In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

Division: Worldwide Development
Retention Category: GRS019
Information Type: Clinical Pharmacology Study Report

Title:	An open-label, two period, study to determine the excretion balance and pharmacokinetics of [^{14}C]-GSK221149A, administered as single doses of an oral solution and an intravenous infusion to healthy female adults

Phase: I
Compound Number: GSK221149
Effective Date: 20-FEB-2008

Description: GSK221149A is an oxytocin receptor antagonist currently in development for the treatment of preterm labor without premature rupture of membranes. Study OTA105101 was a 2-period, open-label study conducted in 6 healthy female subjects (not of child bearing potential). Each subject received a single 100 mg (60 μCi) oral dose of [^{14}C]-GSK221149A in Period 1, and a 10 mg (20 μCi) IV infusion of [^{14}C]-GSK221149A in Period 2. In each period, urine and feces were collected for a minimum of 168 hours following dosing at various sample times after dosing to measure parent drug and total drug-related material. Safety and tolerability were also assessed throughout the study. Samples (for a separate study) were collected to characterize and quantify the metabolic profile of GSK221149A in plasma, urine and feces following administration of [^{14}C]-GSK221149A to healthy adult females. The major route of elimination of GSK221149 and its metabolites was through the feces (58-73% of the administered dose), followed by the urine (20.5-36% of administered dose). There was minimal association of radioactivity with the red blood cells. Levels of radioactivity fell below the limit of quantitation in blood and plasma for all subjects by 24 hours and 8 hours post-dose, respectively. This indicates that little or no accumulation of any metabolites may be expected upon multiple dosing of GSK221149. The absolute bioavailability of GSK221149 was low (28%) following administration as an oral solution and similar to that found in a previous study with GSK221149. Following IV administration, GSK221149 demonstrated moderate to high systemic clearance and a large apparent volume of distribution. Total radioactivity closely paralleled parent drug after oral and IV administration, suggesting that there are no metabolites of GSK221149 with long half-lives. Single 10 mg intravenous doses and single 100 mg oral doses of GSK221149A were generally safe and well tolerated in healthy adult female subjects under the conditions of this study.

Subject: ADME, [^{14}C]-GSK221149A, absolute bioavailability
Authors: [redacted]
Indication Studied: Treatment of preterm labor without premature rupture of membranes

Initiation Date: 24 October 2006
Completion Date: 29 December 2006
Date of Report: February 2008

Sponsor Signatory: [redacted] MD
(and Medical Officer) Clinical Pharmacology and Discovery Medicine
GlaxoSmithKline

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

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Abbreviations

AE	Adverse event
ALT	Alanine amino transferase
AST	Aspartate amino transferase
AUC(0-inf)	Area under concentration-time curve from zero to infinity
AUC(0-t)	Area under concentration-time curve from zero to t
BMI	Body mass index
BP	Blood pressure
^{14} C	Carbon 14
µCi	Micro Curies
CL	Plasma clearance
Cmax	Maximum plasma concentration
CRF	Case report form
CRU	Clinical Research Unit
CV	Coefficient of variation
DMPK	Drug Metabolism & Pharmacokinetics
ECG	Electrocardiogram
EDTA	Ethylene dinitrotetraacetic acid
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
HLQ	Higher limit of quantification
HPLC	High performance liquid chromatography
IRB	Institutional Review Board
ICRP	International Commission on Radiological Protection
IV	Intravenous
kg	Kilogram
LLQ	Lower limit of quantification
LSC	Liquid scintillation counting
mL	Milliliter
MS/MS	Mass spectrometric detection
NQ	Not quantifiable
PGx	Pharmacogenetics
PK	Pharmacokinetics
QC	Quality control
SAE	Serious adverse event
Tmax	Time at which maximum concentration is reached
T1/2	Half-life

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1. INVESTIGATORS AND STUDY ADMINISTRATION

1.1. List of Investigators

Investigator	Investigator/Site Number	Hospital/Institution and Address
[redacted] M.D. (sub-investigator was [redacted] MD)	[redacted]	[redacted]

1.2. Study Administration

	Name and Address	Role/Responsibilities (if applicable for the study)
Ethics Committee	[redacted]	
Contract Research Organization	[redacted]	Responsibilities: PK Analysis

2. ETHICAL CONDUCT OF THE STUDY

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by [redacted]

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, and, the guiding principles of the Declaration of Helsinki.

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. Case report forms (paper) were provided for each subject's data to be recorded.

3. OBJECTIVES

3.1. Objectives

3.2. Primary

- To determine the total recovery and relative excretion of radiocarbon in urine and feces after a single intravenous and single oral doses of [^{14}C]-GSK221149A in healthy adult females

- To generate samples (for a separate study) to characterize and quantify the metabolic profile of GSK221149A in plasma, urine and feces following administration of [^{14}C]-GSK221149A to healthy adult females

3.3. Secondary

- To further assess the safety and tolerability of single intravenous and/or oral doses of GSK221149A in healthy adult female subjects
- To determine the absolute bioavailability of GSK221149A by comparing the disposition of [^{14}C]-GSK221149A following oral and intravenous dosing.
- To determine (as data permit) pharmacokinetic parameters of interest following oral and intravenous dosing.
- To compare total drug-related material (radioactivity) in blood and plasma relative to parent plasma concentrations.

3.4. Endpoints

3.4.1. Primary

- Urinary and fecal cumulative excretion as a percentage of the total radioactive dose administered over time
- Collection of samples for characterization and quantification of metabolites in plasma, urine and fecal homogenates to be documented and performed by DMPK, GSK; results to be reported in a separate report

3.4.2. Secondary

- Clinical safety data from spontaneous AE reporting, 12-lead ECG, vital signs, nursing/physician observation, and safety laboratory tests were summarized and any clinically significant abnormalities described. Safety data were not statistically analyzed.
- $AUC_{(0\text{-inf})}$ and $C_{max,}$ of GSK221149A and drug-related material (radioactivity) in plasma following oral and intravenous dosing.
- T_{max}, $t_{1/2}$ of GSK221149A following oral dosing.
- T_{max}, $t_{1/2}$, volume and clearance of GSK221149A following intravenous dosing.
- Blood:Plasma ratio of total drug-related material (radioactivity)

4. STUDY RATIONALE AND DESIGN

4.1. Study Rationale

Although some data on the disposition of GSK221149A are available from in vitro and in vivo experiments, the metabolic pathways and elimination routes for GSK221149A have not been fully explored. This clinical study was proposed to characterize the single-dose

metabolic disposition of [^{14}C]-labeled GSK221149A by analyzing radioactivity in plasma, urine and feces, and to provide samples on which to investigate the metabolic profile of [^{14}C]-GSK221149A in each matrix.

4.2. Study Design

This was an open-label, non-randomized, 2 period study. Dosing in each period was separated by at least 28 days. In Period 1, subjects received a single dose of 10 mg (20 μCi) intravenous (IV) infusion of [^{14}C]-GSK221149A as a 0.4 mg/mL solution over a period of 5 minutes (Regimen A). In Period 2, subjects received a single oral dose of 100 mg (60 μCi) [^{14}C]-GSK221149A as a 0.8-mg/mL solution (Regimen B). In each period, subjects were admitted to a CRU for 6 consecutive nights.

Safety and tolerability evaluations included assessment of vital signs, 12-lead ECGs, clinical laboratory tests, AE monitoring and physical examinations collected throughout the study.

In each period, blood samples were collected for a minimum of 48 hours post-dose. Blood collections continued until the measured radiocarbon for 2 consecutive plasma samples fell to less than or equal to twice the background radiation count or until both the urine and stool collections were ceased. Samples were collected every 24 hours following the 72 hour sample, if required. Urine and feces were collected for a minimum of 96-hours and a maximum of 240 hours post-dose. Collection was discontinued if the 48-72 and 72-96 hour sample was collected and results of radiocarbon measurement indicated that 2 consecutive samples (of urine and feces) contained less than or equal to 1% of the administered dose of radioactivity.

Follow-up visits were conducted 10 to 14 days after a subject's blood, urine, and fecal samples lowering to the respective required radiocarbon counts for discontinuation of sampling. The total study duration was approximately 2 months.

Blood samples were analysed for GSK221149 by a validated analytical method based on protein precipitation using HPLC-MS/MS analysis. PK analyses of plasma GSK221149 concentration-time data were conducted using noncompartmental methods.

There were no amendments to the original protocol dated 6 April 2006.

5. DIAGNOSIS AND CRITERIA FOR INCLUSION

5.1. Inclusion Criteria

A subject was eligible for inclusion in this study only if all of the following criteria applied:

1. Non-smoking female subjects, 30-55 years old.

2. Females of non-child bearing potential were eligible to be included in this study. Females were considered 'not of child-bearing potential' if one of the following was true:
   - Serum estradiol and FSH levels at screening consistent with a post-menopausal state
   - Post-menopausal females amenorrhoeic for greater than 2 years as of screening
   - Pre-menopausal females with documented hysterectomy with or without bilateral oopherectomy
3. Body weight > 50 kg (110 pounds) and body mass index (BMI) between 19 and 32 where:

$$\text{BMI} = \frac{\text{weight in kg}}{(\text{height in meters})^2}$$

4. Negative for HIV, Hepatitis B and Hepatitis C at screening
5. Available to complete the study (up to 14 days confinement in the research unit)
6. A history of regular bowel movements
7. No clinically relevant findings on clinical examination, medical examination and tests, clinical chemistry, hematology and urinalysis (including microscopy, if abnormalities are found) at pre-study. If parameters were outside the normal range, the subject may have participated in the study when, in the opinion of the Principal Investigator or designee, the abnormality did not compromise safety or interfere with study procedure

5.2. Exclusion Criteria

A subject was not eligible for inclusion in this study if any of the following criteria applied:

1. Any clinically relevant abnormality identified on the screening medical assessment, laboratory examination or 12-lead ECG (including liver function tests and CPK ≥ULN)
2. Positive urine test for drugs of abuse or alcohol at screening or prior to study medication administration
3. Positive urine cotinine at screening
4. History of regular alcohol consumption exceeding 7 drinks/week (average) for women (1 drink = 5 ounces of wine or 12 ounces of beer or 1.5 ounces of hard liquor) within 6 months of screening
5. Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication
6. Donation of blood in excess of 500mL within 56 days prior to the first dose of study medication

7. Previous history of active gastric or duodenal ulcer within 6 months prior to the first dose of study medication
8. Any history of bleeding diathesis or positive fecal occult blood result(s) at screening (If initial results were positive, test may be repeated. Fecal occult blood tests may have been repeated after dietary counseling at the discretion of the investigator. Upon repeat, if results were positive, subject was not permitted to enroll into study).
9. A pre-existing condition(s) interfering with normal gastrointestinal (GI) anatomy or motility, including constipation, malabsorption or other GI dysfunction which may interfere with the absorption, distribution, metabolism or elimination of the study drug
10. An occupation which requires monitoring for radiation exposure, nuclear medicine procedures or excessive x-rays within the past 12 months
11. Participation in another ADME study within the past 12 month
12. The subject received non-prescription drug or vitamins, herbal and dietary supplements within 48 hours prior to the first study day, or St. John's Wort within 14 days prior to the first dose of study drug. Subjects who had taken OTC medication were entered into the study, if, in the opinion of the Principal Investigator or designee, the medication received did not interfere with the study procedures or compromise safety
13. Subjects who received prescription medication within 14 days prior to the first dose of study drug. Subjects were entered into the study, if, in the opinion of the Principal Investigator or designee, the prescription medication did not interfere with study procedures or compromise safety
14. Consumption of grapefruit or grapefruit juice within 7 days of the first study day
15. Exposure to more than 3 new chemical entities within 12 months prior to the first dosing period
16. Subjects who received a total body radiation dose of greater than 5.0 mSv (upper limit of WHO category II) or exposure to significant radiation (e.g. serial x-ray or CT scans, barium meal etc) in the 12 months prior to this study
17. The radiation exposure from the previous 3 year period is over 10 mSv for subjects who have been exposed to ionizing radiation above background as a result of their work with radiation as category A (classified) workers or as a result of research studies they may have been involved in. Clinical (therapeutic or diagnostic) exposure was not included.
18. History of anaphylaxis or anaphalatoid reactions, severe allergic responses to drugs

6. TREATMENT ADMINISTRATION

[^{14}C]-GSK221149A was supplied by GlaxoSmithKline as a sterile solution suitable for both IV and oral routes of administration, a clear, colorless solution which contains GSK221149A at a concentration of 0.8 mg/mL (1.6 μCi/mL) (Batch Number 061126238). In Period 1, subjects received a single dose of 10 mg (20 μCi) IV infusion of [^{14}C]-GSK221149A as a 0.4 mg/mL solution over a period of 5 minutes (Regimen A).

In Period 2, subjects received a single oral dose of 100 mg (60 μCi) [^{14}C]-GSK221149A as a 0.8 mg/mL solution (Regimen B).

Individual oral dose solutions were 100 mg (60 μCi) of [^{14}C]-GSK221149A in 125 mL. Oral doses (one for each subject to be dosed) were prepared on the day of dosing at the clinical site in a pre-weighed vessel. An aliquot (less than 1 mL) was removed to determine radiochemical purity and radioactive concentration in each dose. The full vessel was re-weighed and administered to each of 6 subjects via a straw. A further 100 mL (2 x 50ml) of water was added to the container and the contents rinsed and drunk by the subject. The glass container and straw were washed with consecutive volumes of water/methanol and the radioactivity associated with dose residues determined. Residual radioactivity was deducted from the dispensed radioactivity to determine the total radioactive dose administered.

For IV drug administration, a cannula was sited in a prominent lower forearm vein of the opposite arm for blood sampling, and was removed immediately after completion of the infusion. [^{14}C]-GSK221149A was aspirated into a pre-weighed syringe connected to a three way tap. The apparatus was re-weighed and the dose solution administered as an intravenous infusion of 10 mg (20 μCi) over a period of 5 minutes. At the end of the infusion period, the infusion apparatus (syringe, line, three-way taps and cannulae) was retained for analysis of residual activity as well as any other residual dose material removed subsequent to the initial weighing. The remaining injection solution was used for the assessment of radiochemical purity and radioactive concentration in each dose. The dosing apparatus was washed with consecutive volumes of water/methanol and the radioactivity associated with dose residues determined. Residual radioactivity was deducted from the dispensed radioactivity to determine the total radioactive dose administered.

A small amount of additional radioactive material was collected in a separate container so that the radiochemical purity could be determined and an authentic reference standard (with Certificate of Analysis) was also supplied to facilitate analysis. Additional doses were supplied as a spare dose, for a mock dose preparation and to check radiochemical purity and radioactive concentrations, as required.

The time of dosing (administration of oral solution or start of infusion) was designated Day 1, Time 0; all subsequent timepoints were in relation to this timepoint.

The actual dose received by each subject was determined with reference to the radioactive dose concentration and the weight of dose administered corrected for any residual radioactivity.

7. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures were performed by qualified study personnel as outlined in the Time and Events Schedule provided in Attachment 1.

7.1. Safety Assessments

7.1.1. Adverse Events

An AE was any untoward medical occurrence in a subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The investigator was responsible for the detection and documentation of AEs. AEs were assessed in each study period and at follow-up by asking a non-leading question such as "How do you feel?"

7.1.2. Serious Adverse Events

A serious adverse event (SAE) was any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, or was a congenital anomaly/birth defect. Medical or scientific judgement were exercised in deciding whether reporting was appropriate in other situations, such as important medical events that may not have been immediately life-threatening or result in death or hospitalization but could have jeopardized the subject or could have required medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also have been considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

7.1.3. Clinical Laboratory Evaluations

7.1.4. Other Safety Assessments

7.1.4.1. Vital Signs

Blood pressure and heart rate measurements were performed after subjects had rested for at least 10 minutes in a sitting position at screening; and in a supine position at 1, 2, 4 and 12 hours after dosing in Periods 1 and 2; and at follow-up.

Vital signs measurements were to be repeated if clinically significant changes or machine error occur. Out of range blood pressure and heart rates were repeated at the Investigator's discretion.

7.1.4.2. 12-lead Electrocardiograms

12-lead ECGs were obtained after subjects had rested for at least 10 minutes in a semi - supine position at screening; at 1, 2, 4 and 12 hours after dosing in Periods 1 and 2; and at follow-up. Whenever 12-lead ECGs were performed at the same nominal time as a blood draw or blood pressure and pulse rate measurement, the 12-lead ECG was obtained first. The 12-lead ECG was printed at a paper speed of 25 mm/sec in a '3 x 4' format.

The 12-lead ECG obtained on Day 1 at 1 hour post dose of each dosing period was evaluated for safety. All other post dose 12-lead ECGs were evaluated for safety within 12 hours of obtaining the 12-lead ECG.

The final conduction intervals entered on the CRF was those generated by the ECG machine, unless deemed ***significantly inaccurate*** by the over-reading Investigator or physician designate (e.g., motion artifact, poorly defined waveforms, background noise or arrhythmia that impair automated measurements), and affecting the interpretation of the intervals as of potential clinical concern. In these instances, the hand-read intervals were entered onto the CRF.

7.1.4.3. Physical Exam

A physical exam was conducted at screening; prior to dosing in Periods 1 and 2, and at follow-up.

7.2. Pharmacokinetic Assessments

7.2.1. Cold Assay in Plasma and determination of ^{14}C-Radioactivity in Plasma - Blood Collection and Sampling Times

Following oral administration of [^{14}C]-GSK221149A, blood samples (6 mL) for determination of compound plasma concentrations were collected into EDTA containing polypropylene tubes at the following timepoints: pre-dose and at 15, 30 and 45 minutes post-dose, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60 and 72 hours post-dose. Blood samples could have been drawn either by a needle stick or a peripheral venous catheter.

Following intravenous administration of [^{14}C]-GSK221149A, blood samples (6 mL) were collected pre-dose and at 10, 20, 30 minutes, 1, 2 (prior to cessation of the infusion), 3, 4, 6, 8, 12, 18, 24, 36, 48, 60 and 72 hours after the start of the infusion.

The blood samples obtained from pre-dose through the 48 hour post-dose were mandatory samples. If the radiocarbon measured in the 24 and 48-hour samples (or any two subsequent sequential samples) were each ≤ twice the background radiation count, further samples were not collected. Samples were collected every 24 hours following the 72 hour sample if required.

The samples were processed within 1 hour by centrifugation for 10 minutes at approximately 4ºC and 1500g. The resultant plasma was transferred into uniquely labelled polypropylene tubes of 5 mL and split in 4 aliquots as detailed in Table 1.

Table 1 Details of sample collection of blood and plasma for parent drug and total radioactivity pharmacokinetics.

Sample volume	Whole blood	Plasma	Final aliquots	Measurement	Storage	Analytical Lab
6 mL	6 mL	2.4 mL	1 mL	PK parent	-20°C	GSK
			1 mL	PK parent	-20°C	GSK
			0.2 mL	Radioactivity	-20°C	CRO
			0.2 mL	Radioactivity	-20°C	CRO

The volume indicated in the table is the minimum required assuming a plasma extraction of 40%. Higher volumes are acceptable

The first 2 final aliquots of 1 mL were kept frozen at a nominal temperature of -20°C or below, on dry ice during transit and shipped to GSK.

The 2 final aliquots of 0.2 mL were measured for ^{14}C contents at the CRO facility.

7.2.2. Samples for Metabolite Profiling in Plasma and Radioactivity in Whole Blood - Blood Collection and Sampling Times

Blood samples (approximately 30 mL) were collected into EDTA containing tubes for identification of metabolites and measurement of radioactivity in whole blood at the following sample times: pre-dose, 2, 6, 24 and 48 hours after dosing in Periods 1 and 2.

Duplicate aliquots of whole blood (approximately 0.3 mL) were taken from each sample for whole blood radioactivity analysis. The resultant plasma was put into a pre-labelled NUNC storage tube and split into aliquots as detailed in Table 2.

Table 2 Details of sample collection of blood and plasma for metabolite profiling (GSK study) and whole blood radioactivity measurement.

Sample volume	Whole blood	Plasma	Final aliquots	Measurement	Storage	Analytical Lab
30 mL	0.6 mL	-	0.3 mL	Radioactivity in blood	N/A	CRO
		-	0.3 mL	Radioactivity in blood	N/A	CRO
	29.4 mL	17.6 mL	c 5 mL	Metabolite profiling	-20°C	GSK
			c 5 mL	Metabolite profiling	-20°C	GSK
			c 5 mL	Metabolite profiling	-20°C	GSK

The volumes indicated in the table are the minimum required assuming a plasma extraction of 40%. Higher volumes are acceptable.
C – circa (approximately)

Of the non radiolabelled pre-dose plasma sample, a 5 mL aliquot was spiked with ^{14}C-GSK221149A at appropriate concentrations (ca 50,000-100,0000 dpm/mL) to act as storage and shipment controls and was analysed for radioactivity. The storage samples were prepared within 24 hours of dosing and subjected to the same storage and freeze/thaw regimen as the study samples.

The first 3 final aliquots of c 5 mL and spiked controls were kept frozen at a nominal temperature -20°C or below, on dry ice during transit.

The 2 final aliquots of 0.3 mL were measured for ^{14}C content.

7.2.3. Urine Collection and Sampling Times

Urine samples for ^{14}C-radioactivity (all time points) and metabolic profiling (selected time points) were collected pre-dose and at 0-6 hours, 6-12 hours and 12-24 hours after drug administration and in 24-hour intervals up to 240 hours (Day 10) after drug administration. The intervals between time 0 and 96 hours were mandatory. If the radiocarbon eliminated in the 48 to 72 and 72 to 96-hour collections were both less than or equal to 1% of the administered dose, further collections were not necessary.

All subjects were asked to void their bladders prior to the drug administration. A blank urine sample (100 mL) was collected at pre-dose.

For each subject and each collection interval, there was a pre-weighed 1 liter polypropylene container which was properly labeled with drug name, study code, subject number, study day, date, collection interval and sample number. The urine was stored in a refrigerator immediately after collection (2 to 8°C). Subjects were instructed to empty their bladders completely at the end of each collection interval. The total weight of urine collected was determined during each collection interval.

One 5 mL aliquot was required for determination of ^{14}C-radioactivity and two 20/100 mL aliquots for metabolite profiling and pharmacokinetic analysis. An additional 20/100-mL aliquot was kept at the analysis laboratory. All samples were transferred into appropriately labeled polypropylene tubes or containers and stored at -20°C or below.

In addition a 20 mL aliquot of pre-dose (non-radiolabeled) urine was spiked with [^{14}C]-GSK221149A at appropriate concentrations (ca 50,000-100,0000 dpm/mL) to act as storage and shipment controls and was analyzed for radioactivity. The storage samples were prepared within 48-72 hours of dosing and subjected to the same storage and freeze/thaw regimen as the study samples.

To measure the recoveries of total radiocarbon and concentrations of [^{14}C]-GSK221149A-related compounds in urine over each sample collection period, all urine voided by the subjects was collected in pre-weighed, sterile plastic containers. Recovery of all urine voided was critical to successful completion of the study. To ensure complete collections, access to toilet facilities was restricted. Study center personnel controlled access. When a subject requested to void, the appropriate container, labeled with the subject number and time interval were provided with instructions to collect all urine. Subjects were asked to void at the end of each collection interval, but during the interval they voided as needed. The start and stop time (to the nearest minute) of each urine collection and its total weight after taring the container (to the nearest gram) was recorded in the CRF. While each collection was ongoing, the urine was stored in a refrigerator (2 to 8°C).

A summary of the details for feces sample collection and handling is provided in Table 3.

Table 3 Details of urine samples

	Final aliquots	Measurement	Storage	Analytical Lab
Urine (each fraction)	20/100 mL	Metabolite profile	-20°C	GSK
	20/100 mL	Metabolite profile	-20°C	GSK
	5 mL	Radioactivity	-20°C	CRO
	20/100 mL	Reserve	-20°C	CRO

7.2.4. Feces Collection and Sampling Times

Feces samples for ^{14}C-radioactivity and metabolic profiling was collected pre-dose and in 24-hour intervals up to 240 hours (Day 10) after drug administration. The intervals between time 0 and 96 hours were mandatory. If the radiocarbon eliminated in the 48 to 72 and 72 to 96-hour collections were both less than or equal to 1% of the administered dose, further collections were not necessary.

All stools were collected from each subject for up to 10 days post-dosing to measure total radiocarbon excreted in feces and for metabolite profiling. The time of each collection (to the nearest minute) and its total weight (after taring the container) was recorded on the CRF. Feces and toilet paper were collected and weighed as passed, and then were frozen at -70°C or lower. Feces samples were pooled for each subject at 24-hour intervals.

The weight of the feces was recorded. The feces samples analyzed were quantitatively transferred into a pre-weighed fitting bucket. Water was added and the sample re-weighed. Fecal samples were homogenized using an Industrial Blender. Three 20/100 g aliquots were retained and stored at -20°C: or below one for metabolite profiling; one for determination of ^{14}C-radioactivity and one to be kept at CRO. The remainder of the homogenates were discarded at the end of study upon agreement with GSK.

An additional 20g aliquots of pre-dose (non-radiolabeled) fecal homogenate was spiked with [^{14}C]-GSK221149A at appropriate concentrations (ca 50,000-100,0000 dpm/g) to act as storage and shipment controls and was analyzed for radioactivity. The storage samples were prepared within 24 hours of dosing and subjected to the same storage and freeze/thaw regimen as the study samples.

Feces samples collected for metabolic profiling were kept frozen on dry ice during transit and shipped to GSK.

A summary of the details for feces sample collection and handling is provided in Table 4.

Table 4 Details of feces samples

	Final aliquots	Measurement	Storage	Analytical Lab
Feces (each fraction)	20/100 g	Metabolite profile	-20°C	GSK
	20 g	Radioactivity	-20°C	CRO
	20/100 g	Reserve	-20°C	CRO

7.2.5. Sample Handling

Samples of blood (*ca.* 1 mL) and plasma (*ca.* 0.5 to 1 mL) were stored at *ca*. -20°C before and after analysis of total radioactivity concentration. Sub-samples of urine (*ca.* 5 mL each) were stored at *ca*. -20°C before and after analysis. Feces samples were stored at *ca* -20°C before analysis. At the time of processing, three *ca.* 50 g (if available) sub-samples of each fecal homogenate were removed and stored at *ca*. -20°C. One sub-sample was used to determine the total radioactivity concentration, another sub-sample was shipped to the Sponsor as described below and one was retained as a reserve sample. The remaining bulk fecal homogenate samples will be stored at *ca.* -20°C for *ca.* 6 months or until discarded upon agreement with the Sponsor.

Additionally, storage and shipment stability samples were prepared for each period according to the following procedures. One 5 mL aliquot of pre-dose plasma was spiked with [^{14}C]GSK221149A at an appropriate concentration (*ca.* 50,000 to 100,000 dpm/mL). Portions of the pre-dose urine and feces samples from the same subject were used for storage and shipment stability sample preparation. An *ca.* 20 mL urine aliquot was spiked with [^{14}C]GSK221149A at an appropriate concentration (*ca.* 50,000 to 100,000 dpm/mL) and an *ca.* 20 g aliquot of fecal homogenate was spiked with [^{14}C]GSK221149A at an appropriate concentration (*ca.* 50,000 to 100,000 dpm/g). The spiked aliquots were stored at *ca.* -20°C until shipment as described below. All samples were assayed for radioactivity content prior to shipment.

Note: Urine and plasma were spiked at a concentration of 50,000-100,000 dpm/mL. Feces was spiked at a concentration of 50,000-100,000 dpm/g.

7.2.6. Determination of Radioactivity

All samples prepared in scintillation fluid were subjected to liquid scintillation counting for 5 minutes (urine, feces and whole blood), together with representative blank samples, using a Liquid Scintillation Analyser with automatic quench correction by an external standard method. Prior to analysis, samples were allowed to stabilize with regard to light and temperature. Representative blank sample values were subtracted from sample count rates to give net dpm per sample.

A limit of reliable measurement of *30 dpm* above background had been instituted in the laboratories.

All sample combustions were performed in a Model 307 Sample Oxidizer (Packard Instrument Company; Downers Grove, IL). The resulting $^{14}CO_2$ was trapped in Carbo-Sorb. Perma-Fluor scintillation cocktail was added and the radioactivity content was quantitated by LSC. All samples directly counted by LSC were analyzed using Ultima Gold scintillation cocktail. The samples were counted in a Model 2900TR liquid scintillation counter (Packard) for at least 5 min or 100,000 counts. All samples were analyzed in duplicate (if sample size allowed), with the exception of feces, which were analyzed in triplicate. If results for sample replicates (calculated as dpm/g of sample) differed by more than 10% from the mean value, the sample was rehomogenized (where appropriate) and reanalyzed. This specification was met for all sample aliquots that had radioactivity greater than 500 dpm.

7.2.6.1. Analysis of Blood

Each sample was mixed thoroughly and duplicate aliquots from each blood sample (*ca.* 0.3 mL each) were combusted and analyzed for radioactivity.

7.2.6.2. Analysis of Plasma

Each sample was mixed thoroughly and duplicate aliquots (*ca.* 0.2 mL each) were transferred to scintillation vials and analyzed for radioactivity.

7.2.6.3. Analysis of Urine

Each sub-sample was mixed thoroughly and duplicate aliquots (*ca.* 1.0 mL each) were transferred to scintillation vials and analyzed for radioactivity.

7.2.6.4. Analysis of Feces

The samples were pooled by subject and interval, weighed, mixed with deionized water and the homogenate weight was recorded. Samples were allowed to extract at least overnight (if possible; samples from later collection intervals may have been analyzed on the day of receipt to facilitate the release of the subjects from the CRU). The samples were homogenized with a probe-type homogenizer and triplicate weighed aliquots (*ca.* 0.3 g each) were combusted and analyzed for radioactivity.

7.2.7. Pharmacokinetic Bioanalytical Methods

Human plasma samples were analysed for GSK221149 by Worldwide Bioanalysis, GlaxoSmithKline Pharmaceuticals at King of Prussia, PA using a validated analytical method based on protein precipitation, followed by high-performance liquid chromatography (HPLC) with tandem mass spectrometric detection (MS/MS). The lower limit of quantification (LLQ) for GSK221149 was 1 ng/mL using a 50 µL aliquot of human plasma with a higher limit of quantification (HLQ) of 1000 ng/mL [GlaxoSmithKline Document Number CD2005/00446/00].

Quality Control (QC) samples, prepared at 3 different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the QC results were to deviate from the nominal concentration by more than 15%, and at least 50% of the results from each QC concentration should be within 15% of nominal. The applicable analytical runs met all predefined run acceptance criteria. All data are stored in the GLP Archive, GlaxoSmithKline Pharmaceuticals, Research & Development, Upper Merion, PA.

7.3. Pharmacogenetic Assessments

In addition to any blood samples taken for the clinical study, a whole blood sample (~10mL) was collected for the pharmacogenetic (PGx) research using a tube containing EDTA. The PGx sample was labeled (or "coded") with a study-specific number that could be traced or linked back to the subject by the investigator or site staff. Coded samples did not carry personal identifiers (such as name or social security number). The blood sample was taken on a single occasion unless a duplicate sample was required due to the inability to utilize the original sample. It was recommended that the blood sample be taken at the first opportunity after a subject had been randomized and provided informed consent for PGx research, but could have been taken at any time while the subject was participating in the clinical study.

The need to conduct PGx analysis may be identified after a study (or set of studies) of GSK221149A has been completed and the study data reviewed. For this reason, samples

may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. In special cases, the samples may not be studied. This might happen if there are not enough subjects, if the study was stopped for other reasons, or if no questions are raised about how people respond to GSK221149A.

No analyses of PGx samples from this study are currently planned. If at any time a potential unexpected or unexplained variation in drug handling or response is apparent that may be attributable to genetic variation (e.g., pharmacokinetics, efficacy and/or safety), then PGx analysis will be considered and will be the topic of a separate report.

8. METHODS

Samples collected for analysis of balance/excretion and metabolite data were collected. Details regarding the methods of analysis will be reported separately.

8.1. Data Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK could have conducted a quality assurance audit. Regulatory agencies could also have conducted a regulatory inspection of this study. Such audits/inspections could have occurred at any time during or after completion of the study.

The PK data generated were subject to QC procedures by [redacted]

At the clinical study sites, the investigator or their designee recorded all required subject data in paper Case Report Forms (CRFs). A screening log with GSK-required information and created by the investigator at the site, tracked subjects who were screened prior to entry into the study but who were not randomized. An investigator meeting was held where monitor-related guidelines were shared with the site prior to study start.

The completed original CRFs were returned to GSK Data Management for processing. In addition, validated laboratory data was transmitted electronically to GSK Data Management. The investigator retained copies of the CRFs.

Data entry applications were designed and validated using a data entry screen software system (i.e., ClinTrial). Data values recorded on the CRF were entered using double-dependent data entry.

Computerized data validation was performed on CRF data using ClinTrial validation checks and study-specific data validation checks. Validation discrepancies, if not covered by a Standard Clarification Agreement (SCA), were queried using the documented data query process for review and resolution by investigators, and if appropriate, with reference to the clinical Study Team members. Any necessary changes were made to both the CRF and the database by data management staff.

QC tasks were conducted in accordance with existing data management standard operating procedures to ensure database accuracy against the data collected in the CRF.

QC procedures are in alignment with the International Conference on Harmonisation of Good Clinical Practice (ICH GCP). Adverse events and concomitant medications were coded by the autoencoder using the MedDRA (version 9.0) and GSKDRUG dictionary.

8.2. Data Analysis Methods

Statistical analyses were the responsibility of Clinical Pharmacology Statistics and Programming (CPSP), GlaxoSmithKline Pharmaceuticals, Philadelphia, PA.

8.2.1. Balance/Excretion Data Handling Conventions

Dose tables were compiled with the mean and standard deviation values calculated using the Excel software program, Version 8.0e (Microsoft Corporation). Data tables (radioactivity concentration and percentage of dose) were generated by DEBRA, Version 5.2a (LabLogic), an automated and validated data capture and management system for studies using radiolabeled test article. The Rees system was used to capture environmental conditions in storage units.

8.2.2. Pharmacokinetic Data Handling Conventions

Plasma GSK221149A concentration data stored in SMS2000 were extracted into a MicroSoft Excel spreadsheet. SAS-based programs were employed to convert the bioanalytical spreadsheet to SAS datasets, to merge concentration data with treatment information and actual sampling times, and to convert the resulting datasets to a comma-delimited text files. The text files were then accessed by WinNonlin Professional, Version 4.1 computer software for PK analyses of concentration-time data. PK parameters were calculated and exported to MicroSoft Excel spreadsheet or comma-delimited text file(s) and subsequently converted to SAS datasets for statistical analyses.

8.2.3. Drug Concentration Data

Plasma GSK221149A concentrations were listed by subject and actual sampling time. Plasma GSK221149A concentrations were summarized by planned sampling time. Figures of individual and mean/median plasma GSK221149A concentration-time profiles were produced on both semi-log and linear scales.

For the calculation of mean and median profiles, NQ values were set to zero except when an individual NQ fell between two quantifiable values, in which case it was omitted. The mean/median value at a time with one or more NQ values was reported unless the resulting mean/median value was below the LLQ of the assay, in which case the value was reported as NQ.

8.2.4. Balance/Excretion Parameters

Radioanalysis was conducted by [redacted] United States, under the direction of Clinical Pharmacokinetics/Modeling and

Simulation, GlaxoSmithKline. Analysis was conducted in accordance with [redacted] sample analysis scheme CMS 78916B (dated 09 November 2006), [redacted] standard operating procedures (SOPs) and the [redacted] Department of Health and Family Services, Radiation Protection Section (License No. [redacted]

8.2.5. Pharmacokinetic Parameters

PK analysis was conducted by [redacted] United States, under the direction of Clinical Pharmacokinetics/Modeling and Simulation, GlaxoSmithKline. Pharmacokinetic data are stored in the Archive, GlaxoSmithKline, Research and Development.

PK analysis of plasma GSK221149 concentration-time data was conducted using the noncompartmental Model 200 (Period 2) and Model 202 (Period 1) of WinNonlin Professional Edition version 4.1 [Pharsight Corporation, Mountain View, CA, 2003] according to the standard operating procedures described in Standard Methods for the Non-Compartmental Analysis of Pharmacokinetic Data (SOP-CPK-0001 v01, 29-Aug-03). Actual elapsed time from dosing was used to estimate all individual plasma PK parameters for evaluable subjects. Values for the following PK parameters were estimated:

- The maximum observed plasma concentration (Cmax) and time of occurrence of Cmax (tmax) were the actual observed values.
- Where data permitted, the terminal elimination rate constant (λz) was derived from the log-linear disposition phase of the concentration-time curve using least-squares regression analysis with visual inspection of the data to determine the appropriate number of terminal data points for regression analysis. The terminal phase half-life (t1/2) was calculated as $\ln 2/\lambda z$.
- Area under the plasma concentration-time curve was calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Area under the plasma concentration-time curve from time zero to the last measurable concentration [AUC(0-t)] and from time zero to infinity after single dosing [AUC(0-∞)] were determined. Values for AUC(0-∞) were estimated as the sum of AUC(0-t) and Ct divided by the elimination rate constant, where Ct was the last observed quantifiable concentration. The percentage of AUC(0-∞) obtained by extrapolation [%AUCex] was also calculated. It was calculated as: [(AUC(0-∞)-AUC(0-t))/AUC(0-∞)] * 100.
- Total clearance (CL) was calculated as Dose/AUC(0-∞) for Period 1.
- Volume of distribution at steady-state (Vd_{ss}) was calculated as CL * Mean Residence Time (MRT) for Period 1.
- Absolute bioavailability (F) was calculated as dose-normalized AUC(0-∞) from the oral dose (Period 2)/dose-normalized AUC(0-∞) from the IV infusion dose (Period 1). F was calculated using MicroSoft Excel Version 10.0.

8.2.6. Sample Size Considerations

8.2.6.1. Sample Size Assumption

The target sample size for the study was 6 subjects. Based on experience with other studies, this sample size was expected to provide sufficient PK data to address the study objective while limiting the number of subjects exposed to radioactivity. No sample size calculations were performed.

8.2.7. Interim Analysis

No formal statistical interim analyses were planned for this study.

8.2.8. Final Analyses

8.2.8.1. Balance/Extretion Analyses

No formal statistical analyses of the data were performed. Statistical analyses were limited to mean, standard deviation and coefficient of variation calculations, as appropriate.

8.2.8.2. Pharmacokinetic Analyses

No formal statistical analyses of the pharmacokinetic data were performed. Plasma GSK221149A concentration-time data was listed for each subject and summarized by planned sampling time. Individual, mean, and median concentration-time profiles were plotted on both linear and semi-log scale.

The PK parameters AUC(0-∞), AUC (0-t), CL, Cmax, F, Vss, and T½ were calculated. Individual subject parameter values, as well as a descriptive summary of parameters were reported. The descriptive statistics include the mean, standard deviation, median, minimum, maximum, and for all parameters except T_{max}, the standard deviation of log-transformed values, geometric mean and corresponding 95% confidence intervals.

8.2.9. Changes in conduct of the study or planned analyses

Heart rate (HR) data was not collected in Period 1 due to site error.

[redacted]

9. STUDY POPULATION RESULTS

9.1. Disposition of Subjects

Six (6) subjects entered the study and received at least one dose of study medication; all 6 subjects completed the study.

9.2. Protocol Deviations

There were no deviations related to the inclusion/exclusion criteria.

[redacted] As such, this subjects's PK data was excluded from the Period 1 PK evaluation.

In Period 2 (all subjects were dosed in Period 2 on 11 December 2006), it was noted that exact preparation was not followed. The [[^{14}C]-GSK221149A Oral Dose Preparation form instructed the CRU staff to mix 39 mL of [^{14}C]-GSK221149A with 91 mL GSK221149 to arrive at a total volume of 130 mL. From that total, a 5 mL aliquot was to be separated leaving 125 mL available for the oral dose. However, 99 mL of the GSK221149 was mixed with the [^{14}C]-GSK221149A due to miscalculation, resulting in 138 mL total volume. The resultant gram dose was still within 5%.

The study was otherwise conducted as per protocol.

9.3. Populations Analyzed

PK: All subjects who received the study medication and had sufficient data for evaluation of PK were included in the PK analysis population. [redacted] All 6 subjects were included in the PK analysis of data collected in Period 2.

Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. All 6 subjects were included in the evaluation of safety and tolerability.

9.4. Demographics Characteristics

All subjects entered into the study were White females.

Table 5 Subject Disposition and Characteristics

Number of subjects planned	6
Number of subjects entered	6
Number of subjects completed	6
Age, years	
Mean (SD)	52.2 (2.48)
Median (Range)	52.5 (48-55)
Gender, N	
Females	6
Height (cm)	
Mean (SD)	163.7 (8.50)
Median (Range)	161.5 (154-178)
Weight (kg)	
Mean (SD)	70.65 (11.636)
Median (Range)	69.35 (53.7-89.1)
BMI (kg/m^2)	
Mean (SD)	26.17 (2.087)
Median (Range)	26.55 (22.6-28.2)
Race, N (%)	
White – White/Caucasian/European Heritage	6 (100)
Ethnicity, N	
Hispanic or Latino	0 (0)
Not Hispanic or Latino	6 (100)

Source: Safety Source Table 9.1 and Table 9.4

9.5. Concomitant Medications

One subject took a concomitant medication during the treatment phase of the study (in-text Table 6). Use of this concomitant medication was not thought to affect subject safety or the interpretation of study results.

Table 6 Prohibited Concomitant Medications by Subject

[redacted]

Source: Safety Source Table 11.12

9.6. Treatment Compliance

Study medication was administered by study personnel. Compliance was 100%.

10. PHARMACOKINETIC RESULTS

10.1. Dose Analysis

10.1.1. Radiochemical Purity

The mean radiochemical purity of [^{14}C]GSK221149A was 99.8% in the intravenous dose solution for Session 1 and 99.6% in the oral dose solution for Session 2.

10.1.2. Dose Administration

For IV administration (Period 1), the mean dose administered was 20.4 µCi per subject (mean of 9.94 mg GSK221149A per subject) (Table 7). For oral administration (Period 2), the mean dose administered was 62.2 µCi per subject (mean of 105 mg GSK221149A per subject) (Table 8).

Table 7 Mean and Individual Intravenous Doses of [^{14}C]GSK221149A Administered to Healthy Female Subjects

[redacted]

Source: Attachment 2, [redacted] Radioanalysis Report

Table 8 Mean and Individual Oral Doses of [^{14}C]GSK221149A Administered to Healthy Female Subjects

[redacted]

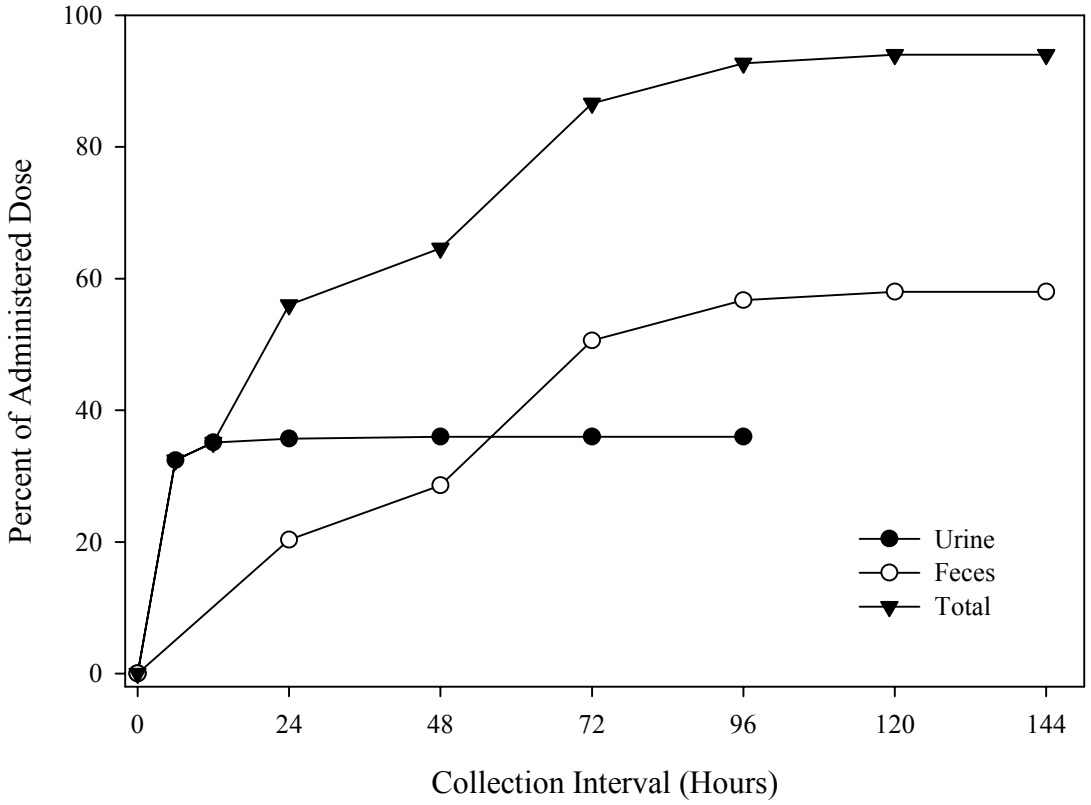
Source: Attachment 2, [redacted] Radioanalysis Report

10.2. Excretion of Radioactivity

10.2.1. Period 1 - Intravenous Administration

Following the single intravenous dose in Period 1 (Figure 1), fecal excretion was the predominant route of elimination, accounting for a mean of 58.0% of the administered dose (range of 55.1 to 60.9% in individual subjects). Urinary excretion accounted for a mean of 36.0% of the administered dose (range of 32.2 to 39.3% in individual subjects). Most of the dose (mean of 92.7%) was recovered in urine and feces by 96 hours post-dose. The mean total recovery of radioactivity was 93.9% of the dose (range of 93.1 to 95.5% in individual subjects).

Figure 1 Mean Cumulative Elimination of Radioactivity by Healthy Female Subjects after a Single 10-mg/20-µCi Intravenous Dose of [^{14}C]GSK221149A (Session 1)



Source: Attachment 2, [redacted] Radioanalysis Report

The maximum mean concentrations of [^{14}C]GSK221149A-derived radioactivity were observed for samples collected from 0-6 hours post-dose for urine (3370 ng equiv/mL) and 24-48 hours post-dose for feces (22,000 ng equiv/g).

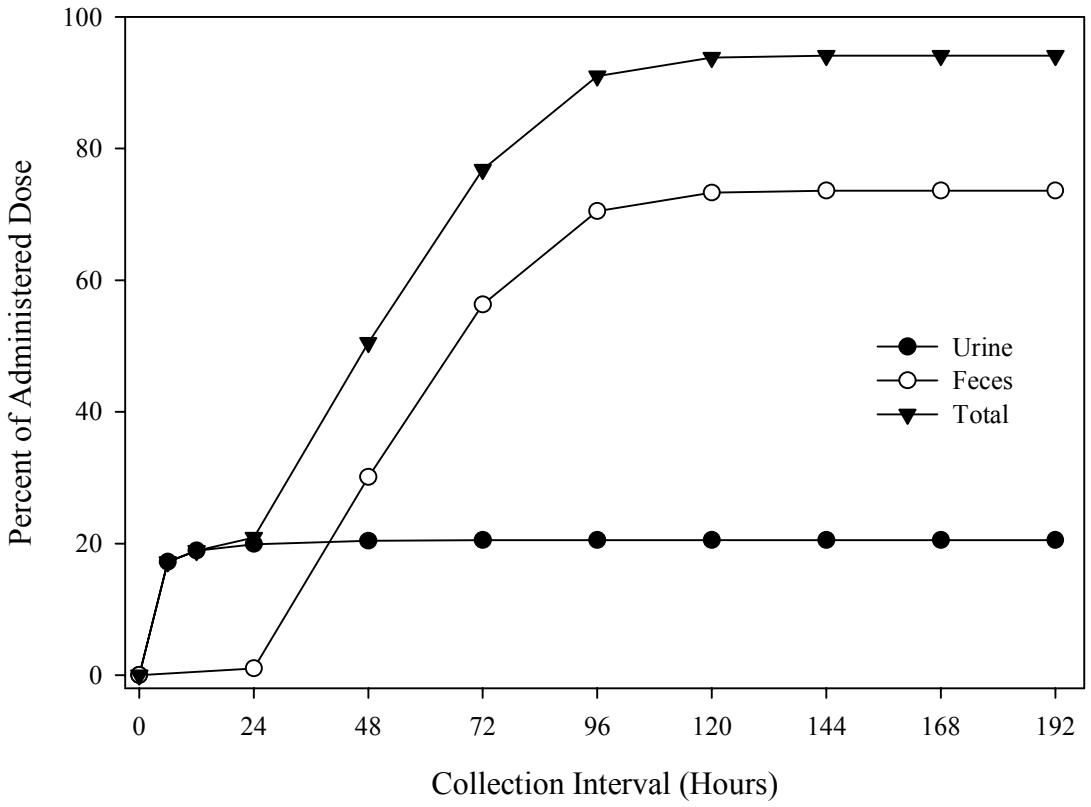
Mean and individual recoveries of radioactivity for each collection interval are presented in Table 2 and cumulatively in Table 3 of Attachment 2, [redacted] Radioanalysis Report.

Concentrations of radioactivity in urine and feces are presented in Table 4 of Attachment 2, [redacted] Radioanalysis Report.

10.2.2. Period 2 - Oral Administration

Following the single oral dose in Period 2 (Figure 2), fecal excretion was again the predominant route of elimination, accounting for a mean of 73.6% of the administered dose (range of 66.7% to 78.2% in individual subjects). Urinary excretion accounted for a mean of 20.5% of the administered dose (range of 18.3 to 23.4% in individual subjects). Most of the dose (mean of 93.8%) was recovered in urine and feces by 120 hours post-dose. The mean total recovery of radioactivity was 94.1% of the dose (range of 87.0 to 97.4% in individual subjects).

Figure 2 Mean Cumulative Elimination of Radioactivity by Healthy Female Subjects after a Single 100-mg/60-µCi Oral Dose of [^{14}C]GSK221149A (Session 2)



Source: Attachment 2, [redacted] Radioanalysis Report

The maximum mean concentrations of [^{14}C]GSK221149A -derived radioactivity were observed for samples collected from 0-6 h post-dose for urine (21,200 ng equiv/mL) and 48-72 hours post-dose for feces (380,000 ng equiv/g).

Mean and individual recoveries of radioactivity for each collection interval are presented in Table 5 of Attachment 2, [redacted] Radioanalysis Report and cumulatively in Table 6

of Attachment 2, [redacted] Radioanalysis Report. Concentrations of radioactivity in urine and feces are presented in Table 7 of Attachment 2, [redacted] Radioanalysis Report.

10.3. Concentrations of Radioactivity in Blood and Plasma

10.3.1. Total Radioactivity

GSK221149 total radioactivity pharmacokinetic parameters are presented in Table 10.5 – Table 10.9, and are summarized in Table 9 below.

Following a single, oral 100mg dose of [^{14}C]-GSK221149A, total radioactivity rapidly appeared in plasma with a median tmax value of 0.5 hour. The mean half-life of total radioactivity after oral administration (2.13 hours) was slightly longer than that observed after IV administration (1.22 hours), but was still relatively short. As was observed with the parent compound, between-subject variability was low after IV administration and moderate after oral administration.

Table 9 Geometric Mean (CVb%) of Total Radioactivity Pharmacokinetic Parameters

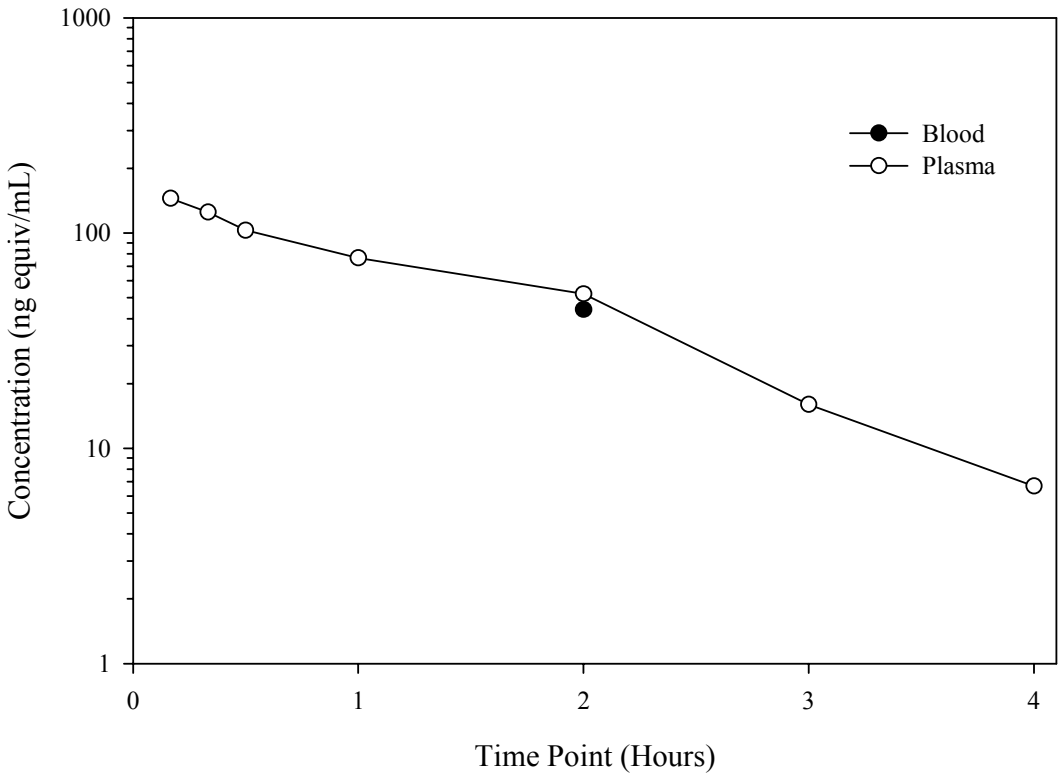
Period	n	AUC(0-∞) (ng·hr/mL)	AUC(0-t) (ng·hr/mL)	Cmax (ng/mL)	tmax (hr)[1]	t1/2 (hr)
1	5	268.37 (20.70)	188.75 (19.46)	179.1 (15.00)	0.170 (0.17-0.33)	1.22 (25.73)
2	6	2291.04 (21.08)	1864.60 (21.69)	840.7 (25.00)	0.5 (0.25-0.78)	2.13 (38.25)

Source Data: Pharmacokinetic Source Table 10.5 – Table 10.9
1. Median (Range)
NC Not calculated
Period 1 Single, 10mg dose of [^{14}C]-GSK221149A, IV infusion over 5 minutes
Period 2 Single, 100mg dose of [^{14}C]-GSK221149A, oral solution

10.3.2. Period 1 - Intravenous Administration

The maximum mean concentration of radioactivity in blood was observed at 2 hours post-dose (44.1 ng equiv/mL) (Figure 3). Individual maximum concentrations of radioactivity in blood were observed at 2 hours post-dose (range of 32.9 to 56.7 ng equiv/mL). The maximum mean concentration of radioactivity in plasma was observed at 10 minutes post-dose (145 ng equiv/mL) (Figure 3). Individual maximum concentrations of radioactivity in plasma were observed from 10 minutes to 2 hours post-dose (range of 69.7 to 209 ng equiv/mL). Levels of radioactivity fell below the limit of quantitation in both blood and plasma for all subjects by 6 h post-dose (Figure 3).

Figure 3 Mean Concentrations of Radioactivity in Blood and Plasma from Healthy Female Subjects after a Single 10-mg/20-µCi Intravenous Dose of [^{14}C]GSK221149A (Period 1)



Source: Attachment 2, [redacted] Radioanalysis Report

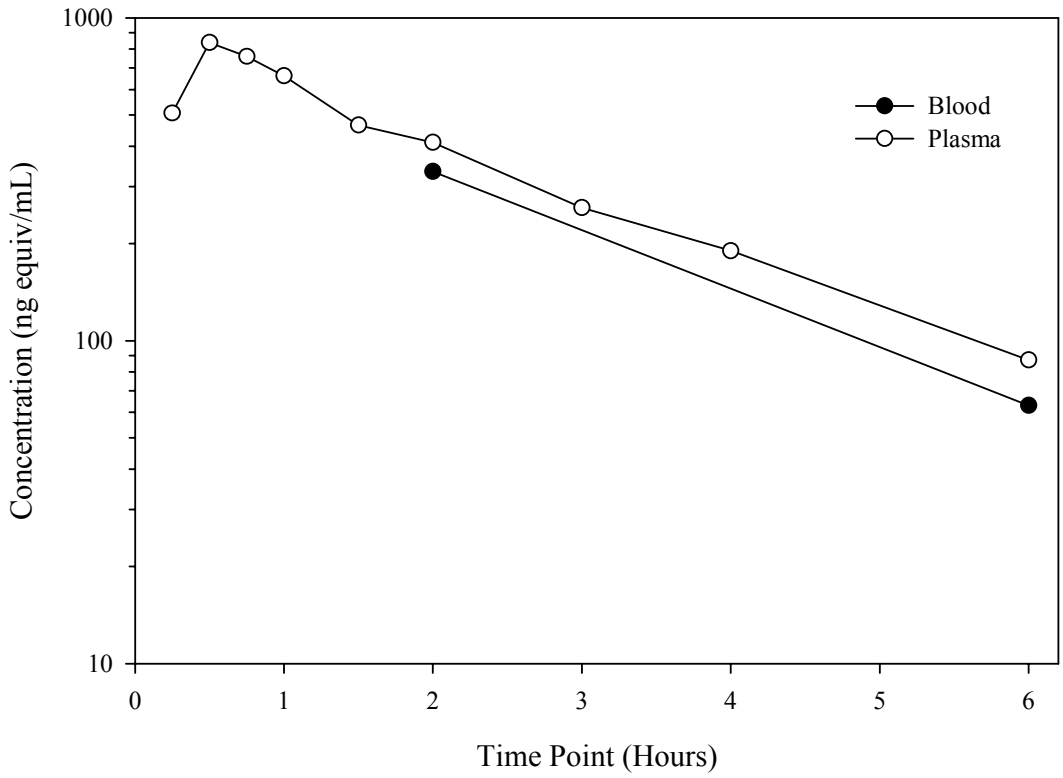
The mean blood:plasma ratio at 2 hours post-dose was 0.850, indicating minimal association of radioactivity with the red blood cells.

The mean and individual concentrations of total radioactivity in blood and plasma samples are presented in Table 8 and Table 9, respectively, of Attachment 2, [redacted] Radioanalysis Report. Blood:plasma concentration ratios are presented in Table 10 of Attachment 2, [redacted] Radioanalysis Report.

10.3.3. Period 2 - Oral Administration

The maximum mean concentration of radioactivity in blood was observed at 2 hours post-dose (334 ng equiv/mL) (Figure 4). Individual maximum concentrations of radioactivity in blood were observed at 2 hours post-dose (range of 283 to 419 ng equiv/mL). The maximum mean concentration of radioactivity in plasma was observed at 30 minutes post-dose (838 ng equiv/mL) (Figure 4). Individual maximum concentrations of radioactivity in plasma were observed from 15 to 45 minutes post-dose (range of 635 to 1260 ng equiv/mL). Levels of radioactivity fell below the limit of quantitation in blood and plasma for all subjects by 24 hours and 8 hours post-dose, respectively (Figure 4).

Figure 4 Mean Concentrations of Radioactivity in Blood and Plasma from Healthy Female Subjects after a Single 100-mg/60-µCi Oral Dose of [^{14}C]GSK221149A (Period 2)



Source: Attachment 2, [redacted] Radioanalysis Report

Mean blood:plasma ratios at 2 hours and 6 hours post-dose were 0.812 and 0.718, respectively, indicating minimal association of radioactivity with the red blood cells.

The mean and individual concentrations of total radioactivity in blood and plasma samples are presented in Table 11 and Table 12, respectively, of Attachment 2, [redacted] Radioanalysis Report. Blood:plasma concentration ratios are presented in Table 13 of Attachment 2, [redacted] Radioanalysis Report.

10.4. GSK221149 Plasma Pharmacokinetics

GSK221149 PK parameters are summarized in in-text Table 10.

Table 10 Geometric Mean (CVb%) of GSK221149 Pharmacokinetic Parameters

Period	n	AUC(0-∞) (ng·hr/mL)	AUC(0-t) (ng·hr/mL)	Cmax (ng/mL)	tmax (hr)[1]	t1/2 (hr)	CL (L/hr)	Vd_{ss} (L)	F (%)
1	5	203 (11.7)	197(13.5)	188 (13.5)	0.170 (0.17 – 0.33)	1.34 (21.0)	49.3 (11.7)	80.6 (14.8)	NC
2	6	538 (48.3)	533 (48.6)	311 (60.3)	0.500 (0.25 – 0.78)	1.46 (21.9)	NC	NC	28.1 (43.5)

Source Data: Pharmacokinetic Source Table 10.2 and Table 10.3
1. Median (Range)
NC Not calculated
Regimen A Single, 10mg dose of [^{14}C]-GSK221149A, IV infusion over 5 minutes (Period 1)
Regimen B Single, 100mg dose of [^{14}C]-GSK221149A, oral solution (Period 2)

Following a single, oral 100mg dose of [^{14}C]-GSK221149A, GSK221149 rapidly appeared in plasma with a median tmax value of 0.5 hour. Similar mean t½ values of GSK221149 were observed following IV drug administration (1.34 hours) and following oral drug administration (1.46 hours). The mean CL of GSK221149 from plasma was 49.3 L/hr which is approximately 60% of human liver blood flow [Davies, 1993]. The mean Vd_{ss} of GSK221149 was 80.6 L, which may indicate that GSK221149 was extensively distributed in tissue [Davies, 1993]. The mean absolute bioavailability (F) of GSK221149 was 28.1%.

Between-subject variability was low for PK parameters following intravenous drug administration, while the between-subject variability for PK parameters was generally moderate following oral drug administration.

Individual plots for PK parameters can be found in Pharmacokinetic Source Figure 10.1 – Figure 10.3.

10.5. Statistical Analysis Details

Statistical analyses of Pharmacokinetic data were the responsibility of Clinical Pharmacology Statistics & Programming, GlaxoSmithKline Pharmaceuticals, Philadelphia, US.

Pharmacokinetic data was released to CPSP on April 10, 2007 by Clinical Pharmacokinetics via HARP. Main results of the summary statistics are presented to the accuracy of the raw data. All summary statistics were carried out using SAS 8.02 for UNIX running under the HARP environment.

[redacted]

10.6. Metabolite Data

Samples were collected for analysis of metabolite data. Results will be reported separately.

11. SAFETY RESULTS

11.1. Extent of Exposure

Six (6) subjects were enrolled in the study and received both treatment regimens. A total of 6 subjects completed the study. A record of study medication administration is provided in Safety Source Table 11.1.

11.2. Adverse Events

The overall rate of occurrence of AEs appeared similar following IV or oral administration of [^{14}C]-GSK221149A (in-text Table 11).

Table 11 Post-dose Adverse Events

	Number of Subjects	
Adverse Event	Regimen A (IV)	Regimen B (Oral)
Abdominal pain	--	3
Fatigue	--	3
Diarrhea	--	2
Headache	--	2
Flatulence	1	1
Nausea	--	1
Vomiting	--	1
Puncture site pain	1	--
Herpes simplex	--	1
Viral upper respiratory tract infection	1	--
Ecchymosis	1	--
Erythema	1	--
Pruritis	1	--
Rash	1	--
Conjuctival hemorrhage	--	1
Pallor	--	1
# of Subjects Exposed	6	6
# of Subjects with AE	4	5

Source: Safety Source Table 11.2
Regimen A Single, 10mg dose of [14C]-GSK221149A, IV infusion over 5 minutes (Period 1)
Regimen B Single, 100mg dose of [14C]-GSK221149A, oral solution (Period 2)

All AEs reported during the study resolved. The majority of AEs were considered mild; there was 1 subject with a moderate AE. [redacted] This subject had an AE of viral upper respiratory tract infection which started the day prior to dosing in Period 2.

11.3. Serious Adverse Events And Adverse Events Leading to Withdrawal

No subjects died, experienced an SAE, or withdrew due to an AE in this study.

11.4. Pregnancies

No pregnancies were reported in this study.

11.5. Clinical Laboratory Evaluations

There were no clinical chemistry or hematology values of potential clinical concern (PCC).

[redacted] The finding transient and not considered clinically significant by the investigator.

11.6. Vital Signs

Five subjects had post-dose vital signs of potential clinical concern (PCC) (in-text Table 12). All values of PCI were transient, asymptomatic and not considered by the investigator to be clinically significant.

Table 12 Subjects with Post-Dose Vital Signs of Potential Clinical Concern

[redacted]

Source: Safety Source Table 11.13
SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; H - hour
PCI Criterion:
SBP: ≥140 mmHg or >30 mmHg change from baseline
DBP: ≥90 mmHg or >20 mmHg change from baseline
Regimen A Single, 10mg dose of [14C]-GSK221149A, IV infusion over 5 minutes (Period 1)
Regimen B Single, 100mg dose of [14C]-GSK221149A, oral solution (Period 2)

11.7. ECGs

One subject had post-dose ECG parameters of PCC. The value was transient, resolved spontaneously, and was not considered by the investigator to be an AE.

Table 13 Subjects with Post-Dose ECGs of Potential Clinical Concern

[redacted]

Source: Safety Source Table 11.11
Regimen A Single, 10mg dose of [14C]-GSK221149A, IV infusion over 5 minutes (Period 1)

12. DISCUSSION AND CONCLUSIONS

12.1. Discussion

Following oral administration of [^{14}C]-GSK221149A, GSK221149 was rapidly absorbed and rapidly eliminated from plasma. Similar mean t1/2 values of GSK221149 were observed following intravenous drug infusion and oral drug administration of [^{14}C]-GSK221149A. After intravenous administration, clearance of GSK221149 from plasma was moderate to high (approximately 60% of human liver blood flow). The Vd_{ss} of GSK221149 was greater than total body water in humans, which may indicate that GSK221149 was extensively distributed to the tissue [Davies, 1993]. The absolute bioavailability (F) was 28.1% indicating that GSK221149 was not highly bioavailable following oral administration of [^{14}C]-GSK221149A.

After both oral and intravenous elimination, the major route of elimination of GSK221149-associated radioactivity was via the feces and urine. Nearly complete recovery of radioactivity (>93%) was achieved after both routes of administration. Radioactivity levels were not detectable after 24 hours after oral administration (8 hours after IV administration), indicating that none of the metabolites of GSK221149 will accumulate upon multiple dosing.

Total radioactivity closely paralleled parent drug after oral and IV administration, suggesting that there are no metabolites of GSK221149 with long half-lives.

The blood and plasma levels of GSK221149-associated radioactivity were similar. This suggests that GSK221149 and its metabolites do not accumulate in the erythrocytes.

Between-subject variability for both parent drug and total radioactivity was low for PK parameters following intravenous drug administration, while the between-subject variability for PK parameters was generally moderate following oral drug administration. This higher variability after oral administration most likely reflects the high between-subject variability in gut CYP3A4 activity.

The mean absolute bioavailability of GSK221149 in this study was 28%. This number agrees well with the previous estimates of bioavailability (16.6-25.5%) found in Study OTA103772.

Systemic exposure to drug-related material was 3.5-4.3 fold higher than exposure to parent drug after oral administration, while it was similar after IV administration. These results suggest that parent drug was the predominant circulating drug-related material following IV administration, but there were likely significant levels of circulating metabolites following oral administration.

No subjects died, experienced an SAE, or withdrew due to an AE in this study. The overall rate of occurrence of AEs appeared similar following IV or oral administration of [^{14}C]-GSK221149A. However, there was an increased incidence of nausea and vomiting following oral solution dosing. All but one AE were considered mild, and all AEs

resolved by the end of the study. There were no AEs related to clinical laboratory tests, ECGs or vital signs.

12.2. Conclusions

- The major route of elimination of GSK221149 and its metabolites was through the feces (58-73% of the administered dose), followed by the urine (20.5-36% of administered dose).
- There was minimal association of radioactivity with the red blood cells.
- Levels of radioactivity fell below the limit of quantitation in blood and plasma for all subjects by 24 hours and 8 hours post-dose, respectively. This indicates that little or no accumulation of any metabolites may be expected upon multiple dosing of GSK221149.
- The absolute bioavailability of GSK221149 was low (28%) following administration as an oral solution and similar to that found in a previous study with GSK221149.
- Following IV administration, GSK221149 demonstrated moderate to high systemic clearance and a large apparent volume of distribution.
- Total radioactivity closely paralleled parent drug after oral and IV administration, suggesting that there are no metabolites of GSK221149 with long half-lives.
- Single 10 mg intravenous doses and single 100 mg oral doses of GSK221149A were generally safe and well tolerated in healthy adult female subjects under the conditions of this study.

13. REFERENCES

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GlaxoSmithKline Document Number CD2005/00446/00 Study ID Validation Study. The Validation of a Method for Determination of GSK221149 in Human Plasma (range 1 to 1000 ng/mL) using HPLC-MS/MS. Report Date 2005.

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Table 9.1
Summary of Demographic Characteristics

		Total (N=6)
Age (y)	n	6
	Mean	52.2
	SD	2.48
	Median	52.5
	Min.	48
	Max.	55
Sex	n	6
	Female	6 (100%)
Ethnicity	n	6
	Hispanic/Latino	0
	Not Hispanic/Latino	6 (100%)
Height (cm)	n	6
	Mean	163.7
	SD	8.50
	Median	161.5
	Min.	154
	Max.	178
Weight (kg)	n	6
	Mean	70.65
	SD	11.636
	Median	69.35
	Min.	53.7
	Max.	89.1

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 9.1
Summary of Demographic Characteristics

		Total (N=6)
Body Mass Index (kg/m^2)	n	6
	Mean	26.17
	SD	2.087
	Median	26.55
	Min.	22.6
	Max.	28.2

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 9.2
Summary of Inclusion/Exclusion Criteria Deviations

No data to report

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 9.3
Summary of End of Study Record

	Total (N=6)
Completion Status	
Completed	6 (100%)
Prematurely Withdrawn	0

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 9.4
Summary of Race and Racial Combination Details

Race	Total (N=6)
n	6
African American/African Heritage	0
American Indian or Alaska Native	0
Asian - Central/South Asian Heritage	0
Asian - East Asian Heritage	0
Asian - Japanese Heritage	0
Asian - South East Asian Heritage	0
Asian - Mixed Race	0
Native Hawaiian or other Pacific Islander	0
White - Arabic/North African Heritage	0
White - White/Caucasian/European Heritage	6 (100%)
White - Mixed Race	0
Mixed Race	0

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

PHARMACOKINETIC DATA SOURCE FIGURES AND TABLES

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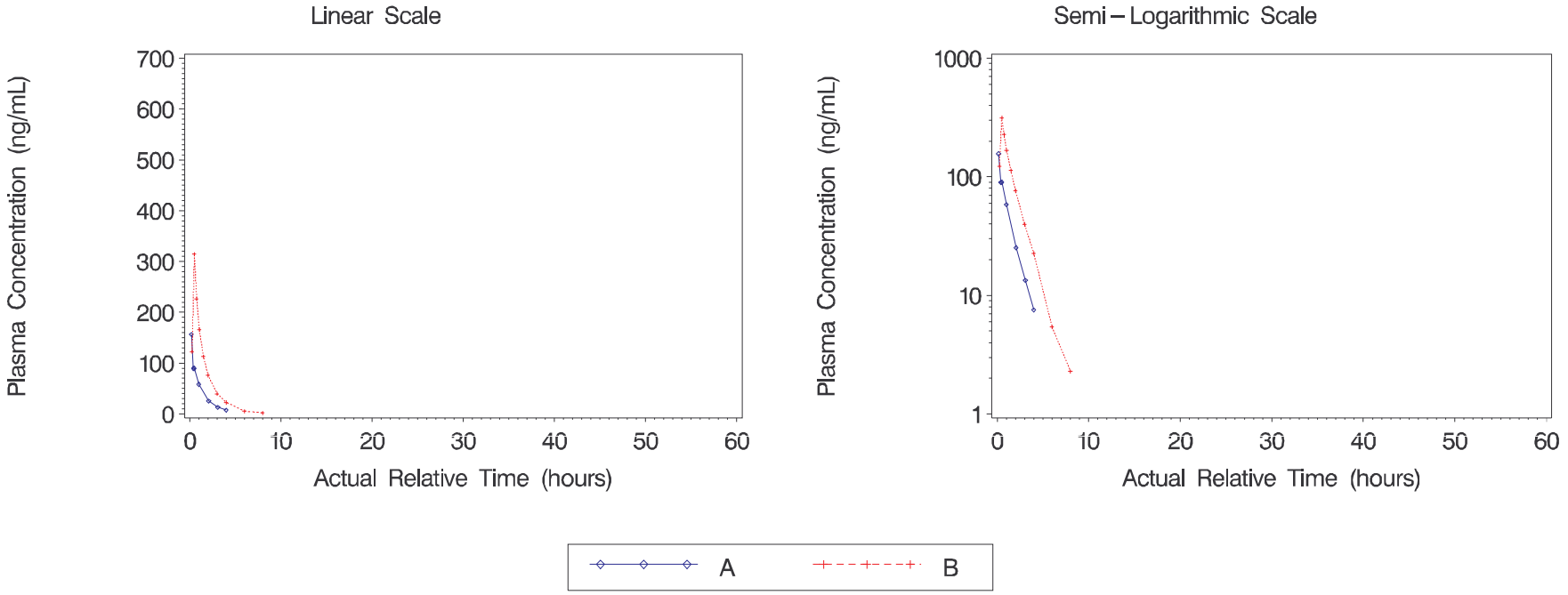
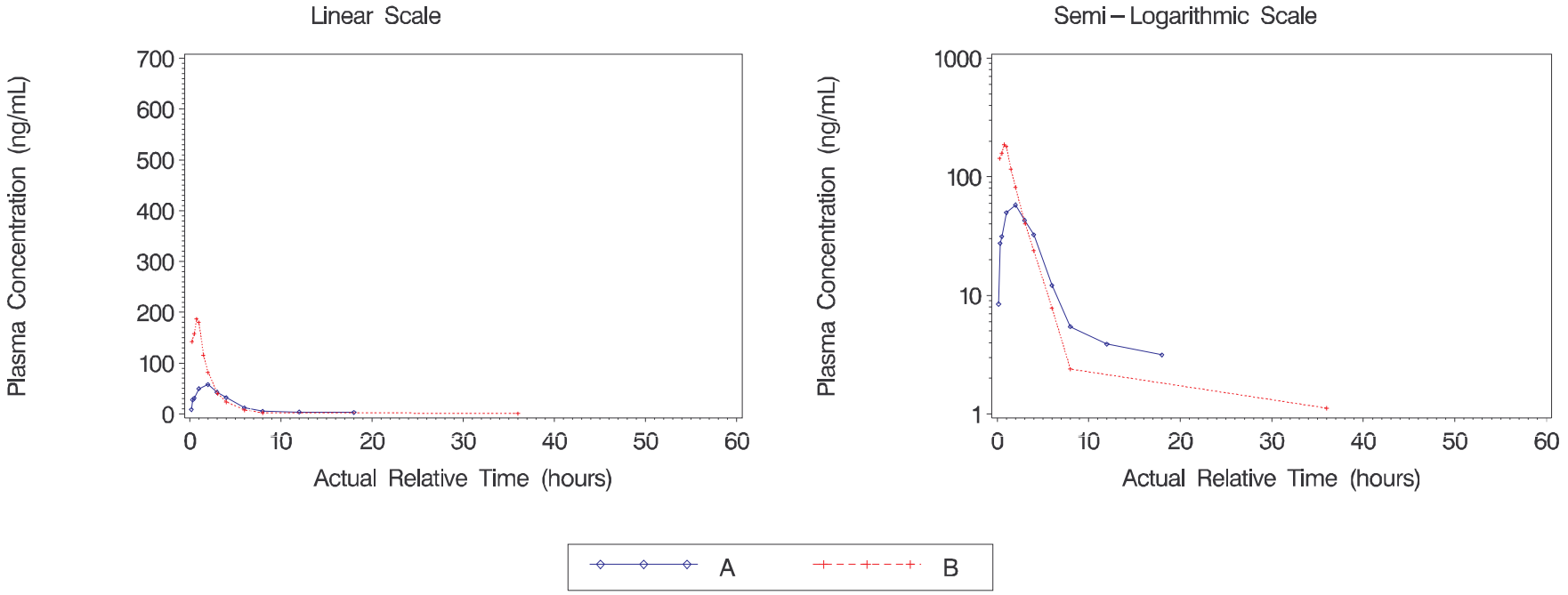
Figure 10.1
Individual Subject Plot of GSK221149 Plasma Concentration vs Actual Relative Time
Subject ID = [redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

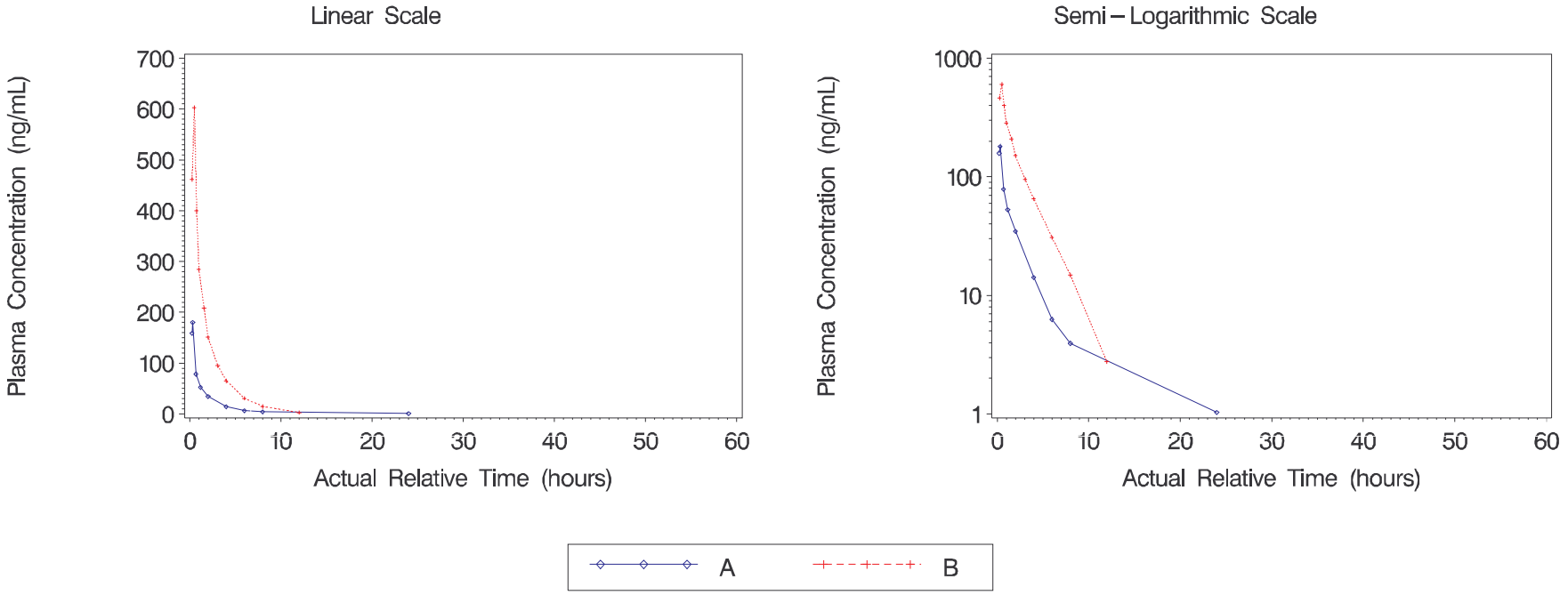
Figure 10.1
Individual Subject Plot of GSK221149 Plasma Concentration vs Actual Relative Time
Subject ID=[redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

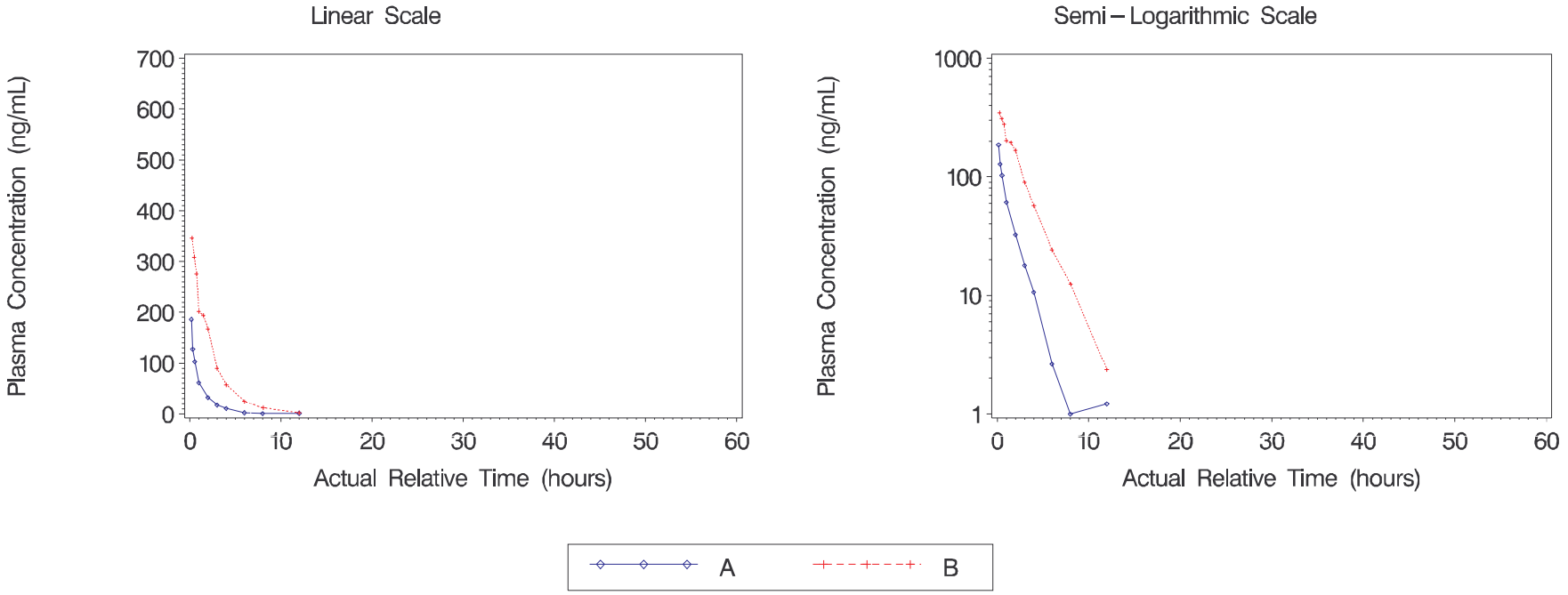
Figure 10.1
Individual Subject Plot of GSK221149 Plasma Concentration vs Actual Relative Time
Subject ID=[redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

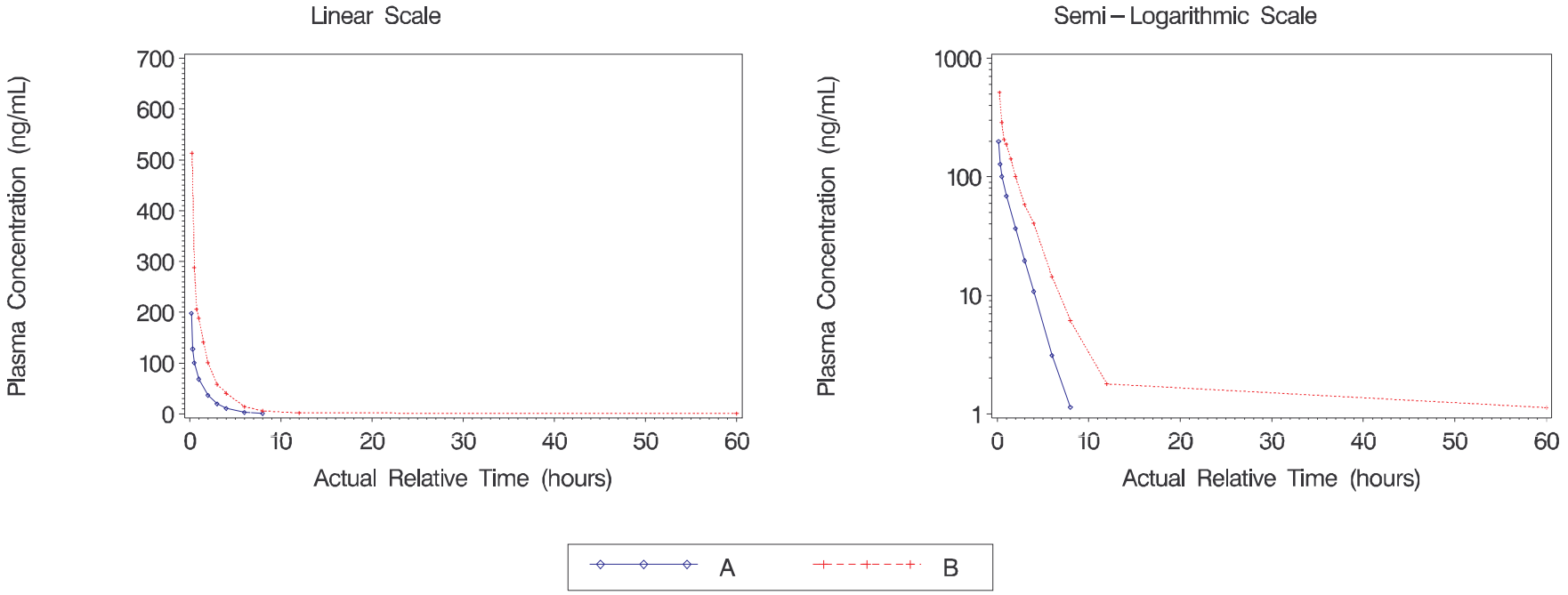
Figure 10.1
Individual Subject Plot of GSK221149 Plasma Concentration vs Actual Relative Time
Subject ID=[redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

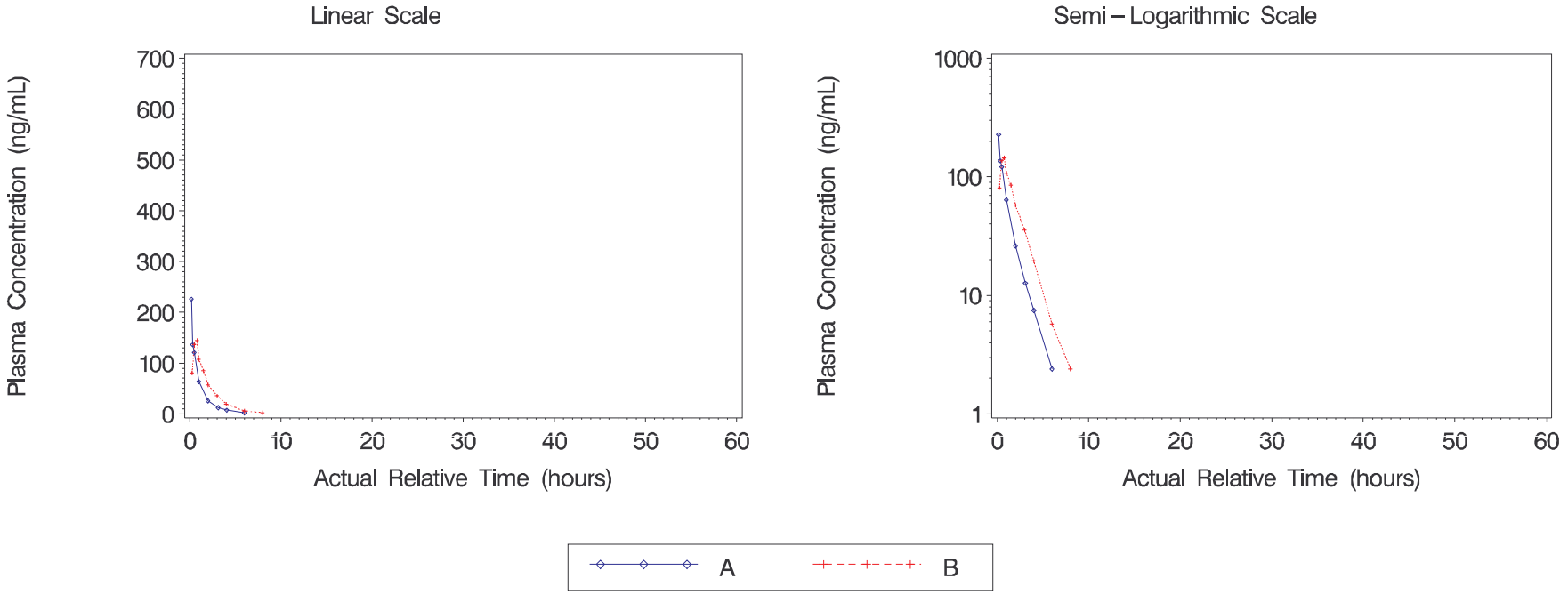
Figure 10.1
Individual Subject Plot of GSK221149 Plasma Concentration vs Actual Relative Time
Subject ID=[redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

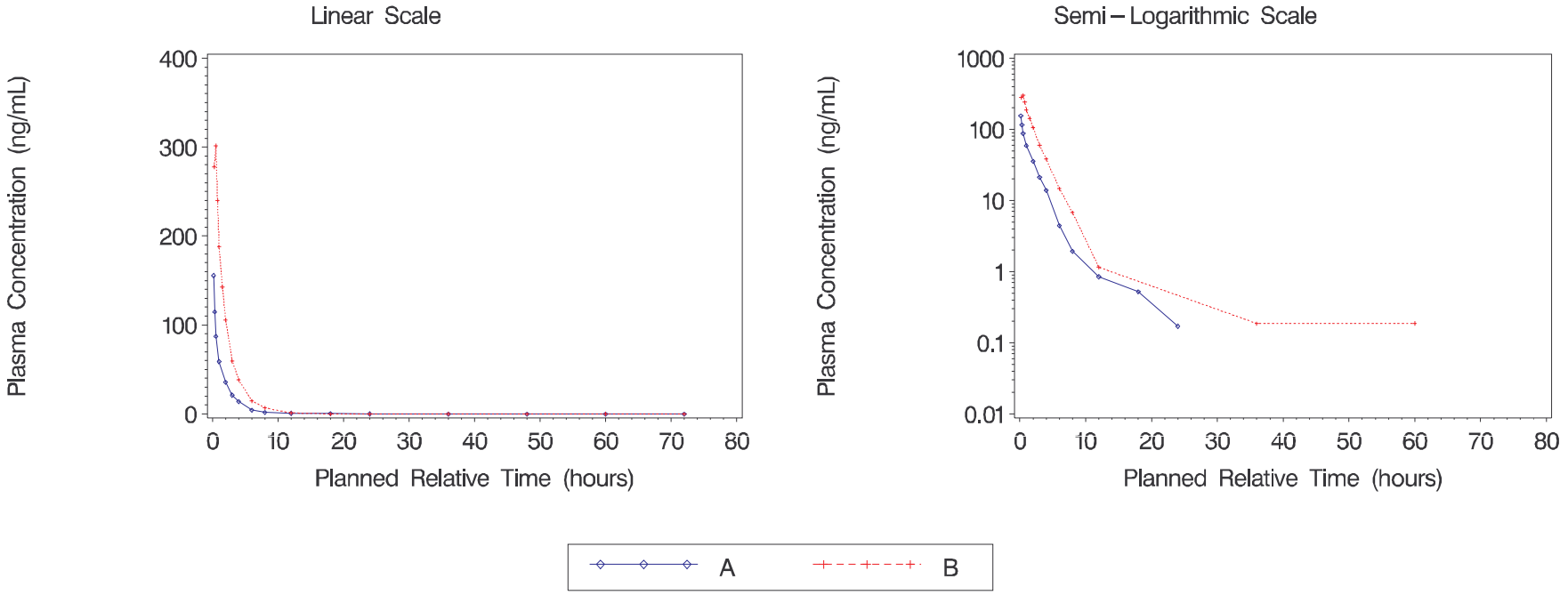
Figure 10.1
Individual Subject Plot of GSK221149 Plasma Concentration vs Actual Relative Time
Subject ID=[redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

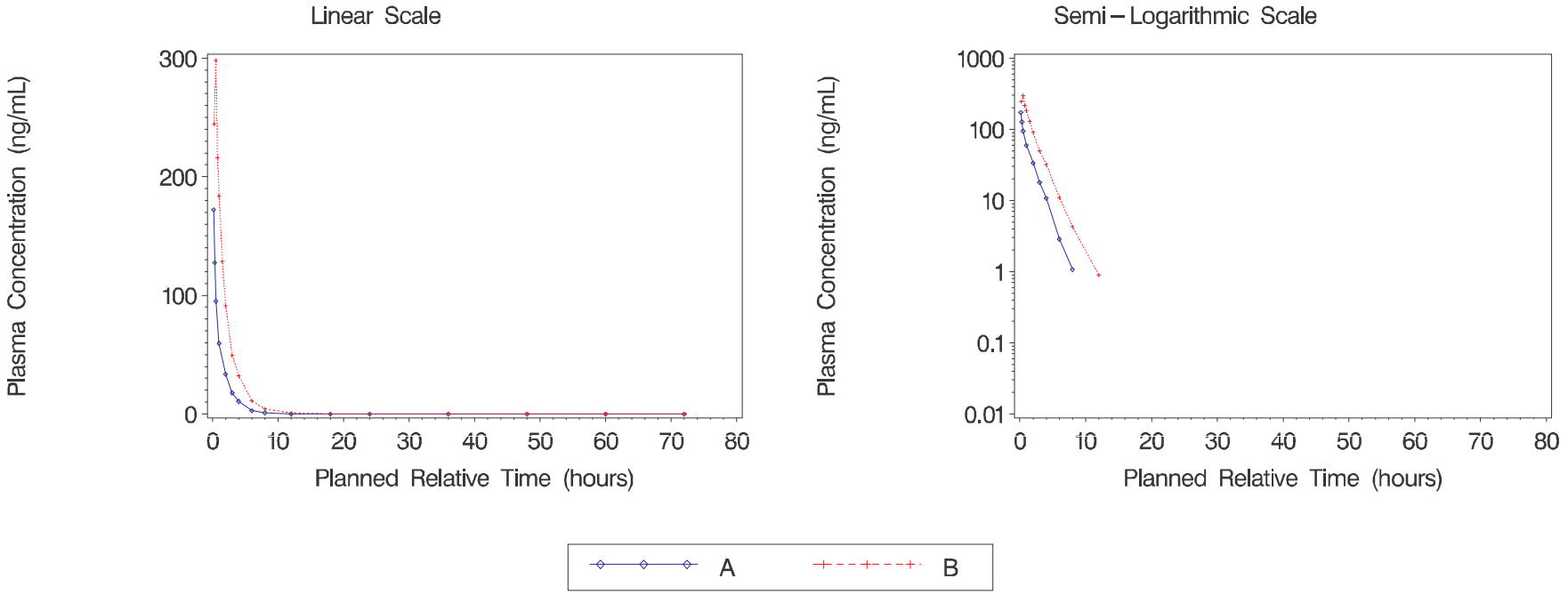
Figure 10.2
Mean GSK221149 Plasma Concentration vs Planned Time by Treatment



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

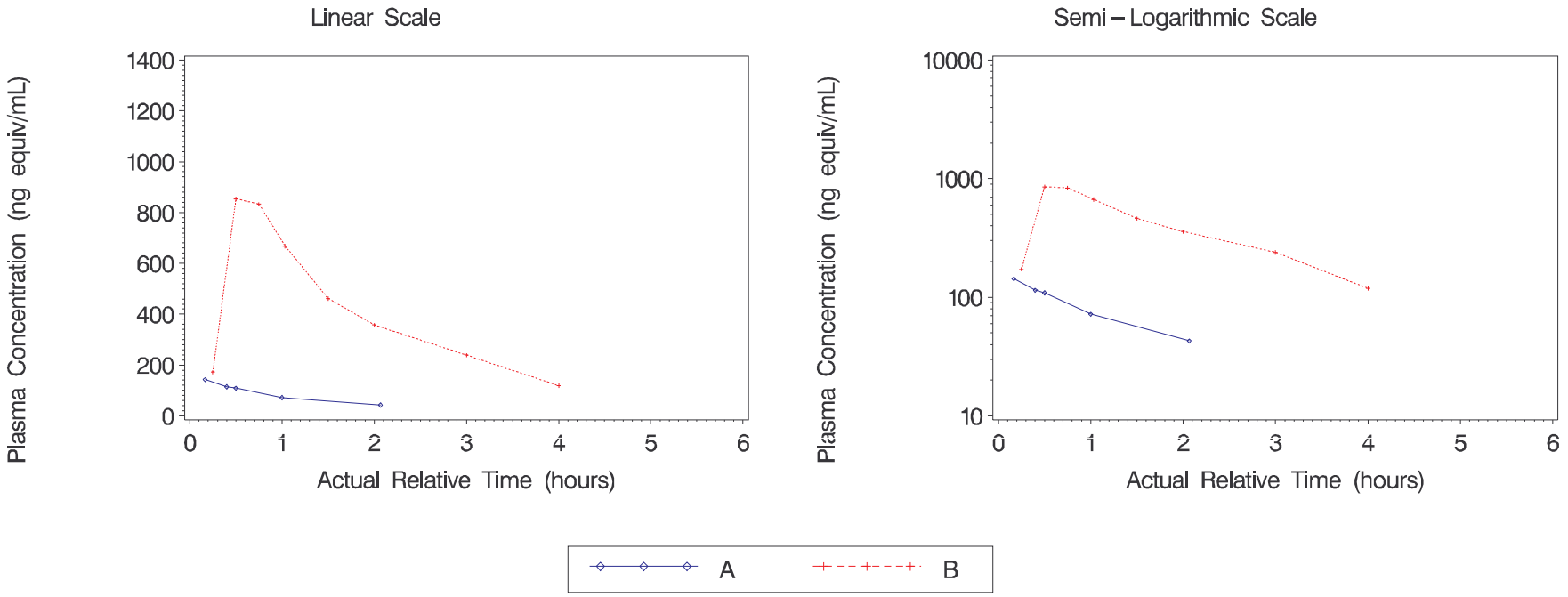
Figure 10.3
Median GSK221149 Plasma Concentration vs Planned Time by Treatment



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

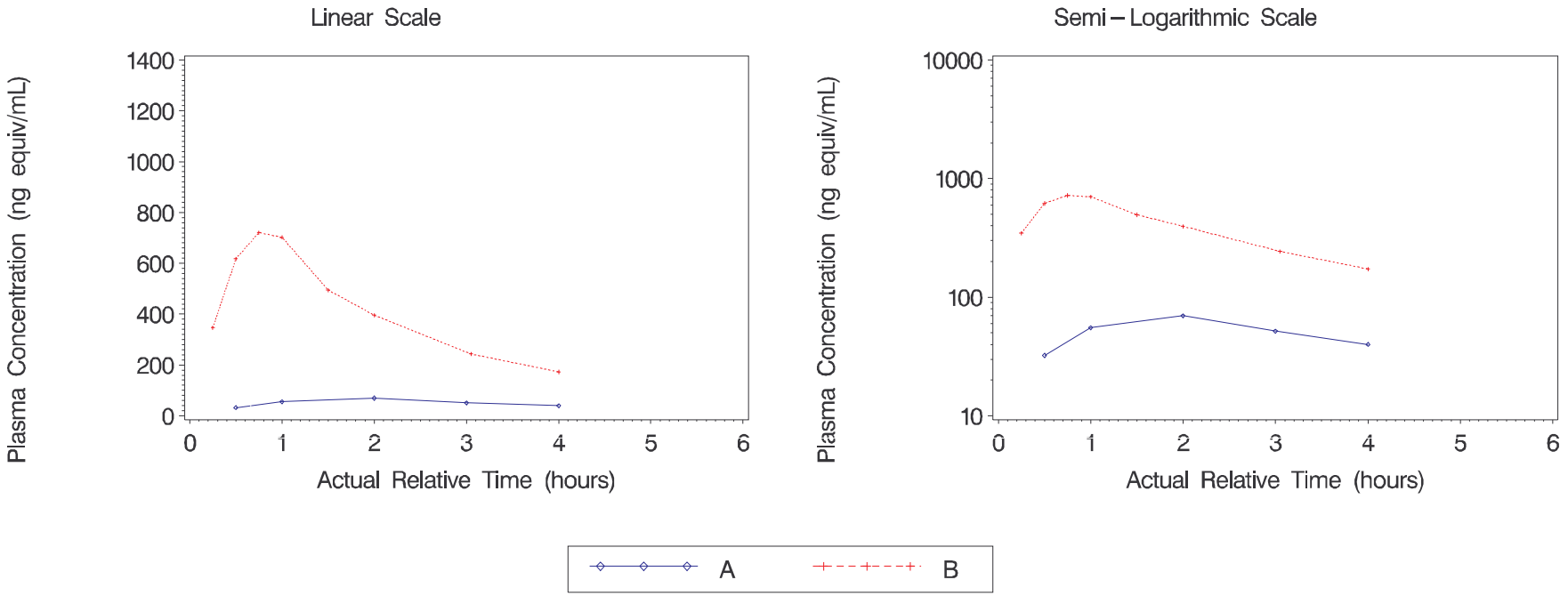
Figure 10.4
Individual Subject Plot of GSK221149A Plasma Radioactivity Concentration vs Actual Relative Time
Subject ID = [redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

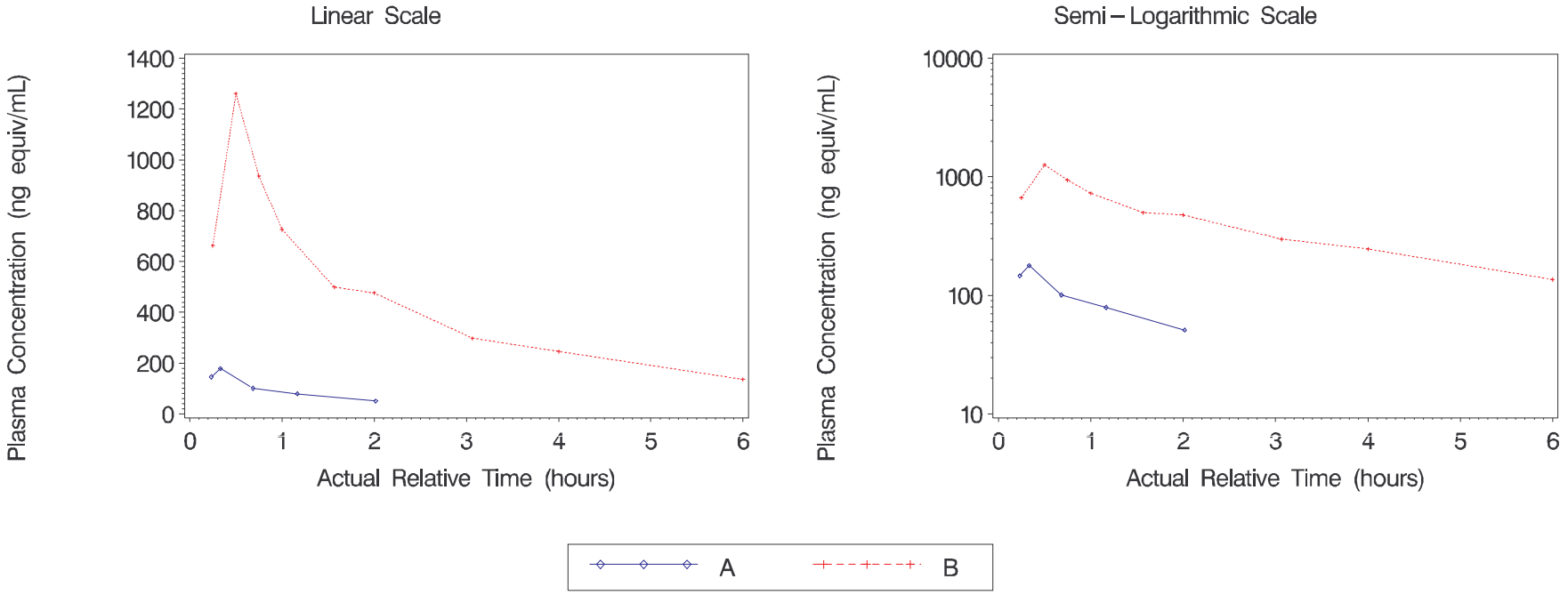
Figure 10.4
Individual Subject Plot of GSK221149A Plasma Radioactivity Concentration vs Actual Relative Time
Subject ID=[redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

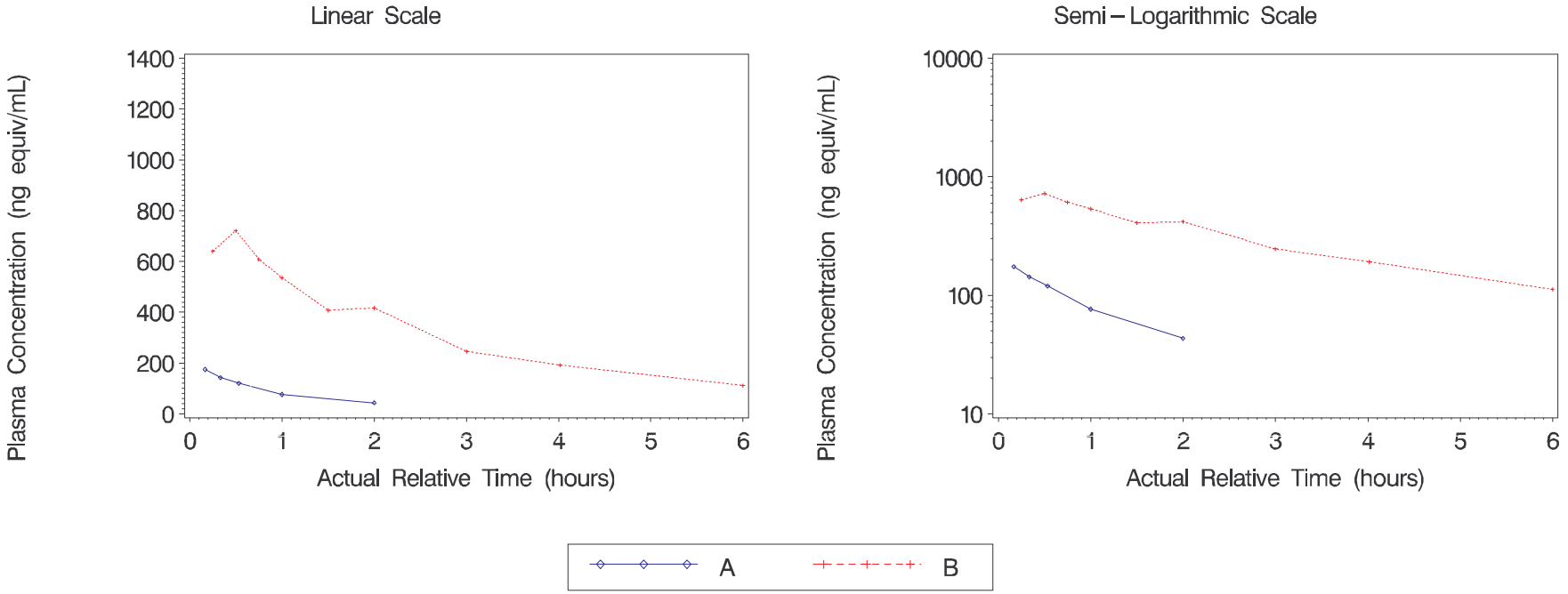
Figure 10.4
Individual Subject Plot of GSK221149A Plasma Radioactivity Concentration vs Actual Relative Time
Subject ID=[redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

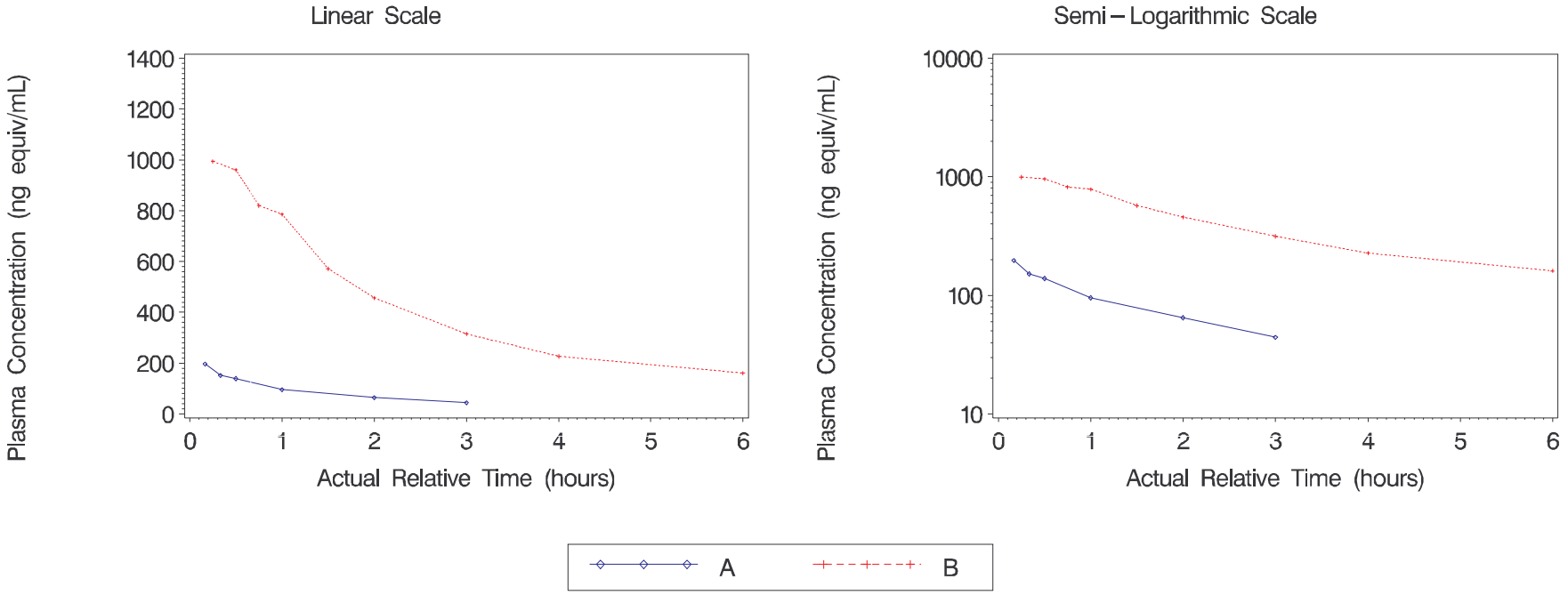
Figure 10.4
Individual Subject Plot of GSK221149A Plasma Radioactivity Concentration vs Actual Relative Time
Subject ID=[redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

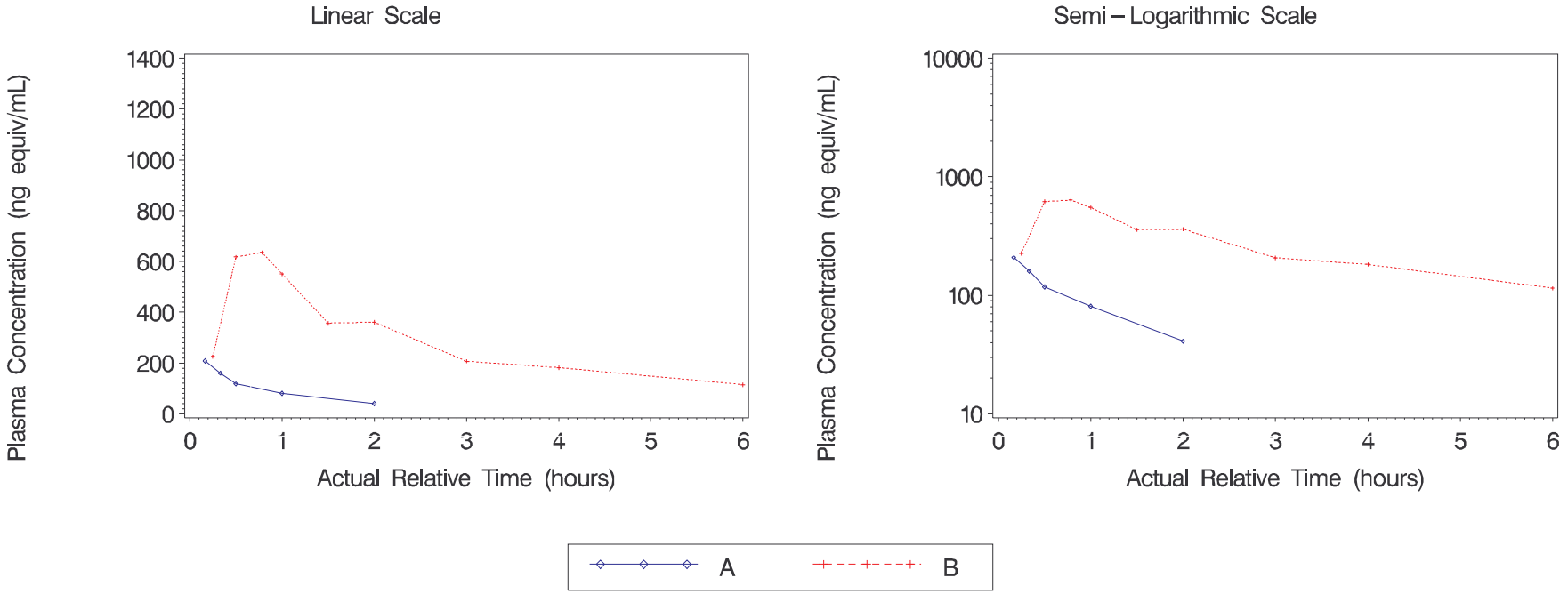
Figure 10.4
Individual Subject Plot of GSK221149A Plasma Radioactivity Concentration vs Actual Relative Time
Subject ID=[redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

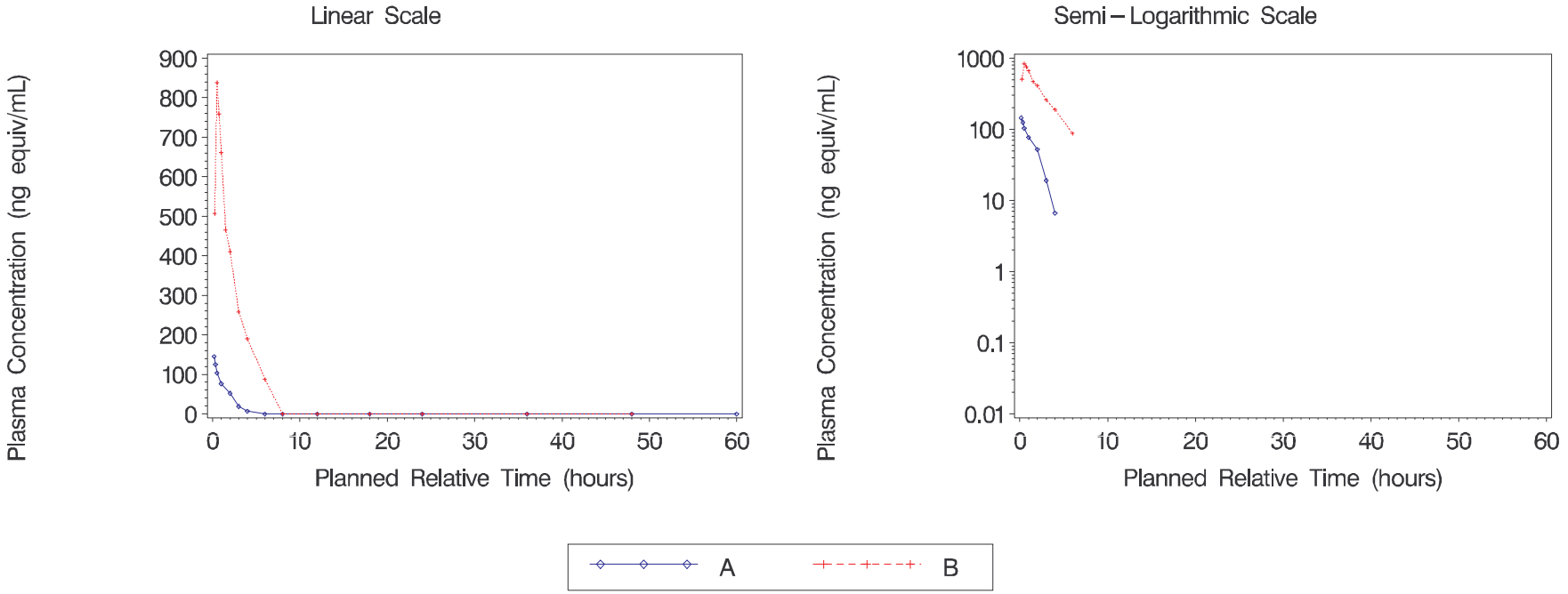
Figure 10.4
Individual Subject Plot of GSK221149A Plasma Radioactivity Concentration vs Actual Relative Time
Subject ID=[redacted]



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

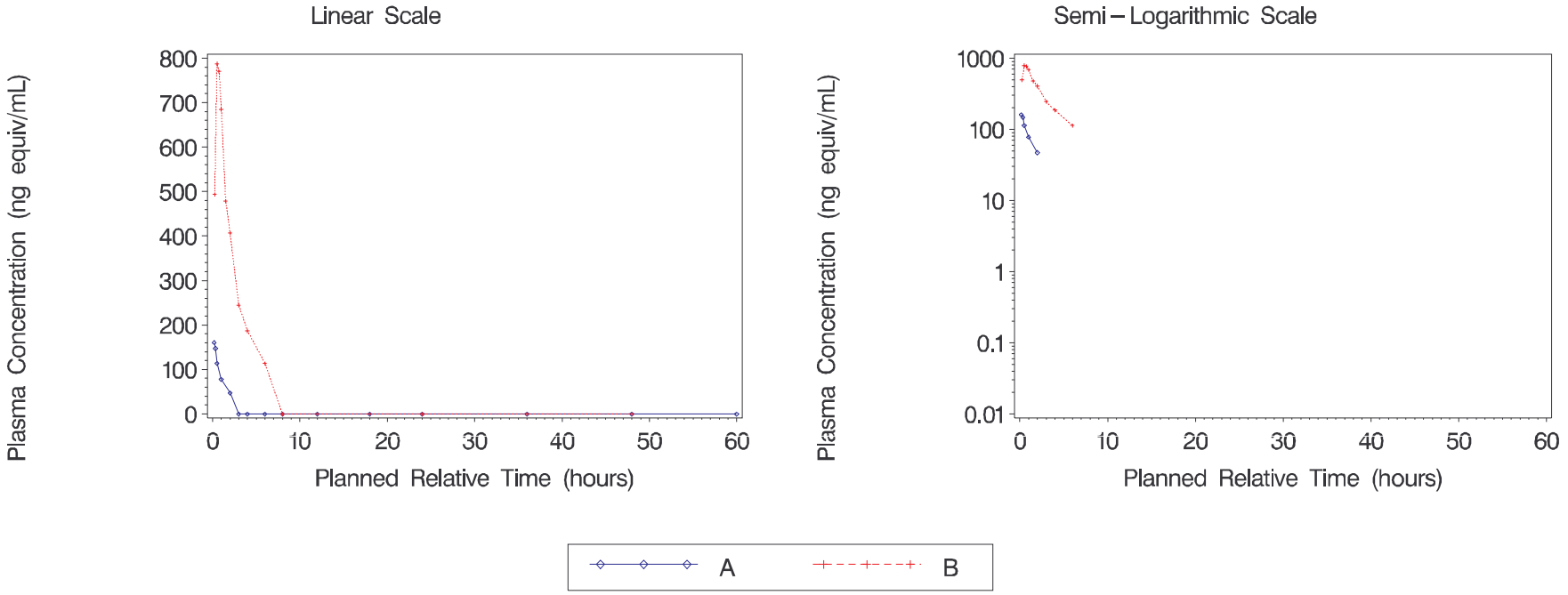
Figure 10.5
Mean GSK221149A Plasma Radioactivity Concentration vs Planned Time by Treatment



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Figure 10.6
Median GSK221149A Plasma Radioactivity Concentration vs Planned Time by Treatment



Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 10.1
Summary of GSK221149 Plasma PK Concentration - Time Data (ng/mL)

Treatment	N	Visit	Pl. Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
A	6	PERIOD 1	PRE-DOSE	6	6	0.000		0.000	0.00	0.00
			10 M	6	0	155.615	76.6396	172.250	8.45	226.16
			20 M	6	0	114.810	51.5904	127.515	27.54	180.11
			30 M	6	0	87.335	30.8791	95.225	31.27	120.91
			1 H	6	0	59.028	7.0461	59.655	49.75	68.65
			2 H	6	0	35.500	11.9119	33.580	25.23	57.96
			3 H	5	0	21.278	12.4366	17.870	12.65	42.90
			4 H	6	0	13.843	9.4576	10.705	7.49	32.48
			6 H	6	1	4.420	4.2629	2.870	0.00	12.09
			8 H	6	2	1.923		1.070	0.00	5.45
			12 H	6	4	0.850		0.000	0.00	3.88
			18 H	6	5	0.525		0.000	0.00	3.15
			24 H	6	5	0.172		0.000	0.00	1.03
			36 H	6	6	0.000		0.000	0.00	0.00
			48 H	6	6	0.000		0.000	0.00	0.00
			60 H	6	6	0.000		0.000	0.00	0.00
			72 H	6	6	0.000		0.000	0.00	0.00

Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 10.1
Summary of GSK221149 Plasma PK Concentration - Time Data (ng/mL)

Treatment	N	Visit	Pl. Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
B	6	PERIOD 2	PRE-DOSE	6	6	0.000		0.000	0.00	0.00
			15 M	6	0	277.887	187.1975	244.400	80.81	513.38
			30 M	6	0	301.490	166.6188	298.180	136.80	602.76
			45 M	6	0	239.825	89.4590	216.215	144.59	399.43
			1 H	6	0	187.822	57.2529	183.855	107.71	284.00
			1.5 H	6	0	142.870	48.7295	128.495	85.15	208.31
			2 H	6	0	105.688	43.8592	91.080	57.42	167.15
			3 H	6	0	59.747	26.5010	49.270	35.54	95.05
			4 H	6	0	38.118	19.4512	32.135	19.50	65.04
			6 H	6	0	14.697	10.6027	11.040	5.42	30.75
			8 H	6	0	6.735	5.5790	4.255	2.28	14.85
			12 H	6	3	1.152		0.895	0.00	2.76
			18 H	6	6	0.000		0.000	0.00	0.00
			24 H	6	6	0.000		0.000	0.00	0.00
			36 H	6	5	0.187		0.000	0.00	1.12
			48 H	6	6	0.000		0.000	0.00	0.00
			60 H	6	5	0.188		0.000	0.00	1.13
			72 H	6	6	0.000		0.000	0.00	0.00

Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 10.2
Summary Statistics of Log-Transformed Derived GSK221149 Plasma PK Parameters
(Excluding Subject [redacted] for IV Data)

Parameter		10 mg IV (N=6)	100 mg Oral (N=6)
AUC(0-inf)(hr*ng/mL)	n	5	6
	Geom. Mean	203.02970	538.32530
	95% CI	(175.60185,234.74159)	(333.04117,870.14506)
	SD Logs	0.116886	0.457576
	Arith. Mean	204.11548	586.76642
	95% CI	(175.52607,232.70489)	(309.15114,864.38170)
	SD	23.025079	264.537690
	%CVb	11.73	48.26
	Median	206.80970	526.21610
	Min.	168.9013	294.3223
	Max.	231.2189	988.5632
AUC(0-t)(hr*ng/mL)	n	5	6
	Geom. Mean	196.52411	533.28417
	95% CI	(166.28509,232.26212)	(329.00955,864.38828)
	SD Logs	0.134563	0.460217
	Arith. Mean	197.89108	581.79362
	95% CI	(166.92633,228.85583)	(305.37024,858.21700)
	SD	24.938105	263.401936
	%CVb	13.52	48.57
	Median	204.05990	522.04855
	Min.	156.8534	289.9052
	Max.	221.0082	981.5769
CL(L/hr)	n	5	
	Geom. Mean	49.25388	
	95% CI	(42.60004,56.94701)	
	SD Logs	0.116886	

CL: Plasma clearance; Vss: Volume of distribution at steady state; F: Bioavailability

[redacted]

Table 10.2
Summary Statistics of Log-Transformed Derived GSK221149 Plasma PK Parameters
(Excluding Subject [redacted] for IV Data)

Parameter		10 mg IV (N=6)	100 mg Oral (N=6)
CL(L/hr)	Arith. Mean	49.53000	
	95% CI	(42.08716,56.97284)	
	SD	5.994243	
	%CVb	11.73	
	Median	48.35360	
	Min.	43.2491	
	Max.	59.2062	
Cmax(ng/mL)	n	5	6
	Geom. Mean	187.997	311.281
	95% CI	(159.063,222.194)	(173.594,558.173)
	SD Logs	0.1346	0.5565
	Arith. Mean	189.364	351.378
	95% CI	(157.664,221.064)	(163.228,539.529)
	SD	25.5299	179.2870
	%CVb	13.52	60.25
	Median	185.970	330.470
	Min.	156.50	144.59
	Max.	226.16	602.76
F(%)	n	5	
	Geom. Mean	28.14801	
	95% CI	(16.78750,47.19647)	
	SD Logs	0.416250	
	Arith. Mean	29.98708	
	95% CI	(16.35243,43.62173)	
	SD	10.980947	
	%CVb	43.49	
	Median	29.25080	

CL: Plasma clearance; Vss: Volume of distribution at steady state; F: Bioavailability

[redacted]

Table 10.2
Summary Statistics of Log-Transformed Derived GSK221149 Plasma PK Parameters
(Excluding Subject [redacted] for IV Data)

Parameter		10 mg IV (N=6)	100 mg Oral (N=6)
F(%)	Min.	14.7939	
	Max.	42.7544	
Vss(L)	n	5	
	Geom. Mean	80.56307	
	95% CI	(67.07940,96.75710)	
	SD Logs	0.147514	
	Arith. Mean	81.25580	
	95% CI	(66.73455,95.77705)	
	SD	11.694990	
	%CVb	14.83	
	Median	85.21150	
	Min.	66.0431	
	Max.	94.9824	
t1/2(hr)	n	5	6
	Geom. Mean	1.34477	1.45564
	95% CI	(1.03921,1.74019)	(1.16019,1.82632)
	SD Logs	0.207597	0.216172
	Arith. Mean	1.36878	1.48388
	95% CI	(1.00238,1.73518)	(1.15449,1.81328)
	SD	0.295089	0.313880
	%CVb	20.99	21.87
	Median	1.20780	1.50485
	Min.	1.1076	1.1142
	Max.	1.7918	1.8084

CL: Plasma clearance; Vss: Volume of distribution at steady state; F: Bioavailability

[redacted]

Table 10.3
Summary Statistics of Derived GSK221149 Plasma PK Parameter Tmax
(Excluding Subject [redacted] for IV Data)

Parameter		10 mg IV (N=6)	100 mg Oral (N=6)
Tmax(hr)	n	5	6
	Arith. Mean	0.202	0.505
	95% CI	(0.113,0.291)	(0.263,0.747)
	SD	0.0716	0.2305
	%CVb	35.42	45.65
	Median	0.170	0.500
	Min.	0.17	0.25
	Max.	0.33	0.78

[redacted]

Table 10.4
Summary of GSK221149A Plasma Radioactivity PK Concentration - Time Data (ng equiv/mL)

Treatment	N	Visit	Pl. Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
A	6	PERIOD 1	PRE-DOSE	6	6	0.000		0.000	0.00	0.00
			10 M	6	1	145.000	75.8024	160.500	0.00	209.00
			20 M	6	1	124.833	64.6820	147.500	0.00	179.00
			30 M	6	0	103.233	36.9703	113.500	32.40	139.00
			1 H	6	0	76.633	13.1016	77.900	55.40	95.60
			2 H	6	0	52.200	12.3038	47.250	41.10	69.70
			3 H	5	3	19.180		0.000	0.00	51.60
			4 H	6	5	6.667		0.000	0.00	40.00
			6 H	6	6	0.000		0.000	0.00	0.00
			8 H	6	6	0.000		0.000	0.00	0.00
			12 H	6	6	0.000		0.000	0.00	0.00
			18 H	6	6	0.000		0.000	0.00	0.00
			24 H	6	6	0.000		0.000	0.00	0.00
			36 H	6	6	0.000		0.000	0.00	0.00
			48 H	6	6	0.000		0.000	0.00	0.00
			60 H	6	6	0.000		0.000	0.00	0.00

Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 10.4
Summary of GSK221149A Plasma Radioactivity PK Concentration - Time Data (ng equiv/mL)

Treatment	N	Visit	Pl. Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
B	6	PERIOD 2	PRE-DOSE	6	6	0.000		0.000	0.00	0.00
			15 M	6	0	507.000	314.9540	493.500	172.00	994.00
			30 M	6	0	838.500	246.4595	787.500	618.00	1260.00
			45 M	6	0	758.833	126.6071	770.500	608.00	936.00
			1 H	6	0	661.500	99.3011	685.000	536.00	786.00
			1.5 H	6	0	465.500	75.3996	478.500	357.00	572.00
			2 H	6	0	410.833	48.8074	406.500	358.00	476.00
			3 H	6	0	258.000	40.4475	244.500	207.00	315.00
			4 H	6	0	189.833	44.5036	187.000	119.00	246.00
			6 H	6	2	87.333		113.500	0.00	161.00
			8 H	6	6	0.000		0.000	0.00	0.00
			12 H	6	6	0.000		0.000	0.00	0.00
			18 H	6	6	0.000		0.000	0.00	0.00
			24 H	6	6	0.000		0.000	0.00	0.00
			36 H	6	6	0.000		0.000	0.00	0.00
			48 H	6	6	0.000		0.000	0.00	0.00

Regimen Key:
A = IV infusion of 10mg GSK221149 over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 10.5
Summary Statistics of Derived GSK221149A Plasma Radioactivity PK Parameter Tmax
(Excluding Subject [redacted] for IV Data)

Parameter		10 mg IV (N=6)	100 mg Oral (N=6)
Tmax(hr)	n	5	6
	Arith. Mean	0.202	0.547
	95% CI	(0.113,0.291)	(0.342,0.751)
	SD	0.0716	0.1951
	% CVb	35	36
	Median	0.170	0.500
	Min.	0.17	0.25
	Max.	0.33	0.78

[redacted]

Table 10.6
Summary Statistics of Log-Transformed Derived GSK221149A Plasma Radioactivity
PK Parameter AUC(0-t) (Excluding Subject [redacted] for IV Data)

Parameter		10 mg IV (N=6)	100 mg Oral (N=6)
AUC(0-t)(hr*ug/L)	n	5	6
	Geom. Mean	188.74672	1864.60260
	95% CI	(148.57171,239.78538)	(1488.90193,2335.10533)
	SD Logs	0.192756	0.214410
	Arith. Mean	191.76900	1901.48500
	95% CI	(141.08812,242.44988)	(1459.87945,2343.09055)
	SD	40.816902	420.802888
	%CVb	19.46	21.69
	Median	181.59100	1739.48500
	Min.	159.7465	1518.8150
	Max.	263.0000	2433.5000

[redacted]

Table 10.7
Summary Statistics of Log-Transformed Derived GSK221149A Plasma Radioactivity PK Parameter T1/2
(Excluding Subject [redacted] for IV Data)

Parameter		10 mg IV (N=6)	100 mg Oral (N=6)
t1/2(hr)	n	5	6
	Geom. Mean	1.22671	2.13407
	95% CI	(0.89584,1.67977)	(1.44805,3.14510)
	SD Logs	0.253146	0.369543
	Arith. Mean	1.25994	2.25419
	95% CI	(0.83783,1.68206)	(1.42189,3.08649)
	SD	0.339956	0.793097
	%CVb	25.73	38.25
	Median	1.16992	2.28989
	Min.	0.9802	1.2317
	Max.	1.8023	3.4531

[redacted]

Table 10.8
Summary Statistics of Log-Transformed Derived GSK221149A Plasma Radioactivity PK Parameter Cmax
(Excluding Subject [redacted] for IV Data)

Parameter		10 mg IV (N=6)	100 mg Oral (N=6)
Cmax(ug/L)	n	5	6
	Geom. Mean	179.1	840.7
	95% CI	(149.6,214.5)	(645.2,1095.4)
	SD Logs	0.15	0.25
	Arith. Mean	180.6	864.2
	95% CI	(149.4,211.8)	(621.6,1106.7)
	SD	25.12	231.15
	%CVb	15	26
	Median	179.0	787.5
	Min.	143	635
	Max.	209	1260

[redacted]

Table 10.9
Summary Statistics of Log-Transformed Derived GSK221149A Plasma Radioactivity
PK Parameter AUC(0-inf) (Excluding Subject [redacted] for IV Data)

Parameter		10 mg IV (N=6)	100 mg Oral (N=6)
AUC(0-inf)(hr*ug/L)	n	5	6
	Geom. Mean	268.36678	2291.04038
	95% CI	(207.53961,347.02161)	(1840.74374,2851.49198)
	SD Logs	0.207006	0.208528
	Arith. Mean	273.30261	2332.86781
	95% CI	(196.36323,350.24199)	(1823.01846,2842.71716)
	SD	61.964736	485.831937
	%CVb	20.92	21.08
	Median	240.46349	2238.35718
	Min.	232.1546	1730.2793
	Max.	378.1864	2912.7878

[redacted]

SAFETY DATA SOURCE TABLES

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Table 11.1
Summary of Exposure to Study Drug

		A (N=6)	B (N=6)
Duration (days)	n	6	6
	Mean	1.0	1.0
	SD	0.00	0.00
	Median	1.0	1.0
	Min.	1	1
	Max.	1	1

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.2
Summary of All Adverse Events

System Organ Class Preferred Term	A (N=6)	B (N=6)
ANY EVENT	4 (67%)	5 (83%)
Gastrointestinal disorders		
Any event	1 (17%)	4 (67%)
Abdominal pain	0	3 (50%)
Diarrhoea	0	2 (33%)
Flatulence	1 (17%)	1 (17%)
Nausea	0	1 (17%)
Vomiting	0	1 (17%)
General disorders and administration site conditions		
Any event	1 (17%)	3 (50%)
Fatigue	0	3 (50%)
Puncture site pain	1 (17%)	0
Infections and infestations		
Any event	1 (17%)	1 (17%)
Herpes simplex	0	1 (17%)
Viral upper respiratory tract infection	1 (17%)	0
Nervous system disorders		
Any event	0	2 (33%)
Headache	0	2 (33%)
Skin and subcutaneous tissue disorders		
Any event	2 (33%)	0
Ecchymosis	1 (17%)	0

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.2
Summary of All Adverse Events

System Organ Class Preferred Term	A (N=6)	B (N=6)
Erythema	1 (17%)	0
Pruritus	1 (17%)	0
Rash	1 (17%)	0
Eye disorders		
Any event	0	1 (17%)
Conjunctival haemorrhage	0	1 (17%)
Vascular disorders		
Any event	0	1 (17%)
Pallor	0	1 (17%)

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Albumin (G/L)			SCREENING	6	43.2	2.04	43.5	40	46
	A	6	PRE-DOSE	6	42.8	2.40	43.5	39	45
			48 H	6	44.8	3.76	45.0	40	51
	B	6	PRE-DOSE	6	41.7	3.08	42.5	37	45
			48 H	6	43.5	2.35	43.5	40	46
			FOLLOW-UP	6	42.5	2.07	42.5	39	45
Alkaline Phosphatase (IU/L)			SCREENING	6	75.7	36.86	62.5	47	148
	A	6	PRE-DOSE	6	71.5	26.35	62.0	53	123
			48 H	6	73.7	27.93	64.0	55	127
	B	6	PRE-DOSE	6	76.0	23.87	70.5	56	123
			48 H	6	71.3	24.38	64.5	48	118
			FOLLOW-UP	6	68.0	23.45	62.0	45	113
Alanine Amino Transferase (IU/L)			SCREENING	6	15.0	2.10	14.5	13	19
	A	6	PRE-DOSE	6	16.2	2.64	16.0	13	21
			48 H	6	16.2	3.19	16.0	12	21
	B	6	PRE-DOSE	6	15.8	4.96	13.5	12	25
			48 H	6	14.0	3.16	12.5	12	20

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Alanine Amino Transferase (IU/L)			FOLLOW-UP	6	14.7	2.42	14.0	12	18
Aspartate Amino Transferase (IU/L)			SCREENING	6	20.5	3.73	21.5	14	25
	A	6	PRE-DOSE	6	19.8	3.19	20.5	14	23
			48 H	6	19.7	3.14	21.0	14	22
	B	6	PRE-DOSE	6	19.8	4.83	20.0	14	28
			48 H	6	17.8	4.22	17.0	13	25
			FOLLOW-UP	6	20.5	3.67	19.0	16	25
Basophils (GI/L)			SCREENING	6	0.00	0.000	0.00	0.0	0.0
	A	6	PRE-DOSE	6	0.00	0.000	0.00	0.0	0.0
			48 H	6	0.05	0.055	0.05	0.0	0.1
	B	6	PRE-DOSE	6	0.00	0.000	0.00	0.0	0.0
			48 H	6	0.05	0.055	0.05	0.0	0.1
			FOLLOW-UP	6	0.02	0.041	0.00	0.0	0.1
Basophils (percentage) (%)			SCREENING	6	0.48	0.172	0.50	0.3	0.7
	A	6	PRE-DOSE	6	0.57	0.137	0.55	0.4	0.8

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Basophils (percentage) (%)	A	6	48 H	6	0.98	0.631	0.85	0.3	2.0
	B	6	PRE-DOSE	6	0.55	0.176	0.50	0.4	0.8
			48 H	6	1.00	0.721	0.80	0.2	1.9
			FOLLOW-UP	6	0.55	0.187	0.55	0.3	0.8
Total Bilirubin (UMOL/L)			SCREENING	6	8.265	2.9453	8.550	5.13	11.97
	A	6	PRE-DOSE	6	7.695	2.0943	6.840	5.13	10.26
			48 H	6	6.840	1.5295	6.840	5.13	8.55
	B	6	PRE-DOSE	6	7.410	2.9945	5.985	5.13	11.97
			48 H	6	6.840	2.4183	6.840	3.42	10.26
			FOLLOW-UP	6	6.270	1.3962	5.985	5.13	8.55
Calcium (MMOL/L)			SCREENING	6	2.33283	0.132728	2.35778	2.1208	2.4701
	A	6	PRE-DOSE	6	2.36193	0.112321	2.37025	2.2206	2.4950
			48 H	6	2.31203	0.101858	2.30788	2.1707	2.4451
	B	6	PRE-DOSE	6	2.28708	0.104274	2.30788	2.1208	2.4202
			48 H	6	2.27877	0.087384	2.32035	2.1457	2.3453
			FOLLOW-UP	6	2.28293	0.109040	2.28292	2.1208	2.4202

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Chloride (MMOL/L)			SCREENING	6	102.5	1.87	102.5	100	105
	A	6	PRE-DOSE	6	102.7	0.52	103.0	102	103
			48 H	6	101.7	1.21	101.5	100	103
	B	6	PRE-DOSE	6	102.0	1.26	101.5	101	104
			48 H	6	102.2	1.17	102.0	101	104
			FOLLOW-UP	6	102.8	1.72	102.5	101	106
Carbon Dioxide content / Bicarbonate (MMOL/L)			SCREENING	6	31.0	0.63	31.0	30	32
	A	6	PRE-DOSE	6	29.7	1.37	29.5	28	32
			48 H	6	28.2	0.98	28.5	27	29
	B	6	PRE-DOSE	6	28.8	1.94	28.5	27	32
			48 H	6	29.3	0.52	29.0	29	30
			FOLLOW-UP	6	30.3	1.37	30.5	28	32
Creatinine (UMOL/L)			SCREENING	6	67.773	10.7058	66.300	53.04	79.56
	A	6	PRE-DOSE	6	69.247	6.6545	70.720	61.88	79.56
			48 H	6	70.720	7.9067	70.720	61.88	79.56
	B	6	PRE-DOSE	6	63.353	6.6545	61.880	53.04	70.72
			48 H	6	67.773	7.2178	66.300	61.88	79.56

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Creatinine (UMOL/L)			FOLLOW-UP	6	67.773	4.5650	70.720	61.88	70.72
Eosinophils (GI/L)			SCREENING	6	0.18	0.160	0.10	0.1	0.5
	A	6	PRE-DOSE	6	0.15	0.176	0.10	0.0	0.5
			48 H	6	0.22	0.147	0.20	0.1	0.5
	B	6	PRE-DOSE	6	0.17	0.121	0.10	0.1	0.4
			48 H	6	0.18	0.117	0.15	0.1	0.4
			FOLLOW-UP	6	0.20	0.110	0.20	0.1	0.4
Eosinophils (percentage) (%)			SCREENING	6	2.80	2.391	1.85	1.4	7.6
	A	6	PRE-DOSE	6	2.70	3.056	1.70	0.5	8.8
			48 H	6	4.05	2.913	3.05	2.0	9.9
	B	6	PRE-DOSE	6	2.97	2.179	1.95	1.5	7.2
			48 H	6	3.57	2.508	2.65	1.2	8.3
			FOLLOW-UP	6	3.13	1.747	2.50	2.0	6.6
Gamma Glutamyl Transferase (IU/L)			SCREENING	6	12.3	3.27	13.0	8	16
	A	6	PRE-DOSE	6	11.3	2.66	13.0	7	13
			48 H	6	10.5	2.26	10.5	7	14

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Gamma Glutamyl Transferase (IU/L)	B	6	PRE-DOSE	6	14.7	4.08	15.0	10	20
			48 H	6	13.0	2.83	13.0	10	17
			FOLLOW-UP	6	12.5	3.62	13.0	8	18
Glucose (MMOL/L)			SCREENING	6	4.71835	0.438494	4.69060	4.1633	5.2179
	A	6	PRE-DOSE	6	4.65359	0.397843	4.66284	4.1077	5.2735
			48 H	6	5.08842	0.324943	5.21794	4.6073	5.4400
	B	6	PRE-DOSE	6	4.76461	0.448796	4.80162	4.2188	5.2735
			48 H	6	5.06991	0.295127	5.16243	4.6628	5.4400
			FOLLOW-UP	6	4.97740	0.337958	4.96815	4.5518	5.3845
Hemoglobin (G/L)			SCREENING	6	139.2	5.31	138.0	134	147
	A	6	PRE-DOSE	6	141.2	2.56	142.0	138	144
			48 H	6	139.7	7.71	138.0	133	154
	B	6	PRE-DOSE	6	135.5	5.47	136.5	129	141
			48 H	6	132.7	4.08	132.5	127	138
			FOLLOW-UP	6	134.2	4.75	134.0	129	140
Hematocrit (1)			SCREENING	6	0.4105	0.01511	0.4075	0.392	0.429

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Hematocrit (1)	A	6	PRE-DOSE	6	0.4105	0.00814	0.4130	0.399	0.418
			48 H	6	0.4080	0.02376	0.4025	0.390	0.453
	B	6	PRE-DOSE	6	0.4018	0.01598	0.4040	0.384	0.420
			48 H	6	0.3912	0.01306	0.3900	0.377	0.410
			FOLLOW-UP	6	0.3972	0.01597	0.3955	0.379	0.418
Potassium (MMOL/L)			SCREENING	6	4.00	0.322	3.90	3.7	4.6
	A	6	PRE-DOSE	6	4.10	0.551	3.85	3.8	5.2
			48 H	6	4.22	0.117	4.25	4.0	4.3
	B	6	PRE-DOSE	6	4.12	0.426	3.90	3.8	4.8
			48 H	6	4.05	0.105	4.05	3.9	4.2
			FOLLOW-UP	6	4.03	0.273	4.00	3.7	4.4
Lymphocytes (GI/L)			SCREENING	6	1.80	0.434	1.85	1.2	2.3
	A	6	PRE-DOSE	6	1.82	0.240	1.80	1.4	2.1
			48 H	6	1.88	0.232	1.85	1.6	2.2
	B	6	PRE-DOSE	6	1.75	0.207	1.75	1.5	2.1
			48 H	6	1.73	0.266	1.75	1.4	2.0
			FOLLOW-UP	6	2.02	0.382	1.80	1.7	2.6

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Lymphocytes (percentage) (%)			SCREENING	6	30.52	3.854	31.50	24.2	34.8
	A	6	PRE-DOSE	6	30.52	4.243	31.35	23.3	34.2
			48 H	6	32.52	5.695	32.75	24.4	40.9
	B	6	PRE-DOSE	6	30.18	4.893	29.85	25.3	38.5
			48 H	6	30.93	10.293	32.20	13.0	43.7
			FOLLOW-UP	6	32.48	5.189	32.00	24.8	39.2
Mean Corpuscle Hemoglobin Concentration (G/L)			SCREENING	6	339.2	3.66	338.5	335	344
	A	6	PRE-DOSE	6	344.0	1.67	343.5	342	346
			48 H	6	342.2	2.32	342.0	340	346
	B	6	PRE-DOSE	6	337.3	1.37	337.0	336	339
			48 H	6	338.5	2.43	338.0	336	343
			FOLLOW-UP	6	338.0	3.16	338.5	332	341
Mean Corpuscle Hemoglobin (PG)			SCREENING	6	30.37	0.677	30.45	29.2	31.0
	A	6	PRE-DOSE	6	30.48	0.741	30.50	29.4	31.4
			48 H	6	30.48	0.711	30.60	29.3	31.3

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Mean Corpuscle Hemoglobin (PG)	B	6	PRE-DOSE	6	30.08	0.749	30.00	29.1	31.1
			48 H	6	30.22	0.674	30.25	29.3	31.0
			FOLLOW-UP	6	30.32	0.966	30.35	28.9	31.6
Mean Corpuscle Volume (FL)			SCREENING	6	89.50	2.251	89.95	86.1	92.5
	A	6	PRE-DOSE	6	88.62	1.955	88.75	85.6	90.7
			48 H	6	89.00	1.943	88.85	86.1	91.1
	B	6	PRE-DOSE	6	89.22	2.305	89.30	85.8	92.4
			48 H	6	89.25	1.997	88.75	86.9	92.4
			FOLLOW-UP	6	89.63	2.423	89.30	87.0	93.5
Monocytes (GI/L)			SCREENING	6	0.48	0.117	0.50	0.3	0.6
	A	6	PRE-DOSE	6	0.50	0.089	0.50	0.4	0.6
			48 H	6	0.53	0.121	0.55	0.4	0.7
	B	6	PRE-DOSE	6	0.53	0.121	0.55	0.4	0.7
			48 H	6	0.52	0.240	0.40	0.4	1.0
			FOLLOW-UP	6	0.50	0.126	0.45	0.4	0.7

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Monocytes (percentage) (%)			SCREENING	6	8.27	1.745	8.15	6.2	10.8
	A	6	PRE-DOSE	6	8.50	1.114	8.85	6.5	9.6
			48 H	6	9.08	1.504	9.35	6.4	10.5
	B	6	PRE-DOSE	6	8.85	1.075	8.95	7.5	10.0
			48 H	6	8.47	0.999	8.65	6.8	9.7
			FOLLOW-UP	6	8.12	1.465	8.30	5.8	9.8
Mean Platelet Volume (FL)			SCREENING	6	8.90	0.780	8.85	7.7	10.0
	A	6	PRE-DOSE	6	9.13	0.841	9.10	8.0	10.4
			48 H	6	9.27	1.097	9.25	7.8	11.1
	B	6	PRE-DOSE	6	9.18	0.816	9.00	8.3	10.7
			48 H	6	9.18	0.808	9.15	8.0	10.5
			FOLLOW-UP	6	8.75	0.612	8.65	7.9	9.7
Sodium (MMOL/L)			SCREENING	6	139.3	2.25	138.5	137	143
	A	6	PRE-DOSE	6	139.7	1.21	139.5	138	141
			48 H	6	138.5	1.76	138.0	137	141
	B	6	PRE-DOSE	6	138.3	1.75	138.5	136	141
			48 H	6	138.0	0.63	138.0	137	139

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Sodium (MMOL/L)			FOLLOW-UP	6	138.8	1.47	139.5	137	140
Total Neutrophils (GI/L)			SCREENING	6	3.42	0.578	3.40	2.5	4.2
	A	6	PRE-DOSE	6	3.48	0.682	3.50	2.5	4.3
			48 H	6	3.20	0.951	3.50	1.8	4.3
	B	6	PRE-DOSE	6	3.52	1.179	3.25	2.1	5.4
			48 H	6	3.72	2.366	3.15	1.8	8.3
			FOLLOW-UP	6	3.62	1.194	3.80	2.2	4.9
Total Neutrophils (percentage) (%)			SCREENING	6	57.93	5.840	55.00	53.2	67.2
	A	6	PRE-DOSE	6	57.72	6.874	58.10	47.5	67.9
			48 H	6	53.37	8.025	53.80	43.5	64.5
	B	6	PRE-DOSE	6	57.45	6.513	58.90	49.3	64.8
			48 H	6	56.03	11.886	55.60	42.9	76.7
			FOLLOW-UP	6	55.72	6.667	56.25	47.8	66.6
Platelet count (GI/L)			SCREENING	6	295.3	70.82	313.0	175	385
	A	6	PRE-DOSE	6	288.8	63.17	293.5	191	363
			48 H	6	303.5	63.65	309.0	212	386

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Platelet count (GI/L)	B	6	PRE-DOSE	6	290.0	60.67	291.0	187	368
			48 H	6	288.5	43.82	288.5	220	350
			FOLLOW-UP	6	314.3	65.18	320.0	210	379
Phosphorus, Inorganic (MMOL/L)			SCREENING	6	1.11401	0.105623	1.09786	1.0010	1.2916
	A	6	PRE-DOSE	6	1.08172	0.149723	1.04943	0.9041	1.3562
			48 H	6	1.08710	0.125336	1.06557	0.9687	1.3239
	B	6	PRE-DOSE	6	1.06557	0.181515	0.98485	0.9041	1.3239
			48 H	6	1.10324	0.165174	1.08172	0.9041	1.3562
			FOLLOW-UP	6	1.09248	0.096690	1.06557	1.0010	1.2270
Red Blood Cell Count (TI/L)			SCREENING	6	4.592	0.2426	4.620	4.32	4.87
	A	6	PRE-DOSE	6	4.637	0.1902	4.675	4.40	4.89
			48 H	6	4.590	0.3688	4.500	4.28	5.27
	B	6	PRE-DOSE	6	4.510	0.2864	4.545	4.15	4.80
			48 H	6	4.385	0.2342	4.365	4.08	4.71
			FOLLOW-UP	6	4.438	0.2771	4.425	4.09	4.80
Total Protein (G/L)			SCREENING	6	73.3	3.72	74.0	67	78

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Total Protein (G/L)	A	6	PRE-DOSE	6	75.0	3.03	75.0	71	78
			48 H	6	77.7	6.53	76.0	72	90
	B	6	PRE-DOSE	6	74.8	4.36	75.5	67	80
			48 H	6	76.2	4.45	76.5	69	82
			FOLLOW-UP	6	74.8	4.62	75.5	69	80
Urea (MMOL/L)			SCREENING	6	4.1055	1.02851	3.7485	3.213	6.069
	A	6	PRE-DOSE	6	4.6410	0.93094	4.4625	3.927	6.426
			48 H	6	5.5335	0.54142	5.5335	4.998	6.426
	B	6	PRE-DOSE	6	5.2955	1.38112	4.8195	3.927	7.497
			48 H	6	5.4145	1.24524	5.3550	3.570	6.783
			FOLLOW-UP	6	5.2360	1.65406	4.8195	3.213	7.854
Uric Acid (UMOL/L)			SCREENING	6	196.2840	26.60026	187.3620	166.544	231.972
	A	6	PRE-DOSE	6	206.1973	39.21472	205.2060	148.700	255.764
			48 H	6	210.1627	23.39211	214.1280	172.492	237.920
	B	6	PRE-DOSE	6	214.1280	31.02097	211.1540	178.440	255.764
			48 H	6	214.1280	33.22372	214.1280	172.492	261.712
			FOLLOW-UP	6	213.1367	22.06914	217.1020	172.492	231.972

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.3
Summary of Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
White Blood Cell Count (GI/L)			SCREENING	6	5.92	0.962	6.25	4.5	6.9
	A	6	PRE-DOSE	6	5.98	0.668	6.00	5.3	7.1
			48 H	6	5.88	0.995	6.40	4.1	6.6
	B	6	PRE-DOSE	6	6.00	1.457	5.75	4.2	8.4
			48 H	6	6.23	2.425	5.60	4.3	10.9
			FOLLOW-UP	6	6.42	1.539	6.65	4.7	8.3

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.4
Summary of Drug-Related Adverse Events

System Organ Class Preferred Term	A (N=6)	B (N=6)
ANY EVENT	1 (17%)	5 (83%)
Gastrointestinal disorders		
Any event	1 (17%)	4 (67%)
Abdominal pain	0	3 (50%)
Flatulence	1 (17%)	1 (17%)
Nausea	0	1 (17%)
Vomiting	0	1 (17%)
Nervous system disorders		
Any event	0	2 (33%)
Headache	0	2 (33%)
General disorders and administration site conditions		
Any event	0	1 (17%)
Fatigue	0	1 (17%)
Vascular disorders		
Any event	0	1 (17%)
Pallor	0	1 (17%)

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.5
Summary of ECG Values

	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Heart Rate (bpm)			SCREENING	6	61.8	9.15	64.0	45	72
	A	6	PRE-DOSE	6	62.8	10.38	63.0	50	80
			1 H	6	61.3	10.19	62.0	44	76
			2 H	6	64.7	14.36	63.0	47	90
			4 H	6	65.3	14.67	63.5	46	90
			12 H	6	71.7	8.55	75.5	57	80
	B	6	PRE-DOSE	6	62.2	11.41	63.5	42	74
			1 H	6	62.7	11.84	66.0	44	74
			2 H	6	62.2	9.93	63.0	46	73
			4 H	6	62.8	11.07	65.0	44	73
			12 H	6	68.2	9.24	70.0	54	81
			FOLLOW-UP	6	60.2	11.00	64.5	42	70
PR Interval (msec)			SCREENING	6	139.3	10.33	142.0	126	152
	A	6	PRE-DOSE	6	143.0	8.65	145.0	126	150
			1 H	6	141.3	9.18	144.0	124	150
			2 H	6	141.0	9.70	144.0	122	150
			4 H	6	142.0	9.21	145.0	124	150
			12 H	6	139.3	11.29	142.0	118	150

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.5
Summary of ECG Values

	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
PR Interval (msec)	B	6	PRE-DOSE	6	139.7	9.07	142.0	128	152
			1 H	6	143.0	10.41	144.0	124	154
			2 H	6	140.0	12.71	145.0	124	152
			4 H	6	141.3	10.63	141.0	126	154
			12 H	6	140.3	7.74	142.0	128	148
			FOLLOW-UP	6	146.3	6.86	148.0	138	154
QRS Duration (msec)			SCREENING	6	94.0	7.59	96.0	80	100
	A	6	PRE-DOSE	6	94.0	6.57	96.0	82	100
			1 H	6	93.0	5.76	95.0	82	98
			2 H	6	94.3	7.09	97.0	80	98
			4 H	6	93.7	7.42	95.0	80	100
			12 H	6	94.0	8.10	97.0	78	100
	B	6	PRE-DOSE	6	94.3	6.62	96.0	82	102
			1 H	6	93.0	8.46	95.0	78	100
			2 H	6	92.7	6.89	94.0	80	100
			4 H	6	94.3	7.63	94.0	82	104
			12 H	6	92.0	8.29	92.0	78	102
			FOLLOW-UP	6	91.7	7.84	94.0	78	100
QT Interval (msec)			SCREENING	6	416.3	24.86	410.0	392	462

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.5
Summary of ECG Values

	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
QT Interval (msec)	A	6	PRE-DOSE	6	406.7	21.57	407.0	370	430
			1 H	6	408.7	26.40	408.0	372	454
			2 H	6	415.3	24.87	420.0	380	452
			4 H	6	416.0	27.28	420.0	370	454
			12 H	6	385.0	19.79	384.0	358	408
	B	6	PRE-DOSE	6	406.3	30.87	403.0	378	464
			1 H	6	410.0	30.38	406.0	378	460
			2 H	6	410.0	21.58	411.0	380	442
			4 H	6	416.3	31.68	414.0	378	472
			12 H	6	391.3	17.19	390.0	370	416
			FOLLOW-UP	6	421.7	48.85	407.0	386	516
QTc Interval (msec)			SCREENING	6	419.5	15.86	418.5	399	444
	A	6	PRE-DOSE	6	412.7	14.91	413.5	388	429
			1 H	6	409.2	11.39	412.0	388	419
			2 H	6	426.0	25.61	417.0	400	464
			4 H	6	428.8	25.01	431.5	397	453
			12 H	6	418.5	20.51	414.0	397	456
	B	6	PRE-DOSE	6	408.5	15.14	406.0	387	427
			1 H	6	414.0	17.91	413.0	393	434
			2 H	6	413.8	18.96	416.0	386	438
			4 H	6	421.2	16.73	416.5	403	445
			12 H	6	415.2	27.74	403.5	394	469

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.5
Summary of ECG Values

	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
QTc Interval (msec)			FOLLOW-UP	6	416.2	14.40	413.0	398	436
QTc (Bazett) (msec)			SCREENING	6	420.120	15.8519	419.254	400.10	444.69
	A	6	PRE-DOSE	6	413.586	14.9428	414.013	388.88	430.01
			1 H	6	410.051	11.4743	413.057	388.78	420.12
			2 H	6	427.007	25.9638	418.112	400.05	465.40
			4 H	6	429.477	25.0655	432.268	397.52	453.65
			12 H	6	419.367	20.5496	414.902	397.67	456.94
	B	6	PRE-DOSE	6	409.579	14.8187	407.256	388.21	427.91
			1 H	6	414.961	17.7572	413.843	393.92	435.07
			2 H	6	414.838	19.0219	417.285	387.01	439.23
			4 H	6	422.254	16.6093	417.510	404.20	445.94
			12 H	6	415.851	27.5903	403.953	394.65	469.41
			FOLLOW-UP	6	417.022	14.5314	413.853	398.45	436.37
QTc (Fridericia) (msec)			SCREENING	6	418.596	10.4189	417.659	408.00	437.69

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.5
Summary of ECG Values

	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
QTc (Fridericia) (msec)	A	6	PRE-DOSE	6	411.018	8.1730	409.027	400.88	423.23
			1 H	6	409.292	5.2070	409.935	402.50	416.72
			2 H	6	422.629	13.7936	419.630	404.61	442.06
			4 H	6	424.458	13.7751	420.599	408.00	442.15
			12 H	6	407.433	16.3481	400.804	394.03	439.29
	B	6	PRE-DOSE	6	408.096	7.8837	406.696	399.82	421.17
			1 H	6	412.899	10.7757	410.822	400.46	429.30
			2 H	6	412.947	11.4591	409.974	403.05	433.41
			4 H	6	419.907	12.0237	419.788	403.54	437.81
			12 H	6	407.324	19.9959	400.998	391.35	446.50
			FOLLOW-UP	6	418.156	21.5700	411.285	400.46	458.16

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.6
Summary of Change from Baseline Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Albumin (G/L)	A	6	48 H	6	2.0	2.10	1.5	0	6
	B	6	48 H	6	1.8	0.98	1.5	1	3
Alkaline Phosphatase (IU/L)	A	6	48 H	6	2.2	5.53	1.0	-4	12
	B	6	48 H	6	-4.7	4.89	-4.0	-12	2
Alanine Amino Transferase (IU/L)	A	6	48 H	6	0.0	1.79	-0.5	-2	3
	B	6	48 H	6	-1.8	1.83	-1.0	-5	0
Aspartate Amino Transferase (IU/L)	A	6	48 H	6	-0.2	0.98	-0.5	-1	1
	B	6	48 H	6	-2.0	1.55	-2.0	-4	0
Basophils (GI/L)	A	6	48 H	6	0.05	0.055	0.05	0.0	0.1
	B	6	48 H	6	0.05	0.055	0.05	0.0	0.1
Basophils (percentage) (%)	A	6	48 H	6	0.42	0.665	0.30	-0.3	1.5

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.6
Summary of Change from Baseline Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Basophils (percentage) (%)	B	6	48 H	6	0.45	0.692	0.20	-0.2	1.5
Total Bilirubin (UMOL/L)	A	6	48 H	6	-0.855	2.3571	0.000	-5.13	1.71
	B	6	48 H	6	-0.570	2.5745	-1.710	-3.42	3.42
Calcium (MMOL/L)	A	6	48 H	6	-0.04990	0.049900	-0.04990	-0.1248	0.0250
	B	6	48 H	6	-0.00832	0.037563	0.00000	-0.0749	0.0250
Chloride (MMOL/L)	A	6	48 H	6	-1.0	1.26	-0.5	-3	0
	B	6	48 H	6	0.2	0.98	0.0	-1	2
Carbon Dioxide content / Bicarbonate (MMOL/L)	A	6	48 H	6	-1.5	1.38	-1.5	-3	0
	B	6	48 H	6	0.5	1.87	0.5	-2	3
Creatinine (UMOL/L)	A	6	48 H	6	1.473	3.6089	0.000	0.00	8.84
	B	6	48 H	6	4.420	4.8419	4.420	0.00	8.84
Eosinophils (GI/L)	A	6	48 H	6	0.07	0.082	0.05	0.0	0.2

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.6
Summary of Change from Baseline Chemistry/Haematology Data

Lab Test	Treatment	N	Pl.	Time	n	Mean	SD	Median	Min.	Max.
Eosinophils (GI/L)	B	6	48	H	6	0.02	0.041	0.00	0.0	0.1
Eosinophils (percentage) (%)	A	6	48	H	6	1.35	0.521	1.10	0.9	2.3
	B	6	48	H	6	0.60	0.490	0.70	-0.3	1.1
Gamma Glutamyl Transferase (IU/L)	A	6	48	H	6	-0.8	1.72	-1.0	-3	1
	B	6	48	H	6	-1.7	2.73	-1.5	-5	2
Glucose (MMOL/L)	A	6	48	H	6	0.43483	0.162471	0.44408	0.1665	0.6661
	B	6	48	H	6	0.30531	0.194681	0.36081	0.0000	0.5551
Hemoglobin (G/L)	A	6	48	H	6	-1.5	6.16	-2.5	-8	10
	B	6	48	H	6	-2.8	2.64	-2.5	-7	1
Hematocrit (1)	A	6	48	H	6	-0.0025	0.01956	-0.0065	-0.022	0.035
	B	6	48	H	6	-0.0107	0.00981	-0.0105	-0.025	0.001
Potassium (MMOL/L)	A	6	48	H	6	0.12	0.564	0.25	-1.0	0.5

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.6
Summary of Change from Baseline Chemistry/Haematology Data

Lab Test	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Potassium (MMOL/L)	B	6	48 H	6	-0.07	0.501	0.20	-0.8	0.4
Lymphocytes (GI/L)	A	6	48 H	6	0.07	0.103	0.10	-0.1	0.2
	B	6	48 H	6	-0.02	0.256	0.00	-0.3	0.3
Lymphocytes (percentage) (%)	A	6	48 H	6	2.00	3.426	1.25	-2.1	7.4
	B	6	48 H	6	0.75	6.860	3.40	-12.3	5.7
Mean Corpuscle Hemoglobin Concentration (G/L)	A	6	48 H	6	-1.8	2.04	-3.0	-3	2
	B	6	48 H	6	1.2	3.19	0.5	-2	7
Mean Corpuscle Hemoglobin (PG)	A	6	48 H	6	0.00	0.210	-0.05	-0.2	0.4
	B	6	48 H	6	0.13	0.175	0.15	-0.1	0.4
Mean Corpuscle Volume (FL)	A	6	48 H	6	0.38	0.232	0.45	0.1	0.6
	B	6	48 H	6	0.03	0.625	0.05	-0.8	1.1

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.6
Summary of Change from Baseline Chemistry/Haematology Data

Lab Test	Treatment	N	Pl.	Time	n	Mean	SD	Median	Min.	Max.
Monocytes (GI/L)	A	6	48	H	6	0.03	0.082	0.00	0.0	0.2
	B	6	48	H	6	-0.02	0.194	-0.05	-0.2	0.3
Monocytes (percentage) (%)	A	6	48	H	6	0.58	0.915	0.55	-0.6	1.7
	B	6	48	H	6	-0.38	0.426	-0.35	-1.0	0.2
Mean Platelet Volume (FL)	A	6	48	H	6	0.13	0.320	0.00	-0.2	0.7
	B	6	48	H	6	-0.00	0.219	0.05	-0.3	0.3
Sodium (MMOL/L)	A	6	48	H	6	-1.2	1.72	-1.0	-4	1
	B	6	48	H	6	-0.3	1.51	-1.0	-2	2
Total Neutrophils (GI/L)	A	6	48	H	6	-0.28	0.588	-0.05	-1.2	0.2
	B	6	48	H	6	0.20	1.962	-0.40	-1.6	4.0
Total Neutrophils (percentage) (%)	A	6	48	H	6	-4.35	4.011	-3.70	-11.0	-0.4
	B	6	48	H	6	-1.42	7.936	-4.75	-6.6	13.8

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.6
Summary of Change from Baseline Chemistry/Haematology Data

Lab Test	Treatment	N	Pl.	Time	n	Mean	SD	Median	Min.	Max.
Platelet count (GI/L)	A	6	48	H	6	14.7	11.78	17.0	0	29
	B	6	48	H	6	-1.5	21.59	-4.0	-27	33
Phosphorus, Inorganic (MMOL/L)	A	6	48	H	6	0.00538	0.071962	0.00000	-0.0969	0.0969
	B	6	48	H	6	0.03767	0.065912	0.04844	-0.0646	0.1292
Red Blood Cell Count (TI/L)	A	6	48	H	6	-0.047	0.2196	-0.095	-0.25	0.38
	B	6	48	H	6	-0.125	0.1043	-0.120	-0.30	0.01
Total Protein (G/L)	A	6	48	H	6	2.7	4.97	2.0	-2	12
	B	6	48	H	6	1.3	1.51	2.0	-1	3
Urea (MMOL/L)	A	6	48	H	6	0.8925	0.95126	1.0710	-0.714	1.785
	B	6	48	H	6	0.1190	0.62517	0.1785	-0.714	1.071
Uric Acid (UMOL/L)	A	6	48	H	6	3.9653	23.69266	11.8960	-35.688	23.792
	B	6	48	H	6	-0.0000	21.61016	-0.0000	-23.792	23.792

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.6
Summary of Change from Baseline Chemistry/Haematology Data

Lab Test	Treatment	N	Pl.	Time	n	Mean	SD	Median	Min.	Max.
White Blood Cell Count (GI/L)	A	6	48	H	6	-0.10	0.710	0.10	-1.2	0.6
	B	6	48	H	6	0.23	2.081	-0.10	-1.9	4.1

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.7
Summary of Urinalysis Dipstick Results

Lab Test	Pl. Time	SI text result	A (N=6)	B (N=6)	Screening/Follow-up
Urine Occult Blood (dipstick)	SCREENING	2+	0	0	0
		NEGATIVE	0	0	6 (100%)
		TRACE	0	0	0
	PRE-DOSE	2+	0	0	0
		NEGATIVE	5 (83%)	6 (100%)	0
		TRACE	1 (17%)	0	0
	48 H	2+	0	1 (17%)	0
		NEGATIVE	6 (100%)	5 (83%)	0
		TRACE	0	0	0
	FOLLOW-UP	2+	0	0	0
		NEGATIVE	0	0	5 (83%)
		TRACE	0	0	1 (17%)
Urine Glucose (dipstick)	SCREENING	2+	0	0	0
		NEGATIVE	0	0	6 (100%)
		TRACE	0	0	0
	PRE-DOSE	2+	0	0	0
		NEGATIVE	6 (100%)	6 (100%)	0
		TRACE	0	0	0
	48 H	2+	0	0	0
		NEGATIVE	6 (100%)	6 (100%)	0
		TRACE	0	0	0

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.7
Summary of Urinalysis Dipstick Results

Lab Test	Pl. Time	SI text result	A (N=6)	B (N=6)	Screening/Follow-up
Urine Glucose (dipstick)	FOLLOW-UP	2+	0	0	0
		NEGATIVE	0	0	6 (100%)
		TRACE	0	0	0
Urine Ketones (dipstick)	SCREENING	2+	0	0	0
		NEGATIVE	0	0	6 (100%)
		TRACE	0	0	0
	PRE-DOSE	2+	0	0	0
		NEGATIVE	6 (100%)	6 (100%)	0
		TRACE	0	0	0
	48 H	2+	0	0	0
		NEGATIVE	6 (100%)	6 (100%)	0
		TRACE	0	0	0
	FOLLOW-UP	2+	0	0	0
		NEGATIVE	0	0	6 (100%)
		TRACE	0	0	0
Urine Protein (dipstick)	SCREENING	2+	0	0	0
		NEGATIVE	0	0	6 (100%)
		TRACE	0	0	0
	PRE-DOSE	2+	0	0	0
		NEGATIVE	6 (100%)	6 (100%)	0
		TRACE	0	0	0

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.7
Summary of Urinalysis Dipstick Results

Lab Test	Pl. Time	SI text result	A (N=6)	B (N=6)	Screening/Follow-up
Urine Protein (dipstick)	48 H	2+	0	0	0
		NEGATIVE	6 (100%)	6 (100%)	0
		TRACE	0	0	0
	FOLLOW-UP	2+	0	0	0
		NEGATIVE	0	0	6 (100%)
		TRACE	0	0	0

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.8
Summary of ECG Findings

Result	A (N=6)	B (N=6)
PRE-DOSE		
n	6 (100%)	6 (100%)
Normal	6 (100%)	6 (100%)
Abnormal - not clinically significant	0	0
Abnormal - clinically significant	0	0
Not available	0	0
1 H		
n	6 (100%)	6 (100%)
Normal	6 (100%)	6 (100%)
Abnormal - not clinically significant	0	0
Abnormal - clinically significant	0	0
Not available	0	0
2 H		
n	6 (100%)	6 (100%)
Normal	6 (100%)	6 (100%)
Abnormal - not clinically significant	0	0
Abnormal - clinically significant	0	0
Not available	0	0
4 H		
n	6 (100%)	6 (100%)
Normal	6 (100%)	6 (100%)
Abnormal - not clinically significant	0	0
Abnormal - clinically significant	0	0
Not available	0	0

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.8
Summary of ECG Findings

Result	A (N=6)	B (N=6)
12 H		
n	6 (100%)	6 (100%)
Normal	6 (100%)	5 (83%)
Abnormal - not clinically significant	0	1 (17%)
Abnormal - clinically significant	0	0
Not available	0	0
Any visit post-baseline		
n	6 (100%)	6 (100%)
Normal	6 (100%)	6 (100%)
Abnormal - not clinically significant	0	1 (17%)
Abnormal - clinically significant	0	0
Not available	0	0

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

Table 11.9
Summary of Vital Signs

	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)			SCREENING	6	118.0	15.72	117.5	98	143
	A	6	PRE-DOSE	6	127.0	12.57	126.0	114	148
			1 H	6	119.7	18.18	117.5	102	152
			2 H	6	118.0	16.63	116.0	101	149
			4 H	6	123.7	15.23	119.5	107	150
			12 H	6	115.8	13.47	115.5	98	137
	B	6	PRE-DOSE	6	120.0	18.78	118.5	96	147
			1 H	6	111.5	15.87	109.0	95	138
			2 H	6	108.5	18.33	102.5	91	143
			4 H	6	118.7	9.95	120.5	101	130
			12 H	6	118.5	20.76	120.5	86	138
			FOLLOW-UP	6	120.3	15.44	119.5	97	144

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.9
Summary of Vital Signs

	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)			SCREENING	6	62.7	13.72	60.0	46	84
	A	6	PRE-DOSE	6	57.0	11.88	55.0	46	79
			1 H	6	55.2	17.27	50.0	36	85
			2 H	6	54.7	11.13	52.0	44	75
			4 H	6	61.2	10.68	60.5	48	77
			12 H	6	54.5	12.71	52.0	42	78
	B	6	PRE-DOSE	6	63.8	10.57	63.0	52	83
			1 H	6	59.5	11.93	58.0	46	81
			2 H	6	59.0	11.78	56.0	47	81
			4 H	6	49.8	10.89	48.0	40	69
			12 H	6	58.2	12.98	55.5	45	82
			FOLLOW-UP	6	61.8	7.99	59.5	54	77

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.9
Summary of Vital Signs

	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Heart Rate (bpm)			SCREENING	6	70.0	13.10	64.5	59	94
	A	6	PRE-DOSE	0					
			1 H	6	65.0	14.14	64.5	47	90
			2 H	6	69.0	15.67	64.5	56	100
			4 H	6	65.8	13.45	63.0	48	89
			12 H	6	73.5	11.47	74.5	57	90
	B	6	PRE-DOSE	6	61.8	10.94	65.5	43	72
			1 H	6	63.5	11.48	68.0	44	75
			2 H	6	63.5	9.71	65.5	46	72
			4 H	6	63.5	10.41	65.5	45	74
			12 H	6	70.0	10.26	74.0	54	81
			FOLLOW-UP	6	62.0	13.07	64.5	42	81

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A

[redacted]

Table 11.10
Summary of Change from Baseline for Vital Signs

	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	A	6	1 H	6	-7.3	11.24	-11.0	-18	9
			2 H	6	-9.0	12.26	-7.0	-31	3
			4 H	6	-3.3	10.52	-6.5	-15	15
			12 H	6	-11.2	10.11	-11.0	-25	6
	B	6	1 H	6	-8.5	4.64	-8.5	-15	-1
			2 H	6	-11.5	12.82	-6.0	-36	-2
			4 H	6	-1.3	10.82	2.5	-17	11
			12 H	6	-1.5	8.43	-2.0	-10	11

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A
Note: Definition of Baseline is Period Specific Predose

[redacted]

Table 11.10
Summary of Change from Baseline for Vital Signs

	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Diastolic BP (mmHg)	A	6	1 H	6	-1.8	7.91	-1.0	-12	7
			2 H	6	-2.3	2.80	-1.5	-7	1
			4 H	6	4.2	8.73	1.0	-5	16
			12 H	6	-2.5	4.23	-3.0	-7	4
	B	6	1 H	6	-4.3	2.73	-3.5	-9	-2
			2 H	6	-4.8	2.48	-4.5	-9	-2
			4 H	6	-14.0	5.55	-12.0	-25	-10
			12 H	6	-5.7	3.88	-5.5	-12	-1

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A
Note: Definition of Baseline is Period Specific Predose

[redacted]

Table 11.10
Summary of Change from Baseline for Vital Signs

	Treatment	N	Pl. Time	n	Mean	SD	Median	Min.	Max.
Heart Rate (bpm)	A	6	1 H	0					
			2 H	0					
			4 H	0					
			12 H	0					
	B	6	1 H	6	1.7	2.50	1.0	-2	5
			2 H	6	1.7	2.16	1.5	-1	5
			4 H	6	1.7	2.73	2.0	-2	5
			12 H	6	8.2	1.94	8.5	6	11

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A
Note: Definition of Baseline is Period Specific Predose

[redacted]

Table 11.11
Listing of ECG Values (PCC Only)

Inv./ Subj.	Age(y)/ Sex/ Race	Treatment/ Visit	Pl. Time/ ECG Date/ ECG Time	Study Day/ Period Day	Test(Unit)	Result	CC Range	CC Code

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Regimen Key:
A=IV infusion of 10mg GSK221149A over 5 minutes
B=Single oral dose of 100mg GSK221149A

Table 11.12
Listing of Concomitant Medications

Cent./ Subj./ Seq.	Treatment/ Period	ATC Level 1/ Ingredient/ Verbatim Text/ Indication	Dose/ Units/ Freq/ Route	Start Date/ Start Time/ Study Day/ Period Day	Stop Date/ Study Day/ Period Day	Started Pre-Trial?	Ongoing Medication?
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.							

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A
Note: Conmeds with the same indication may be listed with multiple ATC Classifications/Ingredients

Table 11.13
Listing of Vital Signs Data with Potential Clinical Concern (PCC Only)

Inv./ Subj.	Age(y)/ Sex/ Race	Trt./ Visit	Test	Unit	Pl. Time	Actual Date/ Time	Study Day	Value	BL	Chg from BL	F3 Criteria Low	F3 Criteria High	F2 Criteria Low	F2 Criteria High	Flag F3	Flag F2

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Regimen Key:
A = IV infusion of 10mg GSK221149A over 5 minutes
B = Single oral dose of 100mg GSK221149A
Clinical Concern Criterion:
Heart Rate - Semi-Supine: <35 or >100 bpm, Sitting: <35 or >100 bpm.
Blood Pressure - Systolic > 30 mmHg change from baseline
Diastolic > 20 mmHg change from baseline
Flag Type: F2 - Change from baseline,F3 - Clinical relevance
I: Normal, H: High, L: Low, P: Pre-therapy

Attachment 1: Time and Events Table

Assessment	Screening	Period 1			Washout 28 days	Period 2			Follow-up
		Pre-dose[3]	Post-dose	Days 2-7[13]		Pre-dose[3]	Post dose	Days 2-7[13]	
Informed consent	✓								
Medical history	✓								
Con Meds	✓	✓	✓	✓		✓	✓	✓	
Demographics	✓								
Physical exam	✓	✓[3]				✓[3]			✓
Serology (HbsAg, anti-HCV, anti-HIV)	✓								
Serum β-hCG	✓	✓				✓			
Urine cotinine	✓								
Urine drug screen & alcohol test	✓	✓[3]				✓[3]			
12-lead ECG	✓	✓[3]	✓[5]			✓[3]	✓[5]		✓
Vital signs (blood pressure, heart rate)	✓[1]	✓[3]	✓[5]			✓[3]	✓[5]		✓
Clinical laboratory incl. urinalysis	✓	✓		✓[12]		✓		✓[12]	✓
Blood sampling for pharmacogenetics[2]									
Blood sample for plasma PK (cold assay)		✓	✓[7]			✓	✓		

Continued

Assessment	Screening	Period 1			Washout 28 days	Period 2			Follow-up
		Pre-dose[3]	Post-dose	Days 2-7[13]		Pre-dose[3]	Post dose	Days 2-7[13]	
Blood for metabolite analysis		✓	✓[11]			✓	✓[11]		
Blood sample for ^{14}C radioactivity in plasma		✓	✓[7]			✓	✓[6]		
Blood sample for ^{14}C radioactivity in whole blood		✓	✓[11]			✓	✓[11]		
Drug Administration			✓				✓		
Urine collection		✓	✓[8]	✓[8]			✓[8]	✓[9]	
Feces collection		✓	✓[9]	✓[9]				✓	
AE reporting[4]		✓	✓[10]	✓	✓	✓	✓[10]	✓	✓

1. Sitting, all other measurements semi-supine
2. Blood sampling for pharmacogenetics can be carried out at any suitable time point, after the PGx informed consent has been obtained.
3. Assessments may be at Admission or pre-dose as appropriate
4. SAEs related to study participation will be reported from time of consent.
5. VS & ECG at 1, 2, 4 & 12 h post dose
6. After oral administration, samples collected at pre dose, 15, 30, 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60 and 72 hours post-dose. Samples will be collected every 24 hours following the 72 hour sample if required.
7. After intravenous administration, samples will be collected at pre dose, 10, 20, 30 minutes, 1, 2, 3, 4, 6, 8, 12,18, 24, 36, 48, 60 and 72 hours after the start of the infusion Samples will be collected every 24 hours following the 72 hour sample if required.
8. Urine will be collected at pre dose, 0-6h, 6-12 h, 12-24 h post dose at over 24 h intervals 240 h post dose.
9. Feces will be collected at 24 h intervals up to 240 h post dose or until at least 90% radioactivity has been recovered
10. Subject response to adverse event questioning through a 'non-leading' question will be assessed and recorded at 4 and 12 hours post-dose. In addition, details of any adverse events reported spontaneously by any given subject will be recorded.
11. 30 mL samples at pre dose, 2, 6, 24 and 48 hrs post dose
12. 48 h post dose/start of infusion (Day 3)
13. Sample collection may continue to day 10, but will be a minimum of 2 days.

GSK221149A

Radioanalysis in Support of Compound GSK221149A

[redacted] Report No.: [redacted]
Sample Analysis Scheme No. CMS 78916B
GlaxoSmithKline
King of Prussia, PA

[redacted] [redacted] and [redacted]

Principal Analytical Investigator: [redacted] BS
GSK Clinical Study Identifier: OTA105101
GSK Representative: [redacted]
Issue Date: 10 April 2007
Total Number of Pages: 44

Participation

In addition to the principal analytical investigator, the following principal staff of [redacted] participated in this study:

Drug Metabolism

[redacted] BS, Laboratory Supervisor

[redacted] BS, Study Chemist

[redacted] BS, Study Coordination Supervisor

[redacted] BS, Study Coordinator

[redacted] BS, Manager Laboratory Operations

[redacted] BS, Supervisor Radiochemical Analysis

[redacted] Analyst Radiochemical Analysis

[redacted] Analyst Radiochemical Analysis

[redacted] PhD Associate Director

Quality Assurance Unit

[redacted] Vice President, Business Process Improvement and Compliance, BS

Radiation Safety Officer

[redacted] MS

Study Dates and Data Storage

This study was conducted on contract at [redacted] USA, in conjunction with the [redacted] USA.

Date Sample Analysis Scheme No. CMS 78916B signed by

Principal Analytical Investigator:	09 November 2006
Sponsor's Monitor:	12 January 2007
Analysis start date:	14 November 2006
Analysis completion date:	19 December 2006

All raw data, documentation, records, final sample analysis scheme, and final report will be retained in the archives of [redacted] for at least 1 year following the signing of the final report in accordance with [redacted] standard operating procedures (SOPs). The [redacted] archives staff will contact the Sponsor after at least 1 year following report finalization to determine disposition of the archived materials (except for the raw data on durable media, study correspondence, study protocol, any amendments, and final report, which will be kept by [redacted] for at least 10 years, in accordance with [redacted] SOPs). The Sponsor will then authorize the disposal or retention of samples, and the transport of remaining materials to their site (or that of their designee), or authorize the transport of the materials to the archive facilities of EPL Archives, Inc., Sterling, VA (EPL).

In the event the Sponsor fails to indicate disposition, these materials will be transferred to the EPL storage facilities. The Sponsor will be charged annual fees by EPL for the use of their archive facilities. [redacted] will have access to these materials for continued research or regulatory audit.

Approval

This study was performed under our overall scientific guidance and management. We agree with the discussion and conclusions made in this report.

Principal Analytical Investigator [redacted] Date: 10 Apr 2007
[redacted] BS
Drug Metabolism
[redacted]

Associate Director [redacted] Date: 10 April 07
[redacted] PhD
Drug Metabolism
[redacted]

Quality Assurance Statement

This report has been reviewed by the Quality Assurance Unit of [redacted] and accurately reflects the raw data. The following inspections were conducted and findings reported to the principal analytical investigator (PAI) and associated management.

Critical procedures, which are performed routinely in an operational area, may be audited as part of a process inspection program. This can be in addition to phases scheduled on an individual study basis. Selected process inspections conducted and considered applicable to this study may be included below.

Inspection Dates		Phase	Date Reported to PAI and PAI Management
From	To		
10 Nov 2006	10 Nov 2006	Protocol Review	10 Nov 2006
15 Nov 2006	15 Nov 2006	Radioanalysis	15 Nov 2006
12 Feb 2007	13 Feb 2007	Draft Report Review	13 Feb 2007
08 Feb 2007	13 Feb 2007	Data Review	13 Feb 2007

[redacted]

Repr[redacted]
Qual[redacted]t

10 Apr 07
Date

Summary

Objectives

The purpose of this study was to determine the radioactivity concentrations in blood, plasma, urine and feces and the radioactivity recovery in urine and fecal samples obtained during the conduct of [redacted] study [redacted] "An Open-Label, Two Period, Study to Determine the Excretion Balance and Pharmacokinetics of [^{14}C]-GSK221149A, Administered as Single Doses of an Oral Solution and an Intravenous Infusion to Healthy Female Adults." [GlaxoSmithKline (GSK) Study OTA105101, GSK Document No. ZM2005/00186/00].

Methods

In a study conducted by the [redacted] six healthy female subjects each received a single, target, 10-mg/20-µCi intravenous dose of [^{14}C]GSK221149A as a 0.4-mg/mL solution in Session 1. Following a washout period of approximately 2 weeks, each subject then received a single, target, 100-mg/60-µCi oral dose of [^{14}C]GSK221149A as a 0.8-mg/mL solution in Session 2. Blood, plasma, urine and feces were collected and analyzed for total radioactivity following the radiolabeled dose in each session.

Results

Following the single intravenous dose in Session 1, fecal excretion was the predominant route of elimination, accounting for a mean of 58.0% of the administered dose (range of 55.1 to 60.9% in individual subjects). Urinary excretion accounted for a mean of 36.0% of the administered dose (range of 32.2 to 39.3% in individual subjects). Most of the dose (mean of 92.7%) was recovered in urine and feces by 96 h post-dose. The mean total recovery of radioactivity was 93.9% of the dose (range of 93.1 to 95.5% in individual subjects).

Following the single oral dose in Session 2, fecal excretion was again the predominant route of elimination, accounting for a mean of 73.6% of the administered dose (range of 66.7% to 78.2% in individual subjects). Urinary excretion accounted for a mean of 20.5% of the administered dose (range of 18.3 to 23.4% in individual subjects). Most of the dose (mean of 93.8%) was recovered in urine and feces by 120 h post-dose. The mean total recovery of radioactivity was 94.1% of the dose (range of 87.0 to 97.4% in individual subjects).

The maximum mean concentration of radioactivity in blood following intravenous administration was observed at 2 h post-dose (44.1 ng equiv/mL). Individual maximum concentrations of radioactivity in blood were observed at 2 h post-dose (range of 32.9 to 56.7 ng equiv/mL). The maximum mean concentration of radioactivity in plasma was observed at 10 min post-dose (145 ng equiv/mL). Individual maximum concentrations of

radioactivity in plasma were observed from 10 min to 2 h post-dose (range of 69.7 to 209 ng equiv/mL). Levels of radioactivity fell below the limit of quantitation (BLQ) in both blood and plasma for all subjects by 6 h post-dose.

The maximum mean concentration of radioactivity in blood following oral administration was observed at 2 h post-dose (334 ng equiv/mL). Individual maximum concentrations of radioactivity in blood were observed at 2 h post-dose (range of 283 to 419 ng equiv/mL). The maximum mean concentration of radioactivity in plasma was observed at 30 min post-dose (838 ng equiv/mL). Individual maximum concentrations of radioactivity in plasma were observed from 15 to 45 min post-dose (range of 635 to 1260 ng equiv/mL). Levels of radioactivity fell below the limit of quantitation for all subjects in blood and plasma by 24 h and 8 h post-dose, respectively.

Conclusions

- Following the single, target, 10-mg intravenous dose of [^{14}C]GSK221149A (20 μCi) to healthy female subjects in Session 1, the predominant route of elimination of drug-related material was *via* feces (mean of 58.0%, range of 55.1 to 60.9%). Urinary excretion accounted for a mean of 36.0% of the administered dose (range of 32.2 to 39.3%). The mean total recovery of radioactivity was 93.9% (range of 93.1 to 95.5%) of the dose.

- Following the single, target, 100-mg oral dose of [^{14}C]GSK221149A (60 μCi) to healthy female subjects in Session 2, the predominant route of elimination of drug-related material was *via* feces (mean of 73.6%, range of 66.7 to 78.2%). Urinary excretion accounted for a mean of 20.5% of the administered dose (range of 18.3 to 23.4%). The mean total recovery of radioactivity was 94.1% (range of 87.0 to 97.4%) of the dose.

- Maximum mean concentrations of radioactivity following intravenous administration were observed in blood and plasma at 2 h and 10 min post-dose, respectively. Individual maximum concentrations were observed at 2 h post-dose for blood and 10 min to 2 h post-dose for plasma. Levels of radioactivity fell below the limit of quantitation in both blood and plasma for all subjects by 6 h post-dose.

- Maximum mean concentrations of radioactivity following oral administration were observed in blood and plasma at 2 h and 30 min post-dose, respectively. Individual maximum concentrations were observed at 2 h post-dose for blood and 15 to 45 min post-dose for plasma. Levels of radioactivity fell below the limit of quantitation in blood and plasma for all subjects by 24 h and 8 h post-dose, respectively.

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Introduction

GSK221149A is currently under development by GlaxoSmithKline as a therapeutic agent for the treatment of pre-term labor.

The purpose of this study was to determine the radioactivity concentrations in blood, plasma, urine and feces and the radioactivity recovery in urine and fecal samples obtained during the conduct of [redacted] study [redacted] "An Open-Label, Two Period, Study to Determine the Excretion Balance and Pharmacokinetics of [^{14}C]-GSK221149A, Administered as Single Doses of an Oral Solution and an Intravenous Infusion to Healthy Female Adults." [GlaxoSmithKline (GSK) Study OTA105101, GSK Document No. ZM2005/00186/00].

Materials and Methods

This radioanalysis study was conducted by [redacted] in accordance with [redacted] sample analysis scheme CMS 78916B (dated 09 November 2006), [redacted] standard operating procedures (SOPs) and the [redacted] Department of Health and Family Services, Radiation Protection Section (License No. [redacted]

Study Design

The dose formulations were prepared and the subjects were dosed throughout the two-session study at the [redacted] according to the target doses listed below.

Study Session	Number of Subjects	Dose Route	Dose Form	Target Dose Level (mg/Subject)	Target Dose Volume (mL/Subject)	Target Dose Concentration (mg/mL)	Target Radioactivity Level (μCi/Subject)
1	6	IV	Solution	10	25	0.4	20
2	6	Oral	Solution	100	125	0.8	60

IV Intravenous (5 minute infusion)

From each subject during each session, whole blood was collected pre-dose and at 2 h, 6 h, 24 h and 48 h post-dose. Blood for plasma was collected pre-dose and at 10 min, 20 min, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 18 h, 24 h, 36 h, 48 h and 60 h post-dose during Session 1. For Session 2, blood for plasma was collected pre-dose and at 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 18 h, 24 h, 36 h and 48 h post-dose. For both sessions, urine was collected pre-dose, at 0-6 h, 6-12 h, 12-24 h and at 24-h intervals until discharge criteria were met. Feces samples were collected from each subject during each session pre-dose and at 24 h intervals until discharge criteria were met. All samples were analyzed for total radioactivity. Discharge criteria were met when greater than 90% of the radioactive dose administered was recovered in the urine

and feces or less than 1% was excreted in two consecutive 24 h collection periods for both urine and feces (maximum stay of 240 h).

Dose Analysis

An unopened vial of [^{14}C]GSK221149A solution was transferred to [redacted] for confirmation of radiochemical purity analysis following the initiation of the clinical dosing for each study session. Samples (*ca.* 1 mL) from each individual dose for each session were also transferred to [redacted] for analysis of radioactivity concentration by liquid scintillation counting (LSC). After the intravenous dose in Session 1, the dose apparatus (syringe, line, three-way tap and cannula) for each subject was transferred to [redacted] for analysis of residual radioactivity and dose material. The amount of radioactive dose administered to each subject was calculated based on the results of the concentration analysis of individual dose aliquots and each dose apparatus, the solution weights administered to each subject (weights provided by the [redacted] and any other applicable information provided by the Sponsor (e.g., the Certificate of Analysis specific activity). The radio-high performance liquid chromatography (HPLC) method used for radiopurity analysis is presented in Appendix 1, Table 1-1.

The vials of test article and subject dose samples were stored at *ca.* -20ºC, protected from light, before and after analysis. Any test article or formulation remaining after analysis will be discarded or shipped to a site specified by the Sponsor.

Sample Handling

Samples of blood (*ca.* 1 mL) and plasma (*ca.* 0.5 to 1 mL) were stored at *ca*. -20°C before and after analysis of total radioactivity concentration. Subsamples of urine (*ca.* 5 mL each) were stored at *ca*. -20°C before and after analysis. Feces samples were stored at *ca* -20°C before analysis. At the time of processing, three *ca.* 50 g (if available) subsamples of each fecal homogenate were removed and stored at *ca*. -20°C. One subsample was used to determine the total radioactivity concentration, another subsample was shipped to the Sponsor as described below and one was retained as a reserve sample. The remaining bulk fecal homogenate samples will be stored at *ca.* -20°C for *ca.* 6 months or until discarded upon agreement with the Sponsor.

Additionally, storage and shipment stability samples were prepared for each session according to the following procedures. One 5 mL aliquot of pre-dose plasma was spiked with [^{14}C]GSK221149A at an appropriate concentration (*ca.* 50,000 to 100,000 dpm/mL). Portions of the pre-dose urine and feces samples from the same subject were used for storage and shipment stability sample preparation. An *ca.* 20 mL urine aliquot was spiked with [^{14}C]GSK221149A at an appropriate concentration (*ca.* 50,000 to 100,000 dpm/mL) and an *ca.* 20 g aliquot of fecal homogenate was spiked with [^{14}C]GSK221149A at an appropriate concentration (*ca.* 50,000 to 100,000 dpm/g). The

spiked aliquots were stored at *ca.* -20°C until shipment as described below. All samples were assayed for radioactivity content prior to shipment.

Matrix	Approximate Aliquot Size (g)	Mean Radioactivity Added (dpm/g)
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.		

Note: Urine and plasma were spiked at a concentration of 50,000-100,000 dpm/mL. Feces was spiked at a concentration of 50,000-100,000 dpm/g.

Radioanalytical Methods

All sample combustions were performed in a Model 307 Sample Oxidizer (Packard Instrument Company; Downers Grove, IL). The resulting $^{14}CO_2$ was trapped in Carbo-Sorb. Perma-Fluor scintillation cocktail was added and the radioactivity content was quantitated by LSC. All samples directly counted by LSC were analyzed using Ultima Gold scintillation cocktail. The samples were counted in a Model 2900TR liquid scintillation counter (Packard) for at least 5 min or 100,000 counts. All samples were analyzed in duplicate (if sample size allowed), with the exception of feces, which were analyzed in triplicate. If results for sample replicates (calculated as dpm/g of sample) differed by more than 10% from the mean value, the sample was rehomogenized (where appropriate) and reanalyzed. This specification was met for all sample aliquots that had radioactivity greater than 500 dpm.

Analysis of Blood

Each sample was mixed thoroughly and duplicate aliquots from each blood sample (*ca.* 0.3 mL each) were combusted and analyzed for radioactivity.

Analysis of Plasma

Each sample was mixed thoroughly and duplicate aliquots (*ca.* 0.2 mL each) were transferred to scintillation vials and analyzed for radioactivity.

Analysis of Urine

Each subsample was mixed thoroughly and duplicate aliquots (*ca.* 1.0 mL each) were transferred to scintillation vials and analyzed for radioactivity.

Analysis of Feces

The samples were pooled by subject and interval, weighed, mixed with deionized water and the homogenate weight was recorded. Samples were allowed to extract at least

overnight (if possible; samples from later collection intervals may have been analyzed on the day of receipt to facilitate the release of the subjects from the CRU). The samples were homogenized with a probe-type homogenizer and triplicate weighed aliquots (*ca.* 0.3 g each) were combusted and analyzed for radioactivity.

Sample Shipment

The spiked plasma, urine and fecal homogenate aliquots for storage and shipment stability and the plasma, urine and fecal homogenate subsamples for pharmacokinetic analysis and metabolic profiling were shipped to the following address:

[redacted]
GlaxoSmithKline
Development DMPK UW2720
709 Swedeland Road
King of Prussia, PA 19406-0939

Any analysis of these samples is not considered to be within the scope of this study. Data generated from these samples, if any, will not be used for interpretation of the results for this study, and will not be reported within this study.

Data Analysis and Major Computer Systems

Statistical analyses were limited to mean, standard deviation and coefficient of variation calculations, as appropriate. Dose tables were compiled with the mean and standard deviation values calculated using the Excel software program, Version 8.0e (Microsoft Corporation). Data tables (radioactivity concentration and percentage of dose) were generated by DEBRA, Version 5.2a (LabLogic), an automated and validated data capture and management system for studies using radiolabeled test article. The Rees system was used to capture environmental conditions in storage units.

A description of the calculations performed on the data is archived with the raw data. The computer-generated data shown in the Tables and Appendices have been rounded appropriately for inclusion in this report. As a result, calculation of values from data in this report will, in some instances, yield minor variations.

Results and Discussion

Dose Analysis

Radiochemical Purity

The mean radiochemical purity of [^{14}C]GSK221149A was 99.8% in the intravenous dose solution for Session 1 and 99.6% in the oral dose solution for Session 2. The radio-HPLC used to determined the radiochemical purity can be found in Appendix 1, Table 1-1. The radiochemical purity data are presented in Appendix 1, Table 1-2. Representative chromatograms are presented in Appendix 1, Figures 1-1 and 1-2.

Concentrations of Radioactivity and Specific Activities

Concentrations of radioactivity and specific activities in the individual dose aliquots are presented in Appendix 1, Table 1-3.

Dose Administration

The mean and individual doses of [^{14}C]GSK221149A administered to each subject for each session are presented in Table 1. For the intravenous administration (Session 1), the mean dose administered was 20.4 µCi/subject (mean of 9.94 mg GSK221149A/subject). For oral administration (Session 2), the mean dose administered was 62.2 µCi/subject (mean of 105 mg GSK221149A/subject).

Excretion of Radioactivity

Session 1-Intravenous Administration

Mean and individual recoveries of radioactivity for each collection interval are presented in Table 2 and cumulatively in Table 3. Concentrations of radioactivity in urine and feces are presented in Table 4. Mean urinary, fecal and total (urine and feces) cumulative excretion profiles are shown in Figure 1.

Following the single intravenous dose in Session 1, fecal excretion was the predominant route of elimination, accounting for a mean of 58.0% of the administered dose (range of 55.1 to 60.9% in individual subjects). Urinary excretion accounted for a mean of 36.0% of the administered dose (range of 32.2 to 39.3% in individual subjects). Most of the dose (mean of 92.7%) was recovered in urine and feces by 96 h post-dose. The mean total recovery of radioactivity was 93.9% of the dose (range of 93.1 to 95.5% in individual subjects).

The maximum mean concentrations of [^{14}C]GSK221149A-derived radioactivity were observed for samples collected from 0-6 h post-dose for urine (3370 ng equiv/mL) and 24-48 h post-dose for feces (22,000 ng equiv/g).

Session 2-Oral Administration

Mean and individual recoveries of radioactivity for each collection interval are presented in Table 5 and cumulatively in Table 6. Concentrations of radioactivity in urine and feces are presented in Table 7. Mean urinary, fecal and total (urine and feces) cumulative excretion profiles are shown in Figure 2.

Following the single oral dose in Session 2, fecal excretion was again the predominant route of elimination, accounting for a mean of 73.6% of the administered dose (range of 66.7% to 78.2% in individual subjects). Urinary excretion accounted for a mean of 20.5% of the administered dose (range of 18.3 to 23.4% in individual subjects). Most of the dose (mean of 93.8%) was recovered in urine and feces by 120 h post-dose. The mean total recovery of radioactivity was 94.1% of the dose (range of 87.0 to 97.4% in individual subjects).

The maximum mean concentrations of [^{14}C]GSK221149A-derived radioactivity were observed for samples collected from 0-6 h post-dose for urine (21,200 ng equiv/mL) and 48-72 h post-dose for feces (380,000 ng equiv/g).

Concentrations of Radioactivity in Blood and Plasma

Session 1-Intravenous Administration

The mean and individual concentrations of total radioactivity in blood and plasma samples are presented in Tables 8 and 9, respectively. Blood:plasma concentration ratios are presented in Table 10. The concentration-time profiles of radioactivity in blood and plasma are presented in Figure 3.

The maximum mean concentration of radioactivity in blood was observed at 2 h post-dose (44.1 ng equiv/mL). Individual maximum concentrations of radioactivity in blood were observed at 2 h post-dose (range of 32.9 to 56.7 ng equiv/mL). The maximum mean concentration of radioactivity in plasma was observed at 10 min post-dose (145 ng equiv/mL). Individual maximum concentrations of radioactivity in plasma were observed from 10 min to 2 h post-dose (range of 69.7 to 209 ng equiv/mL). Levels of radioactivity fell below the limit of quantitation in both blood and plasma for all subjects by 6 h post-dose.

The mean blood:plasma ratio at 2 h post-dose was 0.850, indicating minimal association of radioactivity with the red blood cells.

Session 2-Oral Administration

The mean and individual concentrations of total radioactivity in blood and plasma samples are presented in Tables 11 and 12, respectively. Blood:plasma concentration ratios are presented in Table 13. The concentration-time profiles of radioactivity in blood and plasma are presented in Figure 4.

The maximum mean concentration of radioactivity in blood was observed at 2 h post-dose (334 ng equiv/mL). Individual maximum concentrations of radioactivity in blood were observed at 2 h post-dose (range of 283 to 419 ng equiv/mL). The maximum mean concentration of radioactivity in plasma was observed at 30 min post-dose (838 ng equiv/mL). Individual maximum concentrations of radioactivity in plasma were observed from 15 to 45 min post-dose (range of 635 to 1260 ng equiv/mL). Levels of radioactivity fell below the limit of quantitation in blood and plasma for all subjects by 24 h and 8 h post-dose, respectively.

Mean blood:plasma ratios at 2 h and 6 h post-dose were 0.812 and 0.718, respectively, indicating minimal association of radioactivity with the red blood cells.

Conclusions

- Following the single, target, 10-mg intravenous dose of [^{14}C]GSK221149A (20 μCi) to healthy female subjects in Session 1, the predominant route of elimination of drug-related material was *via* feces (mean of 58.0%, range of 55.1 to 60.9%). Urinary excretion accounted for a mean of 36.0% of the administered dose (range of 32.2 to 39.3%). The mean total recovery of radioactivity was 93.9% (range of 93.1 to 95.5%) of the dose.

- Following the single, target, 100-mg oral dose of [^{14}C]GSK221149A (60 μCi) to healthy female subjects in Session 2, the predominant route of elimination of drug-related material was *via* feces (mean of 73.6%, range of 66.7 to 78.2%). Urinary excretion accounted for a mean of 20.5% of the administered dose (range of 18.3 to 23.4%). The mean total recovery of radioactivity was 94.1% (range of 87.0 to 97.4%) of the dose.

- Maximum mean concentrations of radioactivity following intravenous administration were observed in blood and plasma at 2 h and 10 min post-dose, respectively. Individual maximum concentrations were observed at 2 h post-dose for blood and 10 min to 2 h post-dose for plasma. Levels of radioactivity fell below the limit of quantitation in both blood and plasma for all subjects by 6 h post-dose.

- Maximum mean concentrations of radioactivity following oral administration were observed in blood and plasma at 2 h and 30 m post-dose, respectively. Individual maximum concentrations were observed at 2 h post-dose for blood and 15 to 45 min post-dose for plasma. Levels of radioactivity fell below the limit of quantitation in blood and plasma for all subjects by 24 h and 8 h post-dose, respectively.

Tables

Table 1 Mean and Individual Intravenous and Oral Doses of [^{14}C]GSK221149A Administered to Healthy Female Subjects

Subject Number	Dose Weight (g)	Dose Apparatus/Vial (dpm)	Dose Administered (dpm/subject)	(mg/subject)	(µCi/subject)
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.					

Notes: The mean radioactivity concentrations and specific activities of the dose formulations are presented in Appendix 1, Table 1-3.
SD Standard deviation

Table 2 Recovery of Radioactivity from Healthy Female Subjects after a Single 10-mg/20-µCi Intravenous Dose of [^{14}C]GSK221149A (Session 1)

Collection Interval	Percent of Administered Dose Subject Number
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.	

BLQ Below the limit of quantitation. Considered zero for calculation of the mean and SD.
NS No sample obtained. Considered zero for calculation of the mean and SD.
SD Standard deviation

Table 3 Cumulative Recovery of Radioactivity from Healthy Female Subjects after a Single 10-mg/20-µCi Intravenous Dose of [^{14}C]GSK221149A (Session 1)

Collection Interval	Percent of Administered Dose Subject Number
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.	

SD Standard deviation

Table 4 Urine and Feces Concentrations of Radioactivity in Healthy Female Subjects after a Single 10-mg/20-µCi Intravenous Dose of [^{14}C]GSK221149A (Session 1)

Collection Interval	Concentration (ng equiv/g or mL) Subject Number
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.	

BLQ Below the limit of quantitation. Considered zero for calculation of the mean and SD.
NA Not applicable
NS No sample obtained
SD Standard deviation

Table 5 Recovery of Radioactivity from Healthy Female Subjects after a Single 100-mg/60-µCi Oral Dose of [^{14}C]GSK221149A (Session 2)

Collection Interval	Percent of Administered Dose Subject Number
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.	

BLQ Below the limit of quantitation. Considered zero for calculation of the mean and SD.
NA Not applicable
NC No sample obtained. Subject discharged from clinic.
NS No sample obtained. Considered zero for calculation of the mean and SD.
SD Standard deviation
a:

Table 6 Cumulative Recovery of Radioactivity from Healthy Female Subjects after a Single 100-mg/60-µCi Oral Dose of [^{14}C]GSK221149A (Session 2)

Collection Interval	Percent of Administered Dose Subject Number
[redacted]	This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

SD Standard deviation

a: [redacted]

Table 7 Feces and Urine Concentrations of Radioactivity in Healthy Female Subjects after a Single 100-mg/60-µCi Oral Dose of [^{14}C]GSK221149A (Session 2)

Collection Interval	Concentration (ng equiv/g or mL) Subject Number

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

BLQ Below the limit of quantitation. Considered zero for calculation of the mean and SD.
NA Not applicable
NC No sample obtained. Subject discharged from clinic.
NS No sample obtained
SD Standard deviation

Table 8 Blood Concentrations of Radioactivity in Healthy Female Subjects after a Single 10-mg/20-μCi Intravenous Dose of [^{14}C]GSK221149A (Session 1)

Collection Time Point	Concentration (ng equiv/mL) Subject Number

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Note: The representative limits of quantitation for Session 1 have been calculated to be 19.0 and 22.0 ng equiv/mL for blood and plasma, respectively. These values are presented for reference purposes only. DEBRA calculates a limit of quantitation for each sample; therefore, values may vary slightly.
BLQ Below the limit of quantitation. Considered zero for calculation of the mean and SD.
SD Standard deviation

Table 9 Plasma Concentrations of Radioactivity in Healthy Female Subjects after a Single 10-mg/20-μCi Intravenous Dose of [^{14}C]GSK221149A (Session 1)

Collection Time Point	Concentration (ng equiv/mL) Subject Number
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.	

Note: The representative limits of quantitation for Session 1 have been calculated to be 19.0 and 22.0 ng equiv/mL for blood and plasma, respectively. These values are presented for reference purposes only. DEBRA calculates a limit of quantitation for each sample; therefore, values may vary slightly.
BLQ Below the limit of quantitation. Considered zero for calculation of the mean and SD.
NS No sample obtained
SD Standard deviation

Table 10 Blood:Plasma Concentration Ratios in Healthy Female Subjects after a Single 10-mg/20-μCi Intravenous Dose of [^{14}C]GSK221149A (Session 1)

Collection Time Point	Blood:Plasma Concentration Ratio Subject Number
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.	

NA Not applicable. Blood, plasma or both were below the limit of quantitation.
SD Standard deviation

Table 11 Blood Concentrations of Radioactivity in Healthy Female Subjects after a Single 100-mg/60-μCi Oral Dose of [^{14}C]GSK221149A (Session 2)

Collection Time Point	Concentration (ng equiv/mL) Subject Number

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

Note: The representative limits of quantitation for Session 2 have been calculated to be 42.9 and 68.1 ng equiv/mL for blood and plasma, respectively. These values are presented for reference purposes only. DEBRA calculates a limit of quantitation for each sample; therefore, values may vary slightly.
BLQ Below the limit of quantitation. Considered zero for calculation of the mean and SD.
SD Standard deviation

Table 12 Plasma Concentrations of Radioactivity in Healthy Female Subjects after a Single 100-mg/60-μCi Oral Dose of [^{14}C]GSK221149A (Session 2)

Collection Time Point	Concentration (ng equiv/mL) Subject Number
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.	

Note: The representative limits of quantitation for Session 2 have been calculated to be 42.9 and 68.1 ng equiv/mL for blood and plasma, respectively. These values are presented for reference purposes only. DEBRA calculates a limit of quantitation for each sample; therefore, values may vary slightly.
BLQ Below the limit of quantitation. Considered zero for calculation of the mean and SD.
SD Standard deviation

Table 13 Blood:Plasma Concentration Ratios in Healthy Female Subjects after a Single 100-mg/60-μCi Oral Dose of [^{14}C]GSK221149A (Session 2)

Collection Time Point	Blood:Plasma Concentration Ratio Subject Number
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.	

NA Not applicable. Blood, plasma or both were below the limit of quantitation.
SD Standard deviation

Figures

Figure 1 Mean Cumulative Elimination of Radioactivity by Healthy Female Subjects after a Single 10-mg/20-µCi Intravenous Dose of [^{14}C]GSK221149A (Session 1)

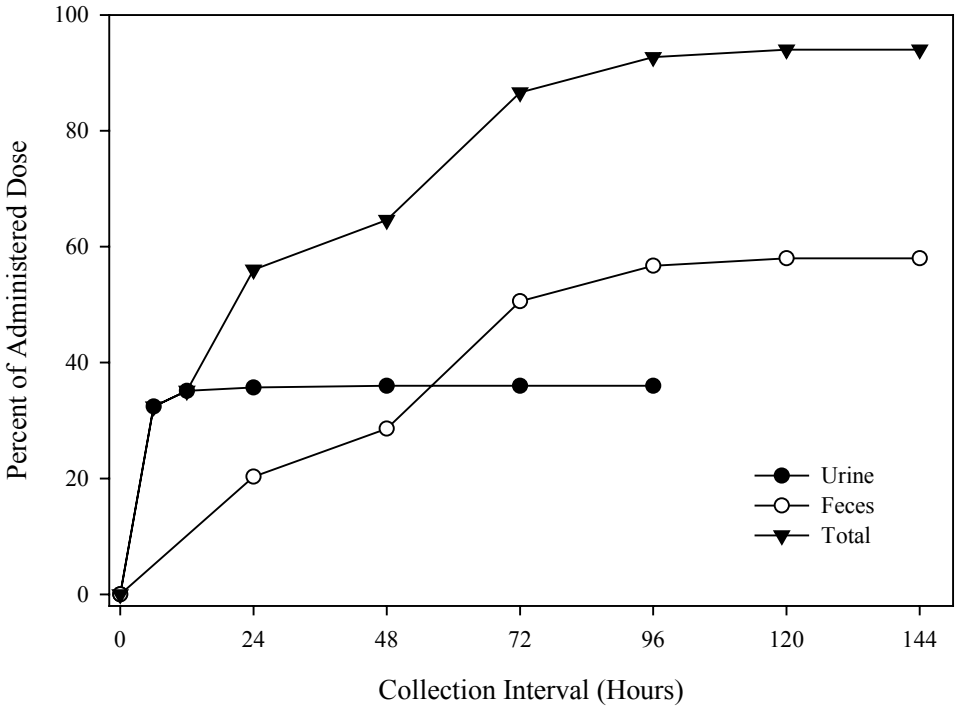


Figure 2 Mean Cumulative Elimination of Radioactivity by Healthy Female Subjects after a Single 100-mg/60-µCi Oral Dose of [^{14}C]GSK221149A (Session 2)

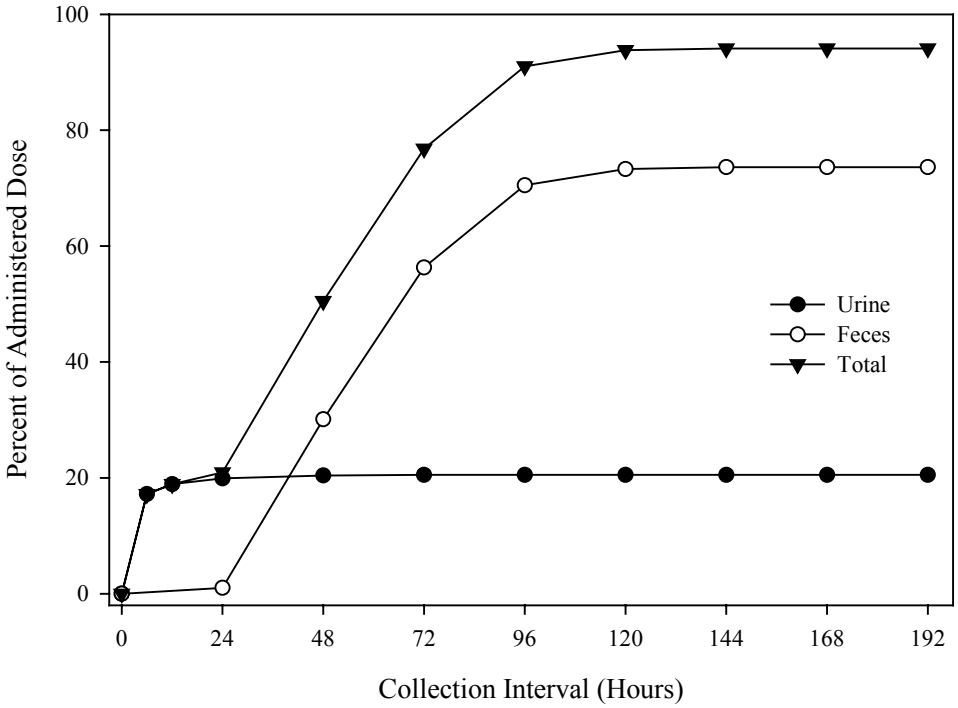


Figure 3 Mean Concentrations of Radioactivity in Blood and Plasma from Healthy Female Subjects after a Single 10-mg/20-µCi Intravenous Dose of [^{14}C]GSK221149A (Session 1)

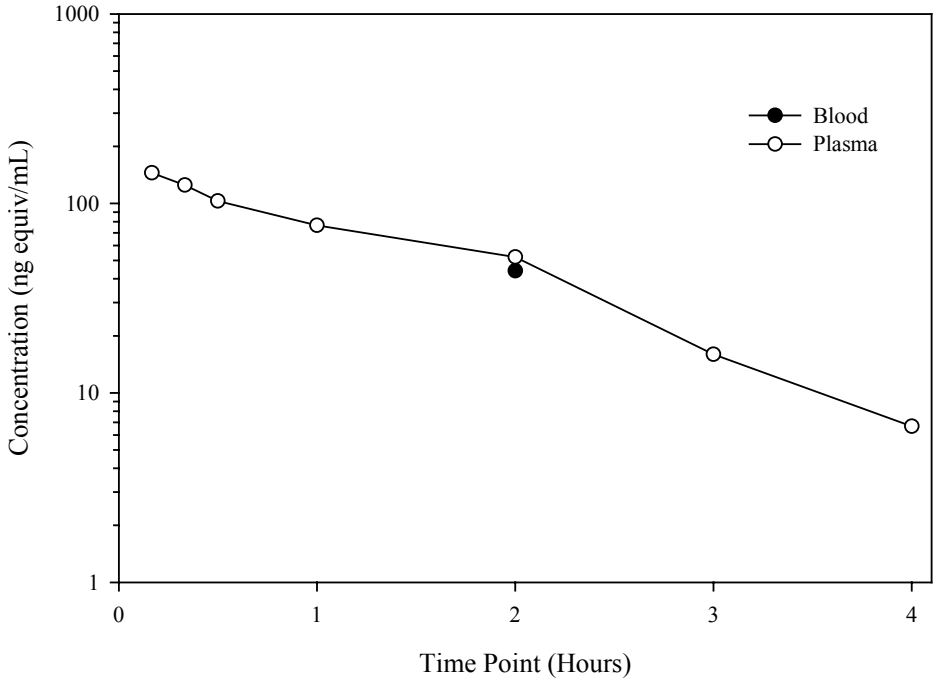
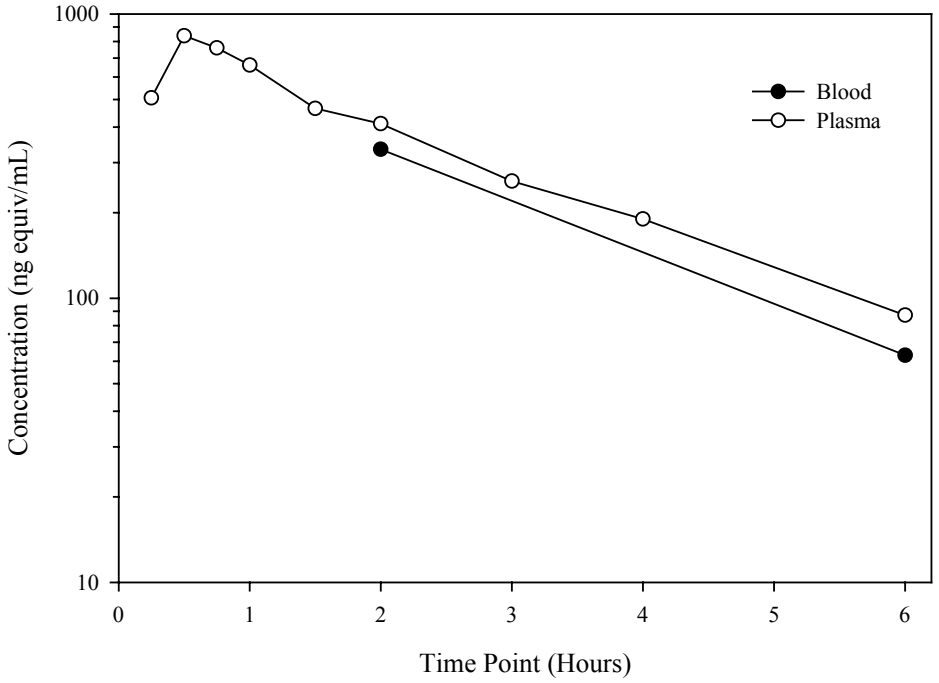


Figure 4 Mean Concentrations of Radioactivity in Blood and Plasma from Healthy Female Subjects after a Single 100-mg/60-µCi Oral Dose of [^{14}C]GSK221149A (Session 2)



Appendix

Appendix 1 Radio-HPLC Method and Analysis of the Dose Formulations

Table 1-1 Radio-HPLC Method

HPLC system:		
Pump, UV detector, autoinjector	HP 1100 Series	
Column heater	Eppendorf CH-30	
Wavelength:	220 nm	
Radioactivity detector:	Packard 500 Series	
Flow cell	0.5 mL TRLSC	
Scintillation cocktail:	Ultima Flo M	
Flow rate	3 mL/min	
Analytical column:	Luna C18(2), 4.6 x 100 mm, 3 µm	
Column temperature:	25°C	
Mobile phase flow rate:	1 mL/min	
Mobile phase:		
Solvent A	0.05% trifluoroacetic acid in reverse osmosis water	
Solvent B	0.05% trifluoroacetic acid in acetonitrile	
Gradient:		
Time (min)	% A	% B
Initial	100	0
15	0	100
20	100	0
30	100	0

Note: See Appendix 1, Figures 1-1 and 1-2 for representative radiochromatograms from the analysis of each dose solution.

Table 1-2 Radiochemical Purity Analysis of the Dose Solutions

Session	Column Recovery (%)	Mean (%)	Radiochemical Purity (%)	Mean (%)
1	97.4	97.5	99.9	99.8
(Intravenous)	97.7		99.8	
2	96.3	96.2	99.7	99.6
(Oral)	96.1		99.6	

Note: See Appendix 1, Figures 1-1 and 1-2 for representative radiochromatograms from the analysis of each dose solution.

Table 1-3 Analysis of the Dose Solutions for Concentration of Radioactivity

Session	Subject No.	Mean Radioactivity Concentration (dpm/g)	SD	CV (%)	Specific Activity (μCi/mg)
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.					

Note: The data presented were determined from triplicate analysis.
CV Coefficient of variation
SD Standard deviation

Figure 1-1 Representative Chromatogram for HPLC Analysis of the Intravenous Dose Solution for Session 1

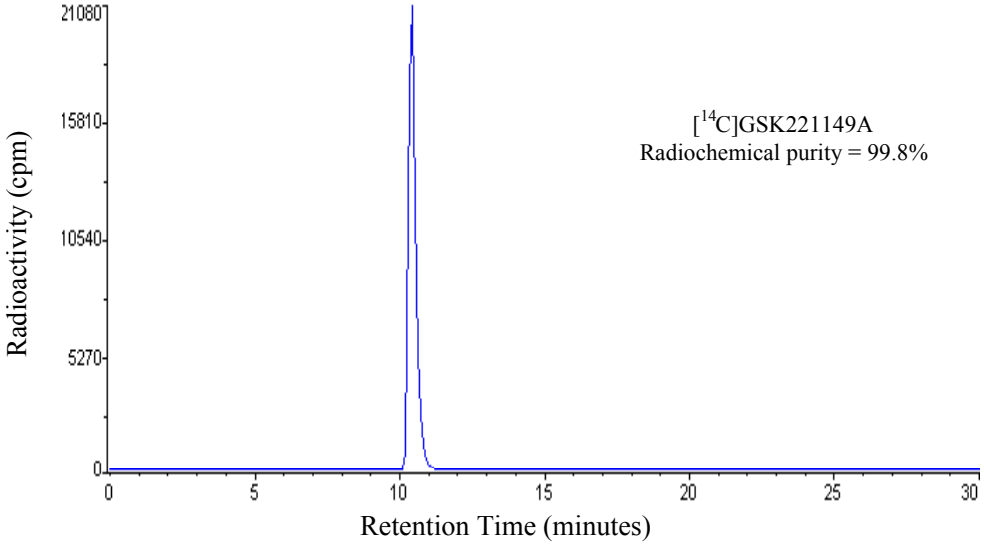
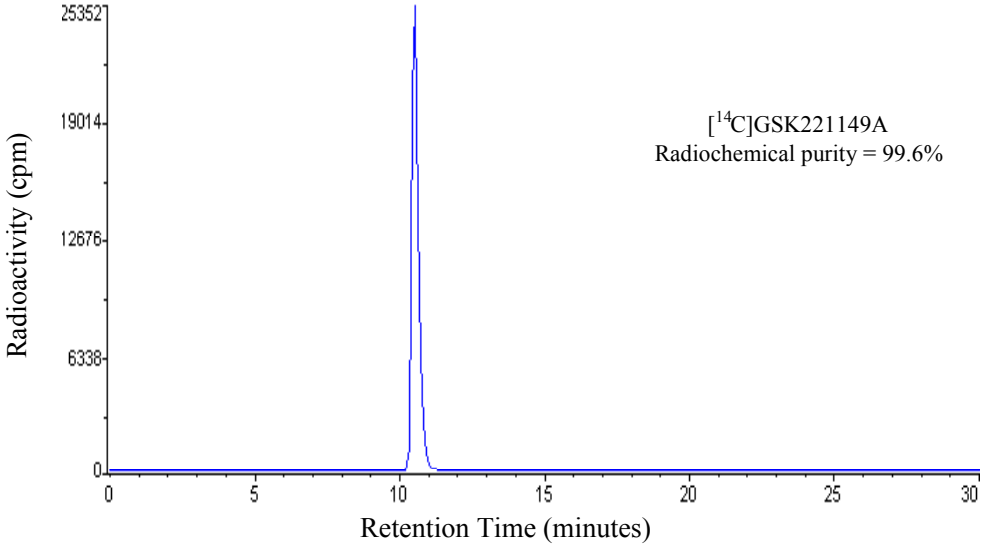


Figure 1-2 Representative Chromatogram for HPLC Analysis of the Oral Dose Solution for Session 2



Synopsis

Identifier: EM2007/00008/00 **Study Number:** OTA105101

Title: An open-label, two period, study to determine the excretion balance and pharmacokinetics of [^{14}C]-GSK221149A, administered as single doses of an oral solution and an intravenous infusion to healthy female adults

Investigator: [redacted] MD (sub-investigator: [redacted] MD)

Study center: [redacted]

Publications: None at the time of this report.

Study period: 24 October 2006 - 29 December 2006

Phase of development: I

Objectives:

Primary:

- To determine the total recovery and relative excretion of radiocarbon in urine and feces after a single intravenous and single oral doses of [^{14}C]-GSK221149A in healthy adult females
- To generate samples (for a separate study) to characterize and quantify the metabolic profile of GSK221149A in plasma, urine and feces following administration of [^{14}C]-GSK221149A to healthy adult females
- ***Secondary:***
- To further assess the safety and tolerability of single intravenous and/or oral doses of GSK221149A in healthy adult female subjects
- To determine the absolute bioavailability of GSK221149A by comparing the disposition of [^{14}C]-GSK221149A following oral and intravenous dosing.
- To determine (as data permit) pharmacokinetic parameters of interest following oral and intravenous dosing.
- To compare total drug-related material (radioactivity) in blood and plasma relative to parent plasma concentrations.

Methodology:

This was an open-label, non-randomized, 2 period study. Dosing in each period was separated by at least 28 days. In Period 1, subjects received a single dose of 10 mg (20 μCi) intravenous (IV) infusion of [^{14}C]-GSK221149A as a 0.4 mg/mL solution over a period of 5 minutes (Regimen A). In Period 2, subjects received a single oral dose of 100 mg (60 μCi) [^{14}C]-GSK221149A as a 0.8-mg/mL solution (Regimen B). In each period, subjects were admitted to a clinical research unit (CRU) for 6 consecutive nights.

Blood and urine samples for clinical laboratory tests, as well as adverse events (AEs), 12-lead ECG and vital signs were collected throughout the study.

In each period, blood samples were collected for a minimum of 2 days (i.e. 48 hours post-dose). Blood collections continued until the measured radiocarbon for 2 consecutive plasma samples fell to less than or equal to twice the background radiation count. Urine and feces were collected for a minimum of 96-hours and a maximum of 240 hours (10 days) post-dose. Collection was discontinued if the 48-72 and 72-96 hour sample was collected and results of radiocarbon measurement indicated that 2 consecutive samples (of urine and feces) contained less than or equal to 1% of the administered dose of radioactivity.

Follow-up visits were conducted 10 to 14 days within a subject's blood, urine, and fecal samples lowering to the respective required radiocarbon counts for discontinuation of sampling.

Blood samples were analysed for GSK221149 by a validated analytical method based on protein precipitation using HPLC-MS/MS analysis. PK analyses of plasma GSK221149 concentration-time data were conducted using noncompartmental methods.

The total study duration was approximately 2 months.

Number of subjects:

Planned, N	6
Entered, N	6
Completed, n (%)	6 (100%)
Total Withdrawn, n (%)	0 (0%)

Diagnosis and main criteria for inclusion:

Eligible subjects were healthy adult females (not of child-bearing potential) between 30 and 55 years of age, inclusive.

Treatment administration:

[^{14}C]-GSK221149A was supplied by GlaxoSmithKline as a sterile solution suitable for both IV and oral routes of administration, a clear, colorless solution which contains GSK221149A at a concentration of 0.8 mg/mL (1.6 μCi/mL) (Batch Number 061126238). In Period 1, subjects received a single dose of 10 mg (20 μCi) IV infusion of [^{14}C]-GSK221149A as a 0.4 mg/mL solution over a period of 5 minutes (Regimen A). In Period 2, subjects received a single oral dose of 100 mg (60 μCi) [^{14}C]-GSK221149A as a 0.8-mg/mL solution (Regimen B).

Criteria for evaluation:

PK: All subjects who received the study medication and had sufficient data for evaluation of PK were included in the PK analysis population. Area under the concentration-time curve from time zero to the last quantifiable concentration [AUC(0-t)], from zero extrapolated to infinity [AUC(0-∞)], the maximum concentration (Cmax), time to reach Cmax (tmax), and the elimination half-life (t½) after each administration were assessed as the primary pharmacokinetic parameters of interest for GSK221149. Total systemic clearance (CL) and volume of distribution at steady-state (Vd_{ss}) after IV

administration were also assessed. Absolute bioavailability (F) was assessed by comparing dose normalized AUC(0-∞) from both administrations. [redacted] All 6 subjects were included in the PK analysis of data collected in Period 2.

Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Safety data, including AEs, vital signs, clinical laboratory data and ECG monitoring, were listed and summarized. Clinical abnormalities were described. All 6 subjects were included in the evaluation of safety and tolerability.

Statistical methods:

PK: No formal statistical analyses of the PK data were performed. Individual subject parameter values, as well as a descriptive summary of parameters were reported. The descriptive statistics include the mean, standard deviation, median, minimum, maximum, and for all parameters except tmax, the standard deviation of log-transformed values, geometric mean and corresponding 95% confidence intervals.

Safety: No formal statistical analyses of the safety data were performed.

Summary:

Demographics:

All subjects entered into the study were White females.

Sex, N	Females	6
Age, years	Mean (SD)	52.2 (2.48)
	Median (min-max)	52.5 (48-55)
Race, N	White – White/Caucasian/European Heritage	6
Ethnicity, N	Hispanic or Latino	0
	Not Hispanic or Latino	6

Pharmacokinetics:

Following the single intravenous dose in Session 1, fecal excretion was the predominant route of elimination, accounting for a mean of 58.0% of the administered dose (range of 55.1 to 60.9% in individual subjects). Urinary excretion accounted for a mean of 36.0% of the administered dose (range of 32.2 to 39.3% in individual subjects). Most of the dose (mean of 92.7%) was recovered in urine and feces by 96 hours post-dose. The mean total recovery of radioactivity was 93.9% of the dose (range of 93.1 to 95.5% in individual subjects).

Following the single oral dose in Session 2, fecal excretion was again the predominant route of elimination, accounting for a mean of 73.6% of the administered dose (range of 66.7% to 78.2% in individual subjects). Urinary excretion accounted for a mean of 20.5% of the administered dose (range of 18.3 to 23.4% in individual subjects). Most of the dose (mean of 93.8%) was recovered in urine and feces by 120 hours post-dose. The mean total recovery of radioactivity was 94.1% of the dose (range of 87.0 to 97.4% in individual subjects).

The maximum mean concentration of radioactivity in blood following IV administration was observed at 2 hours post-dose (44.1 ng equiv/mL). Individual maximum concentrations of radioactivity in blood were observed at 2 hours post-dose (range of 32.9 to 56.7 ng equiv/mL). The maximum mean concentration of radioactivity in plasma was observed at 10 minutes post-dose (145 ng equiv/mL). Individual maximum concentrations of radioactivity in plasma were observed from 10 minutes to 2 hours post-dose (range of 69.7 to 209 ng equiv/mL). Levels of radioactivity fell below the limit of quantitation (BLQ) in both blood and plasma for all subjects by 6 hours post-dose.

The maximum mean concentration of radioactivity in blood following oral administration was observed at 2 hours post-dose (334 ng equiv/mL). Individual maximum concentrations of radioactivity in blood were observed at 2 hours post-dose (range of 283 to 419 ng equiv/mL). The maximum mean concentration of radioactivity in plasma was observed at 30 minutes post-dose (838 ng equiv/mL). Individual maximum concentrations of radioactivity in plasma were observed from 15 to 45 minutes post-dose (range of 635 to 1260 ng equiv/mL). Levels of radioactivity fell below the limit of quantitation for all subjects in blood and plasma by 24 hours and 8 hours post-dose, respectively.

Geometric means (CVb%) for parent GSK221149 PK parameters of interest are summarized in the following table:

Regimen	N	AUC(0-∞) (ng·hr/mL)	AUC(0-t) (ng·hr/mL)	Cmax (ng/mL)	tmax (hr)[1]	t1/2 (hr)	CL (L/hr)	Vd_{ss} (L)	F (%)
A (IV)	5	203 (11.7)	197 (13.5)	188 (13.5)	0.170 (0.17 – 0.33)	1.34 (21.0)	49.3 (11.7)	80.6 (14.8)	NC
B (oral)	6	538 (48.3)	533 (48.6)	311 (60.3)	0.500 (0.25 – 0.78)	1.46 (21.9)	NC	NC	28.1 (43.5)

1. Median (Range)
NC Not calculated
Regimen A Single, 10mg dose of [^{14}C]-GSK221149A, IV infusion over 5 minutes (Period 1)
Regimen B Single, 100mg dose of [^{14}C]-GSK221149A, oral solution (Period 2)

Following a single, oral 100mg dose of [^{14}C]-GSK221149A, total radioactivity rapidly appeared in plasma with a median tmax value of 0.5 hour. The mean half- life of total radioactivity after oral administration (2.13 hours) was slightly longer than that observed after IV administration (1.22 hours), but was still relatively short. As was observed with the parent compound, between-subject variability was low after IV administration and moderate after oral administration. Geometric Mean (CVb%) of total radioactivity PK parameters are summarized in the table below.

Regimen	N	AUC(0-∞) (ng·hr/mL)	AUC(0-t) (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)[1]	t1/2 (hr)
A (IV)	5	268.37 (20.70)	188.75 (19.46)	179.1 (15.00)	0.170 (0.17-0.33)	1.22 (25.73)
B (oral)	6	2291.04 (21.08)	1864.60 (21.69)	840.7 (25.00)	0.5 (0.25-0.78)	2.13 (38.25)

Source Data: Pharmacokinetic Source Table 10.5 - Table 10.9
1. Median (Range)
NC Not calculated
Regimen A Single, 10mg dose of [^{14}C]-GSK221149A, IV infusion over 5 minutes (Period 1)
Regimen B Single, 100mg dose of [^{14}C]-GSK221149A, oral solution (Period 2)

Safety:

There were no deaths or SAEs reported during the study. There were no AEs related to clinical laboratory values, ECGs or vital signs. The majority of AEs were mild, and all AEs resolved by the end of the study. The most commonly reported AEs (i.e., reported in ≥ 2 subjects in either Regimen) are presented in the table below.

	Number of Subjects	
	Regimen A (IV)	Regimen B (Oral)
Abdominal pain	--	3
Diarrhea	--	2
Fatigue	--	3
Headache	--	2
Total # of subjects with AEs	4	5
Total # of subjects exposed	6	6

Regimen A Single, 10mg dose of [^{14}C]-GSK221149A, IV infusion over 5 minutes (Period 1)
Regimen B Single, 100mg dose of [^{14}C]-GSK221149A, oral solution (Period 2)

Conclusions:

- The major route of elimination of GSK221149 and its metabolites was through the feces (58-73% of the administered dose), followed by the urine (20.5-36% of administered dose).
- There was minimal association of radioactivity with the red blood cells.
- Levels of radioactivity fell below the limit of quantitation in blood and plasma for all subjects by 24 hours and 8 hours post-dose, respectively. This indicates that little or no accumulation of any metabolites may be expected upon multiple dosing of GSK221149.
- The absolute bioavailability of GSK221149 was low (28%) following administration as an oral solution and similar to that found in a previous study with GSK221149.
- Following IV administration, GSK221149 demonstrated moderate to high systemic clearance and a large apparent volume of distribution.
- Total radioactivity closely paralleled parent drug after oral and IV administration, suggesting that there are no metabolites of GSK221149 with long half-lives.
- Single 10 mg intravenous doses and single 100 mg oral doses of GSK221149A were generally safe and well tolerated in healthy adult female subjects under the conditions of this study.

Date of Report: February 2008

Division: Worldwide Development
Retention Category: GRS019
Information Type: Protocol

Title:	An open-label, two period, study to determine the excretion balance and pharmacokinetics of [^{14}C]-GSK221149A, administered as single doses of an oral solution and an intravenous infusion to healthy female adults

Compound Number: GSK221149

Effective Date: 06-Apr-2006

Description:

GSK221149A is an oxytocin receptor antagonist and is currently in development for the treatment of preterm labor without premature rupture of membranes.

This will be a two-period, open-label study conducted at a single site. Six healthy female subjects (not of child bearing potential) will participate in the study. Each subject will receive a single 100 mg (60 μCi) oral dose and an 10 mg (20 μCi) intravenous infusion of [^{14}C]-GSK221149A. Urine and fecal samples will be collected for a minimum of 168 hours following study-drug administration (or until more than 90% of the radioactive dose administered is recovered) to establish an excretion balance and metabolic disposition. Blood and plasma will be collected at various sample times after dosing to measure parent drug and total drug-related material. Samples of urine, feces and plasma will be transferred into a separate study to characterize and quantify metabolites in these matrices. Safety will be assessed by physical examination, clinical observation and question regarding adverse experiences, as well as vital signs, ECGs, and safety laboratories.

Subject: GSK221149A, absorption, distribution, metabolism, elimination.

Author(s): [redacted]

CONFIDENTIAL ZM2005/00186/00
OTA105101

SPONSOR SIGNATORY:

[redacted] M.D
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Apr 6, 2006
Date

SPONSOR INFORMATION PAGE

Clinical Study Identifier: OTA105101

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Email:	[redacted]
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Telephone number (day)	[redacted]
Telephone number (evening)	[redacted] (cell), [redacted] home)
Facsimile number	[redacted]
Email:	[redacted]

Regulatory Agency Identifying Number(s): 69,401 and 73,287

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I confirm agreement to conduct the study in compliance with the protocol.

Investigator Name: _____

_____ _____
Investigator Signature Date

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ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of variance
ALT	Alanine amino transferase
AST	Aspartate amino transferase
AUC(0-inf)	Area under concentration-time curve from zero to infinity
AUC(0-t)	Area under concentration-time curve from zero to t
BP	Blood pressure
Bpm	beats per minute
BUN	Blood urea nitrogen
^{14}C	Carbon 14
CBC	Complete blood count
µCi	Micro Curies
CIB/IB	Clinical investigator's brochure/investigator's brochure
CL	Plasma clearance
Cm	Centimeter
Cmax	Maximum plasma concentration
CRF	Case report form (electronic or hard-copy)
CRO	Clinical Research Organisation
CV	Coefficient of variation
DMPK	Drug Metabolism & Pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ED	Effective Dose
EISR	Expedited Investigator Safety Report
FDA	Food and Drug Administration
FTIH	First Time Into Human
FTIW	First Time into Woman
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GSK	GlaxoSmithKline
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug Application
IRB	Institutional Review Board
ICRP	International Commission on Radiological Protection
IV	Intravenous
Kg	Kilogram
M	Meter
mL	Milliliter
mmHg	millimeter of mercury
MRSD	Maximum Recommended Starting Dose
MRT	Mean residence time
mRem	millirem
MSDS	Material Safety Data Sheet
MSE	Mean square error
Msec	millisecond

mSv	millisievert
OT	Oxytocin
PTL	Preterm Labor
SRM	Study Reference Manual
US	United States
UDS	Urine Drug Screen
WHO	World Health Organisation

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Tractocile

PROTOCOL SUMMARY

Rationale

Single and repeat doses of both the oral and intravenous formulations of GSK221149A have been administered to healthy women of child-bearing potential in two studies (OTA100801, OTA103772). Although ADME data are available on the metabolism of GSK221149A from animals, in vitro experiments and early Phase 1 trials, the metabolic pathways and elimination routes for GSK221149A in humans have not yet been fully elucidated. The principal aim of this study is to investigate the excretion and absorption of GSK221149A in humans using [^{14}C] radiolabeled drug substance administered by the oral and intravenous routes. Additionally, samples from this study will be transferred to a separate study to characterize and quantify the metabolites of GSK221149A in plasma, urine and feces.

The absorption, metabolism and excretion of GSK221149A must be adequately described in human subjects as part of the clinical development.

Objective(s)

Primary

- To determine the total recovery and relative excretion of radiocarbon in urine and feces after a single intravenous and single oral dose of [^{14}C]-GSK221149A in healthy adult females
- To generate samples (for a separate study) to characterize and quantify the metabolic profile of GSK221149A in plasma, urine and feces following administration of [^{14}C]-GSK221149A to healthy adult females

Secondary

- To further assess the safety and tolerability of single intravenous and/or oral doses of GSK221149A in healthy adult female subjects
- To determine the absolute bioavailability of GSK221149A by comparing the disposition of [^{14}C]-GSK221149A following oral and intravenous dosing
- To determine (as data permit) pharmacokinetic parameters of interest following oral and intravenous dosing
- To compare total drug-related material (radioactivity) in blood and plasma relative to parent plasma concentrations.

Endpoint(s)

Primary

- Urinary and fecal cumulative excretion as a percentage of the total radioactive dose administered over time

- Collection of samples for characterization and quantification of metabolites in plasma, urine and fecal homogenates to be documented and performed by DMPK, GSK; results to be reported in a separate report

Secondary Endpoints:

- Clinical safety data from spontaneous AE reporting, 12-lead ECG, vital signs, nursing/physician observation, and safety laboratory tests will be summarized and any clinically significant abnormalities described. Safety data will not be statistically analyzed.
- $AUC_{(0\text{-inf})}$ and C_{max} of GSK221149A and drug-related material (radioactivity) in plasma following oral and intravenous dosing
- $T_{max,}$ $t_{1/2}$ of GSK221149A following oral dosing
- $T_{max,}$ $t_{1/2}$, volume and clearance of GSK221149A following intravenous dosing
- Blood:Plasma ratio of total drug-related material (radioactivity)

Study Design

This will be an open-label, two period study involving six healthy female subjects (not of child bearing potential).

Each subject will participate in two separate dosing periods. In the first dosing period, each subject will receive a single dose of 10 mg (20 μCi) intravenous infusion of [^{14}C]-GSK221149A administered over 5 minutes. In the second dosing period, each subject will receive a single oral dose of 100 mg (60 μCi) [^{14}C]-GSK221149A. Each study period will involve approximately a six-night, seven-day admission. The two dosing periods will be separated by a wash-out of at least 28 days.

Blood samples will be collected for a minimum of 48 hours post-dose. Blood collections will continue until the measured radiocarbon for two consecutive plasma samples falls to less than or equal to twice the background radiation count. Thus, if the results of the radiocarbon measurements for the 36-hour sample and the 48-hour sample reveal that both samples contain radioactivity less than or equal to twice the background radiation count, sample collection may be discontinued. Otherwise, sample collection will continue until two consecutive samples produce radiocarbon measurement results indicating that both samples contain less than or equal to twice the background radiation count or until both the urine and stool collections have ceased. Samples will be collected every 24 hours following the 72 hour sample if required. Therefore, sampling may theoretically continue after day 7, but will not continue beyond day 10.

All urine and feces will be collected for a minimum of 96-hours post-dose and a maximum of 240 hours (10 days) post-dose. Collection may be discontinued if the 48-72 and 72-96 hour sample has been collected and results of radiocarbon measurement indicate that two consecutive samples (of urine and feces) contain less than or equal to 1% of the administered dose of radioactivity. Thus, if the results of the radiocarbon measurements for both the 48 – 72 and 72- 96 hour sample reveal that both samples

contain ≤1% of the administered dose of radioactivity, urine and stool sample collection may be discontinued (i.e., it would not be necessary to collect the 96 – 120 hour sample).

Clinical safety data from spontaneous AE reporting, 12-lead ECG, vital signs, nursing/physician observation, and safety laboratory tests will be summarized and any clinically significant abnormalities described. Safety data will not be statistically analyzed.

Study Population

Six healthy female subjects, not of child-bearing potential, aged 30 - 55 years will be recruited to obtain an evaluable number of 6 subjects.

This sample size is expected to provide sufficient data while limiting the number of subjects exposed to radioactivity. The study will be conducted at a single center ([redacted] USA).

Study Assessments

Subjects will be screened within 30 days prior to administration of study medication to confirm that they have met the entrance criteria for the study. Subjects will be admitted to the research unit on Day -1 or the morning of dosing, at the discretion of the investigator, of each dosing period. The following morning (Day 1 of each dosing period) subjects will be administered either the intravenous infusion or the oral solution as described in the study design. Subjects will remain housed at the research unit until sample collection has been completed. The subjects will be confined to the research unit for a minimum of four days in each study session.

Investigational Products

In study period 1, all subjects will receive 10 mg (20 μCi) intravenous infusion of [^{14}C]-GSK221149A over administered over 5 minutes. In study period 2, all subjects will receive a single dose of 100 mg (60 μCi) [^{14}C]-GSK221149A, oral solution.

[^{14}C]-GSK221149A will be supplied by GlaxoSmithKline to the site as sterile solution, for both IV and oral routes of administration.

1. INTRODUCTION

1.1. Background

GSK221149A is an oxytocin receptor antagonist, which is being developed for the treatment of preterm labor without premature rupture of membranes. Preterm labor (PTL) is the largest single cause of infant morbidity and mortality and is frequently associated with long-term disability. Pre-term births (24-37 weeks gestation) affect 5-10% of pregnancies in developed countries. They are the cause of 70% of neonatal deaths not associated with congenital malformations, and are associated with long-term neurocognitive, respiratory and ophthalmic morbidity. The etiology of pre-term labor is not fully understood but is likely to be due to multiple pathological processes. Risk factors include previous pre-term delivery, multiple gestations, two or more previous miscarriages or abortions, low socio-economic status, cervical incompetence, smoking and age (under 18 or over 40 years). Diagnosis of pre-term labor is traditionally based on the presence of uterine contractions and cervical changes. Following diagnosis, the use of pharmacological treatment to delay birth is determined by gestational age. There is currently no licensed treatment for PTL in the U.S.

The polypeptide Tractocile, a mixed oxytocin and vasopressin receptor antagonist, is approved in the EU for the treatment of preterm labor between 24 and 33 weeks. It was found to be as efficacious for PTL as beta-adrenergic agonists (a common therapy for preterm labor), with fewer adverse maternal effects. Because Tractocile is a polypeptide, dose administration has been limited to parenteral routes, thus practically limiting the possibility of longer term tocolysis. Neonatal outcomes have not been shown to improve as a result of short term Tractocile therapy (up to 48 hours) or as a result of therapy with any other medication used as a tocolytic. Neonatal benefits are more likely to be demonstrated if the pregnancy is allowed to progress closer to term by using longer term tocolysis.

Oxytocin appears to have a key role in term and preterm labor, since it is the most potent uterine contractile agent known, and is produced locally within the uterus during labor. The density of oxytocin receptors increases ~100-fold during pregnancy, and preterm labor is associated with increased uterine oxytocin receptor density. Failure to go into labor at term is associated with low oxytocin receptor density. The oxytocin receptor is a G-protein coupled receptor. There are no subtypes of oxytocin receptor (OT), but it is related to the vasopressin family of receptors. While vasopressin has high affinity at both oxytocin and vasopressin receptors, oxytocin only has high affinity for oxytocin receptors.

GSK221149A is an oxytocin receptor antagonist which has nanomolar affinity for the oxytocin receptor, with >500-fold selectivity over the closely related vasopressin receptors, in contrast to Tractocile. GSK221149A has been shown to inhibit oxytocin-induced contractions in vivo in the anesthetized rat. Both intravenous and oral formulation are in development.

There were no effects seen with GSK221149A in intravenous toxicity studies of up to 14 days in dogs at doses less than or equal to 60 mg/kg/day. In oral reproductive toxicity studies, there were no effects of GSK221149A on fertility in female rats or on the fetal development in rats or rabbits. In addition, results of genotoxicity assessments suggest that GSK221149A does not present a genotoxic hazard to humans, and there were no safety pharmacology findings of concern for clinical use.

To date, both the oral and intravenous formulations of GSK221149A have been administered to healthy females of child bearing potential in two separate studies (OTA100801 and OTA103772, respectively). Dosing in these studies has complete and there have been no clinically significant AEs or SAEs reported to date (January 30 2006). For additional information refer to the Investigator Brochure [GlaxoSmithKline Document Number ZM2005/00122/00].

1.1.1. Metabolism and Pharmacokinetics of GSK221149A

Plasma clearance was low in rat (~20% liver blood flow [LBF]), moderate in dog (~35% LBF) and moderate to high in cynomolgus monkey (~60% LBF). Oral bioavailability was acceptable in the rat and dog from a solution formulation (>40%), though in the dog the bioavailability was lower (~24%) from an aqueous formulation as compared to a DMSO/PEG formulation. In the rat the dose normalized oral exposure was similar whether administered in solution at 5 mg/kg or as a suspension at 300 mg/kg, suggesting that the oral pharmacokinetics were linear over this dose range and were not limited by the rate of dissolution. Oral bioavailability in the cynomolgus monkey was low (~10% when administered using 1% DMSO/hydroxypropyl beta cyclodextrin formulation).

In the rat and dog, following oral or IV administration of [^{14}C]GSK221149, drug-related material was primarily eliminated by secretion to bile (30-50% in rat and 60% in dog) with approximately 15% of the administered dose excreted in the urine. Absorption was estimated to be >63%.

In a non-radiolabelled study in the rat the majority of metabolites detected were products of monoxygenation (i.e. using NMR). The sites of hydroxylation identified were on the indanyl substitutent (both the indanyl methylene and phenyl ring), the methyl of the oxazole group and the morpholine ring (with and without ring opening).

GSK221149 has been demonstrated to activate rat and human PXR (Pregnane X receptor) *in vitro*. In cultured human hepatocytes, GSK221149 caused notable increases in CYP3A4 mRNA along with increased CYP3A4 catalytic activity at the highest test concentration (3 ug/mL, no notable increases were seen at ≤1 ug/mL). GSK221149 did not demonstrate *in vitro* direct or metabolism-dependent inhibition (IC50 > 100 uM) of the cytochrome P450 enzymes investigated (i.e CYP1A2, CYP 2A6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) in human liver microsomes. CYP3A4 appears to be the primary enzyme responsible for the oxidative metabolism of GSK221149 with a minor contribution from CYP2C19. GSK221149A is a substrate of human P-gp (P-glycoprotein) and murine Bcrp (breast cancer resistance protein). It is not an inhibitor of human P-gp at concentrations up to 50 μM, as evaluated in an *in vitro* cell based assay system. The compound demonstrates medium permeability across an artificial

membrane. Plasma protein binding was low (< 55%) in all species tested (rat, dog, monkey and human).

1.2. Rationale

Both the oral and intravenous formulations of GSK221149A have been administered to healthy female subjects of child-bearing potential in two separate studies. Dosing in these studies has completed, and there have been no clinically significant AEs or SAEs reported to date (January 30, 2006). After preliminary review of the safety data, there have been no effects on vital signs (BP or HR), ECG parameters or safety laboratories that are attributable to drug.

In study OTA100801, the safety, tolerability and pharmacokinetics of single and repeat oral dosing of GSK221149A were evaluated in healthy, non-pregnant, female subjects of child bearing potential. In the first part of the study, single oral doses of up to 1000 mg were administered. At the highest dose (1000mg), the median exposure (range) was 8480 ng•hr/mL (6397-14406), and the median (range) Cmax was 2256 (1608-5620) ng/mL. This AUC and Cmax are approximately 30% and 23%, respectively, of NOAEL of the oral formulation in the most sensitive species (dog). In the second part of OTA100801, GSK221149A was administered orally 4 times daily for 14 days at doses of 100, 300 and 500 mg. The median steady state exposure (range) and Cmax (range) at the highest dose studied were 2805 ng•hr/mL (1650-3964 ng•hr/mL) and 834 ng/mL (554-2029 ng/mL), which are 10% and 8% of the exposure and Cmax, respectively, at the dog NOAEL. A total of thirty-nine women have received at least one oral dose of 100mg or greater. Upon repeat dosing (100-500 mg QID), a minor amount of metabolic induction of GSK221149 (12-24%) was noted by Day 14.

In study OTA103772, the safety, tolerability, and pharmacokinetics of intravenous administration of GSK221149A were evaluated in healthy, non-pregnant, female subjects of child bearing potential. In the first part of this study, single doses of GSK221149A were infused at various rates. At the highest dose studied (20 mg infused over 30 minutes), 3 of 6 subjects receiving GSK221149A experienced mild pain at the infusion site that was temporally-associated with the infusion; neither of the two subjects receiving placebo experienced pain. This effect was not observed in any of the subsequent sessions, where 10 mg was administered over 5, 10 and 30 minutes. The median exposure (range) and Cmax (range) at the highest dose administered (20 mg over 30 minutes) was 399 ng•hr/mL (271 – 617 ng•hr/mL) and 299 ng/mL, (157 – 530 ng/mL) which are 0.05% and 9%, respectively, of the dog NOAEL for the intravenous formulation. In the second part of the study, a dosing regimen consisting of an initial rapid infusion of GSK221149A or placebo (over 5 minutes) followed by a continuous infusion of GSK221149A or placebo for a total of 48 hours was administered. The highest dose administered in this study was 14 mg over 5 minutes followed by 16 mg/hr for 47 hours, 55 minutes. At this dose, the median (range) Css was 252 ng/mL (192-290 ng/mL) and the median (range) Cmax was 308 ng/mL (285-320 ng/mL). These values are 22% and 9%, respectively, of the dog NOAEL. Fourteen women have received at least one intravenous dose of greater than or equal to 10 mg over 5 minutes.

Although some data on the disposition of GSK221149A are available from in vitro and in vivo experiments, the metabolic pathways and elimination routes for GSK221149A have

not been fully explored. This clinical study is proposed to characterize the single-dose metabolic disposition of [^{14}C]-labeled GSK221149A by analyzing radioactivity in plasma, urine and feces, and to provide samples on which to investigate the metabolic profile of [^{14}C]-GSK221149A in each matrix.

1.3. Rationale for Dose

The dose of radiolabeled drug administered in human mass balance studies is calculated from data on the distribution and elimination of the radioactive drug from laboratory animals, taking into account the nature of the isotope, the concentration of radioactivity in individual tissues/organs. The dose of radioactivity that will be administered to each subject in this study is approximately 80 μCi. A target radioactive dose of approximately 0.92 mSv for this study, is above the upper limit for a WHO category I exposure (<0.1 mSv or within variations of natural background).

To assist Institutional Review Boards (IRBs) in their evaluation of research proposals involving administration of radioisotopes to human subjects, the World Health Organization (WHO) divided such studies into three categories, depending on the amount of total body radiation to which the subjects are exposed. Based on results from Study OTA1008001 (single and repeat dose-escalating FTIH study) and studies in rats and monkeys, it is anticipated that the plasma concentrations of metabolites of [^{14}C]-GSK221149A will be low relative to that for GSK221149A. In order to aid in the detection, quantitation, and identification of metabolites of [^{14}C]-GSK221149A in plasma, the total radiodose of 80 μCi was chosen. The projected effective dose (ED) to the whole body following 80 μCi of [^{14}C]-GSK221149A is 90 mRem (0.9 mSv), and within the range (10 to 100 mRem, or equivalent to 0.1 to 1 mSv) recommended for a Category IIa radiation exposure (i.e., the total body commitment of a subject receiving this dose of radiation is just outside the dose limits for members of the public). This early attempt at categorization is still regarded as a helpful procedure, but it has been modified by others to take account of changes in the assessment of the risk of harm from radiation that has occurred since 1977. Referring to the 1992 International Commission on Radiological Protection (ICRP) for radiological protection in biomedical research, a more explicit categorization in terms of benefit has now been added to the categorization in terms of risks of harm. The proposed dose in this study is within the 0.1 to 1mSv individual dose limits recommended for a Category IIa radiation exposure. This category of exposure is perceived as presenting a minor level of risk to participants (**Appendix 7**).

Administration of an approximately 80 μCi dose is expected to result in an effective dose (ED) to the whole body of 90 mRem. This is approximately one-fifth the annual average background effective dose to the whole body (including radon) of ~360mRem. For comparison to other medical procedures utilizing radiation, 1 chest x-ray results in an ED of ~1 mRem; 1 abdominal x-ray results in an ED of ~30 mRem and a barium enema is equivalent to an ED of ~ 80 mRem.

The study will be limited to healthy female subjects (not of child-bearing potential) and all prospective participants will be questioned as to their past exposure to radiation (x-rays and other radiation based imaging/diagnostic techniques, past participation in other

radioisotope studies, etc.) and potentially excluded from the study, based upon past exposure.

A single 10 mg IV dose and a single 100 mg oral dose of GSK221149A will likely provide quantifiable concentrations of parent and metabolites (for profiling) in plasma, urine, and feces. It will also provide information on the bioavailability of GSK221149A. From the known pharmacokinetics of GSK221149A, it is likely that the collection of all urine and stools up to 4 days post dosing will account for the majority of the administered radioactive dose. In summary, the 10 mg IV and 100 mg oral dose (approximately 20 μCi and 60 μCi, respectively) of [^{14}C]-GSK221149A (90 mRem) proposed accomplishes the scientific objectives of this study by allowing adequate characterization of GSK221149A and its [^{14}C]-metabolites, while minimizing the average radiation exposure to 0.9 mSv.

2. OBJECTIVE(S)

2.1. Primary

- To determine the total recovery and relative excretion of radiocarbon in urine and feces after a single intravenous and single oral doses of [^{14}C]-GSK221149A in healthy adult females
- To generate samples (for a separate study) to characterize and quantify the metabolic profile of GSK221149A in plasma, urine and feces following administration of [^{14}C]-GSK221149A to healthy adult females

2.2. Secondary

- To further assess the safety and tolerability of single intravenous and/or oral doses of GSK221149A in healthy adult female subjects
- To determine the absolute bioavailability of GSK221149A by comparing the disposition of [^{14}C]-GSK221149A following oral and intravenous dosing.
- To determine (as data permit) pharmacokinetic parameters of interest following oral and intravenous dosing.
- To compare total drug-related material (radioactivity) in blood and plasma relative to parent plasma concentrations.

3. ENDPOINT(S)

3.1. Primary

- Urinary and fecal cumulative excretion as a percentage of the total radioactive dose administered over time

- Collection of samples for characterization and quantification of metabolites in plasma, urine and fecal homogenates to be documented and performed by DMPK, GSK; results to be reported in a separate report

3.2. Secondary

- Clinical safety data from spontaneous AE reporting, 12-lead ECG, vital signs, nursing/physician observation, and safety laboratory tests will be summarized and any clinically significant abnormalities described. Safety data will not be statistically analyzed.
- $AUC_{(0\text{-}inf)}$ and $C_{max,}$ of GSK221149A and drug-related material (radioactivity) in plasma following oral and intravenous dosing.
- T_{max}, $t_{1/2}$ of GSK221149A following oral dosing.
- T_{max}, $t_{1/2}$, volume and clearance of GSK221149A following intravenous dosing.
- Blood:Plasma ratio of total drug-related material (radioactivity)

4. STUDY DESIGN

This will be an open-label, two period study involving six healthy female subjects (not of child bearing potential).

Each subject will participate in two separate dosing periods. In the first dosing period, each subject will receive a single dose of 10 mg (20 μCi) intravenous infusion of [^{14}C]-GSK221149A over a period of 5 minutes. In the second dosing period, each subject will receive a single dose of 100 mg (60 μCi) [^{14}C]-GSK221149A, oral solution. Each study period will involve approximately six-night, seven-day admission. The two dosing periods will be separated by a wash-out of at least 28 days.

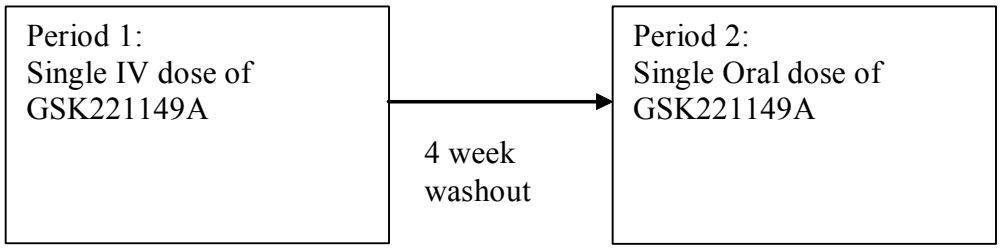

Figure 1 Study Schematic

Blood samples will be collected for a minimum of 2 days (i.e. 48 hours post-dose). Blood collections will continue until the measured radiocarbon for two consecutive plasma samples falls to less than or equal to twice the background radiation count. Thus, if the results of the radiocarbon measurements for the 36-hour sample and the 48-hour sample reveal that both samples contain radioactivity less than or equal to twice the background radiation count, sample collection may be discontinued. Otherwise, sample collection will continue until two consecutive samples produce radiocarbon measurement

results indicating that both samples contain less than or equal to twice the background radiation count or until both the urine and stool collections have ceased. Samples will be collected every 24 hours following the 72 hour sample if required. Therefore, sampling may theoretically continue after day 7, but will not continue beyond day 10.

All urine and feces will be collected for a minimum of 96-hours post-dose and a maximum of 240 hours (10 days) post-dose. Collection may be discontinued if the 48-72 and 72-96 hour sample has been collected and results of radiocarbon measurement indicate that two consecutive samples (of urine and feces) contain less than or equal to 1% of the administered dose of radioactivity. Thus, if the results of the radiocarbon measurements for both the 48 - 72 and 72 - 96 hour sample reveal that both samples contain less than or equal to 1% of the administered dose of radioactivity, urine and stool sample collection may be discontinued i.e., it would not be necessary to collect the 96 - 120 hour sample. Therefore, sampling may theoretically continue after day 7, but will not continue beyond day 10.

Clinical safety data from spontaneous AE reporting, 12-lead ECG, vital signs, nursing/physician observation, and safety laboratory tests will be summarized and any clinically significant abnormalities described. Safety data will not be statistically analyzed.

5. STUDY POPULATION

5.1. Number of Subjects

Six (6) female subjects, aged between 30 – 55 years old, will be enrolled. The justification for including subjects under 55 years of age in this study is that the radioactive dose is low (< 1 mSv and within variations of yearly doses from background radiation) and the risk to this population is minimal. Based on experience with other studies, this sample size is expected to provide sufficient pharmacokinetic data to address the study objective while limiting the number of subjects exposed to radioactivity.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Non-smoking female subjects, 30-55 years old.
2. Females of non-child bearing potential will be eligible to be included in this study. Females will be considered ‘not of child-bearing potential’ if one of the following is true:
    - Serum estradiol and FSH levels at screening consistent with a post-menopausal state

- Post-menopausal females who have been amenorrhoeic for greater than 2 years as of screening
- Pre-menopausal females with documented hysterectomy with or without bilateral oopherectomy

3. Body weight > 50 kg (110 pounds) and body mass index (BMI) between 19 and 32 where:

$$BMI = \frac{\text{weight in kg}}{(\text{height in meters})^2}$$

4. Negative for HIV, Hepatitis B and Hepatitis C at screening
5. Available to complete the study (up to 14 days confinement in the research unit)
6. A history of regular bowel movements
7. No clinically relevant findings on clinical examination, medical examination and tests, clinical chemistry, hematology and urinalysis (including microscopy, if abnormalities are found) at pre-study. If parameters are outside the normal range, the subject may nevertheless participate in the study when, in the opinion of the Principal Investigator or designee, the abnormality will not compromise safety or interfere with study procedure

5.2.2. Exclusion Criteria

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

- Any clinically relevant abnormality identified on the screening medical assessment, laboratory examination or 12-lead ECG (including liver function tests and CPK ≥ULN)
- Subjects with a positive urine test for drugs of abuse or alcohol at screening or prior to study medication administration
- Positive urine cotinine at screening
- History of regular alcohol consumption exceeding 7 drinks/week (average) for women (1 drink = 5 ounces of wine or 12 ounces of beer or 1.5 ounces of hard liquor) within 6 months of screening
- Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication
- Donation of blood in excess of 500mL within 56 days prior to the first dose of study medication
- Previous history of active gastric or duodenal ulcer within 6 months prior to the first dose of study medication
- Any history of bleeding diathesis or positive fecal occult blood result(s) at screening (If initial results are positive test may be repeated fecal occult blood tests may be

repeated after dietary counseling at the discretion of the investigator. Upon repeat, if results are positive, subject may not be permitted to enroll into study).

- A pre-existing condition(s) interfering with normal gastrointestinal (GI) anatomy or motility, including constipation, malabsorption or other GI dysfunction which may interfere with the absorption, distribution, metabolism or elimination of the study drug
- An occupation which requires monitoring for radiation exposure, nuclear medicine procedures or excessive x-rays within the past 12 months
- Participation in another ADME study within the past 12 month
- The subject has received non-prescription drug or vitamins, herbal and dietary supplements within 48 hours prior to the first study day, or St. John's Wort within 14 days prior to the first dose of study drug. Subjects who have taken OTC medication may still be entered into the study, if, in the opinion of the Principal Investigator or designee, the medication received will not interfere with the study procedures or compromise safety
- Subjects who have received prescription medication within 14 days prior to the first dose of study drug. Subjects may still be entered into the study, if, in the opinion of the Principal Investigator or designee, the prescription medication will not interfere with study procedures or compromise safety
- Subjects who have consumed grapefruit or grapefruit juice within 7 days of the first study day
- Subjects who have had exposure to more than three new chemical entities within 12 months prior to the first dosing period
- Subjects who have received a total body radiation dose of greater than 5.0 mSv (upper limit of WHO category II) or exposure to significant radiation (e.g. serial x-ray or CT scans, barium meal etc) in the 12 months prior to this study
- The radiation exposure from the previous 3 year period is over 10 mSv for subjects who have been exposed to ionizing radiation above background as a result of their work with radiation as category A (classified) workers or as a result of research studies they may have been involved in. Clinical (therapeutic or diagnostic) exposure will not be included.
- History of anaphylaxis or anaphalatoid reactions, severe allergic responses to drugs

5.2.3. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) being used in this study: Investigator Brochure [GlaxoSmithKline Document Number ZM2005/00122/00].

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Demographic and Baseline Assessments

Subjects will be screened within 30 days prior to administration of study medication to confirm that they meet the entrance criteria for the study. The screening visit will include:

- a general medical history and physical examination
- medication history
- vital signs (sitting blood pressure and heart rate)
- resting 12-lead ECG (semi-supine)
- clinical laboratory testing (hematology, clinical chemistry and urinalysis)
- urine drug screen
- serology for hepatitis B, C and HIV
- alcohol screen (urine, blood or breath test)
- Serum pregnancy test
- Urine cotinine
- Fecal Occult blood

Samples for pharmacogenetic analysis will also be taken in this study after a separate consent has been obtained.

Only subjects who fulfill all inclusion and exclusion criteria, and who are considered fit by the Investigator (on the basis of baseline screening procedures) will be enrolled into the study.

6.2. In phase study procedures

Study procedures are also outlined in Appendix 1: Time and Events Table. Subjects will attend the unit prior to dosing (Day -1) or the morning of dosing at the discretion of the investigator.

Medication update, physical exam, baseline recording of adverse experiences, urine drug screen and β-hCG may be performed on either Day -1 or Day 1 of each dosing session.

On the morning of Day 1, an ECG and vital signs will be measured with the subject in a semi-supine position, approximately 30 minutes prior to dosing.

For IV dosing period, on the morning of study drug administration, subjects will have an intravenous cannula sited in a prominent lower forearm vein of the arm, and will be removed immediately after completion of the intravenous infusion. After baseline

measurements of vital signs, 12-lead ECG and clinical laboratory sampling, a pre-dose PK sample will be drawn.

For both dosing periods, GSK221149A will be administered after an 8 hour fast. Fasting will continue for 4 hours after administration of GSK221149A to limit variability in bioavailability.

Blood samples for pharmacokinetic and clinical laboratory tests will be taken at the timepoints outlined in Section 6.4.1.

6.3. Follow up Visit

Follow-up evaluations will be completed within 10-14 days of a subject's blood, urine, and fecal samples lowering to the respective required radiocarbon counts for discontinuation of sampling. At this visit, semi-supine vital signs will be measured and a physical examination and 12-lead ECG will be performed. Information regarding the use of concomitant medication or the occurrence of adverse experiences will be obtained. Blood (approximately 20 mL) and urine specimens will be obtained for clinical laboratory tests and for serum β-hCG pregnancy tests.

6.4. Safety

Safety evaluations include vital signs, 12-lead ECGs, clinical laboratory tests, AE monitoring and physical examination.

6.4.1. Clinical Safety Laboratory Tests

For safety laboratory tests, each timepoint requires collection of approximately 10 mL of blood (exception is approximately 20 mL at screening and follow up). A complete listing of the safety laboratory tests is provided in the Study Reference Manual. All safety laboratory tests will be performed using validated assays at the designated laboratory.

6.4.2. ECG Monitoring

6.4.2.1. 12-lead Electrocardiograms

All scheduled electrocardiograms [12-lead ECGs] will be obtained after the subject has rested in the semi - supine position for at least 10 minutes. Whenever 12-lead ECGs are performed at the same nominal time as a blood draw or blood pressure and pulse rate measurement, the 12-lead ECG must be obtained first. The 12-lead ECG will be printed at a paper speed of 25 mm/sec in a '3 x 4' format.

The 12-lead ECG obtained on Day 1 at 1 hour post dose of each dosing session must be evaluated for safety. All other post dose 12-lead ECGs must be evaluated for safety within 12 hours of obtaining the 12-lead ECG. ***All 12-lead ECGs when evaluated for safety can be reviewed by the investigator or physician designee.***

The final conduction intervals entered on the CRF will be those generated by the ECG machine, unless deemed ***significantly inaccurate*** by the over-reading Investigator or physician designate (e.g., motion artifact, poorly defined waveforms, background noise or arrhythmia that impair automated measurements), and affecting the interpretation of the intervals as of potential clinical concern. In these instances, the hand-read intervals will be entered onto the CRF.

6.4.3. Pregnancy

Females **not of child bearing potential** will be enrolled in this study.

6.5. Pharmacokinetics

6.5.1. Pharmacokinetics (Cold Assay) in Plasma and determination of ^{14}C-Radioactivity in Plasma

Following oral administration, blood samples (6 mL) for determination of compound plasma concentrations will be collected into EDTA (di-potassium) -containing polypropylene tubes at the following timepoints: pre-dose and at 15, 30 and 45 minutes post-dose, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60 and 72 hours post-dose. Blood samples can be drawn either by a needle stick or a peripheral venous catheter.

When GSK221149A is administered intravenously, blood samples (6 mL) will be collected pre-dose and at 10, 20, 30 minutes, 1, 2 (prior to cessation of the infusion), 3, 4, 6, 8, 12, 18, 24, 36, 48, 60 and 72 hours after the start of the infusion.

The blood samples obtained from pre-dose through the 48 hour post-dose are mandatory samples. If the radiocarbon measured in the 24 and 48-hour samples (or any two subsequent sequential samples) are each ≤ twice the background radiation count, further samples need not be collected. Samples will be collected every 24 hours following the 72 hour sample if required.

The samples will be processed within 1 hour by centrifugation for 10 minutes at approximately 4ºC and 1500g. The resultant plasma will be transferred into uniquely labelled polypropylene tubes of 5 mL and split in 4 aliquots as detailed in Table 1.

Table 1 Details of sample collection of blood and plasma for parent drug and total radioactivity pharmacokinetics

Sample volume	Whole blood	Plasma	Final aliquots	Measurement	Storage	Analytical Lab
6 mL	6 mL	2.4 mL	1 mL	PK parent	-20°C	GSK
			1 mL	PK parent	-20°C	GSK
			0.2 mL	Radioactivity	-20°C	CRO
			0.2 mL	Radioactivity	-20°C	CRO

The volume indicated in the table is the minimum required assuming a plasma extraction of 40%. Higher volumes are acceptable

The first 2 final aliquots of 1 mL will be kept frozen at a nominal temperature of -20°C or below, on dry ice during transit and shipped to GSK as detailed in the Study Reference Manual.

The 2 final aliquots of 0.2 mL will be measured for ^{14}C contents at the CRO facility.

6.5.1.1. Samples for Metabolite Profiling in Plasma and Radioactivity in Whole Blood

Blood samples (30 mL) will be drawn for identification of metabolites and measurement of radioactivity in whole blood at the following sample times: pre-dose, 2, 6, 24 and 48 hrs post dose for both study periods.

Approximately 3 x 10 mL of whole blood will be collected into EDTA (di-potassium) tubes at each sampling time.

Duplicate aliquots of whole blood (approx. 0.3 mL) will be taken from each sample for whole blood radioactivity analysis. The samples will be handled according to the procedure as detailed in the Study Reference Manual. The resultant plasma should be put into a pre-labelled NUNC storage tube and split into aliquots as detailed in 2.

Table 2 Details of sample collection of blood and plasma for metabolite profiling (GSK study) and whole blood radioactivity measurement

Sample volume	Whole blood	Plasma	Final aliquots	Measurement	Storage	Analytical Lab
30 mL	0.6 mL	-	0.3 mL	Radioactivity in blood	N/A	CRO
		-	0.3 mL	Radioactivity in blood	N/A	CRO
	29.4 mL	17.6 mL	C 5 mL	Metabolite profiling	-20°C	GSK
			C 5 mL	Metabolite profiling	-20°C	GSK
			c 5 mL	Metabolite profiling	-20°C	GSK

The volumes indicated in the table are the minimum required assuming a plasma extraction of 40%. Higher volumes are acceptable.

Of the non radiolabelled pre-dose plasma sample, a 5 mL aliquot will be spiked with ^{14}C-GSK221149A at appropriate concentrations (ca 50,000-100,0000 dpm/mL) to act as storage and shipment controls and will be analysed for radioactivity. The storage samples will be prepared within 24 h of dosing and subjected to the same storage and freeze/thaw regimen as the study samples.

The first 3 final aliquots of 5.9 mL and spiked controls will be kept frozen at a nominal temperature -20°C or below, on dry ice during transit and shipped to:

The 2 final aliquots of 0.3 mL will be measured for ^{14}C contents at the CRO facility.

6.5.2. Urine collection

Urine samples for ^{14}C-radioactivity (all time points) and metabolic profiling (selected time points) will be collected pre-dose and at 0-6 hours, 6-12 hours and 12-24 hours after drug administration and in 24-hour intervals up to 240 hours (Day 10) after drug administration. The intervals between time 0 and 96 hours are mandatory. If the radiocarbon eliminated in the 48 to 72 and 72 to 96-hour collections are both less than or equal to 1% of the administered dose, further collections are not necessary.

All subjects will be asked to void their bladders prior to the drug administration. A blank urine sample (100 mL) will be collected at pre-dose.

For each subject and each collection interval there will be a pre-weighed 1 liter polypropylene container, which is properly labeled with drug name, study code, subject number, study day, date, collection interval and sample number. The urine will be stored in a refrigerator immediately after collection (2 to 8°C). The participants should be instructed to empty their bladders completely at the end of each collection interval. The total weight of urine collected will be determined during each collection interval.

One 5 mL aliquot will be required for determination of ^{14}C-radioactivity and two 20/100 mL aliquots for metabolite profiling and pharmacokinetic analysis. An additional 20/100-mL aliquot will be kept at CRO. All samples will be transferred into appropriately labeled polypropylene tubes or containers and stored at -20°C or below.

In addition a 20 mL aliquot of pre-dose (non-radiolabeled) urine will be spiked with [^{14}C]-GSK221149A at appropriate concentrations (ca 50,000-100,0000 dpm/mL) to act as storage and shipment controls and will be analyzed for radioactivity. The storage samples will be prepared within 48-72 h of dosing and subjected to the same storage and freeze/thaw regimen as the study samples

To measure the recoveries of total radiocarbon and concentrations of [^{14}C]-GSK221149A-related compounds in urine over each sample collection period, all urine voided by the subjects will be collected in pre-weighed, sterile plastic containers. Recovery of all urine voided is critical to successful completion of the study. To ensure complete collections, access to toilet facilities will be restricted. Study center personnel will control access. When a subject requests to void, the appropriate container, labeled with the subject number and time interval will be provided with instructions to collect all urine. Subjects will be asked to void at the end of each collection interval, but during the interval they may void as needed. The start and stop time (to the nearest minute) of each urine collection and its total weight after taring the container (to the nearest gram) will be recorded in the CRF. While each collection is ongoing, the urine will be stored in a refrigerator (2 to 8°C).

6.5.3. Feces collection

Feces samples for ^{14}C-radioactivity and metabolic profiling will be collected pre-dose and in 24-hour intervals up to 240 hours (Day 10) after drug administration. The intervals between time 0 and 96 hours are mandatory. If the radiocarbon eliminated in the

48 to 72 and 72 to 96-hour collections are both less than or equal to 1% of the administered dose, further collections are not necessary.

All stools will be collected from each subject for up to 10 days post-dosing to measure total radiocarbon excreted in feces and for metabolite profiling. The time of each collection (to the nearest minute) and its total weight (after taring the container) will be recorded on the CRF. Feces and toilet paper will be collected and weighed as passed, and then will be frozen at -70°C or lower. Feces samples will be pooled for each subject at 24-hour intervals.

The weight of the feces will be recorded. The feces samples to be analyzed will be quantitatively transferred into a pre-weighed fitting bucket. Water will be added and the sample re-weighed. Fecal samples will be homogenized using an Industrial Blender. Three 20/100 g aliquots will be retained and stored at -20°C: or below one for metabolite profiling; one for determination of ^{14}C-radioactivity and one to be kept at CRO. The remainder of the homogenates will be discarded at the end of study upon agreement with GSK.

An additional *20g* aliquots of pre-dose (non-radiolabeled) fecal homogenate will be spiked with [^{14}C]-GSK221149A at appropriate concentrations (ca 50,000-100,0000 dpm/g) to act as storage and shipment controls and will be analyzed for radioactivity. The storage samples will be prepared within 24 h of dosing and subjected to the same storage and freeze/thaw regimen as the study samples.

Feces samples collected for metabolic profiling will be kept frozen on dry ice during transit and shipped to GSK as detailed in the Study Reference Manual.

Table 3 Details of urine and feces samples

	Final aliquots	Measurement	Storage	Analytical Lab
Urine (each fraction)	20/100 mL	Metabolite profile	-20°C	GSK
	20/100 mL	Metabolite profile	-20°C	GSK
	5 mL	Radioactivity	-20°C	CRO
	20/100 mL	Reserve	-20°C	CRO
Faeces (each fraction)	20/100 g	Metabolite profile	-20°C	GSK
	20 g	Radioactivity	-20°C	CRO
	20/100 g	Reserve	-20°C	CRO

6.5.4. Determination of Radioactivity

All samples prepared in scintillation fluid will be subjected to liquid scintillation counting for 5 min (urine, feces and whole blood), together with representative blank samples, using a Liquid Scintillation Analyser with automatic quench correction by an external standard method. Prior to analysis, samples will be allowed to stabilize with regard to

light and temperature. Representative blank sample values will be subtracted from sample count rates to give net dpm per sample.

A limit of reliable measurement of *30 dpm* above background has been instituted in the CRO laboratories.

6.6. Pharmacodynamics

No pharmacodynamic samples will be collected in this study.

6.7. Pharmacogenetics

Information regarding pharmacogenetic research is included in **Appendix 2**. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e., approval of **Appendix 2**). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and in most cases, the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

7. LIFESTYLE AND/OR DIETARY RESTRICTIONS

7.1. Meals and Dietary Restrictions Lifestyle Guidelines

- Subjects must fast from all food and drink (except water) at least 8 hours prior to dosing
- Water may be consumed *ad libitum starting 2 hours after dosing*.
- Non-caffeinated beverages (except grapefruit juice) may be consumed *ad libitum starting 4 hours after dosing*.
- No nuts to be consumed
- Breakfast, lunch, and dinner will be provided on each day after Day 1.
- Lunch will be provided approximately 4 hours after dosing on Day 1
- Dinner will be provided at approximately 10 hours after morning dosing on Day 1
- An afternoon snack will be permitted at 8 hours post-dose

Subjects should consume 25-30g of dietary fiber per day and eight 6 to 8oz. glasses of water or other non-caffeinated beverage per day while in the study (i.e. from the day of 1st dose) in order to maintain good bowel function.

There is no requirement for subjects to fast prior to attending for blood sampling for clinical laboratory monitoring at screening and follow-up.

7.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, subjects will abstain from ingesting caffeine or xanthine containing products for 24 hours prior to study medication administration until collection of the final pharmacokinetic sample
- During each dosing session, subjects will abstain from alcohol for 48 hours prior to study medication administration until collection of the final pharmacokinetic sample
- Subjects should not have a history of tobacco or nicotine use from 6 months prior to dosing until completion of the study

7.3. Activity

- Subjects will abstain from strenuous exercise for 24 hours prior to the first dose of study medication administration until the end of follow-up visit. Subjects may participate in light recreational activities (e.g., watch television, read)
- Subjects will NOT be permitted to participate in outdoors-recreational activities while in the research unit
- On Day 1 of each study session subjects will remain on bed rest until at least 4 hours post dose, or at the discretion of the investigator

7.4. Medication

Subjects must abstain from taking any prescribed medications or St. John's Wort preparations for 14 days prior to the start of dosing, and over-the-counter remedies for 48 hours prior to the start of Period 1, until completion of the study, including all follow-up visits. However, certain medications (e.g. acetaminophen for headache) may be taken with the prior knowledge and approval of the Principal Investigator. All concomitant medication taken during the study must be recorded in the case report form with indication, daily dose and dates and times of administration.

8. INVESTIGATIONAL PRODUCT(S)

8.1. Radiolabelled Test Item

[^{14}C]-GSK221149A will be supplied by GlaxoSmithKline, as a sterile solution suitable for both IV and oral routes of administration, with 20 mLs per vial at a concentration of 0.8mg/mL (1.6 μCi/mL). The solution is sterilized by filtration and aseptically filled into glass vials.

8.1.1. Non-Radiolabelled Test Item

GSK221149A, (non-radiolabelled test item) will be supplied by GlaxoSmithKline as a sterile solution suitable for both IV and oral routes of administration, a clear, colorless solution which contains GSK221149A at a concentration of 0.8 mg/mL. The solution is sterilized by filtration and aseptically filled into glass vials.

An archive sample of the non-radiolabeled test item will be retained (under the same storage conditions as above) at CRO if sufficient [^{14}C]-test item is supplied.

8.2. Dosage and Administration

Individual oral dose solutions will be 100 mg (60 μCi) of [^{14}C]-GSK221149A in 125 mL. Oral doses (one for each subject to be dosed) will be prepared on the day of dosing at the clinical site in a pre-weighed vessel. An aliquot (less than 1 mL) will be removed and transferred on crushed ice to DMPK (CRO) to determine radiochemical purity and radioactive concentration in each dose. The full vessel will be re-weighed and administered to each of six subjects via a straw. A further 100 mL (2 x 50ml) of water will be added to the container and the contents rinsed and drunk by the subject. The glass container and straw will be washed with consecutive volumes of water/methanol and the radioactivity associated with dose residues determined. Residual radioactivity will be deducted from the dispensed radioactivity to determine the total radioactive dose administered.

For intravenous drug administration, a cannula will be sited in a prominent lower forearm vein of the opposite arm for blood sampling, and will be removed immediately after completion of the intravenous infusion. [^{14}C]-GSK221149A will be aspirated into a pre-weighed syringe connected to a three way tap. The apparatus will be re-weighed and the dose solution administered as an intravenous infusion of 10 mg (20 μCi) over a period of 5 minutes. At the end of the infusion period for each of the subjects the infusion apparatus (syringe, line, three-way taps and cannulae) will be retained for analysis of residual activity as well as any other residual dose material removed subsequent to the initial weighing. The remaining injection solution will be used for the assessment of radiochemical purity and radioactive concentration in each dose. The dosing apparatus will be washed with consecutive volumes of water/methanol and the radioactivity associated with dose residues determined. Residual radioactivity will be deducted from the dispensed radioactivity to determine the total radioactive dose administered.

A small amount of additional radioactive material will be shipped in a separate container so that the radiochemical purity can be determined on arrival and an authentic reference standard (with Certificate of Analysis) will also be supplied to facilitate analysis. Additional doses will be supplied as a spare dose, for a mock dose preparation and to check radiochemical purity and radioactive concentrations, as required.

The time of dosing (administration of oral solution or start of infusion) will be designated Day 1, Time 0; all subsequent timepoints will be in relation to this timepoint.

The actual dose received by each subject will be determined with reference to the radioactive dose concentration and the weight of dose administered corrected for any residual radioactivity.

8.3. Dose Rationale

The dose of radiolabeled drug administered in human mass balance studies is calculated from data on the distribution and elimination of the radioactive drug from laboratory animals, taking into account the nature of the isotope, the concentration of radioactivity in individual tissues/organs and the residence or elimination half-life of the radioactivity from those tissues/organs. The total dose of radioactivity that will be administered to each subject in this study is approximately 80 μCi. A target radioactive dose of approximately 0.9 mSv, which is above the upper limit for a WHO category I exposure (<0.1 mSv or within variations of natural background) (**Appendix 4** and **Appendix 5**). The 20 μCi oral dose and 60 μCi intravenous dose will be sufficient to permit the detection of the [^{14}C] metabolites in plasma.

To assist Institutional Review Boards (IRBs) in their evaluation of research proposals involving administration of radioisotopes to human subjects, the World Health Organization (WHO) divided such studies into three categories, depending on the amount of total body radiation to which the subjects are exposed. Based on results from Study OTA100801 (single and repeat dose-escalating FTIH study in healthy human subjects) and OTA103772, (intravenous infusion dose-escalating study in healthy human subjects) and studies in rats and monkeys, it is anticipated that the plasma concentrations of metabolites of [^{14}C]-GSK221149A will be low relative to that for GSK221149A. This early attempt at categorization is still regarded as a helpful procedure, but it has been modified by others to take account of changes in the assessment of the risk of harm from radiation that has occurred since 1977. Referring to the 1992 International Commission on Radiological Protection (ICRP) for radiological protection in biomedical research, a more explicit categorization in terms of benefit has now been added to the categorization in terms of risks of harm. The proposed dose in this study is within the 0.1 to 1 mSv individual dose limits recommended for a Category IIa radiation exposure. This category of exposure is perceived as presenting a minor level of risk to participants (**Appendix 6**).

Administration of an approximately 80 μCi dose is expected to result in an effective dose (ED) to the whole body of 90 mRem. This is approximately one-fifth the annual average background effective dose to the whole body (including radon) of ~360 mRem. For comparison to other medical procedures utilizing radiation, 1 chest x-ray results in an ED of ~1 mRem; 1 abdominal x-ray results in an ED of ~30 mRem and a barium enema is equivalent to an ED of ~ 80 mRem.

The protocol will be reviewed by a physician experienced in and familiar with the administration of radiocarbon compounds to human subjects. The study will be limited to healthy female subjects and all prospective participants will be questioned as to their past exposure to radiation (x-rays and other radiation based imaging/diagnostic techniques, past participation in other radioisotope studies, etc.) and potentially excluded from the study, based upon past exposure.

A single 10 mg IV dose and a single 100 mg oral dose of GSK221149A will likely provide quantifiable concentrations of parent and metabolites (for profiling) in plasma, urine, and feces. It will also provide information on the bioavailability of GSK221149A. From the known pharmacokinetics of GSK221149A, it is likely that the collection of all

urine and stools up to 4 days post dosing will account for the majority of the administered radioactive dose. In summary, the 10 mg IV and 100 mg oral dose (approximately 20 μCi and 60 μCi, respectively) of [^{14}C]-GSK221149A (90 mRem) proposed accomplishes the scientific objectives of this study by allowing adequate characterization of GSK221149A and its [^{14}C]-metabolites, while minimizing the average radiation exposure to 0.9 mSv.

8.4. Blinding

This is an open-label study.

8.5. Treatment Assignment

This will not be a randomized study.

8.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

8.7. Preparation

The contents of the vial will contain 20 mL of a 0.8 mg/mL, concentrate solution. Details of the dose preparation are described in the SRM.

The infusion bags and syringes containing the solution for administration will be clearly labeled by Unit staff with the protocol number, subject number and dosing session number.

8.8. Handling and Storage

Investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with investigational product-specific requirements.

8.9. Product Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain investigational product accountability

records throughout the course of the study. The responsible person(s) will document the amount of investigational product received from and returned to GSK (when applicable), the amount supplied and/or administered to and returned by subjects, if applicable.

8.10. Assessment of Compliance

Oral dosing will be supervised in the Clinical research unit. Compliance will be checked by the designated study physician.

The study medication will be intravenously administered under the supervision of a study physician. Compliance will be verified by PK blood concentrations.

8.11. Treatment of Investigational Product Overdose

Any signs or symptoms of overdosage will be treated symptomatically. No specific antidote is known.

8.12. Occupational Safety

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

However, precautions are to be taken to avoid direct skin contact, eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure notify the monitor.

Precaution will be taken to avoid direct contact with the investigational product. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator.

9. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

9.1. Permitted Medications

All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

9.2. Prohibited Medications

No concomitant medications will be permitted during the study, with the exception of acetaminophen at doses ≤2 gram/day.

9.3. Non-Drug Therapies

Subjects must abstain from taking any vitamins, herbal and dietary supplements within 7 days prior to the first dose of study medication until completion of the follow up visit.

10. SUBJECT COMPLETION AND WITHDRAWAL

10.1. Subject Completion

A subject will be considered to have completed the study when the following criteria have been met:

- The last study procedure has been completed on the final study session, including all follow up assessments
- More than 90% of the total radioactive dose administered has been recovered from all matrices, or less than 1% of the radioactive dose is excreted in a 24-hour period

10.2. Subject Withdrawal

Subjects may withdraw from the study at any time and for any reason. They are not obliged to state the reason for withdrawal. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the physician on the Completion/ Withdrawal Section of the CRF. Every effort will be made by the physician to follow up subjects who withdrew from the study.

Subjects that are withdrawn from the study for safety reasons (adverse events) will NOT be replaced. Subjects that withdraw for other reasons may be replaced at the discretion of the Investigator and GSK in order to obtain evaluable metabolic data from at least 4 evaluable subjects.

10.2.1. Subject Withdrawal from Investigational Product

For patients withdrawn from the investigational product, the following should be performed if appropriate: 12-lead ECG, clinical safety labs including urinalysis with microscopic examination of urine sediment, and AE assessment. Relevant sections of the CRF will be completed by the investigator (or designated staff).

When a subject completes a visit, relevant sections of the CRF will be completed by the investigator (or designated staff).

10.3. Screen and Baseline Failures

Completed CRFs will not be required for these subjects unless a subject reports an adverse event considered a serious adverse event (SAE) which is related to study participation between the time the subject consented to study participation and withdrawal. However, any source documentation of procedures related to the

participation in the study for all consenting subjects will be retained at the study site according to relevant regulatory requirements, see Section 13.5 ("Records Retention").

11. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs, as detailed in both this section of the protocol and in the AE/SAE section of the SRM.

11.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

11.2. Definition of a SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of existing hospitalization

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

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

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect

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

11.2.1. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., 12-lead ECGs and vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will **not** be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

11.3. Time Period, and Frequency of Detecting AEs and SAEs

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e., before informed consent) should be recorded as Medical/Surgical History. In addition, any medical occurrence which is reported after informed consent is obtained but prior to administration of study medication will be documented as Medical/Surgical History.

All AEs/SAEs occurring after administration of study medication and on or before the final follow up visit must be reported as Adverse Events/Serious Adverse Events. All AEs/SAEs must be recorded irrespective of whether they are considered drug related.

Any AEs/SAEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits as necessary. If these have resolved, this should be documented. If an AE/SAE changes in intensity/frequency then this should be recorded as a separate event (i.e., a new record started).

From the time a subject consents to participate in the study until he or she has completed the study (including any follow-up period), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be reported promptly to GSK.

11.4. Prompt Reporting of SAEs to GSK

SAEs will be reported promptly to GSK as described in the following table once the investigator determines that the event meets the protocol definition of an SAE.

11.4.1. Timeframes for Submitting SAE Reports to GSK

	Initial SAE Reports		Follow-up Information on a Previously Reported SAE	
Type of SAE	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hrs	"SAE" data collection tool	24 hrs	Updated "SAE" data collection tool

11.5. AE and SAE Documentation and Follow-up Procedures

The investigator will review and adhere to the following procedures, which are outlined in detail in the AE/SAE section of the SRM:

- Method of Detecting AEs and SAEs
- Recording of AEs and SAEs
- Evaluating of AEs and SAEs
- Completion and Transmission of SAE Reports to GSK
- Follow-up of AEs and SAEs
- Post-study AEs and SAEs
- Regulatory Reporting Requirements for SAEs

12. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

12.1. Hypotheses

The objectives of this study are to evaluate the metabolic disposition of single, oral dose (100 mg / 60 μCi) and intravenous infusion of [^{14}C] GSK221149A (10 mg/20 μCi, over 5 minutes) in healthy, female subjects. There are no hypotheses to be tested.

12.2. Study Design Considerations

12.2.1. Sample Size Assumptions

Six (6) subjects will be enrolled. Based on experience with other studies, this sample size is expected to provide sufficient pharmacokinetic data to address the study objective while limiting the number of subjects exposed to radioactivity. No sample size calculations were performed.

12.2.2. Sample Size Sensitivity

No sensitivity analysis is performed.

12.2.3. Sample Size Re-estimation

Sample size re-estimation will not be performed.

12.3. Data Analysis Considerations

12.3.1. Analysis Populations

All of the data that is databased will be presented in subject listings and where appropriate presented in summary tables. All subjects who receive the study drug will be included in the safety population. All subjects who receive study drug and who have sufficient data for evaluation of pharmacokinetic endpoints will be included in the pharmacokinetic population.

12.3.2. Analysis Data Sets

Not applicable

12.3.3. Treatment Comparisons

Summaries will present data by treatment group and where appropriate, by assessment time. No formal comparisons between treatment regimens are planned.

12.3.4. Interim Analysis

There will be no formal interim analysis.

12.3.5. Key Elements of Analysis Plan

12.3.5.1. Efficacy Analyses

Not applicable

12.3.5.2. Safety Analyses

No formal statistical analysis of the safety data is planned.

12.3.5.3. Pharmacokinetic Analyses

Blood and Plasma

Plasma GSK221149A concentration-time data will be listed for each subject and summarized by planned sampling time. Individual, mean, and median concentration-time profiles will be plotted on both linear and semi-log scale.

Noncompartmental analysis of concentration-time data will be performed using standard methodologies. The PK parameters AUC(0-t), AUC(0-∞), Cmax, Tmax and $t_{1/2}$ will be calculated. Individual subject parameter values, as well as a descriptive summary of parameters will be reported. The descriptive statistics will include the mean, standard deviation, median, minimum, maximum, and for all parameters except Tmax, the standard deviation of log-transformed values, geometric mean and corresponding 95% confidence intervals.

Radioactivity concentrations in blood and plasma will be reported similarly. The individual, mean, and median plasma and blood radioactivity concentration-time will be plotted with those for GSK221149A. Pharmacokinetic parameters will be calculated and summarized as described above.

Urine and Feces

The total amount and total percent of GSK221149A dose recovered as well as the total amount of radioactivity and total percent of radioactivity dose recovered will be listed and summarized for urine, feces and urine and feces combined.

The percent of dose recovered attributable to GSK221149A will be compared to the total radiocarbon recovered, to determine how much of the recovered dose is due to metabolites. For urine and feces containing sufficient radioactivity, identification of these metabolites will be considered.

13. STUDY CONDUCT CONSIDERATIONS

13.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

GSK will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

The study will be conducted in accordance with all applicable regulatory requirements, including an U.S. IND, 69, 401 and 73,287

The study will also be conducted in accordance with "good clinical practice" (GCP), all applicable subject privacy requirements, and, the guiding principles of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Subject informed consent
- Investigator reporting requirements

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

Written informed consent will be obtained for each subject before he or she can participate in the study.

13.2. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study consistent with the demands of the study and site activity to verify that the:

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

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

13.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

13.4. Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multi-center studies, this can occur at one or more or at all sites. If GSK determines such action is needed, GSK will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action, at that time. When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

GSK will promptly inform all other investigators or the head of the medical institution (where applicable), and/or institutions conducting the study if the study is suspended or prematurely discontinued for safety reasons. GSK will also promptly inform the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IEC/IRB promptly and provide the reason for the suspension or premature discontinuation.

13.5. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

13.6. Provision of Study Results and Information to Investigators

When required by applicable regulations, the investigator signatory for the clinical study report will be determined at the time the report is written. When the clinical study report is completed, GSK will provide the investigator with a full summary of the study results. The investigator is encouraged to share the summary results with the subjects, as appropriate. In addition, the investigator will be given reasonable access to review the relevant statistical tables, figures, and reports and will be able to review the results for the entire study at a GSK site or other mutually agreeable location.

GSK will provide the investigator with the randomization codes for their site after the statistical analysis for the entire study has been completed.

13.7. Data Management

The data collection tool for this study will be GSK-defined case report forms (CRFs). In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures. Original CRFs will be retained by GSK, while the investigator will retain a copy.

14. REFERENCES

GlaxoSmithKline Document Number ZM2005/00122/00, GSK221149A Investigator Brochure. Report Date 31-Aug-2005.

ICRP. *ICRP Publication 62: Radiological Protection in Biomedical Research.* 1 ed. USA:Elsevier; 1993.

Appendices

Appendix 1: Time and Events Table

Assessment	Screening	Period 1			Washout 28 days	Period 2			Follow-up
		Pre-dose[3]	Post-dose	Days 2-7[13]		Pre-dose[3]	Post dose	Days 2-7[13]	
Informed consent	✓								
Medical history	✓								
Con Meds	✓	✓	✓	✓		✓	✓	✓	
Demographics	✓								
Physical exam	✓	✓[3]				✓[3]			✓
Serology (HbsAg, anti-HCV, anti-HIV)	✓								
Serum β-hCG	✓	✓				✓			
Urine cotinine	✓								
Urine drug screen & alcohol test	✓	✓[3]				✓[3]			
12-lead ECG	✓	✓[3]	✓[5]			✓[3]	✓[5]		✓
Vital signs (blood pressure, heart rate)	✓[1]	✓[3]	✓[5]			✓[3]	✓[5]		✓
Clinical laboratory incl. urinalysis	✓	✓		✓[12]		✓		✓[12]	✓
Blood sampling for pharmacogenetics[2]									
Blood sample for plasma PK (cold assay)		✓	✓[7]			✓	✓		

Continued

Assessment	Screening	Period 1			Washout 28 days	Period 2			Follow-up
		Pre-dose[3]	Post-dose	Days 2-7[13]		Pre-dose[3]	Post dose	Days 2-7[13]	
Blood for metabolite analysis		✓	✓[11]			✓	✓[11]		
Blood sample for ^{14}C radioactivity in plasma		✓	✓[7]			✓	✓[6]		
Blood sample for ^{14}C radioactivity in whole blood		✓	✓[11]			✓	✓[11]		
Drug Administration			✓				✓		
Urine collection		✓	✓[8]	✓[8]			✓[8]	✓[9]	
Feces collection		✓	✓[9]	✓[9]				✓	
AE reporting[4]		✓	✓[10]	✓	✓	✓	✓[10]	✓	✓

1. Sitting, all other measurements semi-supine
2. Blood sampling for pharmacogenetics can be carried out at any suitable time point, after the PGx informed consent has been obtained.
3. Assessments may be at Admission or pre-dose as appropriate
4. SAEs related to study participation will be reported from time of consent.
5. VS & ECG at 1, 2, 4 & 12 h post dose
6. After oral administration, samples collected at pre dose, 15, 30, 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60 and 72 hours post-dose. Samples will be collected every 24 hours following the 72 hour sample if required.
7. After intravenous administration, samples will be collected at pre dose, 10, 20, 30 minutes, 1, 2, 3, 4, 6, 8, 12,18, 24, 36, 48, 60 and 72 hours after the start of the infusion Samples will be collected every 24 hours following the 72 hour sample if required.
8. Urine will be collected at pre dose, 0-6h, 6-12 h, 12-24 h post dose at over 24 h intervals 240 h post dose.
9. Feces will be collected at 24 h intervals up to 240 h post dose or until at least 90% radioactivity has been recovered
10. Subject response to adverse event questioning through a 'non-leading' question will be assessed and recorded at 4 and 12 hours post-dose. In addition, details of any adverse events reported spontaneously by any given subject will be recorded.
11. 30 mL samples at pre dose, 2, 6, 24 and 48 hrs post dose
12. 48 h post dose/start of infusion (Day 3)
13. Sample collection may continue to day 10, but will be a minimum of 2 days.

Appendix 2: PGx

Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in different populations. There is increasing evidence that an individual's genetic composition (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx analysis include:

Drug	Disease	Gene	Outcome
Abacavir	HIV [Hetherington, 2002 and Mallal, 2002]	HLA (human leukocyte antigen)	Caucasian males with HLA B57 variant were at increased risk for experiencing hypersensitivity to abacavir
Tranilast	Restenosis prevention following coronary bypass [Danoff, 2004]	UGT1A1	Drug induced hyperbilirubinemia explained by high proportion of affected patients having 7/7 TA repeat genotype, consistent with clinically benign Gilbert's Syndrome
ABT-761	Asthma [Drazen, 1999]	ALOX5	ALOX5 Sp1 promoter genotype (x,x) associated with reduced response to 5-lipoxygenase inhibitor ABT-761

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no a priori hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in handling or response to GSK221149A

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a possible genetic relationship to handling or response to GSK221149A. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with GSK221149A that may be attributable to genetic variations of subjects, the following objectives may be investigated:

- Relationship between genetic variants and the pharmacokinetics of investigational product
- Relationship between genetic variants and safety and/or tolerability of investigational product

Study Population

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

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

Study Assessments and Procedures

In addition to any blood samples take for the clinical study, a whole blood sample (~10ml) will be collected for the PGx research using a tube containing EDTA. The PGx sample is labeled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

If deoxyribonucleic acid (DNA) is extracted from the blood sample, the DNA may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of GSK221149A has been completed and the study data reviewed. For this reason, samples may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. In special cases, the samples may not be studied. This might happen if there are not enough subjects, if the study is stopped for other reasons, or if no questions are raised about how people respond to GSK221149A. GSK or those working with GSK (for example, other researchers) will only work with samples collected from

the study for the use stated in this protocol and in the informed consent form. Samples will be stored securely. Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options concerning the PGx sample, if already collected:

- PGx research continues per the subject's consent; or,
- Any remaining sample is destroyed

If a subject withdraws consent from the PGx research or requests sample destruction, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. In either case, GSK will only keep study information collected/generated up to that point.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Pharmacogenetics Analyses

The need to conduct PGx analysis may be identified after a study (or set of studies) of GSK221149A has been completed and the study data reviewed. For this reason, samples may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. In special cases, the samples may not be studied. This might happen if there are not enough subjects, if the study is stopped for other reasons, or if no questions are raised about how people respond GSK221149A.

Generally GSK will utilize two approaches to explore genetic variation in drug response.

1. 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 adverse events, and those linked to study disease and, thus, linked to drug response.

In addition, continuing research may identify other enzymes, transporters, proteins, or receptors that may be involved in response to GSK221149A. The genes that may code for these proteins may also be studied.

2. By evaluating large numbers of polymorphic markers (e.g., single nucleotide polymorphisms or SNPs) throughout the genome, sets of markers may be identified that correspond to differential drug response.

Hardy-Weinberg Equilibrium Testing

The genotypic frequencies of each polymorphism will be evaluated for conformity to those expected under normal conditions by employing Hardy-Weinberg Equilibrium testing.

Comparison of Demographic and Baseline Characteristics by Genotype

Differences in baseline clinical characteristics and potential contributing covariates may be summarized and compared among genotype (or haplotype) subgroups.

Evaluation of Genotypic Effects

Analyses may be carried out to evaluate the degree of association between subject genotype (or haplotype) and selected parameters (e.g., pharmacokinetics, efficacy and safety). Where such genotypic tests are inappropriate (for example, where the number of marker genotypes is too large and/or the frequency of individual genotypes too small), allelic tests may be conducted. Allelic tests evaluate whether the frequency of each marker allele is the same in responders and non-responders.

Evaluation of Treatment by Genotype and Gene-Gene Interaction

In addition to evaluating the main effects of the genotypes (haplotypes or alleles) on the selected parameters, the possibility of a treatment group by genotype (haplotype or allele) interaction will also be explored. If appropriate, the joint effects of multiple markers (gene-gene interactions) may also be evaluated.

Linkage Disequilibrium

For pairs of polymorphisms, the degree to which alleles from the two sites are correlated (linkage disequilibrium) may also be evaluated. If the genotypes at two polymorphic sites within a gene are shown to be statistically associated with a response to investigational product, the degree of linkage disequilibrium will aid interpretation in that it will indicate the extent to which the two sites are exerting independent effects.

Multiple Comparisons and Multiplicity

To the extent that multiple markers are evaluated (especially in the case of a genome scan for association), an adjustment to observed p-values may be made to limit erroneous conclusions due to multiple tests.

Power and Sample Size Considerations

The ability to detect differential drug response among genotypes at a polymorphic site depends on the total number of subjects genotyped and the frequency distribution of the different genotypes. Consequently, genotyping analyses are plausible for those polymorphic sites where the number of subjects comprising the genotypic groups is sufficiently large; however, these frequencies will not be known until sufficient samples have been collected and genotyping is complete.

Estimates of sample sizes required to demonstrate genotype effects vary considerably, depending on the assumptions made about allele frequency, genetic effect size, and mechanism of inheritance [Cardon, 2000]. In the work by Palmer and Cookson [Palmer, 2001], which assumed a genotype relative risk of 1.5, it was estimated that more than 300 cases and 600 controls would be needed to conduct a genetic association analysis. In contrast, McCarthy and Hilfiker [McCarthy, 2000] showed that with a genotype relative risk of 2.16 and a relatively commonly occurring genotype, only 30 cases and 30 controls would be needed to demonstrate an association.

Published PGx examples include abacavir hypersensitivity reaction [Hetherington, 2002 and Mallal, 2002] and tranilast induced hyperbilirubinemia [Danoff, 2004] where genetic markers have been found to significantly associate with hypersensitivity reaction (abacavir) and hyperbilirubinemia (tranilast). These examples show that small sample sizes typically encountered in Phase I and Phase II studies may be sufficient to identify clinically relevant genetic associations.

Informed Consent

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

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarize the cumulative PGx research results in the clinical study report.

In general, GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of the PGx research results because the information generated from PGx studies is preliminary in nature, and the significance and scientific validity of the results are undetermined at such an early stage of research, under any circumstances unless required by law.

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Appendix 3: (Phase I) Liver Chemistry Safety Algorithms

Liver chemistry stopping criteria have been designed to assure subject safety. ALT and AST are released into the blood in response to liver injury, proportional to liver damage. ALT is relatively specific for liver injury, unlike AST. In a normal population, ALT ≥3x ULN is detected in ≤0.4%, and therefore, merits evaluation, particularly if associated with hepatitis signs or symptoms: fatigue, nausea, vomiting, abdominal pain, jaundice, fever, rash or eosinophilia. With massive hepatic injury, the ability of the liver to excrete conjugated (or direct) bilirubin diminishes. Therefore, the presence of ALT >3x ULN and concomitant bilirubin ≥ 1.5xULN (>35% direct), in the absence of elevated alkaline phosphatase or biliary injury, suggests significant liver injury, mandating the need for immediate drug cessation.

Stop study drug, repeat liver chemistries, and closely follow if:

- **ALT 3xULN and bilirubin 1.5xULN (>35% direct) requires rapid evaluation, specialist consultation, where possible, and prompt GSK notification)**
- **ALT 3xULN**

Subjects meeting the above liver chemistry stopping criteria should not be retreated (or rechallenged) with study drug, as more severe injury (including fatality) may occur with rechallenge, if drug-induced liver injury. Subjects meeting these liver chemistry stopping criteria should complete the procedures required in the protocol for the last study treatment visit, while continuing safety followup as outlined below.

If a subject exhibits **ALT 3x ULN and bilirubin 1.5x ULN** (>35% direct):

- Study drug should be immediately discontinued and the subject followed closely
- Consultation with a specialist is recommended (e.g. hepatologist), where possible, to include close followup of liver chemistries, prothrombin time (as the short-lived coagulation proteins sensitively reflect liver synthetic function), clinical and mental status (i.e. to detect encephalopathy), assessment of appearance or worsening of fatigue, nausea, vomiting, abdominal pain, jaundice, fever, or rash
- GSK personnel should be notified of this event within 24 hours
- Followup liver chemistries (ALT, AST, alkaline phosphatase, and bilirubin) should be obtained twice weekly until values are clearly falling and resolution to normal or baseline should be documented
- Measure autoimmune markers: antinuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies (if available)
- Perform liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease

For subjects exhibiting either **ALT 3x ULN and bilirubin 1.5x ULN** (>35% direct bilirubin) or **ALT 3xULN**:

- Study drug should be immediately discontinued and the subject followed

- Obtain CPK, LDH, and viral hepatitis serology: Hepatitis A IgM antibody, Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM), Hepatitis C RNA; CMV testing: IgM antibody or CMV PCR; EBV testing: heterophile antibody, monospot testing, or EBV PCR; Hepatitis E IgM antibody
- Followup liver chemistries (ALT, AST, alkaline phosphatase, and bilirubin) should be monitored until values normalize, substantively improve, or stabilize
- Include on adverse event pages any clinical symptoms of hepatitis: fatigue, nausea, vomiting, abdominal pain, jaundice, fever, or rash
- Include on concomitant medication pages any use of acetaminophen, herbal remedies, other over the counter medications, putative hepatotoxins, or alcohol
- A blood sample should be collected as soon as possible (preferably within 12 hours of the last dose) for pharmacokinetic analysis. The time of the last dose of study drug, and the actual time and date of the blood sample should be recorded in the case report form.
- Blood samples may be collected for DNA analysis (whole blood in EDTA tube) *, transcriptomics (Paxgene 5 ml tube)*, metabolomics, or other laboratory evaluations (e.g. paraoxonase 1, HDL-cholesterol, etc.).

References

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Mansuy JM. Peron JM. Abravanel F. Poirson H. Dubois M. Miedouge M. Vischi F. Alric L. Vinel JP. Izopet J. Hepatitis E in the south west of France in individuals who have never visited an endemic area. Journal of Medical Virology. 74(3):419-24, 2004.

- informed consent required for pharmacogenetics and transcriptomics

Appendix 4: Dosimetry Review for Oral [^{14}C]-GSK221149A

CONFIDENTIAL RD2006/00269/00
XBL RPT01427

GlaxoSmithKline

Division:	WWDMPK	**Compound No.:**	GSK221149
Retention Category:	GRS028	**Protocol Number:**	05615
Information Type:	Dosimetry Report	**Total No. of Pages:**	18
Site of Issue:	XenoBiotic Labs, Inc. 107 Morgan Lane Plainsboro, NJ, 08536		

Title: Dosimetry Review for oral [^{14}C]GSK221149

XBL Study Number: 05615
Report Number RPT01427

Description: A dosimetry analysis for oral administration of [^{14}C]GSK221149 in humans based on organ/tissue distribution and excretion data obtained in fasted female rat following oral administration of [^{14}C]GSK221149 at 5 mg/kg as contained in reports CD2005/00145/00 and CD2005/00063/00, respectively.

Subject: GSK221149, female rat, oral administration, dosimetry

Sponsor: GlaxoSmithKline
Five Moore Drive
Research Triangle Park
North Carolina, 27709
USA

Sponsor's Monitor: [redacted]

Author: **Signature:** **Date:**

[redacted] Ph.D.
VP, Pharmaceutical Development
XenoBiotic Labs, Inc.
107 Morgan Lane
Plainsboro, NJ, 08536

[redacted] 14 Feb 2006

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SUMMARY

A dosimetry analysis was conducted to estimate the human absorbed radiation dose estimates for [^{14}C]GSK221149-related radioactivity using organ/tissue distribution and excretion data obtained previously following oral administration of [^{14}C]GSK221149A at 5 mg/kg to the fasted female rat.

The animal data was subjected to relative organ mass scaling and physiological time scaling, and then fit with non-compartmental analysis using WinNonlin4.1 (Pharsight). The human absorbed dose estimates were calculated following the MIRD system.

The human absorbed dose estimates were summarized in terms of absorbed dose equivalent per unit activity (mrem/μCi, and mrem/100 μCi) for the organs calculated by MIRDOSE3.1 (Oak Ridge Associated Universities, 1994) and for several other organs/tissues of interest not calculated by MIRDOSE3.1.

The two organs/tissues that received the highest doses were the lower large intestine (LLI) wall (8.44 mrem/μCi) and the upper large intestine (ULI) wall (2.95 mrem/μCi).

Based on the estimated absorbed data generated in this report, a human study involving an oral administration of 100 μCi of [^{14}C]GSK221149 to adult females would be well within the guidelines stated in 21CFR361.1. An oral administration of 100 μCi of [^{14}C]GSK221149 would result in an Effective Dose (ED) to the whole body of circa 115 mrem (1.2 mSv), or approximately one-third of an annual average background ED to the whole body (including radon) of approximately 300 mrem. In addition, this ED would be in the Risk Category IIb according to ICRP 62. For an ED less than 100 mrem (1 mSv) (Risk Category IIa), an oral administration of 87 μCi or less should be utilized.

1. STUDY DETAILS

Sponsor:	GlaxoSmithKline Five Moore Drive, Research Triangle Park (RTP), NC 27709, (USA)
Performing Facility:	XenoBiotic Labs, Inc. 107 Morgan Lane Plainsboro, NJ, 08536
Data Analyst:	[redacted] Ph.D.
Study Monitor:	[redacted]
XBL Study Number:	05615
XBL Report Number:	RPT01427
Primary Applications Used to Derive Data:	WinNonlin4.1 (Pharsight Corp). MIRDOSE3.1 (Oak Ridge Associated Universities, 1994, build August, 1995) MS Excel 2003

Location of Records:

The original signed report will be held under the control of the US (Research Triangle Park) R&D Document Management archives, GSK, for retention in accordance with their GLP archiving procedures.

2. INTRODUCTION

Animal (rat) tissue distribution data from a radiolabel quantitative whole body autoradiography (QWBA) study along with excretion balance data can be utilized to estimate the exposure to radioactivity that a human would receive during a clinical study with radiolabeled drug. In the QWBA study, the use of pigmented animals allows for the characterization of uptake and retention of drug-related material in melanin containing tissues.

In this study, a dosimetry analysis was conducted to estimate the human absorbed radiation dose estimates for [^{14}C]GSK221149-related radioactivity using organ/tissue distribution and excretion data obtained previously in fasted female rat following oral administration of [^{14}C]GSK221149A at 5 mg/kg as contained in reports CD2005/00145/00 and CD2005/00063/00 respectively.

3. OBJECTIVE

To purpose of this report is to provide the effective dose of radioactivity to human subjects as calculated based on rat tissue distribution and excretion data.

4. TEST GUIDELINES

There are no test guidelines that apply to the work performed in this study.

5. METHODS

The time-activity data from the QWBA study was used to generate residence times (τ values) for all the organs/tissues of interest, which are equal to the cumulative activity ($\tilde{A}$) as a fraction of the administered activity (A_0).

$$\tau = \tilde{A}/A_0 \text{ (units of time)}$$

Residence times are related to the area under the curve (AUC_∞). AUC_∞ values were calculated using non-compartmental methods within WinNonlin 4.1. If necessary the lower limit of quantification, (LLOQ) was substituted for a BLQ (below the lower limit of quantification) value to allow a reasonable calculation of AUC_∞. Prior to calculating residences times, the time-activity data was allometrically scaled to the human body by a relative organ mass scaling and a physiological time scaling calculation.

One method of physiological time scaling is based on relative basal metabolic rates as modeled by the ratio of the total body masses raised to the 0.25 power.[4,5]

$$t_h = t_a \left[\frac{mass_h}{mass_a} \right]^{0.25}$$

Relative organ mass scaling assumes that activity uptake and retention is proportional to an organ's mass relative to its total body mass.[6]

$$\%\text{ IA Human organ} = \%\text{ IA Animal Organ} \frac{\left[\frac{\text{Organ Mass}_{Human}}{\text{Body Mass}_{Human}} \right]}{\left[\frac{\text{Organ Mass}_{Animal}}{\text{Body Mass}_{Animal}} \right]}$$

For example, if the human brain is four times larger as a fraction of its total body mass as the rat brain, then the human brain is assumed to have a percent injected activity (%IA) uptake four times greater than the rat brain.

If animal data is collected on a per gram basis (as in QWBA studies), the above equation can be easily modified to the following:

$$\%IA \text{ Human Organ} = \frac{\%IA \text{ Animal Organ}}{g} \cdot \left[\frac{Body\,\text{Mass}_{Animal}}{Body\,\text{Mass}_{Human}}\right] \cdot Organ\,\text{Mass}_{Human}$$

Residence times were input into the MIRDOSE3.1 (ORAU, 1994) software that calculates absorbed dose estimates bases on the MIRD system[3]. MIRDOSE3.1 computes the Mean Absorbed Dose per unit Administered Activity (D/A_0) for each of the target organs and the whole body based on the Cumulative Activity ($\tilde{A}$) in each of the source organs. MIRDOSE3.1 considers both penetrating radiation (gamma) and non-penetrating radiation (weak beta) separately. Carbon-14 (^{14}C) is an example of non-penetrating radiation. MIRDOSE3.1 uses mathematical phantoms of adult males, adult females (non-pregnant and pregnant), and children with standardized organ sizes to simulate the human body.

$$D/A_0 = \tau \bullet S \quad \text{(units of rad/mCi or mrad/}\mu\text{Ci)}$$

MIRDOSE3.1 calculates the S values.

The user calculates and inputs the τ values (residence times).

MIRDOSE3.1 also calculates the gastrointestinal (stomach, small intestine, upper large intestine [ascending and transverse colons] and lower large intestine [descending and sigmoid colons]) residence times from a G.I. tract model[7] and determines a urinary bladder residence time using a dynamic bladder model[8]. For these calculations total cumulative excretion data (urine and feces) is required.

Total cumulative excretion data was also utilized for the calculation of the total body and "remainder of body" residence times. The "remainder" residence time was determined by subtracting the sum of the residence times of all the organs/tissues from the total body residence time. The remainder residence time is used by MIRDOSE3.1 to assign the radioactivity not otherwise attributed to a particular organ/tissue. In the MIRDOSE3.1 output, an organ may show a contribution to the absorbed dose from the "remainder" term.

MIRDOSE3.1 also calculates the Effective Dose Equivalent (EDE) and Effective Dose (ED) in rem/mCi. See definitions in Appendix 1.

For organs/tissues of interest that are not covered by MIRDOSE3.1, absorbed dose estimates were calculated manually in MS Excel following the MIRD[3] system.

6. RESULTS AND DISCUSSION

The human absorbed dose estimates are summarized in terms of absorbed dose equivalent per unit activity (mrem/μCi, and mrem/100 μCi) for the highest dose organs/tissues as calculated by MIRDOSE3.1 and as calculated separately (Table 1). The MIRDOSE3.1 summary data is shown in Figure 1.

The two organs/tissues that received the highest doses were the lower large intestine (LLI) wall (8.44 mrem/μCi) and the upper large intestine (ULI) wall (2.95 mrem/μCi). It should be noted that that the dose estimates for the G.I. walls are very conservative (worst case scenario) due to the short range of ^{14}C beta emissions. The actual absorbed dose to these organs/tissues is most likely to be much lower than the values calculated by MIRDOSE3.1.

An oral administration of 100 μCi of [^{14}C]GSK221149 would result in an Effective Dose (ED) to the whole body of circa 115 mrem (1.2 mSv), which is approximately one-third of an annual average background effective dose to the whole body (including radon) of approximately 300 mrem (Appendix 4). The absorbed doses for both tissues with highest estimated dose as well as whole body are well within the FDA guidelines, as stated in 21CFR361.1 (Appendix 2). In addition, this ED would be in the Risk Category IIb according to ICRP 62 (Appendix 3). For an ED less than 100 mrem (1 mSv) (Risk Category IIa), an oral administration of 87 μCi or less should be utilized.

7. CONCLUSIONS

Based on the estimated absorbed data generated in this report, a human study involving an oral administration of 100 μCi of [^{14}C]GSK221149 to adult females would be well within the guidelines stated in 21CFR361.1.

8. REFERENCES

1. GSK Document Number CD2005/00145/00
GSK221149A: Quantitative Tissue Distribution of Drug-Related Material Using Whole-Body Autoradiography Following a Single Oral (5mg/kg) or Intravenous (2mg/kg) Dose of [^{14}C]GSK221149A to Female and Male Long Evans Rats (Quintiles Study Number PK04-071)

2. GSK Document Number CD2005/00063/00
GSK221149A: Elimination of Radioactivity Following a Single Oral (5mg/kg) or Intravenous (2mg/kg) Administration of [^{14}C]-GSK221149A to Intact and Bile Duct-Cannulated Rats [redacted] Study Number: CMS69447A)

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5. Sparks RB Aydogan B, Comparison of the Effectiveness of Some Common Animal Data Scaling Techniques in Estimating Human Radiation Dose. Proceedings of the Sixth International Radiopharmaceutical Dosimetry Symposium, Orise 99-0164; 705-716, 1999.

6. Sparks RB Aydogan B, Animal Extrapolation Performance in Dosimetry. Proceedings of the Sixth International Radiopharmaceutical Dosimetry Symposium, Orise 99-0164; 1999.

7. ICRP Publication 30, Pergamon Press, 1979.

8. Cloutier et al., Health Phys 25:147-161, 1973.

TABLES

Table 1 Adult Female Dosimetry Summary for Oral [^{14}C]GSK221149 Based on Female Rat Data [a]

Highest dose organs calculated by MIRDOSE3.1

Organ/Tissue/Structure	mrem/μCi	mrem/100 μCi	Limit[b]
Lower Large Intestine Wall	8.44	844	5000
Upper Large Intestine Wall	2.95	295	5000
Small Intestine Wall	0.529	53	5000
Stomach Wall	0.253	25	5000
Liver	0.130	13	5000
Urinary Bladder Wall	0.108	11	5000
All others**	0.05	5	

**adrenals, brain, breasts, gallbladder wall, red marrow, bone surfaces, skin, muscle, lungs, heart wall, kidneys, pancreas, ovaries, spleen, thymus, thyroid, uterus

Select other organs/tissues calculated separately following the MIRD system

Organ/Tissue/Structure	mrem/μCi	mrem/100 μCi	Limit[b]
Eyes (whole, including lens)	0.018	2	3000
All others *** less than	0.010	1	

***Skin (pigmented), spinal cord, uveal tract, esophagus, fat, salivary glands, lymphatic tissue, pituitary

Total Body (MIRDOSE3.1)	mrem/μCi	mrem/100 μCi	Limit[b]
Total Body	0.072	7	3000
Effective Dose (whole body) †	1.15	115	3000

† - ICRP Publication 60, Pergamon Press, 1991.

[a] - Based on an analysis using the MIRD schema[3] and MIRDOSE3.1 software of tissue distribution and excretion data from female rats dosed orally at 5 mg/kg, from reports CD2005/00145/00 (tissue) and CD2005/00063/00 (excretion), respectively.

[b] - Single dose limits in millirem (mrem) based on 21CFR361.1 (Appendix 2).

FIGURES

Figure 1 MIRDOSE3.1 Output

10-19-2005

MIRDOSE (IBM PC VERSION 3.1 - AUGUST 1995)

Radiation Dose Estimates for the ADULT FEMALE
for 14-C-6 GSK221149 oral administration based on female pigmented rats

	TARGET ORGAN	TOTAL DOSE mGy/MBq	rad/mCi	PRIMARY CONTRIBUTOR	%	SECONDARY CONTRIBUTOR	%
1)	Adrenals	1.18E-03	4.37E-03	Adrenals	100.0%	Rem. Body	0.0%
2)	Brain	8.48E-04	3.14E-03	Brain	100.0%	Uterus	0.0%
3)	Breasts	1.30E-02	4.80E-02	Rem. Body	100.0%		0.0%
4)	Gallbladder Wall	1.30E-02	4.80E-02	Rem. Body	100.0%		0.0%
5)	LLI Wall	2.28E+00	8.44E+00	LLI	99.7%	Rem. Body	0.3%
6)	Small Intestine	1.43E-01	5.29E-01	Small Int.	95.5%	Rem. Body	4.5%
7)	Stomach	6.85E-02	2.53E-01	Stomach	90.5%	Rem. Body	9.5%
8)	ULI Wall	7.98E-01	2.95E+00	ULI	99.2%	Rem. Body	0.8%
9)	Heart Wall	1.82E-03	6.73E-03	Heart Wall	100.0%	Uterus	0.0%
10)	Kidneys	4.34E-03	1.61E-02	Kidneys	100.0%	Uterus	0.0%
11)	Liver	3.51E-02	1.30E-01	Liver	100.0%		0.0%
12)	Lungs	1.04E-03	3.85E-03	Lungs	100.0%	Uterus	0.0%
13)	Muscle	5.55E-04	2.05E-03	Muscle	100.0%	Uterus	0.0%
14)	Ovaries	3.37E-04	1.25E-03	Ovaries	100.0%	Uterus	0.0%
15)	Pancreas	4.23E-03	1.56E-02	Pancreas	100.0%	Rem. Body	0.0%
16)	Red Marrow	3.52E-03	1.30E-02	Rem. Body	90.1%	Red Marrow	9.9%
17)	Bone Surfaces	8.92E-03	3.30E-02	Rem. Body	98.3%	Red Marrow	1.7%
18)	Skin	1.30E-02	4.80E-02	Rem. Body	100.0%		0.0%
19)	Spleen	5.89E-04	2.18E-03	Spleen	100.0%	Uterus	0.0%
21)	Thymus	6.27E-04	2.32E-03	Thymus	100.0%	Uterus	0.0%
22)	Thyroid	1.01E-03	3.72E-03	Thyroid	100.0%	Rem. Body	0.0%
23)	Urin Bladder Wall	2.91E-02	1.08E-01	Urinary Bl	77.7%	Rem. Body	22.3%
24)	Uterus	4.63E-04	1.71E-03	Uterus	100.0%	Urinary Bl	0.0%
27)	Total Body	1.96E-02	7.25E-02	Rem. Body	39.2%	LLI	32.6%
28)	EFF DOSE EQUIV	2.02E-01	7.49E-01	Remainder	98.6%	Breasts	1.0%
29)	EFF DOSE	3.10E-01	1.15E+00	Colon	88.3%	Stomach	2.7%

Units of EDE and ED are mSv/MBq or rem/mCi.

RESIDENCE TIMES:

Adrenals	5.80E-04	Muscle	3.31E-01 hr
Brain	3.57E-02	Ovaries	1.30E-04 hr
LLI**	2.15E+01	Pancreas	1.26E-02 hr
Small Intestine**	3.59E+00	Red Marrow	2.10E-02 hr
Stomach	1.00E+00	Spleen	3.10E-03 hr
ULI**	1.17E+01	Thymus	4.40E-04 hr
Heart Wall	1.53E-02	Thyroid	6.00E-04 hr
Kidneys	4.19E-02	Urinary Bl Cont *	2.54E-01 hr
Liver	1.73E+00	Uterus	1.30E-03 hr
Lungs	2.92E-02	Remainder	1.51E+01 hr

* DYNAMIC BLADDER MODEL USED (4.80 HR VOID)
9.9% Tb = 7.94E+00 hr

** ICRP 30 GI tract model used, 100.00% to the stomach
10.30% absorbed from small intestine

APPENDICES

APPENDIX 1 DEFINITIONS

Exposure: Ionizations in air. Unit **R** 'Roentgens'.

Absorbed Dose: Energy absorbed per unit mass. Unit **rad** or **Gy** 'Gray' (1 Gy = 100rad = 1 Joule/kg).

Absorbed Dose Equivalent: rem (**r**ad **e**quivalent **m**an) equivalent to **rad** multiplied by a quality factor (= 1.0 for beta and gamma). Units **rem** or **Sv** 'Sievert' (1 Sv = 100rem).

Activity: Transitions per unit time or rate of decay of radioactive material. Units disintegrations per second (dps), **Bq** 'Becquerel' (1 Bq = 1 dps), **Ci** 'Curie' (1 Ci = 3.7 x 10^{10} Bq or dps).

Mean Absorbed Dose (D): The average energy per unit mass deposited in a target organ by ionizing radiation. (Units rad or rem).

Cumulative activity (Ã): Time integral of the activity (A) in a source organ. Related to the AUC of the time activity curve.

Curie, (Ci): Unit of activity.

Residence time (τ): The quotient of the cumulative activity (Ã) in the source organ divided by the administered activity (A_0), $\tau = \tilde{A}/A_0$.

S: Dose to the target organ per unit cumulated activity in the source organ.

Source Organ: The organ containing the radionuclide that is the source of the energy deposited in the target organ.

Target Organ: An organ for which the radiation absorbed dose is calculated.

Effective Dose (ED): The effective dose, as defined by the ICRP (ICRP Publication 60, Pergamon Press, 1991), is a special quantity that, in principle, allows non-uniform internal doses to be expressed as an equivalent whole body dose. This is accomplished by multiplying the doses (actually dose equivalents) for a given organ by a stochastic risk-weighting factor, and adding the weighted dose equivalents together. The weighting factors recommended by the ICRP in Publication 60 are:

Gonads	0.20	Liver	0.05
Red Marrow	0.12	Esophagus	0.05
Colon	0.12	Thyroid	0.05
Lungs	0.12	Skin	0.01
Stomach	0.12	Bone Surfaces	0.01
Bladder	0.05	Remainder	0.05
Breasts	0.05		

The weighting factor for the remainder is to be divided equally among ten organs not explicitly mentioned in this list but which were assigned by the ICRP (adrenals, brain, ULI, small intestine, kidneys, muscle, pancreas, spleen, thymus, and uterus). Note - esophagus and skin are not treated in MIRDOSE, because they do not exist as target organs. As all of the absorbed doses calculated in MIRDOSE currently involve radionuclides all of whose emissions have assigned quality factors of 1.0, the absorbed doses reported by MIRDOSE may also be interpreted as dose equivalents and multiplied by these weighting factors to calculate the ED.

Effective Dose Equivalent (EDE): The effective dose equivalent, as defined by the ICRP (ICRP Publication 30, Pergamon Press, 1979), is similar to ED with a slightly different set of organs and weighting factors.

APPENDIX 2 FDA RADIATION DOSE LIMITS FOR AN ADULT RESEARCH SUBJECT (21CFR361.1)

21CFR361.1	mrem	mSv
Whole body, active blood-forming organs, lens of eye, gonads		
1. Single Dose	3,000	30
2. Annual and Total Dose Commitment	5,000	50
Other Organs		
1. Single Dose	5,000	50
2. Annual and Total Dose Commitment	15,000	150

APPENDIX 3 ICRP PUBLICATION 62 RISK CATEGORIES BASED ON EFFECTIVE DOSE

Level of Risk	Risk Category (Total Risk)	Effective Dose Range (mSv)	Level of Social Benefit Needed
Trivial	I. (10^{-6} or less)	<0.1	Minor
Minor to Intermediate	IIa (10^{-5})	0.1 to 1	Intermediate to Moderate
	IIb (10^{-4})	1-10	
Moderate	III (10^{-3} or more)	> 10	Substantial

ICRP Publication 62, Pergamon Press, 1992

APPENDIX 4 AVERAGE ANNUAL EFFECTIVE DOSE EQUIVALENT FOR A MEMBER OF THE POPULATION IN THE US

NCRP(93)	mrem	mSv
A. Natural Background		
1. Cosmic	27	0.27
2. Cosmogenic radionuclides	1	0.01
3. Terrestrial	28	0.28
4. Internal	39	0.39
5. Inhaled	200	2.00
Subtotal Natural	295	2.95
B. Man Made		
1. Medical		
a. Diagnostic X-rays	39	0.39
b. Nuclear Medicine	14	0.14
2. Consumer Products	11	0.11
3. Other	<1	<0.01
Subtotal Man Made	65	0.65
Total	360	3.60

Appendix 5: Dosimetry Review for Intravenous [^{14}C]-GSK221149A

GlaxoSmithKline

Division:	WWDMPK	**Compound No.:**	GSK221149
Retention Category:	GRS028	**Protocol Number:**	05615
Information Type:	Dosimetry Report	**Total No. of Pages:**	18
Site of Issue:	XenoBiotic Labs, Inc. 107 Morgan Lane Plainsboro, NJ, 08536		

Title: Dosimetry Review for intravenous [^{14}C]GSK221149

XBL Study Number: 05615
Report Number RPT01428

Description: A dosimetry analysis for intravenous administration of [^{14}C]GSK221149 in humans based on organ/tissue distribution and excretion data obtained in fasted female rat following intravenous administration of [^{14}C]GSK221149 at 2 mg/kg as contained in reports CD2005/00145/00 and CD2005/00063/00, respectively.

Subject: GSK221149, female rat, intravenous administration, dosimetry

Sponsor: GlaxoSmithKline
Five Moore Drive
Research Triangle Park
North Carolina, 27709
USA

Sponsor's Monitor: [redacted]

Author: [redacted] Ph.D.
VP, Pharmaceutical Development
XenoBiotic Labs, Inc.
107 Morgan Lane
Plainsboro, NJ, 08536

Signature: [redacted]

Date: 14 Feb 2006

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SUMMARY

A dosimetry analysis was conducted to estimate the human absorbed radiation dose estimates for [^{14}C]GSK221149-related radioactivity using organ/tissue distribution and excretion data obtained previously following intravenous administration of [^{14}C]GSK221149A at 2 mg/kg to the fasted female rat.

The animal data was subjected to relative organ mass scaling and physiological time scaling, and then fit with non-compartmental analysis using WinNonlin4.1 (Pharsight). The human absorbed dose estimates were calculated following the MIRD system.

The human absorbed dose estimates were summarized in terms of absorbed dose equivalent per unit activity (mrem/μCi, and mrem/100 μCi) for the organs calculated by MIRDOSE3.1 (Oak Ridge Associated Universities, 1994) and for several other organs/tissues of interest not calculated by MIRDOSE3.1.

The two organs/tissues that received the highest doses were the lower large intestine (LLI) wall (7.87 mrem/μCi) and the upper large intestine (ULI) wall (2.75 mrem/μCi).

Based on the estimated absorbed data generated in this report, a human study involving an intravenous administration of 100 μCi of [^{14}C]GSK221149 to adult females would be well within the guidelines stated in 21CFR361.1. An intravenous administration of 100 μCi of [^{14}C]GSK221149 would result in an Effective Dose (ED) to the whole body of circa 104 mrem (1.0 mSv), or approximately one-third of an annual average background ED to the whole body (including radon) of approximately 300 mrem. In addition, this ED would be at the upper limit of Risk Category IIa according to ICRP 62.

1. STUDY DETAILS

Sponsor:	GlaxoSmithKline Five Moore Drive, Research Triangle Park (RTP), NC 27709, (USA)
Performing Facility:	XenoBiotic Labs, Inc. 107 Morgan Lane Plainsboro, NJ, 08536
Data Analyst:	[redacted] Ph.D.
Study Monitor:	[redacted]
XBL Study Number:	05615
XBL Report Number:	RPT01428
Primary Applications Used to Derive Data:	WinNonlin4.1 (Pharsight Corp). MIRDOSE3.1 (Oak Ridge Associated Universities, 1994, build August, 1995) MS Excel 2003

Location of Records:

The original signed report will be held under the control of the US (Research Triangle Park) R&D Document Management archives, GSK, for retention in accordance with their GLP archiving procedures.

2. INTRODUCTION

Animal (rat) tissue distribution data from a radiolabel quantitative whole body autoradiography (QWBA) study along with excretion balance data can be utilized to estimate the exposure to radioactivity that a human would receive during a clinical study with radiolabeled drug. In the QWBA study, the use of pigmented animals allows for the characterization of uptake and retention of drug-related material in melanin containing tissues.

In this study, a dosimetry analysis was conducted to estimate the human absorbed radiation dose estimates for [^{14}C]GSK221149-related radioactivity using organ/tissue distribution and excretion data obtained previously in fasted female rat following intravenous administration of [^{14}C]GSK221149A at 2 mg/kg as contained in reports CD2005/00145/00 and CD2005/00063/00 respectively.

3. OBJECTIVE

To purpose of this report is to provide the effective dose of radioactivity to human subjects as calculated based on rat tissue distribution and excretion data.

4. TEST GUIDELINES

There are no test guidelines that apply to the work performed in this study.

5. METHODS

The time-activity data from the QWBA study was used to generate residence times (τ values) for all the organs/tissues of interest, which are equal to the cumulative activity ($\tilde{A}$) as a fraction of the administered activity (A_0).

$$\tau = \tilde{A}/A_0 \text{ (units of time)}$$

Residence times are related to the area under the curve (AUC_∞). AUC_∞ values were calculated using non-compartmental methods within WinNonlin 4.1. If necessary the lower limit of quantification, (LLOQ) was substituted for a BLQ (below the lower limit of quantification) value to allow a reasonable calculation of AUC_∞. Prior to calculating residences times, the time-activity data was allometrically scaled to the human body by a relative organ mass scaling and a physiological time scaling calculation.

One method of physiological time scaling is based on relative basal metabolic rates as modeled by the ratio of the total body masses raised to the 0.25 power.[4,5]

$$t_h = t_a \left[\frac{mass_h}{mass_a} \right]^{0.25}$$

Relative organ mass scaling assumes that activity uptake and retention is proportional to an organ's mass relative to its total body mass.[6]

$$\%\text{ IA Human organ} = \%\text{ IA Animal Organ} \frac{\left[\frac{\text{Organ Mass}_{Human}}{\text{Body Mass}_{Human}} \right]}{\left[\frac{\text{Organ Mass}_{Animal}}{\text{Body Mass}_{Animal}} \right]}$$

For example, if the human brain is four times larger as a fraction of its total body mass as the rat brain, then the human brain is assumed to have a percent injected activity (%IA) uptake four times greater than the rat brain.

If animal data is collected on a per gram basis (as in QWBA studies), the above equation can be easily modified to the following:

$$\%IA \text{ Human Organ} = \frac{\%IA \text{ Animal Organ}}{g} \cdot \left[\frac{Body\,\text{Mass}_{Animal}}{Body\,\text{Mass}_{Human}} \right] \cdot Organ\,\text{Mass}_{Human}$$

Residence times were input into the MIRDOSE3.1 (ORAU, 1994) software that calculates absorbed dose estimates bases on the MIRD system[3]. MIRDOSE3.1 computes the Mean Absorbed Dose per unit Administered Activity (D/A_0) for each of the target organs and the whole body based on the Cumulative Activity ($\tilde{A}$) in each of the source organs. MIRDOSE3.1 considers both penetrating radiation (gamma) and non-penetrating radiation (weak beta) separately. Carbon-14 (^{14}C) is an example of non-penetrating radiation. MIRDOSE3.1 uses mathematical phantoms of adult males, adult females (non-pregnant and pregnant), and children with standardized organ sizes to simulate the human body.

$$D/A_0 = \tau \bullet S \quad \text{(units of rad/mCi or mrad/}\mu\text{Ci)}$$

MIRDOSE3.1 calculates the S values.

The user calculates and inputs the τ values (residence times).

MIRDOSE3.1 also calculates the gastrointestinal (stomach, small intestine, upper large intestine [ascending and transverse colons] and lower large intestine [descending and sigmoid colons]) residence times from a G.I. tract model[7] and determines a urinary bladder residence time using a dynamic bladder model[8]. For these calculations total cumulative excretion data (urine and feces) is required.

Total cumulative excretion data was also utilized for the calculation of the total body and "remainder of body" residence times. The "remainder" residence time was determined by subtracting the sum of the residence times of all the organs/tissues from the total body residence time. The remainder residence time is used by MIRDOSE3.1 to assign the radioactivity not otherwise attributed to a particular organ/tissue. In the MIRDOSE3.1 output, an organ may show a contribution to the absorbed dose from the "remainder" term.

MIRDOSE3.1 also calculates the Effective Dose Equivalent (EDE) and Effective Dose (ED) in rem/mCi. See definitions in Appendix 1.

For organs/tissues of interest that are not covered by MIRDOSE3.1, absorbed dose estimates were calculated manually in MS Excel following the MIRD[3] system.

6. RESULTS AND DISCUSSION

The human absorbed dose estimates are summarized in terms of absorbed dose equivalent per unit activity (mrem/μCi, and mrem/100 μCi) for the highest dose organs/tissues as calculated by MIRDOSE3.1 and as calculated separately (Table 1). The MIRDOSE3.1 summary data is shown in Figure 1.

The two organs/tissues that received the highest doses were the lower large intestine (LLI) wall (7.87 mrem/μCi) and the upper large intestine (ULI) wall (2.75 mrem/μCi). It should be noted that that the dose estimates for the G.I. walls are very conservative (worst case scenario) due to the short range of ^{14}C beta emissions. The actual absorbed dose to these organs/tissues is most likely to be much lower than the values calculated by MIRDOSE3.1.

An intravenous administration of 100 μCi of [^{14}C]GSK221149 would result in an Effective Dose (ED) to the whole body of circa 104 mrem (1.0 mSv), which is approximately one-third of an annual average background effective dose to the whole body (including radon) of approximately 300 mrem (Appendix 4). The absorbed doses for both tissues with highest estimated dose as well as whole body are well within the FDA guidelines, as stated in 21CFR361.1 (Appendix 2). In addition, this ED would be at the upper limit of Risk Category IIa according to ICRP 62 (Appendix 3).

7. CONCLUSIONS

Based on the estimated absorbed data generated in this report, a human study involving an intravenous administration of 100 μCi of [^{14}C]GSK221149 to adult females would be well within the guidelines stated in 21CFR361.1.

8. REFERENCES

1. GSK Document Number CD2005/00145/00
GSK221149A: Quantitative Tissue Distribution of Drug-Related Material Using Whole-Body Autoradiography Following a Single Oral (5mg/kg) or Intravenous (2mg/kg) Dose of [^{14}C]GSK221149A to Female and Male Long Evans Rats (Quintiles Study Number PK04-071)

2. GSK Document Number CD2005/00063/00
GSK221149A: Elimination of Radioactivity Following a Single Oral (5mg/kg) or Intravenous (2mg/kg) Administration of [^{14}C]-GSK221149A to Intact and Bile Duct-Cannulated Rats [redacted] Study Number: CMS69447A)

3. MIRD Primer For Absorbed Dose Calculations, Revised Edition, 1991, prepared by R. Loevinger, T. F. Budinger, E.E. Watson, Society of Nuclear Medicine, 136 Madison Ave, New York, NY, 10016.

4. Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, 3rd addition, J Gabrielsson and D. Weiner, 2001, Swedish Pharmaceutical Press, page 164.

5. Sparks RB Aydogan B, Comparison of the Effectiveness of Some Common Animal Data Scaling Techniques in Estimating Human Radiation Dose. Proceedings of the Sixth International Radiopharmaceutical Dosimetry Symposium, Orise 99-0164; 705-716, 1999.

6. Sparks RB Aydogan B, Animal Extrapolation Performance in Dosimetry. Proceedings of the Sixth International Radiopharmaceutical Dosimetry Symposium, Orise 99-0164; 1999.

7. ICRP Publication 30, Pergamon Press, 1979.

8. Cloutier et al., Health Phys 25:147-161, 1973.

TABLES

Table 1 Adult Female Dosimetry Summary for Intravenous [^{14}C]GSK221149 Based on Female Rat Data [a]

Highest dose organs calculated by MIRDOSE3.1

Organ/Tissue/Structure	mrem/μCi	mrem/100 μCi	Limit[b]
Lower Large Intestine Wall	7.87	787	5000
Upper Large Intestine Wall	2.75	275	5000
Small Intestine Wall	0.488	49	5000
Urinary Bladder Wall	0.154	15	5000
Liver	0.073	7	5000
All others**	0.04	4	

**adrenals, brain, breasts, gallbladder wall, red marrow, bone surfaces, skin, stomach wall, muscle, lungs, heart wall, kidneys, pancreas, ovaries, spleen, thymus, thyroid, uterus

Select other organs/tissues calculated separately following the MIRD system

Organ/Tissue/Structure	mrem/μCi	mrem/100 μCi	Limit[b]
Esophagus	0.014	1	5000
Uveal Tract	0.010	1	3000
Eyes (whole, including lens)	0.009	1	3000
All others *** less than	0.003	0.3	

***Skin (pigmented), spinal cord, fat, salivary glands, lymphatic tissue, pituitary

Total Body (MIRDOSE3.1)	mrem/μCi	mrem/100 μCi	Limit[b]
Total Body	0.060	6	3000
Effective Dose (whole body) †	1.04	104	3000

† - ICRP Publication 60, Pergamon Press, 1991.

[a] - Based on an analysis using the MIRD schema[3] and MIRDOSE3.1 software of tissue distribution and excretion data from female rats dosed intravenously at 2 mg/kg, from reports CD2005/00145/00 (tissue) and CD2005/00063/00 (excretion), respectively.

[b] - Single dose limits in millirem (mrem) based on 21CFR361.1 (Appendix 2).

FIGURES

Figure 1 MIRDOSE3.1 Output

10-19-2005

MIRDOSE (IBM PC VERSION 3.1 - AUGUST 1995)

Radiation Dose Estimates for the ADULT FEMALE
for 14-C-6 GSK221149 IV administration based on female pigmented rats

TARGET ORGAN	TOTAL DOSE mGy/MBq	TOTAL DOSE rad/mCi	PRIMARY CONTRIBUTOR	%	SECONDARY CONTRIBUTOR	%
1) Adrenals	8.96E-04	3.32E-03	Adrenals	100.0%	Rem. Body	0.0%
2) Brain	8.87E-03	3.28E-02	Rem. Body	100.0%		0.0%
3) Breasts	8.87E-03	3.28E-02	Rem. Body	100.0%		0.0%
4) Gallbladder Wall	8.87E-03	3.28E-02	Rem. Body	100.0%		0.0%
5) LLI Wall	2.13E+00	7.87E+00	LLI	99.8%	Rem. Body	0.2%
6) Small Intestine	1.32E-01	4.88E-01	Small Int.	96.6%	Rem. Body	3.4%
7) Stomach	1.07E-02	3.96E-02	Stomach	58.5%	Rem. Body	41.5%
8) ULI Wall	7.44E-01	2.75E+00	ULI	99.4%	Rem. Body	0.6%
9) Heart Wall	1.18E-03	4.35E-03	Heart Wall	100.0%	Rem. Body	0.0%
10) Kidneys	2.61E-03	9.67E-03	Kidneys	100.0%		0.0%
11) Liver	1.98E-02	7.34E-02	Liver	100.0%		0.0%
12) Lungs	7.81E-04	2.89E-03	Lungs	100.0%	Rem. Body	0.0%
13) Muscle	5.54E-04	2.05E-03	Muscle	100.0%	Uterus	0.0%
14) Ovaries	3.11E-04	1.15E-03	Ovaries	100.0%	Rem. Body	0.0%
15) Pancreas	6.04E-04	2.23E-03	Pancreas	100.0%	Rem. Body	0.0%
16) Red Marrow	2.41E-03	8.91E-03	Rem. Body	90.2%	Red Marrow	9.8%
17) Bone Surfaces	6.10E-03	2.26E-02	Rem. Body	98.3%	Red Marrow	1.7%
18) Skin	8.87E-03	3.28E-02	Rem. Body	100.0%		0.0%
19) Spleen	3.99E-04	1.48E-03	Spleen	100.0%	Rem. Body	0.0%
21) Thymus	4.99E-04	1.85E-03	Thymus	100.0%	Uterus	0.0%
22) Thyroid	5.87E-04	2.17E-03	Thyroid	100.0%	Rem. Body	0.0%
23) Urin Bladder Wall	4.16E-02	1.54E-01	Urinary Bl	89.3%	Rem. Body	10.7%
24) Uterus	3.10E-04	1.15E-03	Uterus	100.0%	Urinary Bl	0.0%
27) Total Body	1.61E-02	5.96E-02	LLI	37.0%	Rem. Body	33.8%
28) EFF DOSE EQUIV	1.86E-01	6.88E-01	Remainder	98.9%	Breasts	0.7%
29) EFF DOSE	2.82E-01	1.04E+00	Colon	90.5%	Urin. Bladd	0.7%

Units of EDE and ED are mSv/MBq or rem/mCi.

RESIDENCE TIMES:

Adrenals	4.40E-04	Muscle	3.30E-01 hr
LLI**	2.01E+01	Ovaries	1.20E-04 hr
Small Intestine**	3.35E+00	Pancreas	1.80E-03 hr
Stomach**	1.01E-01	Red Marrow	1.42E-02 hr
ULI**	1.09E+01	Spleen	2.10E-03 hr
Heart Wall	9.90E-03	Thymus	3.50E-04 hr
Kidneys	2.52E-02	Thyroid	3.50E-04 hr
Liver	9.74E-01	Urinary Bl Cont *	4.17E-01 hr
Lungs	2.19E-02	Uterus	8.70E-04 hr
		Remainder	1.07E+01 hr

* DYNAMIC BLADDER MODEL USED (4.80 HR VOID)
16.2% Tb = 7.72E+00 hr

** ICRP 30 GI tract model used, 83.80% to the SI

APPENDICES

APPENDIX 1 DEFINITIONS

Exposure: Ionizations in air. Unit **R** 'Roentgens'.

Absorbed Dose: Energy absorbed per unit mass. Unit **rad** or **Gy** 'Gray' (1 Gy = 100rad = 1 Joule/kg).

Absorbed Dose Equivalent: rem (**r**ad **e**quivalent **m**an) equivalent to **rad** multiplied by a quality factor (= 1.0 for beta and gamma). Units **rem** or **Sv** 'Sievert' (1 Sv = 100rem).

Activity: Transitions per unit time or rate of decay of radioactive material. Units disintegrations per second (dps), **Bq** 'Becquerel' (1 Bq = 1 dps), **Ci** 'Curie' (1 Ci = 3.7 x 10^{10} Bq or dps).

Mean Absorbed Dose (D): The average energy per unit mass deposited in a target organ by ionizing radiation. (Units rad or rem).

Cumulative activity (Ã): Time integral of the activity (A) in a source organ. Related to the AUC of the time activity curve.

Curie, (Ci): Unit of activity.

Residence time (τ): The quotient of the cumulative activity (Ã) in the source organ divided by the administered activity (A_0), $\tau = \tilde{A}/A_0$.

S: Dose to the target organ per unit cumulated activity in the source organ.

Source Organ: The organ containing the radionuclide that is the source of the energy deposited in the target organ.

Target Organ: An organ for which the radiation absorbed dose is calculated.

Effective Dose (ED): The effective dose, as defined by the ICRP (ICRP Publication 60, Pergamon Press, 1991), is a special quantity that, in principle, allows non-uniform internal doses to be expressed as an equivalent whole body dose. This is accomplished by multiplying the doses (actually dose equivalents) for a given organ by a stochastic risk-weighting factor, and adding the weighted dose equivalents together. The weighting factors recommended by the ICRP in Publication 60 are:

Gonads	0.20	Liver	0.05
Red Marrow	0.12	Esophagus	0.05
Colon	0.12	Thyroid	0.05
Lungs	0.12	Skin	0.01
Stomach	0.12	Bone Surfaces	0.01
Bladder	0.05	Remainder	0.05
Breasts	0.05		

The weighting factor for the remainder is to be divided equally among ten organs not explicitly mentioned in this list but which were assigned by the ICRP (adrenals, brain, ULI, small intestine, kidneys, muscle, pancreas, spleen, thymus, and uterus). Note - esophagus and skin are not treated in MIRDOSE, because they do not exist as target organs. As all of the absorbed doses calculated in MIRDOSE currently involve radionuclides all of whose emissions have assigned quality factors of 1.0, the absorbed doses reported by MIRDOSE may also be interpreted as dose equivalents and multiplied by these weighting factors to calculate the ED.

Effective Dose Equivalent (EDE): The effective dose equivalent, as defined by the ICRP (ICRP Publication 30, Pergamon Press, 1979), is similar to ED with a slightly different set of organs and weighting factors.

APPENDIX 2 FDA RADIATION DOSE LIMITS FOR AN ADULT RESEARCH SUBJECT (21CFR361.1)

21CFR361.1	mrem	mSv
Whole body, active blood-forming organs, lens of eye, gonads		
1. Single Dose	3,000	30
2. Annual and Total Dose Commitment	5,000	50
Other Organs		
1. Single Dose	5,000	50
2. Annual and Total Dose Commitment	15,000	150

APPENDIX 3 ICRP PUBLICATION 62 RISK CATEGORIES BASED ON EFFECTIVE DOSE

Level of Risk	Risk Category (Total Risk)	Effective Dose Range (mSv)	Level of Social Benefit Needed
Trivial	I. (10^{-6} or less)	<0.1	Minor
Minor to Intermediate	IIa (10^{-5})	0.1 to 1	Intermediate to Moderate
	IIb (10^{-4})	1-10	
Moderate	III (10^{-3} or more)	> 10	Substantial

ICRP Publication 62, Pergamon Press, 1992

APPENDIX 4 AVERAGE ANNUAL EFFECTIVE DOSE EQUIVALENT FOR A MEMBER OF THE POPULATION IN THE US

NCRP(93)	mrem	mSv
A. Natural Background		
1. Cosmic	27	0.27
2. Cosmogenic radionuclides	1	0.01
3. Terrestrial	28	0.28
4. Internal	39	0.39
5. Inhaled	200	2.00
Subtotal Natural	295	2.95
B. Man Made		
1. Medical		
a. Diagnostic X-rays	39	0.39
b. Nuclear Medicine	14	0.14
2. Consumer Products	11	0.11
3. Other	<1	<0.01
Subtotal Man Made	65	0.65
Total	360	3.60

Appendix 6: WHO Technical Report Series 611, 1977

Category	Effective Dose Equivalent (mSv)	Level of Risk
I	<0.5	Within variations of natural background
II	0.5 to <5	Within dose limits for members of the public
III	5 to <50	Within dose limits for persons occupationally exposed to radiation

Appendix 7: ICRP Publication 62 Risk Categories Based on Effective Dose

Level or Risk	Risk Category(Total Risk)	Corresponding Effective Dose Range (adults)	Level of Social Benefit Needed
Trivial	I (10^{-6} or less)	<0.1	Minor
Minor to Intermediate	IIa (10^{-5})	0.1 to 1	Intermediate to Moderate
	IIb (10^{-4})	1-10	
Moderate	III (10^{-3} or more)	>10	Substantial

[ICRP, 1993]

Protocol Identifier	Subject Identifier	
OTA105101		

12-LEAD ECG ABNORMALITIES

Date of ECG Day Month Year Time of ECG Hr:Min (00:00-23:59)

Record clinically significant abnormalities below. ✔ all that apply:

A. Rhythm

- [A1] ☐ Sinus bradycardia
- [A21] ☐ Sinus bradycardia (heart rate 40-50 beats/min)
- [A22] ☐ Sinus bradycardia (heart rate 30-39 beats/min)
- [A23] ☐ Sinus bradycardia (heart rate < 30 beats/min)
- [A3] ☐ Sinus pause
- [A2] ☐ Sinus tachycardia (heart rate >100 beats/min)
- [A4] ☐ Ectopic supraventricular beats
- [A20] ☐ Ectopic supraventricular rhythm
- [A17] ☐ Wandering atrial pacemaker
- [A26] ☐ Multifocal atrial tachycardia (Wandering atrial pacemaker with heart rate >100 beats/min)
- [A6] ☐ Supraventricular tachycardia (heart rate >100 beats/min)
- [A7] ☐ Atrial flutter
- [A8] ☐ Atrial fibrillation
- [A5] ☐ Junctional rhythm (heart rate ≤100 beats/min)
- [A25] ☐ Junctional rhythm
- [A24] ☐ Junctional tachycardia (heart rate > 100 beats/min)
- [A9] ☐ Ectopic ventricular beats
- [A12] ☐ Ventricular couplets
- [A13] ☐ Bigeminy
- [A28] ☐ Trigeminy
- [A14] ☐ Electrical alternans
- [A29] ☐ R on T phenomenon
- [A18] ☐ Ventricular fibrillation
- [A19] ☐ Idioventricular rhythm (heart rate < 100 beats/min)
- [A10] ☐ Sustained ventricular tachycardia
- [A11] ☐ Non-sustained ventricular tachycardia
- [A32] ☐ Wide QRS Tachycardia (diagnosis unknown)
- [A27] ☐ Ventricular tachycardia
- [A30] ☐ Monomorphic ventricular tachycardia
- [A15] ☐ Torsades de Pointes (Polymorphic ventricular tachycardia with prolonged QT)
- [A31] ☐ Polymorphic (sustained and non-sustained) ventricular tachycardia
- [A16] ☐ Artificial pacemaker
- [A99] ☐ Other abnormal rhythm

Comment _

B. P-Wave and QRS Morphology

- [B1] ☐ Left atrial abnormality (P mitrale)
- [B2] ☐ Right atrial abnormality (P pulmonale)
- [B3] ☐ Right ventricular hypertrophy
- [B5] ☐ Intraatrial conduction delay
- [D14] ☐ Increased voltage consistent with left ventricular hypertrophy
- [B99] ☐ Other morphology

Comment _

Protocol Identifier	**Subject Identifier**	
OTA105101	☐☐☐☐☐☐	

12-LEAD ECG ABNORMALITIES (Continued)

C. Conduction

[C 1] ☐ First degree AV block (PR interval > 200 msec)
[C 2 0] ☐ Short PR interval
[C 2] ☐ Second degree AV block (Mobitz type 1)
[C 3] ☐ Second degree AV block (Mobitz type 2)
[C 1 6] ☐ 2:1 AV block
[C 4] ☐ Third degree AV block
[C 5] ☐ Left axis deviation (QRS axis more negative than -30°)
[C 6] ☐ Right axis deviation (QRS axis more positive than +110°)
[C 7] ☐ Incomplete right bundle branch block
[C 1 3] ☐ Incomplete left bundle branch block
[C 8] ☐ Right bundle branch block
[C 1 4] ☐ Left anterior hemiblock (synonymous to left anterior fascicular block)
[C 1 5] ☐ Left posterior hemiblock (synonymous to left posterior fascicular block)
[C 9] ☐ Left bundle branch block
[C 1 7] ☐ Bifascicular block
[C 1 0] ☐ Non-specific intraventricular conduction delay (QRS ≥120 msec)
[C 1 1] ☐ Accessory pathway (Wolff-Parkinson White, Lown-Ganong-Levine)
[C 1 9] ☐ Prolonged QT interval
[C 1 2] ☐ QT/QTc prolongation ≥ 500 msec
[C 1 8] ☐ AV dissociation
[C 9 9] ☐ Other conduction

Comment _

D. Myocardial Infarction

[D 1] ☐ Myocardial infarction, old
[D 2] ☐ Myocardial infarction, anterior
[D 3] ☐ Myocardial infarction, lateral
[D 4] ☐ Myocardial infarction, posterior
[D 5] ☐ Myocardial infarction, inferior
[D 6] ☐ Myocardial infarction, septal
[D 2 0] ☐ Myocardial infarction, Non-Q wave
[D 9 8] ☐ Other myocardial infarction

Comment _

E. Depolarisation/Repolarisation (QRS-T)

[D 7] ☐ Non-specific ST-T changes
[D 1 9] ☐ J point elevation
[D 8] ☐ ST elevation
[D 2 1] ☐ ST elevation-pericarditis
[D 9] ☐ ST depression
[D 1 0] ☐ U waves abnormal
[D 1 1] ☐ T wave inversion
[D 1 2] ☐ T wave peaked
[D 1 5] ☐ T waves flat
[D 1 6] ☐ T waves biphasic
[D 1 8] ☐ Notched T-waves
[D 1 3] ☐ Low QRS voltage
[D 1 7] ☐ T-wave flattening/inversion
[D 9 9] ☐ Other depolarisation/repolarisation

Comment _

Other Abnormalities

[E 9 9] ☐ Other abnormalities

Comment _

Case Report Form

Confidential

Subject Identifier

OTA105101

An Open-label, Two Period, Study to Determine the Excretion Balance and Pharmacokinetics of [^{14}C]-GSK221149A, Administered as Single Doses of an Oral Solution and an Intravenous Infusion to Healthy Female Adults

Protocol Identifier	Subject Identifier	Centre Number	
OTA105101			

COVER SHEET - TRACKING DETAILS

An Open-label, Two Period, Study to Determine the Excretion Balance and Pharmacokinetics of [^{14}C]-GSK221149A, Administered as Single Doses of an Oral Solution and an Intravenous Infusion to Healthy Female Adults

Module Number 1

Visits included in this CRF - Screening, Period 1, Period 2, Follow-up, Unscheduled Assessments, Pharmacogenetic Research, Concomitant Medication, Non-serious Adverse Events, Serious Adverse Events, Study Conclusion, Investigator Comment Log and Investigator's Signature

COMPLETION GUIDELINES FOR CASE REPORT FORMS (CRFS)

GENERAL INSTRUCTIONS FOR CRF COMPLETION

- Complete CRFs in English; answer all questions on every page unless directed otherwise.
- Print neatly and legibly; use a black ballpoint pen and press firmly so that all copies are legible.
- Do not write information on page margins.
- Avoid use of abbreviations and acronyms whenever possible. If abbreviations must be used, use only clear abbreviations that are in standard medical use, or those supplied on instructional pages in this CRF.
- Enter Subject Identifier in the space provided at the top of each CRF page.
- Do not write the Subject's name or initials anywhere inside the CRF.
- Record all values in the units indicated on the CRF (e.g., Height in centimetres, Weight in kilograms).
- Where boxes are provided in the CRF to record numbers, complete as follows, using leading zeroes if necessary: 6 recorded as **0 6**.
- Ensure that information classified as "Other, specify" does not fit into one of the listed categories. Record a concise reason in the "specify" field that accompanies "Other", if "Other" is ✔.
- If extra pages need to be inserted between numbered CRF pages, do the following: insert the first extra page after the last numbered page in the section of the CRF affected (e.g., Concomitant Medications) and number the extra page as nn.01. Subsequent extra pages are then numbered nn.02, nn.03 etc.

DATE

- If the CRF is not completed at time of subject assessment, record date of assessment, not date of CRF completion.
- Use the first three letters of each month as the abbreviation for the months (e.g., JAN, FEB, MAR).

0	1	J	A	N	0	3
Day		Month			Year	

= 1st January 2003

TIME

- Record time in 24-hour clock format unless specified otherwise, per conversion chart below.

a.m.		**p.m.**	
Midnight = 00:00	6:00 = 06:00	Noon = 12:00	6:00 = 18:00
1:00 = 01:00	7:00 = 07:00	1:00 = 13:00	7:00 = 19:00
2:00 = 02:00	8:00 = 08:00	2:00 = 14:00	8:00 = 20:00
3:00 = 03:00	9:00 = 09:00	3:00 = 15:00	9:00 = 21:00
4:00 = 04:00	10:00 = 10:00	4:00 = 16:00	10:00 = 22:00
5:00 = 05:00	11:00 = 11:00	5:00 = 17:00	11:00 = 23:00

Note: Midnight = 00:00 is the start of the new day, not the end of the previous day.

MISSING INFORMATION

- Use the following abbreviations for missing information.
  - NA not available/not applicable
  - ND not done
  - UNK unknown
  - NR no result (to be used only for missing data recorded on Local Lab pages)

CRF CORRECTION PROCESS

- Draw a single line through an incorrect entry and write the correct information nearby.
- Initial and date all corrections, additions or deletions.
- DO NOT erase, write over, use correction fluid or tape, or re-copy the original page to correct errors.

GENERAL CRF
MONITOR DATA VALIDATION CHECK

All CRF pages must be reviewed for consistency, completeness, logic and legibility in line with SOP-WWD –1103, Section 6.3 and ICH GCP E6 5.18.4 to include:

- Accurate identifier information completed on every CRF page.
- Identification & completion of missing CRF pages and blank data fields in line with the instructions pre-printed in the CRF.
- Validity and chronology of recorded dates and times.
- Ensuring only one ✔ box response is completed in response to a given question (unless otherwise indicated on the CRF).
- Review of free text fields for spelling and translation errors.
- Where an option of Other; *specify* is provided, specify text should only be completed when the 'Other' option is ✔. A concise text entry, which does not match one of the alternative specified options, should be present in the space provided.
- Data is placed at the correct visit and on the correct CRF page.

INCLUSION AND EXCLUSION CRITERIA
MONITOR DATA VALIDATION CHECK

- Confirm that the subject is eligible to participate in the study and if not, that all the failed criteria have been marked.

Protocol Identifier	Subject Identifier	Visit Date (Day / Month / Year)	Visit Description
OTA105101			**Screening**

ELIGIBILITY QUESTION

Did the subject meet all the entry criteria?

[Y] ☐ Yes [N] ☐ No

If No, ✔ all boxes corresponding to violations of any inclusion/exclusion criteria.

INCLUSION CRITERIA

✔ the boxes corresponding to any of the inclusion criteria the subject failed.

1. ☐ Non-smoking female subjects, 30-55 years old.
2. ☐ Females of non-child bearing potential will be eligible to be included in this study. Females will be considered 'not of child-bearing potential' if one of the following is true:
   - Serum estradiol and FSH levels at screening consistent with a post-menopausal state
   - Post-menopausal females who have been amenorrhoeic for greater than 2 years as of screening
   - Pre-menopausal females with documented hysterectomy with or without bilateral oopherectomy
3. ☐ Body weight > 50 kg (110 pounds) and body mass index (BMI) between 19 and 32 where:

   BMI = weight in kg/[height in meters]^2
4. ☐ Negative for HIV, Hepatitis B and Hepatitis C at screening.
5. ☐ Available to complete the study (up to 14 days confinement in the research unit).
6. ☐ A history of regular bowel movements.
7. ☐ No clinically relevant findings on clinical examination, medical examination and tests, clinical chemistry, hematology and urinalysis (including microscopy, if abnormalities are found) at pre-study. If parameters are outside the normal range, the subject may nevertheless participate in the study when, in the opinion of the Principal Investigator or designee, the abnormality will not compromise safety or interfere with study procedure.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			Screening

EXCLUSION CRITERIA

✔ the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

1. ☐ Any clinically relevant abnormality identified on the screening medical assessment, laboratory examination or 12-lead ECG (including liver function tests and CPK ≥ ULN).
2. ☐ Subjects with a positive urine test for drugs of abuse or alcohol at screening or prior to study medication administration.
3. ☐ Positive urine cotinine at screening.
4. ☐ History of regular alcohol consumption exceeding 7 drinks/week (average) for women (1 drink = 5 ounces of wine or 12 ounces of beer or 1.5 ounces of hard liquor) within 6 months of screening.
5. ☐ Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication.
6. ☐ Donation of blood in excess of 500mL within 56 days prior to the first dose of study medication.
7. ☐ Previous history of active gastric or duodenal ulcer within 6 months prior to the first dose of study medication.
8. ☐ Any history of bleeding diathesis or positive fecal occult blood result(s) at screening (If initial results are positive test may be repeated fecal occult blood tests may be repeated after dietary counseling at the discretion of the investigator. Upon repeat, if results are positive, subject may not be permitted to enroll into study).
9. ☐ A pre-existing condition(s) interfering with normal gastrointestinal (GI) anatomy or motility, including constipation, malabsorption or other GI dysfunction which may interfere with the absorption, distribution, metabolism or elimination of the study drug.
10. ☐ An occupation which requires monitoring for radiation exposure, nuclear medicine procedures or excessive x-rays within the past 12 months.
11. ☐ Participation in another ADME study within the past 12 month.
12. ☐ The subject has received non-prescription drug or vitamins, herbal and dietary supplements within 48 hours prior to the first study day, or St. John's Wort within 14 days prior to the first dose of study drug. Subjects who have taken OTC medication may still be entered into the study, if, in the opinion of the Principal Investigator or designee, the medication received will not interfere with the study procedures or compromise safety .
13. ☐ Subjects who have received prescription medication within 14 days prior to the first dose of study drug. Subjects may still be entered into the study, if, in the opinion of the Principal Investigator or designee, the prescription medication will not interfere with study procedures or compromise safety.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			**Screening**

EXCLUSION CRITERIA (Continued)

✔ the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

14. ☐ Subjects who have consumed grapefruit or grapefruit juice within 7 days of the first study day.

15. ☐ Subjects who have had exposure to more than three new chemical entities within 12 months prior to the first dosing period.

16. ☐ Subjects who have received a total body radiation dose of greater than 5.0 mSv (upper limit of WHO category II) or exposure to significant radiation (e.g. serial x-ray or CT scans, barium meal etc) in the 12 months prior to this study.

17. ☐ The radiation exposure from the previous 3 year period is over 10 mSv for subjects who have been exposed to ionizing radiation above background as a result of their work with radiation as category A (classified) workers or as a result of research studies they may have been involved in. Clinical (therapeutic or diagnostic) exposure will not be included.

18. ☐ History of anaphylaxis or anaphalatoid reactions, severe allergic responses to drugs.

DEMOGRAPHY
INVESTIGATOR INSTRUCTIONS

ETHNICITY

- **Hispanic or Latino** — A person of Cuban, Mexican, Puerto Rican, South American or other Spanish culture or origin, regardless of race

  Note: If the subject does not meet the definition above, ✔ Not Hispanic or Latino.

- **Not Hispanic or Latino** — Neither Hispanic or Latino

GEOGRAPHIC ANCESTRY

The racial groups below are based on the FDA and ICH Guidelines.

Note: In order to provide for all eventualities, it is permissible to ✔ multiple boxes.

- **African American/African Heritage** — A person having origins in any of the black racial groups of Africa
- **American Indian or Alaskan Native** — A person having origins in any of the original peoples of North and South America (including Central America) and who maintains tribal affiliation or community attachment
- **Asian - Central/South Asian Heritage** — A person having origins in Central Asia (Kazakstan, Kyrgystan, Tajikstan, Turkmenistan and Uzbekistan) and Indian Subcontinent (India, Pakistan, Bangladesh and Sri Lanka)
- **Asian - East Asian Heritage** — A person having origins in China, Korea
- **Asian - Japanese Heritage** — A person having origins in Japan
- **Asian - South East Asia Heritage** — A person having origins in Malaysia, the Philippines, Indonesia, Thailand, Vietnam, Laos, Burma or Cambodia
- **Native Hawaiian or Other Pacific Islander** — A person having origins in any of the original peoples of Hawaii, Guam, Samoa or other Pacific Islands, Australia (Aborigines), Papua New Guinea, New Zealand, Marshalls and other island groups west and south of Japan
- **White - Arabic/North African Heritage** — A person having origins in any of the original peoples of Middle East or North Africa
- **White - White/Caucasian European Heritage** — A person having origins in any of the original peoples of Europe

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			**Screening**

DEMOGRAPHY

Date of birth ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Sex
[M] ☐ Male
[F] ☐ Female

Ethnicity ✔ *one:*
[1] ☐ Hispanic or Latino
[2] ☐ Not Hispanic or Latino

Geographic Ancestry ✔ *all that apply:*
[11] ☐ African American/African Heritage
[12] ☐ American Indian or Alaskan Native
[13] ☐ Asian - Central/South Asian Heritage
[14] ☐ Asian - East Asian Heritage
[15] ☐ Asian - Japanese Heritage
[16] ☐ Asian - South East Asian Heritage
[17] ☐ Native Hawaiian or Other Pacific Islander
[18] ☐ White - Arabic/North African Heritage
[19] ☐ White - White/Caucasian/European Heritage

MEDICAL CONDITIONS

DEFINITIONS

CURRENT MEDICAL CONDITIONS

Conditions from which the subject is currently suffering, regardless of how long they have been present. If the subject has had a recurring condition that is not present at the time of the assessment, it can be classed as current if, in the Investigator's opinion it is likely to recur during the study.

PAST MEDICAL CONDITIONS

Conditions from which the subject has suffered in the past, but are no longer present. A past condition may have stopped as recently as the day prior to being assessed.

CONCOMITANT MEDICATIONS

Record details of the subject's ongoing concomitant medications that was taken prior to study medication administration, in the appropriate Concomitant Medications section.

PHYSICAL EXAMINATION

Perform a physical examination and record details of any clinically significant abnormalities on the Medical Conditions page.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101		**WORKSHEET**	**Screening**

MEDICAL CONDITIONS

Diagnosis *Only in the absence of a diagnosis, record the signs and symptoms on separate lines*	**Current** [1]	**Past** [2]
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.		
12.		
13.		
14.		
15.		
16.		
17.		
18.		
19.		
20.		
21.		
22.		
23.		
24.		
25.		
26.		
27.		
28.		

ALCOHOL INTAKE
INVESTIGATOR INSTRUCTIONS

ALCOHOL CONVERTER

1 unit of alcohol in US = 1.5oz hard liquor, 12oz beer, 5oz wine

Round up/down to the nearest integer.

HISTORY OF TOBACCO USE
INVESTIGATOR INSTRUCTIONS

DEFINITIONS

- **Never smoked** Never smoked/used tobacco
- **Current smoker** Currently smoking/using tobacco or has smoked/used tobacco within 6 months of screening visit
- **Former smoker** Previously smoked/used tobacco and has not smoked/used tobacco for at least 6 months prior to screening visit

CONVERTER FOR TOBACCO PRODUCTS

1 cigar = 7 cigarettes

1 gram (or 0.03 oz.) of tobacco = 1 cigarette

CALCULATION FOR NUMBER OF PACK YEARS

$$\frac{\text{Average number of cigarettes smoked per day}}{20} \times \text{number of years smoked}$$

Round up/down to the nearest integer

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
OTA105101	☐☐☐☐☐☐		Screening

ALCOHOL INTAKE

Does the subject consume alcohol?

[Y] ☐ Yes [N] ☐ No

If Yes, record the average number of units of alcohol[1] consumed per week ☐☐☐ units per week

[1] *See facing page for conversion guidelines.*

HISTORY OF TOBACCO USE

What is the subject's history of tobacco use *(includes all tobacco products)*?

[1] ☐ Never smoked[1]

[2] ☐ Current smoker[1] → *If current smoker, exclude subject from the study.*

[3] ☐ Former smoker[1] → When did the subject last smoke/use tobacco? ☐☐ Day ☐☐☐ Month ☐☐ Year

If current or former smoker, answer the following questions:

Average number of cigarettes[2] smoked per day? ☐☐☐ cigarettes per day

Number of years during which the subject has smoked/used tobacco? ☐☐☐ years

Number of pack years?[3] ☐☐☐ pack years

Is the subject currently using a nicotine oral regimen or topical application (e.g., gum, patches, etc.)?

[Y] ☐ Yes [N] ☐ No

[1] *See facing page for definitions.*
[2] *For cigar and pipe smokers and smokeless tobacco use the conversion on the facing page.*
[3] *See facing page for calculation guidelines.*

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
OTA105101	☐☐☐☐☐☐		Screening

URINE DRUG AND ALCOHOL SCREEN

Date and time of sample taken ☐☐ ☐☐☐ ☐☐ ☐☐:☐☐
Day Month Year Hr:Min (00:00-23:59)

✔*appropriate box(es)*	Postitive	Negative
Cocaine	☐	☐
Amphetamines	☐	☐
Benzodiazepines	☐	☐
Cannabinoids	☐	☐
Opiates	☐	☐
Barbiturates	☐	☐
Alcohol	☐	☐
Cotinine	☐	☐

If any of the above are positive, exclude subject from the study.

ALCOHOL BREATH TEST

Date sample taken ☐☐ ☐☐☐ ☐☐
Day Month Year

Results ✔*one:*
☐ Positive
If positive, exclude subject from the study.
☐ Negative

Protocol Identifier	Subject Identifier		Visit Description
OTA105101	☐☐☐☐☐☐		**Screening**

VITAL SIGNS

Height ☐☐☐ cm Weight ☐☐☐.☐ kg

Body mass index ☐☐.☐ kg/m²

Date	Planned Relative Time	Actual Time	Blood Pressure Sitting mmHg		Heart Rate
Day Month Year		Hr : Min (00:00 - 23:59)	Systolic	Diastolic	beats/min
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***75***
1.	Screening	:			

12-LEAD ECG

Start Date of ECG ☐☐ ☐☐☐ ☐☐ (Day Month Year) Start time of ECG ☐☐:☐☐ (Hr:Min (00:00-23:59))

Ventricular Rate ☐☐☐ Beats/min

PR Interval ☐☐☐ msec

QRS Duration ☐☐☐ msec

Uncorrected QT Interval ☐☐☐ msec

QTc Interval ☐☐☐ msec

Result of the ECG ✔ *one*:

[1] ☐ Normal
[2] ☐ Abnormal - Not clinically significant
[3] ☐ Abnormal - Clinically significant
[4] ☐ No result (not available)

ELECTRONICALLY TRANSFERRED LABORATORY DATA - INVESTIGATOR INSTRUCTIONS

Ensure a blood sample has been taken for clinical chemistry and haematology, including

- HIV, Hepatitis B surface antigen, Hepatitis C antibody
- Faecal Occult blood

Ensure a urine sample has been taken for urinalysis.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

PREGNANCY TEST

Perform a serum pregnancy test for all females. If results are positive, exclude subject from the study.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101		**WORKSHEET**	**Period 1**

ADVERSE EVENTS

Review predose, 4 and 12 hours post dose.

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

BRIEF PHYSICAL EXAMINATION

Perform a physical examination and record details of any clinically significant abnormality in the appropriate Non-Serious Adverse Events/Serious Adverse Event section.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101	☐☐☐☐☐☐	**WORKSHEET**	**Period 1**

URINE DRUG AND ALCOHOL SCREEN

Date and time of sample taken ☐☐ ☐☐☐ ☐☐ ☐☐:☐☐
Day Month Year Hr:Min (00:00-23:59)

✔*appropriate box(es)*	Postitive	Negative
Cocaine	☐	☐
Amphetamines	☐	☐
Benzodiazepines	☐	☐
Cannabinoids	☐	☐
Opiates	☐	☐
Barbiturates	☐	☐
Alcohol	☐	☐

If any of the above are positive, exclude subject from the study.

ALCOHOL BREATH TEST

Date sample taken ☐☐ ☐☐☐ ☐☐
Day Month Year

Results ✔*one:*
☐ Positive
If positive, exclude subject from the study.
☐ Negative

Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
OTA105101			**Period 1**

VITAL SIGNS

	Date (Day Month Year)	Planned Relative Time	Actual Time (Hr : Min (00:00 - 23:59))	Blood Pressure Semi-supine mmHg: Systolic	Blood Pressure Semi-supine mmHg: Diastolic	Heart Rate (beats/min)
	e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***75***
1.		Predose	:			
2.		1 hr	:			
3.		2 hr	:			
4.		4 hr	:			
5.		12 hr	:			

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			Period 1

12-LEAD ECG

	ECG1	ECG2	ECG3	ECG4	ECG5
Start Date of ECG Day Month Year					
Planned Relative Time	Predose	1 hr	2 hr	4 hr	12 hr
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:	:	:
Ventricular Rate Beats/min					
PR Interval msec					
QRS Duration msec					
Uncorrected QT Interval msec					
QTc Interval msec					
Result of the ECG					

(enter code for result from the following list) 1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

PHARMACOKINETICS - BLOOD

INVESTIGATOR INSTRUCTIONS

- If sample is missed or lost, write "NA" in the Date Sample Taken column.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			**Period 1**

PHARMACOKINETICS - BLOOD (COLD ASSAY)

	Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample Number
1.	Predose		:	101
2.	10 min		:	102
3.	20 min		:	103
4.	30 min		:	104
5.	1 hr		:	105
6.	2 hr		:	106
7.	3 hr		:	107
8.	4 hr		:	108
9.	6 hr		:	109
10.	8 hr		:	110
11.	12 hr		:	111
12.	18 hr		:	112
13.	24 hr		:	113
14.	36 hr		:	114
15.	48 hr		:	115
16.	60 hr		:	116
17.	72 hr		:	117
18.	96 hr		:	118
19.	120 hr		:	119
20.	144 hr		:	120
21.	168 hr		:	121
22.	192 hr		:	122
23.	216 hr		:	123
24.	240 hr		:	124

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			**Period 1**

PHARMACOKINETICS - BLOOD (METABOLITE ANALYSIS)

	Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample Number
1.	Predose		:	125
2.	2 hr		:	126
3.	6 hr		:	127
4.	24 hr		:	128
5.	48 hr		:	129

PHARMACOKINETIC SAMPLING URINE/FAECES INTERVAL COLLECTION DATA
INVESTIGATOR INSTRUCTIONS

- If subject cannot provide a sample (i.e., empty bladder) use 'NA' in the actual start/stop time columns and write zero in the total sample weight/volume column.
- If a sample is lost (tube broken, discarded, etc.) complete the actual start/stop time columns and write 'NA' in the total sample weight/volume column.
- If a sample is missed, write 'NA' in the actual start/stop time columns and in the total sample weight/volume column.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			Period 1

PHARMACOKINETIC SAMPLING URINE INTERVAL COLLECTION DATA

Planned Relative Time Interval Time Relative To dosing	Start Date Day Month Year	Actual Start Time Hr : Min (00:00 - 23:59)	Stop Date Day Month Year	Actual Stop Time Hr : Min (00:00 - 23:59)	Total Sample Weight g	Was all of the sample collected for this interval? Y=Yes N=No	Sample Number
1. Predose		:		:			101
2. 0 - 6 hr		:		:			102
3. 6 - 12 hr		:		:			103
4. 12 - 24 hr		:		:			104
5. 24 - 48 hr		:		:			105
6. 48 - 72 hr		:		:			106
7. 72 - 96 hr		:		:			107
8. 96 - 120 hr		:		:			108
9. 120 - 124 hr		:		:			109
10. 124 - 144 hr		:		:			110
11. 144 - 168 hr		:		:			111
12. 168 - 192 hr		:		:			112
13. 192 - 216 hr		:		:			113
14. 216 - 240 hr		:		:			114

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			Period 1

PHARMACOKINETIC SAMPLING FAECES INTERVAL COLLECTION DATA

Planned Relative Time Interval Time Relative To dosing	Start Date Day Month Year	Actual Start Time Hr : Min (00:00 - 23:59)	Stop Date Day Month Year	Actual Stop Time Hr : Min (00:00 - 23:59)	Total Sample Weight g	Was all of the sample collected for this interval? Y=Yes N=No	Sample Number
1. Predose		:		:			115
2. 0 - 24 hr		:		:			116
3. 24 - 48 hr		:		:			117
4. 48 - 72 hr		:		:			118
5. 72 - 96 hr		:		:			119
6. 96 - 120 hr		:		:			120
7. 120 - 124 hr		:		:			121
8. 124 - 144 hr		:		:			122
9. 144 - 168 hr		:		:			123
10. 168 - 192 hr		:		:			124
11. 192 - 216 hr		:		:			125
12. 216 - 240 hr		:		:			126

ELECTRONICALLY TRANSFERRED LABORATORY DATA - INVESTIGATOR INSTRUCTIONS

Ensure a blood sample has been taken for clinical chemistry and haematology **Predose and 48 hours postdose (start of Day 3 infusion)**.

Ensure a urine sample has been taken for urinalysis **Predose and 48 hours postdose (start of Day 3 infusion)**.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

PREGNANCY TEST

Perform a serum pregnancy test for all females prior to dosing. If results are positive, exclude subject from the study.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			**Period 1**

RANDOMISATION NUMBER

Record randomisation number.

Date of randomisation Day Month Year

INVESTIGATIONAL PRODUCT - IV DOSING

Investigational Product	Infusion Start Date Day Month Year	Infusion Start Time Hr : Min 00:00-23:59	Infusion Stop Date Day Month Year	Infusion Stop Time Hr : Min 00:00-23:59
[^{14}C]-GSK221149A		:		:

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
OTA105101			**Period 2**

ADVERSE EVENTS

Review predose, 4 and 12 hours post dose.

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

BRIEF PHYSICAL EXAMINATION

Perform a physical examination and record details of any clinically significant abnormality in the appropriate Non-Serious Adverse Events/Serious Adverse Event section.

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Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
OTA105101			**Period 2**

URINE DRUG AND ALCOHOL SCREEN

Date and time of sample taken ☐☐ ☐☐☐ ☐☐ ☐☐:☐☐
Day Month Year Hr:Min (00:00-23:59)

✔*appropriate box(es)*	Postitive	Negative
Cocaine	☐	☐
Amphetamines	☐	☐
Benzodiazepines	☐	☐
Cannabinoids	☐	☐
Opiates	☐	☐
Barbiturates	☐	☐
Alcohol	☐	☐

If any of the above are positive, exclude subject from the study.

ALCOHOL BREATH TEST

Date sample taken ☐☐ ☐☐☐ ☐☐
Day Month Year

Results ✔*one:*
☐ Positive
If positive, exclude subject from the study.
☐ Negative

Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
OTA105101			**Period 2**

VITAL SIGNS

	Date (Day Month Year)	Planned Relative Time	Actual Time (Hr : Min (00:00 - 23:59))	Blood Pressure Semi-supine mmHg: Systolic	Blood Pressure Semi-supine mmHg: Diastolic	Heart Rate (beats/min)
	e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***75***
1.		Predose	:			
2.		1 hr	:			
3.		2 hr	:			
4.		4 hr	:			
5.		12 hr	:			

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			Period 2

12-LEAD ECG

	ECG1	ECG2	ECG3	ECG4	ECG5
Start Date of ECG Day Month Year					
Planned Relative Time	Predose	1 hr	2 hr	4 hr	12 hr
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:	:	:
Ventricular Rate Beats/min					
PR Interval msec					
QRS Duration msec					
Uncorrected QT Interval msec					
QTc Interval msec					
Result of the ECG					

(enter code for result from the following list) 1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

PHARMACOKINETICS - BLOOD

INVESTIGATOR INSTRUCTIONS

- If sample is missed or lost, write "NA" in the Date Sample Taken column.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			**Period 2**

PHARMACOKINETICS - BLOOD (COLD ASSAY)

	Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample Number
1.	Predose		:	201
2.	15 min		:	202
3.	30 min		:	203
4.	45 min		:	204
5.	1 hr		:	205
6.	1.5 hr		:	206
7.	2 hr		:	207
8.	3 hr		:	208
9.	4 hr		:	209
10.	6 hr		:	210
11.	8 hr		:	211
12.	12 hr		:	212
13.	18 hr		:	213
14.	24 hr		:	214
15.	36 hr		:	215
16.	48 hr		:	216
17.	60 hr		:	217
18.	72 hr		:	218
19.	96 hr		:	219
20.	120 hr		:	220
21.	144 hr		:	221
22.	168 hr		:	222
23.	192 hr		:	223
24.	216 hr		:	224
25.	240 hr		:	225

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			**Period 2**

PHARMACOKINETICS - BLOOD (METABOLITE ANALYSIS)

	Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample Number
1.	Predose		:	226
2.	2 hr		:	227
3.	6 hr		:	228
4.	24 hr		:	229
5.	48 hr		:	230

PHARMACOKINETIC SAMPLING URINE/FAECES INTERVAL COLLECTION DATA
INVESTIGATOR INSTRUCTIONS

- If subject cannot provide a sample (i.e., empty bladder) use 'NA' in the actual start/stop time columns and write zero in the total sample weight/volume column.
- If a sample is lost (tube broken, discarded, etc.) complete the actual start/stop time columns and write 'NA' in the total sample weight/volume column.
- If a sample is missed, write 'NA' in the actual start/stop time columns and in the total sample weight/volume column.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			Period 2

PHARMACOKINETIC SAMPLING URINE INTERVAL COLLECTION DATA

Planned Relative Time Interval Time Relative To dosing	Start Date Day Month Year	Actual Start Time Hr : Min (00:00 - 23:59)	Stop Date Day Month Year	Actual Stop Time Hr : Min (00:00 - 23:59)	Total Sample Weight g	Was all of the sample collected for this interval? Y=Yes N=No	Sample Number
1. Predose		:		:			201
2. 0 - 6 hr		:		:			202
3. 6 - 12 hr		:		:			203
4. 12 - 24 hr		:		:			204
5. 24 - 48 hr		:		:			205
6. 48 - 72 hr		:		:			206
7. 72 - 96 hr		:		:			207
8. 96 - 120 hr		:		:			208
9. 120 - 124 hr		:		:			209
10. 124 - 144 hr		:		:			210
11. 144 - 168 hr		:		:			211
12. 168 - 192 hr		:		:			212
13. 192 - 216 hr		:		:			213
14. 216 - 240 hr		:		:			214

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			Period 2

PHARMACOKINETIC SAMPLING FAECES INTERVAL COLLECTION DATA

Planned Relative Time Interval Time Relative To dosing	Start Date Day Month Year	Actual Start Time Hr : Min (00:00 - 23:59)	Stop Date Day Month Year	Actual Stop Time Hr : Min (00:00 - 23:59)	Total Sample Weight g	Was all of the sample collected for this interval? Y=Yes N=No	Sample Number
1. Predose		:		:			215
2. 0 - 24 hr		:		:			216
3. 24 - 48 hr		:		:			217
4. 48 - 72 hr		:		:			218
5. 72 - 96 hr		:		:			219
6. 96 - 120 hr		:		:			220
7. 120 - 124 hr		:		:			221
8. 124 - 144 hr		:		:			222
9. 144 - 168 hr		:		:			223
10. 168 - 192 hr		:		:			224
11. 192 - 216 hr		:		:			225
12. 216 - 240 hr		:		:			226

ELECTRONICALLY TRANSFERRED LABORATORY DATA - INVESTIGATOR INSTRUCTIONS

Ensure a blood sample has been taken for clinical chemistry and haematology **Predose and 48 hours postdose (start of Day 3 infusion)**.

Ensure a urine sample has been taken for urinalysis **Predose and 48 hours postdose (start of Day 3 infusion)**.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

PREGNANCY TEST

Perform a serum pregnancy test for all females prior to dosing. If results are positive, exclude subject from the study.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			**Period 2**

INVESTIGATIONAL PRODUCT

Investigational Product	Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59
	e.g., 05 JUN 03	***10:54***
[^{14}C]-GSK221149A		**:**

TREATMENT CONFIRMATION

Did the subject receive the correct treatment (e.g., treatment which the subject was assigned to) during this dosing interval?

[Y] ☐ Yes [N] ☐ No

If No, record reason(s)

_____

_____

_____

CONCOMITANT MEDICATIONS

Record any changes to the subject's concomitant medications or any new medications taken since the last visit in the appropriate Concomitant Medications section.

ADVERSE EVENTS

Record details of any new non-serious adverse events/serious adverse events observed or reported by the subject or any changes to ongoing non-serious adverse events in the appropriate Non-Serious Adverse Events/ Serious Adverse Event section.

BRIEF PHYSICAL EXAMINATION

Perform a physical examination and record details of any clinically significant abnormality in the appropriate Non-Serious Adverse Events/Serious Adverse Event section.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - INVESTIGATOR INSTRUCTIONS

Ensure a blood sample has been taken for clinical chemistry and haematology.

Ensure a urine sample has been taken for urinalysis

ELECTRONICALLY TRANSFERRED LABORATORY DATA - MONITOR DATA VALIDATION CHECK

Ensure that the appropriate lab samples have been sent for processing.

PREGNANCY TEST

Perform a serum pregnancy test for all females.

Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
OTA105101			**Follow-up**

VITAL SIGNS

Date (Day Month Year)	Planned Relative Time	Actual Time (Hr : Min (00:00 - 23:59))	Blood Pressure Semi-supine mmHg: Systolic	Blood Pressure Semi-supine mmHg: Diastolic	Heart Rate (beats/min)
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***75***
	Follow-up	:			

12-LEAD ECG

Start Date of ECG ☐☐ (Day) ☐☐☐ (Month) ☐☐ (Year) Start time of ECG ☐☐:☐☐ (Hr:Min (00:00-23:59))

Ventricular Rate ☐☐☐ Beats/min

PR Interval ☐☐☐ msec

QRS Duration ☐☐☐ msec

Uncorrected QT Interval ☐☐☐ msec

QTc Interval ☐☐☐ msec

Result of the ECG ✔ *one*:

[1] ☐ Normal
[2] ☐ Abnormal - Not clinically significant
[3] ☐ Abnormal - Clinically significant[1]
[4] ☐ No result (not available)

[1] Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			**Unscheduled**

VITAL SIGNS

Date Day Month Year	Planned Relative Time	Actual Time Hr : Min (00:00 - 23:59)	Blood Pressure Semi-supine mmHg Systolic	 Diastolic	Heart Rate beats/min
e.g., 01 JAN 03	***15 min***	***13:02***	***110***	***80***	***75***
1.	Unscheduled	:			
2.	Unscheduled	:			
3.	Unscheduled	:			
4.	Unscheduled	:			
5.	Unscheduled	:			
6.	Unscheduled	:			
7.	Unscheduled	:			
8.	Unscheduled	:			
9.	Unscheduled	:			
10.	Unscheduled	:			
11.	Unscheduled	:			
12.	Unscheduled	:			
13.	Unscheduled	:			
14.	Unscheduled	:			
15.	Unscheduled	:			
16.	Unscheduled	:			
17.	Unscheduled	:			
18.	Unscheduled	:			
19.	Unscheduled	:			
20.	Unscheduled	:			

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			Unscheduled

12-LEAD ECG

	ECG1	ECG2	ECG3	ECG4
Start Date of ECG Day Month Year				
Planned Relative Time	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:	:
Ventricular Rate Beats/min				
PR Interval msec				
QRS Duration msec				
Uncorrected QT Interval msec				
QTc Interval msec				
Result of the ECG				
(enter code for result from the following list)	1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)			

[1] *Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.*

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			Unscheduled

12-LEAD ECG

	ECG5	ECG6	ECG7	ECG8
Start Date of ECG Day Month Year				
Planned Relative Time	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:	:
Ventricular Rate Beats/min				
PR Interval msec				
QRS Duration msec				
Uncorrected QT Interval msec				
QTc Interval msec				
Result of the ECG				
(enter code for result from the following list)	1=Normal 2=Abnormal - not clinically significant 3=Abnormal- clinically significant[1] 4=No result (not available)			

[1] Complete the Non-Serious Adverse Events (AE) or Serious Adverse Event (SAE) page(s) if clinically significant abnormalities meet the protocol definition for an AE or SAE. Complete the additional ECG Abnormalities page if clinically significant abnormalities are present.

Protocol Identifier	Subject Identifier		Visit Description
OTA105101			**Unscheduled**

PHARMACOKINETICS - BLOOD (COLD ASSAY)

	Planned Relative Time	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample Number
1.	Unscheduled		:	901
2.	Unscheduled		:	902
3.	Unscheduled		:	903
4.	Unscheduled		:	904
5.	Unscheduled		:	905
6.	Unscheduled		:	906
7.	Unscheduled		:	907
8.	Unscheduled		:	908

PHARMACOKINETICS - BLOOD (METABOLITE ANALYSIS)

	Planned Relative Time	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample Number
1.	Unscheduled		:	909
2.	Unscheduled		:	910
3.	Unscheduled		:	911
4.	Unscheduled		:	912
5.	Unscheduled		:	913
6.	Unscheduled		:	914
7.	Unscheduled		:	915
8.	Unscheduled		:	916

PGx-PHARMACOGENETIC RESEARCH
INVESTIGATOR INSTRUCTIONS

CONSENT FOR PGx-PHARMACOGENETIC RESEARCH

The question "Has informed consent been obtained for PGx-Pharmacogenetic research?" should be completed at the beginning of the study.

- If the question is answered **No**, ✔ one box for reason and **do not** complete the remainder of the page.

WITHDRAWAL OF CONSENT

The question "Has the subject withdrawn consent for PGx-Pharmacogenetic research?" **must be completed immediately** if the subject withdraws consent. Otherwise, it must be completed when the subject leaves the study. It must be completed for all subjects for whom informed consent was obtained for PGx-Pharmacogenetic research.

- If consent is withdrawn, the investigator will fax the completed form (Request/Notification for Destruction of Sample for Pharmacogenetic Research, F-GRD-001) to the monitor within 5 working days of the subject's premature discontinuation in the study.

BLOOD SAMPLE DESTRUCTION

Do **not** complete this section if a blood sample was not collected.

The question "Has a request been made for sample destruction?" must be completed immediately if there is a request for sample destruction. Otherwise, it must be completed when the subject leaves the study. It must be completed for all subjects for whom a blood sample was obtained for PGx-Pharmacogenetic research.

- If the question is answered Yes, ✔one box for reason.

Protocol Identifier	Subject Identifier	
OTA105101		

PGx-PHARMACOGENETIC RESEARCH

CONSENT FOR PGx-PHARMACOGENETIC RESEARCH

Has informed consent been obtained for PGx-Pharmacogenetic research?

[Y] ☐ Yes [N] ☐ No

If Yes, record the date informed consent obtained for PGx-Pharmacogenetic research Day Month Year

If No, ✔one reason:

[1] ☐ Subject declined
[2] ☐ Subject not asked by Investigator
[Z] ☐ Other, *specify* _

BLOOD SAMPLE COLLECTION (DNA)

Has a blood sample been collected for PGx-pharmacogenetic research?

[Y] ☐ Yes [N] ☐ No

If Yes, record the date sample taken Day Month Year

WITHDRAWAL OF CONSENT

Has subject withdrawn consent for PGx-Pharmacogenetic research?

[Y] ☐ Yes [N] ☐ No

BLOOD SAMPLE DESTRUCTION

Has a request been made for sample destruction?

[Y] ☐ Yes [N] ☐ No

If Yes, ✔one reason:

[1] ☐ Subject requested
[2] ☐ Screen failure
[Z] ☐ Other, *specify* _

CONCOMITANT MEDICATIONS
INVESTIGATOR INSTRUCTIONS

- Record unknown months as UNK.
- The following lists of abbreviations are examples which can be used to aid the completion of the appropriate items on the Concomitant Medications page. These are not all inclusive lists and are for guidance only, other abbreviations not listed may be used if necessary.

UNITS

Abbreviation		Label
TAB	=	Tablet
MCL	=	Microlitre
ML	=	Millilitre
L	=	Litre
MCG	=	Microgram
MG	=	Milligram
G	=	Gram

FREQUENCY

Abbreviation		Label
OD/QD	=	1 x Daily
BID	=	2 x Daily
TID	=	3 x Daily
QID	=	4 x Daily
PRN	=	As required

ROUTE

Abbreviation		Label
IM	=	Intramuscular
IH	=	Inhalation
IV	=	Intravenous
NS	=	Nasal
TP	=	Topical
PO	=	Oral
VG	=	Vaginal

CONCOMITANT MEDICATIONS
MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'No' box at the top of the page has been completed.
- Ensure that the spelling of the Drug Name(s) is correct (use of Trade Names is preferred).
- Check that either medication stop date is completed or 'Ongoing Medication?' is 'Yes'.
  - It is acceptable for stop date to be missing if 'Ongoing Medication?' is 'Yes'.
- Ensure that the 'Reason for Medication' is recorded on one of the following pages using the same terms:
  - Current Medical Conditions
  - Non-Serious Adverse Events
  - Serious Adverse Events Form

Protocol Identifier	Subject Identifier	
OTA105101		

CONCOMITANT MEDICATIONS

Were any concomitant medications taken by the subject prior to screening and/or during the study?

[Y] ☐ Yes [N] ☐ No

If Yes, record each medication on a separate line using Trade Names where possible. If the medication is related to a Non-Serious Adverse Event or Serious Adverse Event, details should be expressed using the same terminology.

Drug Name *(Trade Name preferred)*	Unit Dose	Units[1]	Frequency[1]	Route[1]	Reason for Medication	Start Date Day Month Year	Start Time Hr : Min 00:00-23:59	Taken Prior to Study? Y=Yes N=No	Stop Date Day Month Year	Stop Time Hr : Min 00:00-23:59	Ongoing Medication? Y=Yes N=No
e.g., Aspirin	***200***	***mg***	***BID***	***PO***	***Headache***	***31 MAY 03***	***14:10***	***N***	***31 MAY 03***	***23:00***	***N***
1.							:			:	
2.							:			:	
3.							:			:	
4.							:			:	
5.							:			:	
6.							:			:	
7.							:			:	
8.							:			:	

[1] *For Units, Frequency and Route see facing page for examples of acceptable abbreviations.*

Protocol Identifier	Subject Identifier	
OTA105101		

CONCOMITANT MEDICATIONS (Continued)

Drug Name *(Trade Name preferred)*	Unit Dose	Units[1]	Frequency[1]	Route[1]	Reason for Medication	Start Date Day Month Year	Start Time Hr : Min 00:00-23:59	Taken Prior to Study? Y=Yes N=No	Stop Date Day Month Year	Stop Time Hr : Min 00:00-23:59	Ongoing Medication? Y=Yes N=No
e.g., Aspirin	***200***	***mg***	***BID***	***PO***	***Headache***	***31 MAY 03***	***14:10***	***N***	***31 MAY 03***	***23:00***	***N***
1.							:			:	
2.							:			:	
3.							:			:	
4.							:			:	
5.							:			:	
6.							:			:	
7.							:			:	
8.							:			:	
9.											
10.											
11.											
12.											
13.											
14.											

[1] *For Units, Frequency and Route see facing page for examples of acceptable abbreviations.*

DEFINITION OF A NON-SERIOUS ADVERSE EVENT (AE) (Page 1 of 3)

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Examples of an AE **include:**

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition(s) detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se should not be reported as an AE/SAE).

Examples of an AE **do NOT include** a/an:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

For GSK clinical studies, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen). See protocol for clarification.

IF THIS EVENT MEETS THE DEFINITION OF SERIOUS, COMPLETE THE SERIOUS ADVERSE EVENT SECTION

NON-SERIOUS ADVERSE EVENTS (AE) (Page 2 of 3)

MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'No' box at the top of the page has been completed.
- Start dates must be provided for the reporting of adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Non-Serious Adverse Events pages.
- Non-serious adverse event terms should be reviewed for potential SAEs per protocol.
- Confirm that any adverse events marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject was withdrawn from the study due to an adverse event, confirm that the following variables are consistent for the adverse event which resulted in withdrawal:
  - If investigational product was permanently withdrawn due to an adverse event ...
    - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'
  - If the subject was withdrawn from the study for an adverse event ...
    - 'Withdrawal' on the Non-Serious Adverse Events page is recorded as 'Yes'.
    - 'Action Taken with Investigational Product(s) as a Result of the Non-Serious AE' on the Non-Serious Adverse Events page is recorded as 'Investigational Product Withdrawn'.

INSTRUCTIONS FOR COMPLETING NON-SERIOUS ADVERSE EVENTS (AE) (Page 3 of 3)

Diagnosis	Enter only the diagnosis (if known); otherwise enter sign or symptom. If a diagnosis subsequently becomes available, then this should be entered and the sign or symptom crossed out, initialled and dated by the investigator. If this non-serious event progresses to serious, put a line through the Non-Serious AE record and transcribe the details onto the SAE form.
Start Date **Start Time**	Record the start date of the first occurrence of the AE. Record the start time of the AE.
Outcome	All AEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the AE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the AE was ongoing at the time of death, but was not the cause of death.
End Date **End Time**	Record the end date. This is the date the AE Recovered/Resolved. If the event Recovered/Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the AE is 'Not recovered/Not resolved' or 'Recovering/Resolving'. Record the end time of the AE.
Frequency	Select either single episode or intermittent. Intermittent should be used if the subject experiences the same AE on multiple occasions over a period of time (e.g., dizziness). In these circumstances, the start date will be the start date of the first episode and the end date will be the date of resolution.
Maximum Intensity	Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases. Mild = An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. Moderate = An event that is sufficiently discomforting to interfere with normal everyday activities. Severe = An event that prevents normal everyday activities. Not applicable = those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).
Action Taken with Investigational Product(s) as a Result of the Non-Serious AE	Investigational product(s) withdrawn = Administration of investigational product(s) was permanently discontinued. Dose reduced = Dose is reduced for one or more investigational product(s). Dose increased = Dose increased for one or more investigational product(s). Dose not changed = Investigational product(s) continues even though an adverse event has occurred. Dose interrupted = Administration of one or more investigational product(s) was stopped temporarily but then restarted. Not applicable = Subject was not receiving investigational product(s) when the event occurred (e.g., pre-or post-dosing).
Withdrawal	Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal as indicated on the Study Conclusion page, otherwise indicate 'No'.
Relationship to Investigational Product(s)	It is a regulatory requirement for investigators to assess relationship to investigational product(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

Protocol Identifier	Subject Identifier	
OTA105101		

NON-SERIOUS ADVERSE EVENTS (AE)

*Note: If this is a **Serious Adverse Event (SAE), do not complete this form**, go to the SAE section and complete the SAE form.*

Did the subject experience any non-serious adverse events during the study? [Y] ☐ Yes [N] ☐ No *If Yes, record details below.*

Event	Start Date	Start Time	Outcome	End Date	End Time	Frequency	Maximum Intensity	Action Taken with Investigational Product(s) as a Result of the Non-Serious AE	With-drawal	Relation-ship to Investigational Product(s)
Diagnosis Only *(if known)* Otherwise Sign/Symptom	Day Month Year	Hr : Min 00:00-23:59	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae	Day Month Year	Hr : Min 00:00-23:59	1=Single episode 2=Intermit-tent	1=Mild 2=Moderate 3=Severe X=Not appli-cable	1=Investigational product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted X=Not applicable	Did the subject withdraw from study as a result of this AE? Y=Yes[1] N=No	Is there a reasonable possibility that the AE may have been caused by the investigational product? Y=Yes N=No
e.g., Headache	***25 JAN 03***	***13:25***	***1***	***27 JAN 03***	***10:20***	***1***	***1***	***4***	***Y***	***Y***
1.		:			:					
2.		:			:					
3.		:			:					
4.		:			:					
5.		:			:					
6.		:			:					

[1] *Complete Study Conclusion page and ✔Adverse event as reason for withdrawal.*

Protocol Identifier	Subject Identifier	
OTA105101		

NON-SERIOUS ADVERSE EVENTS (AE) (Continued)

*Note: If this is a **Serious Adverse Event (SAE), do not complete this form**, go to the SAE section and complete the SAE form.*

Event	Start Date	Start Time	Outcome	End Date	End Time	Frequency	Maximum Intensity	Action Taken with Investigational Product(s) as a Result of the Non-Serious AE	With-drawal	Relation-ship to Investigational Product(s)
Diagnosis Only *(if known)* Otherwise Sign/Symptom	Day Month Year	Hr : Min 00:00-23:59	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae	Day Month Year	Hr : Min 00:00-23:59	1=Single episode 2=Intermit-tent	1=Mild 2=Moderate 3=Severe X=Not appli-cable	1=Investigational product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted X=Not applicable	Did the subject withdraw from study as a result of this AE? Y=Yes[1] N=No	Is there a reasonable possibility that the AE may have been caused by the investigational product? Y=Yes N=No
e.g., Headache	***25 JAN 03***	***13:25***	***1***	***27 JAN 03***	***10:20***	***1***	***1***	***4***	***Y***	***Y***
1.		:			:					
2.		:			:					
3.		:			:					
4.		:			:					
5.		:			:					
6.		:			:					

[1] *Complete Study Conclusion page and ✔Adverse event as reason for withdrawal.*

DEFINITION OF A SERIOUS ADVERSE EVENT (SAE) (Page 1 of 5)

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

a) results in death.

b) is life-threatening.

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

c) requires hospitalisation or prolongation of existing hospitalisation.

Note: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is 'serious'.

When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered 'serious'. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity, or

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

e) is a congenital anomaly/birth defect.

f) other.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

SERIOUS ADVERSE EVENTS (SAE) (Page 2 of 5)

MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'no' box at the top of the page has been completed.
- Start dates must be provided for the reporting of serious adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Serious Adverse Events pages.
- **Death** should not be recorded as an SAE but should be recorded as the outcome of an SAE. The condition that resulted in the death should be recorded as the SAE.
- Confirm that any SAEs marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject was withdrawn from the study due to an SAE, confirm that the following variables are consistent for the SAE which resulted in withdrawal:
  - If investigational product was permanently withdrawn due to an adverse event ...
    - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'
  - If the subject was withdrawn from the study for an adverse event ...
    - 'Withdrawal' on the SAE page is recorded as 'Yes'.
    - 'Action Taken with Investigational Product(s) as a Result of the SAE' on the SAE page is recorded as 'Investigational Product Withdrawn'.

THE INVESTIGATOR MUST INFORM GSK OF SERIOUS ADVERSE EVENTS BY FAX OR TELEPHONE (FAX PREFERRED) WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT. (The original pages must remain in the Case Report Form/Study File)

INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 3 of 5)

Diagnosis	Record one SAE diagnosis per line, or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialled and dated by the investigator. A separate form should be used for each SAE. However, if multiple SAEs which are temporally or clinically related are apparent at the time of initial reporting then these may be reported on the same page. If this was recorded previously as a non-serious event but has progressed to serious, put a line through the Non-Serious AE record and transcribe the details onto the SAE form.
Start Date **Start Time**	Record the start date and time of the first occurrence of the event or signs/symptoms of the serious event, not the date and time the event became serious.
Outcome	All SAEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the SAE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the SAE was ongoing at the time of death, but was not the cause of death, enter fatal for the SAE which was the direct cause of death.
End Date **End Time**	Record the end date. This is the date the SAE Recovered/Resolved, or if the outcome was fatal, record the date the subject died. If the event Recovered/ Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the SAE is 'Not recovered/Not resolved' or 'Recovering/Resolving'. Record the end time of the SAE.
Maximum Intensity	Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases. Mild = An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. Moderate = An event that is sufficiently discomforting to interfere with everyday activities. Severe = An event that prevents normal everyday activities. Not applicable = Those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).
Action Taken with Investigational Product(s) as a Result of the SAE	Investigational product(s) withdrawn = Administration of investigational product(s) was permanently discontinued. Dose reduced = Dose is reduced for one or more investigational product(s). Dose increased = Dose increased for one or more investigational product(s). Dose not changed = Investigational product(s) continues even though an adverse event has occurred. Dose interrupted = Administration of one or more investigational product(s) was temporarily interrupted but then restarted. Not applicable = Subject was not receiving investigational product(s) when the event occurred (e.g., pre-or post-dosing) or the subject died and there was no prior decision to discontinue IP(s).
Withdrawal	Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal as indicated on the Study Conclusion page, otherwise indicate 'No'.
Relationship to Investigational Product(s)	It is a regulatory requirement for investigators to assess relationship to investigational product(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number	
OTA105101				

SERIOUS ADVERSE EVENT (SAE)

Did the subject experience a serious adverse event during the study? [Y] ☐ Yes [N] ☐ No *If Yes, record details below.*

SECTION 1

Event	Start Date	Start Time	Outcome	End date	End Time	Maximum Intensity	Action Taken with Investigational Product(s) as a Result of the SAE	With-drawal	Relationship to Investi-gational Product(s)
Diagnosis Only (*if known*) Otherwise Sign/Symptom	Day Month Year	Hr : Min 00:00-23:59	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae 5=Fatal	*If fatal, record date of death.* Day Month Year	Hr : Min 00:00-23:59	1=Mild 2=Moderate 3=Severe X=Not applicable	1=Investigational product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted X=Not applicable	Did the subject withdraw from study as a result of this SAE? Y=Yes[1] N=No	Is there a reasonable possibility the SAE may have been caused by the investi-gational product? Y=Yes N=No
e.g., Anaphylaxis	***25 Jan 03***	***13:25***	***1***	***27 Jan 03***	***10:20***	***1***	***4***	***Y***	***Y***
		:			:				
		:			:				

[1] *Complete Study Conclusion page and ✔Adverse event as reason for withdrawal.*

If fatal, was a post-mortem/autopsy performed [Y] ☐ Yes [N] ☐ No *If Yes, summarise findings in Section 11 Narrative Remarks of this SAE form.*

SECTION 2 Seriousness *(specify reason(s) for considering this a SAE, ✔all that apply:*

[A] ☐ Results in death
[B] ☐ Is life-threatening
[C] ☐ Requires hospitalisation or prolongation of existing hospitalisation
[D] ☐ Results in disability/incapacity
[E] ☐ Congenital anomaly/birth defect
[F] ☐ Other, *specify* _ (*see definition of SAE*)

INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 4 of 5)

SECTION 4 **If Investigational Product was Stopped, Did the Reported Event(s) Recur After Further Investigational Product(s) Were Administered?**	If deliberate or inadvertent administration of further dose(s) of investigational product(s) to the subject occurred, did the reported adverse event recur?

Protocol Identifier	Subject Identifier
OTA105101	

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 3 Demography Data

Date of birth ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year Sex ☐ Male ☐ Female Weight ☐☐☐.☐ kg

SECTION 4 If Investigational Product(s) was Stopped, Did the Reported Event(s) Recur After Further Investigational Product(s) were Administered?

☐ Yes ☐ No ☐ Unknown at this time ☐ Not applicable

SECTION 5 Possible Causes of SAE Other Than Investigational Product(s), ✔*all that apply:*

☐ Disease under study
☐ Medical condition(s) *specify* _ _ _ _ _ _ _ _ _ _ _ *(record in Section 6)*
☐ Lack of efficacy
☐ Withdrawal of investigational product(s)
☐ Concomitant medication(s) s*pecify* _ _ _ _ _ _ _ _ _ _ _ *(record in Section 8)*
☐ Activity related to study participation *(e.g., procedures)*
☐ Other, *specify* _

SECTION 6 RELEVANT Medical Conditions

Specify any RELEVANT past or current medical disorders, allergies, surgeries, etc. that can help explain the SAE	**Date of Onset** Day Month Year	**Condition Present at Time of the SAE?** Y= Yes N=No	***If No, Date of Last Occurrence*** Day Month Year

INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 5 of 5)

SECTION 9 **Details of Investigational Product(s)**	Complete this section using the information in the Investigational Product page. Details of all investigational product(s) taken until the time of the SAE should be included. Provide specific details in Section 11 Narrative Remarks if the subject has taken an overdose of investigational product(s), including whether it was accidental or intentional.

Protocol Identifier	Subject Identifier	
OTA105101		

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 7 Other RELEVANT Risk Factors *(provide any family or social history (e.g., smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE)*

SECTION 8 RELEVANT Concomitant Medications *(include details of any concomitant medication(s) which may have contributed to the event)*

Drug Name (Trade Name preferred)	Dose	Unit	Frequency	Route	Taken Prior to Study? Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Medication? Y=Yes N=No	Reason for Medication
e.g., Zantac	***150***	***mg***	***BID***	***PO***	***N***	***25 Jan 03***	***27 Jan 03***	***N***	***Gastric ulcer***

SECTION 9 Details of Investigational Product(s)

Treatment Period	Investigational Product	Infusion Start Date Day Month Year	Infusion Start Time	Infusion Stop Time	Dose	Units		Treatment Period	Investigational Product	Date of Dose Day Month Year	Dose	Unit
Period 1	[^{14}C]-GSK221149A							Period 2	[^{14}C]-GSK221149A			

Protocol Identifier	Subject Identifier	
OTA105101		

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 10 Details of RELEVANT Assessments *(provide details of any other tests/procedures which were carried out to diagnose or confirm the SAE e.g., laboratory data with units and normal range)*

SECTION 11 Narrative Remarks *(provide a brief narrative description of the SAE and details of treatment given)*

Investigator's signature _____
(confirming that the data on the SAE pages are accurate and complete)

Date Day Month Year

Investigator's name (print) _____

STUDY CONCLUSION
INVESTIGATOR INSTRUCTIONS

- Refer to protocol section(s) 10.1 and 10.2 to evaluate subject completion or withdrawal from the study.
- If subject completed study:
  "Date of subject completion or withdrawal" must match the last scheduled study visit date.
- If subject withdrew and a withdrawal visit was conducted:
  "Date of subject completion or withdrawal" must match the date of subject withdrawal.
- If subject lost to follow-up:
  "Date of subject completion or withdrawal" must match the last actual contact with the subject whether or not the contact was a clinic visit. Do not record dates of unsuccessful attempts to contact the subject.

Note: An 'actual contact' is defined as an interaction between the subject and the investigator or investigator's designee, where the investigator/designee has the opportunity to query the subject about the subject's status. This would include clinic visits and telephone contacts, but normally would not include mail correspondence or third party reports.

STUDY CONCLUSION
MONITOR DATA VALIDATION CHECKS

- If the investigational product was discontinued at the same time as the subject was withdrawn from the study, ensure the reasons for the two discontinuations are consistent.
- If the subject was withdrawn due to an adverse event, confirm that details recorded correspond with details on the Adverse Event pages:
  - 'Withdrawal' on the AE/SAE page is recorded as 'Yes'.
  - 'Action Taken with Investigational Product(s) as a Result of the Non-Serious AE/SAE' on the AE/SAE page is recorded as 'Investigational Product Withdrawn'.
  - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'.

PREGNANCY INFORMATION
MONITOR DATA VALIDATION CHECK

- Check that responses provided correspond with the sex of the subject.
- If the answer to the subject pregnancy question is 'Yes', ensure that a Pregnancy Notification Form has been completed for the subject.

Protocol Identifier	Subject Identifier	
OTA105101		

STUDY CONCLUSION

Date of subject completion or withdrawal ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Time of withdrawal ☐☐:☐☐ (Hr:Min (00:00-23:59))

Was the subject withdrawn from the study?

[Y] ☐ Yes [N] ☐ No

*If Yes, ✔the **primary** reason for withdrawal:*

[1] ☐ Adverse event → *Record details on the Non-Serious Adverse Events or Serious Adverse Event pages as appropriate.*

[2] ☐ Lost to follow-up

[3] ☐ Protocol violation

[4] ☐ Subject decided to withdraw from the study

[Z] ☐ Other, *specify* _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

PREGNANCY INFORMATION

Did the subject become pregnant during the study?

[Y] ☐ Yes [N] ☐ No [X] ☐ Not Applicable (not of childbearing potential or male)

If Yes, complete Pregnancy Notification form.

Protocol Identifier	Subject Identifier	
OTA105101		

INVESTIGATOR COMMENT LOG

Only use this form to record explanatory information on anomalies such as missing data, sponsor waiver of inclusion/exclusion criteria, departures from planned investigational product administration or missed visits.

CRF page number if applicable	Comment

INVESTIGATOR'S SIGNATURE

INVESTIGATOR INSTRUCTIONS

The Investigator is accountable for CRF data. However, the Principal Investigator may delegate CRF signature authority to a medically qualified Sub-investigator (as indicated on the Site Staff Signature Sheet).

Protocol Identifier	Subject Identifier	
OTA105101		

INVESTIGATOR'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature _____ Date Day Month Year

Investigator's name (print) _____

Protocol Identifier	Subject Identifier	
OTA105101	☐☐☐☐☐☐	

12-LEAD ECG ABNORMALITIES

Date of ECG ☐☐ Day ☐☐☐ Month ☐☐ Year Time of ECG ☐☐:☐☐ Hr:Min (00:00-23:59)

Record clinically significant abnormalities below. ✔ all that apply:

A. Rhythm

- [A1] ☐ Sinus bradycardia
- [A21] ☐ Sinus bradycardia (heart rate 40-50 beats/min)
- [A22] ☐ Sinus bradycardia (heart rate 30-39 beats/min)
- [A23] ☐ Sinus bradycardia (heart rate < 30 beats/min)
- [A3] ☐ Sinus pause
- [A2] ☐ Sinus tachycardia (heart rate >100 beats/min)
- [A4] ☐ Ectopic supraventricular beats
- [A20] ☐ Ectopic supraventricular rhythm
- [A17] ☐ Wandering atrial pacemaker
- [A26] ☐ Multifocal atrial tachycardia (Wandering atrial pacemaker with heart rate >100 beats/min)
- [A6] ☐ Supraventricular tachycardia (heart rate >100 beats/min)
- [A7] ☐ Atrial flutter
- [A8] ☐ Atrial fibrillation
- [A5] ☐ Junctional rhythm (heart rate ≤100 beats/min)
- [A25] ☐ Junctional rhythm
- [A24] ☐ Junctional tachycardia (heart rate > 100 beats/min)
- [A9] ☐ Ectopic ventricular beats
- [A12] ☐ Ventricular couplets
- [A13] ☐ Bigeminy
- [A28] ☐ Trigeminy
- [A14] ☐ Electrical alternans
- [A29] ☐ R on T phenomenon
- [A18] ☐ Ventricular fibrillation
- [A19] ☐ Idioventricular rhythm (heart rate < 100 beats/min)
- [A10] ☐ Sustained ventricular tachycardia
- [A11] ☐ Non-sustained ventricular tachycardia
- [A32] ☐ Wide QRS Tachycardia (diagnosis unknown)
- [A27] ☐ Ventricular tachycardia
- [A30] ☐ Monomorphic ventricular tachycardia
- [A15] ☐ Torsades de Pointes (Polymorphic ventricular tachycardia with prolonged QT)
- [A31] ☐ Polymorphic (sustained and non-sustained) ventricular tachycardia
- [A16] ☐ Artificial pacemaker
- [A99] ☐ Other abnormal rhythm

Comment _

B. P-Wave and QRS Morphology

- [B1] ☐ Left atrial abnormality (P mitrale)
- [B2] ☐ Right atrial abnormality (P pulmonale)
- [B3] ☐ Right ventricular hypertrophy
- [B5] ☐ Intraatrial conduction delay
- [D14] ☐ Increased voltage consistent with left ventricular hypertrophy
- [B99] ☐ Other morphology

Comment _

Protocol Identifier	**Subject Identifier**	
OTA105101	☐☐☐☐☐☐	

12-LEAD ECG ABNORMALITIES (Continued)

C. Conduction

[C1] ☐ First degree AV block (PR interval > 200 msec)

[C20] ☐ Short PR interval

[C2] ☐ Second degree AV block (Mobitz type 1)

[C3] ☐ Second degree AV block (Mobitz type 2)

[C16] ☐ 2:1 AV block

[C4] ☐ Third degree AV block

[C5] ☐ Left axis deviation (QRS axis more negative than -30°)

[C6] ☐ Right axis deviation (QRS axis more positive than +110°)

[C7] ☐ Incomplete right bundle branch block

[C13] ☐ Incomplete left bundle branch block

[C8] ☐ Right bundle branch block

[C14] ☐ Left anterior hemiblock (synonymous to left anterior fascicular block)

[C15] ☐ Left posterior hemiblock (synonymous to left posterior fascicular block)

[C9] ☐ Left bundle branch block

[C17] ☐ Bifascicular block

[C10] ☐ Non-specific intraventricular conduction delay (QRS ≥120 msec)

[C11] ☐ Accessory pathway (Wolff-Parkinson White, Lown-Ganong-Levine)

[C19] ☐ Prolonged QT interval

[C12] ☐ QT/QTc prolongation ≥ 500 msec

[C18] ☐ AV dissociation

[C99] ☐ Other conduction

Comment _

D. Myocardial Infarction

[D1] ☐ Myocardial infarction, old

[D2] ☐ Myocardial infarction, anterior

[D3] ☐ Myocardial infarction, lateral

[D4] ☐ Myocardial infarction, posterior

[D5] ☐ Myocardial infarction, inferior

[D6] ☐ Myocardial infarction, septal

[D20] ☐ Myocardial infarction, Non-Q wave

[D98] ☐ Other myocardial infarction

Comment _

E. Depolarisation/Repolarisation (QRS-T)

[D7] ☐ Non-specific ST-T changes

[D19] ☐ J point elevation

[D8] ☐ ST elevation

[D21] ☐ ST elevation-pericarditis

[D9] ☐ ST depression

[D10] ☐ U waves abnormal

[D11] ☐ T wave inversion

[D12] ☐ T wave peaked

[D15] ☐ T waves flat

[D16] ☐ T waves biphasic

[D18] ☐ Notched T-waves

[D13] ☐ Low QRS voltage

[D17] ☐ T-wave flattening/inversion

[D99] ☐ Other depolarisation/repolarisation

Comment _

Other Abnormalities

[E99] ☐ Other abnormalities

Comment _

DEFINITION OF A SERIOUS ADVERSE EVENT (SAE) (Page 1 of 5)

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

a) results in death.

b) is life-threatening.

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

c) requires hospitalisation or prolongation of existing hospitalisation.

Note: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is 'serious'.

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d) results in disability/incapacity, or

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

e) is a congenital anomaly/birth defect.

f) other.

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Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

SERIOUS ADVERSE EVENTS (SAE) (Page 2 of 5)

MONITOR DATA VALIDATION CHECKS

- Check that either 'Yes' or 'no' box at the top of the page has been completed.
- Start dates must be provided for the reporting of serious adverse event data. If the exact date is not known, liaise with the investigator to ensure that a best estimate is provided.
- Ensure that **no** medical or investigational procedures are captured on Serious Adverse Events pages.
- **Death** should not be recorded as an SAE but should be recorded as the outcome of an SAE. The condition that resulted in the death should be recorded as the SAE.
- Confirm that any SAEs marked as **Recovering/Resolving** or **Not recovered/Not resolved** have been followed up for details of resolution.
- If the subject was withdrawn from the study due to an SAE, confirm that the following variables are consistent for the SAE which resulted in withdrawal:
  - If investigational product was permanently withdrawn due to an adverse event ...
    - 'Primary Reason for Withdrawal' on the Study Conclusion page is recorded as 'Adverse Event'
  - If the subject was withdrawn from the study for an adverse event ...
    - 'Withdrawal' on the SAE page is recorded as 'Yes'.
    - 'Action Taken with Investigational Product(s) as a Result of the SAE' on the SAE page is recorded as 'Investigational Product Withdrawn'.

THE INVESTIGATOR MUST INFORM GSK OF SERIOUS ADVERSE EVENTS BY FAX OR TELEPHONE (FAX PREFERRED) WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT. (The original pages must remain in the Case Report Form/Study File).

INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 3 of 5)

Diagnosis	Record one SAE diagnosis per line, or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialled and dated by the investigator. A separate form should be used for each SAE. However, if multiple SAEs which are temporally or clinically related are apparent at the time of initial reporting then these may be reported on the same page. If this was recorded previously as a non-serious event but has progressed to serious, put a line through the Non-Serious AE record and transcribe the details onto the SAE form.
Start Date Start Time	Record the start date and time of the first occurrence of the event or signs/symptoms of the serious event, not the date and time the event became serious.
Outcome	All SAEs must be followed until the events are resolved, the condition stabilises, the events are otherwise explained, or the subject is lost to follow-up. Indicate if the event was 'Recovered/Resolved' or 'Recovered/Resolved with sequelae'. If the SAE is ongoing at the time the subject completes the study or becomes lost to follow-up, the outcome must be recorded as 'Not recovered/Not resolved' or 'Recovering/Resolving'. Also enter 'Not recovered/Not resolved' if the SAE was ongoing at the time of death, but was not the cause of death, enter fatal for the SAE which was the direct cause of death.
End Date End Time	Record the end date. This is the date the SAE Recovered/Resolved, or if the outcome was fatal, record the date the subject died. If the event Recovered/ Resolved with sequelae, enter the date the subject's medical condition resolved or stabilised. Leave blank if the SAE is 'Not recovered/Not resolved' or 'Recovering/Resolving'. Record the end time of the SAE.
Maximum Intensity	Record the maximum intensity that occurred over the duration of the event. Amend the intensity if it increases. Mild = An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. Moderate = An event that is sufficiently discomforting to interfere with everyday activities. Severe = An event that prevents normal everyday activities. Not applicable = Those event(s) where intensity is meaningless or impossible to determine (i.e., blindness and coma).
Action Taken with Investigational Product(s) as a Result of the SAE	Investigational product(s) withdrawn = Administration of investigational product(s) was permanently discontinued. Dose reduced = Dose is reduced for one or more investigational product(s). Dose increased = Dose increased for one or more investigational product(s). Dose not changed = Investigational product(s) continues even though an adverse event has occurred. Dose interrupted = Administration of one or more investigational product(s) was temporarily interrupted but then restarted. Not applicable = Subject was not receiving investigational product(s) when the event occurred (e.g., pre-or post-dosing) or the subject died and there was no prior decision to discontinue IP(s).
Withdrawal	Indicate 'Yes' if the event(s) were directly responsible for the subject's withdrawal as indicated on the Study Conclusion page, otherwise indicate 'No'.
Relationship to Investigational Product(s)	It is a regulatory requirement for investigators to assess relationship to investigational product(s) based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. 'A reasonable possibility' is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support 'a reasonable possibility' include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number	
OTA105256				

SERIOUS ADVERSE EVENT (SAE)

Did the subject experience a serious adverse event during the study? [Y] ☐ Yes [N] ☐ No *If Yes, record details below.*

SECTION 1

Event	Start Date	Start Time	Outcome	End date	End Time	Maximum Intensity	Action Taken with Investigational Product(s) as a Result of the SAE	With-drawal	Relationship to Investi-gational Product(s)
Diagnosis Only (*if known*) Otherwise Sign/Symptom	Day Month Year	Hr : Min 00:00-23:59	1=Recovered/ Resolved 2=Recovering/ Resolving 3=Not recovered/ Not resolved 4=Recovered/ Resolved with sequelae 5=Fatal	*If fatal, record date of death.* Day Month Year	Hr : Min 00:00-23:59	1=Mild 2=Moderate 3=Severe X=Not applicable	1=Investigational product(s) withdrawn 2=Dose reduced 3=Dose increased 4=Dose not changed 5=Dose interrupted X=Not applicable	Did the subject withdraw from study as a result of this SAE? Y=Yes[1] N=No	Is there a reasonable possibility the SAE may have been caused by the investi-gational product? Y=Yes N=No
e.g., Anaphylaxis	***25 Jan 03***	***13:25***	***1***	***27 Jan 03***	***10:20***	***1***	***4***	***Y***	***Y***
		:			:				
		:			:				

[1] *Complete Study Conclusion page and ✔Adverse event as reason for withdrawal.*

SECTION 2 Seriousness *(specify reason(s) for considering this a SAE, ✔all that apply:*

[A] ☐ Results in death
[B] ☐ Is life-threatening
[C] ☐ Requires hospitalisation or prolongation of existing hospitalisation
[D] ☐ Results in disability/incapacity
[E] ☐ Congenital anomaly/birth defect
[F] ☐ Other, *specify* _ (*see definition of SAE*)

INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 4 of 5)

SECTION 4 **If Investigational Product was Stopped, Did the Reported Event(s) Recur After Further Investigational Product(s) Were Administered?**	If deliberate or inadvertent administration of further dose(s) of investigational product(s) to the subject occurred, did the reported adverse event recur?

IDSL Version 03.05 - 28 MAR 06 [SAE_max intensity]

Protocol Identifier	Subject Identifier	
OTA105256		

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 3 Demography Data

Date of birth ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year Sex ☐ Male ☐ Female Weight ☐☐☐.☐ kg

SECTION 4 If Investigational Product(s) was Stopped, Did the Reported Event(s) Recur After Further Investigational Product(s) were Administered?

☐ Yes ☐ No ☐ Unknown at this time ☐ Not applicable

SECTION 5 Possible Causes of SAE Other Than Investigational Product(s), ✔*all that apply:*

☐ Disease under study
☐ Medical condition(s) *specify* _____
☐ Lack of efficacy
☐ Withdrawal of investigational product(s)
☐ Concomitant medication(s) *specify* _____
☐ Activity related to study participation *(e.g., procedures)*
☐ Other, *specify* _____

SECTION 6 RELEVANT Medical Conditions

Specify any RELEVANT past or current medical disorders, allergies, surgeries, etc. that can help explain the SAE	**Date of Onset** Day Month Year	**Condition Present at Time of the SAE?** Y= Yes N=No	***If No, Date of Last Occurrence*** Day Month Year

INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE) (Page 5 of 5)

SECTION 9 **Details of Investigational Product(s)**	Complete this section using the information in the Investigational Product page. Details of all investigational product(s) taken until the time of the SAE should be included. Provide specific details in Section 11 Narrative Remarks if the subject has taken an overdose of investigational product(s), including whether it was accidental or intentional.

IDSL Version 03.05 - 28 MAR 06 [SAE_max intensity]

Protocol Identifier	Subject Identifier	
OTA105256		

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 7 Other RELEVANT Risk Factors *(provide any family or social history (e.g., smoking, alcohol, diet, drug abuse, occupational hazard) relevant to the SAE)*

SECTION 8 RELEVANT Concomitant Medications *(include details of any concomitant medication(s) which may have contributed to the event)*

Drug Name *(Trade Name preferred)*	Dose	Unit	Frequency	Route	Taken Prior to Study? Y=Yes N=No	Start Date Day Month Year	Stop Date Day Month Year	Ongoing Medication? Y=Yes N=No	Reason for Medication
e.g., Zantac	***150***	***mg***	***BID***	***PO***	***N***	***25 Jan 03***	***27 Jan 03***	***N***	***Gastric ulcer***

SECTION 9 Details of Investigational Product(s)

Was treatment blind broken at investigational site? ☐ Yes ☐ No ☐ Not applicable

Protocol Identifier	Subject Identifier	
OTA105256		

SERIOUS ADVERSE EVENT (SAE) (Continued)

SECTION 10 Details of RELEVANT Assessments *(provide details of any other tests/procedures which were carried out to diagnose or confirm the SAE e.g., laboratory data with units and normal range)*

SECTION 11 Narrative Remarks *(provide a brief narrative description of the SAE and details of treatment given)*

Investigator's signature _
(confirming that the data on the SAE pages are accurate and complete)

Date Day Month Year

Investigator's name (print) _

LIST OF INVESTIGATORS AND IECS/IRBS FOR OTA105101

Investigator	Investigator/ Site no.	Hospital/ Institution and Address	IEC/IRB Committee Chair and Name of Committee
[redacted] M.D. [redacted] M.D.	Site No. [redacted]	[redacted]	[redacted]

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

[redacted]

HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT
(HIPAA)

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

Study Sponsor:	GlaxoSmithKline
[redacted] Study Doctor:	[redacted] M.D.
Study Title:	An open-label, two period, study to determine the excretion, balance and pharmacokinetics of [^{14}C]-GSK221149A, administered as single doses of an oral solution and an intravenous infusion to healthy female adults
Protocol No.:	OTA105101

Protected Health Information

During your participation in this research study, the study doctor and staff will collect your personal health information, which will include medical histories, laboratory and other test results. Your study records will also include other personal information, such as your name, social security number, date of birth, address, telephone number, etc. that can be used to identify you. Health information that can identify you is called Protected Health Information, or "PHI." The HIPAA Privacy Rule, which is a federal law designed to protect the confidentiality of your PHI, requires that you give written permission for collecting and/or sharing your PHI.

You do not have to allow the study doctor or study staff to collect, keep or share your PHI. However, you cannot be in this study unless you give permission to do so.

The Purpose of This Authorization

You are being asked to allow the collection, use and sharing of your health information. The purpose of allowing this to happen is so that the study information can be complete, the study records can be checked to see that the study was conducted properly, and the product being tested can be evaluated.

Who May See Your Protected Health Information

Staff and/or associates of [redacted] will look at your study records and may share them with staff or associates from the study sponsor, GlaxoSmithKline. They may also share them with investigators from other research sites, the U.S. Food and Drug Administration (FDA), the Institutional Review Board approving this study, representatives of foreign government health agencies, and/or any duly authorized government agency. People from these organizations will be allowed to see and copy your study records.

By signing this authorization form, you are also giving us permission to see copies of your medical records from your doctor(s), and/or from any medical treatment or hospitalization, related to your participation in this study.

Confidentiality of Your Protected Health Information

As much as possible, your name and identity will be kept private. You will be identified by your initials on many study records. This study may be written about in medical or scientific journals, but your name will not be used in any public reports about this study.

It is possible that the organizations we share your PHI with may share it with others who are not required to follow the HIPAA Privacy Rule, meaning your PHI would no longer be protected, and it also could be used or shared in ways other than those listed here.

You May See and/or Copy Your Protected Health Information

You may request to see and/or copy your PHI, however you must wait until the sponsor has completed all work required for this study.

Your Right to Change Your Mind

Your permission to collect and/or share your PHI will never expire for this study unless you tell us in writing that you have changed your mind. You may change your mind at any time during or after the study.

If you change your mind, and do not want to continue giving us permission to collect and/or share your PHI, the study doctor will not collect or share any new PHI that may identify you after that date. PHI already collected before you change your mind may still be used and given to the organizations listed here. To withdraw your permission to collect and/or share your PHI, you must send a written notice to: [redacted]

IMPORTANT TO NOTE: Dropping out of the research study will not automatically withdraw your permission for us to collect, keep or share your PHI. You must send a written notice withdrawing your permission as stated above.

Permission to Collect, Use, and Share Your PHI

Before you sign this form, please ask any questions you may have about your Protected Health Information. The staff will try to answer fully and clearly any questions you may have before, during and after this study. You will receive a signed copy of this Authorization form.

Please read the following paragraph out loud to the person obtaining the authorization.

I have read the information about my Protected Health Information and have asked the staff any questions I have had at this time. I give permission to collect, keep and share my Protected Health Information.

Your Signature Date/Time

I have received a copy of this authorization form.

Your Signature **Date**

[redacted] **STAFF ONLY**

Printed Name of Person Obtaining Authorization and Verification of Literacy

Signature of Person Obtaining Authorization and Verification of Literacy Date/Scientific Time

Informed Consent Form and Information Sheet for Pharmacogenetic Research

GlaxoSmithKline Protocol Title: An open-label, two period, study to determine the excretion balance and pharmacokinetics of [^{14}C]-GSK221149A, administered as single doses of an oral solution and an intravenous infusion to healthy female adults

GlaxoSmithKline Protocol Number: OTA105101

Study Doctor: **Dr** [redacted]
Site Address: [redacted]

Site Phone Number: [redacted]
Subject Number: _____

This form is in addition to the consent form you signed for the clinical study for OTA105101.

Purpose and Description of the Research
The purpose of this consent form is to explain what pharmacogenetic research is and to ask you to give a blood sample that may be used in this research. The sponsor of the research is the GlaxoSmithKline group of companies [referred to as GSK in this consent]. The study doctor is paid by GSK to conduct this research. This study may have about 6 subjects at one site.

What is pharmacogenetic research?
Genes, which we inherit from our parents, may control the way we react to or handle a medicine. Pharmacogenetics is the study of differences in how our bodies respond to or handle medicines. This pharmacogenetic research is looking at genetic differences to better understand why people react differently when they get the same medicine. If it appears that there is a difference in the way people respond to or handle **GSK221149**, GSK may study these differences using your genes or genetic material taken from your blood sample.

What are the benefits of participating in this research study?
There will be no direct benefit to you by taking part in this pharmacogenetic research. You may help scientists understand why people react to or handle **GSK221149** differently. This may help identify who is more likely to respond to **GSK221149** and who may experience side effects.

What exactly will participation in the research involve?
If you choose to take part in this research, a qualified medical worker will take about 10 ml (or 2 teaspoons) of your blood. In the unlikely case that there is a problem processing your sample, then we may ask you to give a second sample.

Is participation in this study voluntary?
Participation in this pharmacogenetic research is voluntary. You may decline to take part now or you may decide to take part and then change your mind. GSK may store your sample for up to

15 years after the last subject completes the study or GSK may destroy your sample at an earlier time. If you decide not to participate or to withdraw your consent after starting the study, you do not have to give a reason and there will be no change to your medical treatment or to your participation in the **GSK221149** study. If you withdraw from this research, your sample will be destroyed and GSK will only keep and study information collected/generated up to that point.

In special cases, your sample may not be used. This might happen if there are not enough subjects, if the study is stopped for other reasons, or if no questions are raised about how people respond to or handle **GSK221149**.

What are the risks involved with blood sampling?
The physical risks of giving a blood sample are the same as those for any blood sample taken from a vein. You may feel faint, experience mild pain, bruising, irritation or redness at the site of puncture. In rare cases an infection could develop**.**

Compensation for Study-Related Injury
If you are physically injured by the properly performed blood draw and you have followed the directions of the study staff, the sponsor will cover the reasonable medical expenses necessary to treat the injury. No other compensation is offered by GSK, but you do not waive any legal rights by signing this consent form.

What other options are there?
You have the choice not to take part in this research.

How are privacy, data protection and confidentiality protected?
As part of the clinical trial, medical information will be collected and analyzed
To protect your privacy, your sample and medical information will be labeled (or "coded") with a study subject number, not your name. Only your study doctor and his or her staff will keep the link between your subject number and your name.

Your study doctor has been told to keep your pharmacogenetic information including your consent in a separate, secure file, which is **not** part of your medical records. GSK will control access to its files that hold your coded information and results. Your name will **not** appear in any publications or reports about this research.

GSK or those working with GSK (for example, other researchers) will only work with your sample for the use stated in this consent. Samples will be stored securely. GSK will require anyone who works with your sample to agree to hold the research information and any individual results in confidence.

Medical information about you may be produced as part of the research or study procedures. If at the time of the study, this information is known to be relevant to your medical care it will be given to the study doctor who will be encouraged to share it with you or your doctor. You will be told if any of this medical information requires confirmation using a clinical test. This is

important because some research results are for research purposes and may have only limited relevance for clinical diagnosis or treatment.

Individual research results that are not known to be relevant to your medical care at the time of the study will not be released to anyone, unless required by a governmental agency or other legal authority. "Anyone" includes you, your family, your doctor, your insurance company, and your employer.

GSK has taken appropriate measures to ensure the confidentiality of the research-related information. However, if you pass on your individual results (if obtained by you), there is a possibility that this could have an effect on your insurance or employment. This risk is similar as if you were to disclose any type of personal medical information to a third party.

Medical information, samples and research results from you and other research participants may be studied by GSK to make medicines or tests to determine the body's response to or handling of medicine. Your information and any results will be put in a computer and stored in electronic databases. International regulations for information on computers and relevant laws on processing personal information will be strictly adhered to. Your information, sample, and results could be sent to other researchers working with GSK and to other GSK sites.

By agreeing to take part in this research, you will allow your medical information, sample, and pharmacogenetic results to be reviewed as part of collecting and analyzing study results. The people who may check this research include GSK, people working with GSK on this research, ethics committees/institutional review boards, and regulatory authorities such as the FDA. These persons are required to maintain the confidentiality of the information.

Disclosure of Protected Health Information
Authorization to use or disclose your medical information as described above is not time-limited (that is, will not expire). If you decide not to sign this consent, you will not be included in the study. You may withdraw this authorization at any time in writing. If you sign this consent and decide later to withdraw the authorization, you will be withdrawn from the study at that time. Information collected up to the time you withdraw your authorization will continue to be used as study data. Once information is disclosed under this authorization to someone who is not a health care provider, the information is no longer protected by the US privacy rules (called the HIPAA privacy regulations) and could be disclosed to others by the recipient.

Will there be compensation for participation in the research?
You will not receive any payment for taking part in this pharmacogenetic research. ***OR***
You will be paid £X/$X for your time and travel related expenses.

Commercial Issues
GSK and/or others intend to claim sole ownership of any research results consistent with this consent. The results of this research may have commercial or intellectual property value. By signing this consent, you agree that GSK can apply for patents and you understand that you will not receive any financial benefit that might come from the research.

Who can you call for more information about this research study?
You may contact _____ at telephone number _____ at any time if you have questions about this study, an injury related to the blood draw for this research, or wish to withdraw from this research. If you have questions about your rights as a research subject, you may contact _____ of the Institutional Review Board/Ethics Committee at telephone number_____.

CONSENT

A copy of this Consent Form (signed and dated) must be given to the subject or legal representative.

My signature below indicates that:
1. I have read this form and the research has been explained to me.
2. I have been able to discuss the research and ask questions. I am satisfied with the answers.
3. I have been given the time to consider whether or not to take part in this research.
4. I have freely decided to take part in the research study described in this form.

Subject's Name (*Please Print*): _____

Subject's Signature: _____ Date: _____
(*or that of Legal Representative*) **(Day/Month/Year)**

Name and Signature of Individual Obtaining the Subject's Consent:

Name (*Please Print)*: _____

Signature: _____ Date: _____
(Day/Month/Year)

[redacted]

[redacted]

Volunteer Information and Consent Form

Study Sponsor:	GlaxoSmithKline
[redacted] Study Doctor:	[redacted] M.D.
Study Title:	An open-label, two period, study to determine the excretion, balance and pharmacokinetics of [^{14}C]-GSK221149A, administered as single doses of an oral solution and an intravenous infusion to healthy female adults
Protocol No.:	OTA105101

Invitation

You are invited to be in a research study at [redacted] This is a study to see how the body uses the research drug, GSK221149A. Only healthy females of non-childbearing potential can be in this study. GSK221149A is an experimental drug. It is not approved by the Food and Drug Administration (FDA).

The Purpose of This Study

We are doing this study because GSK221149A might help in the treatment of pre-term labor. One of the first steps in learning about a new drug is to find out how the human body uses it, and what side effects it might cause.

This study will use low levels of radiation to see how the human body uses GSK221149A.

[redacted] is paid to test new drugs. The study doctors in this study work for [redacted] but do not have a financial interest in the outcome of this study.

About Radiation

This type of study is called a radiolabeled study. For this study, GSK221149A has been specially prepared to contain radiolabeled carbon [^{14}C]. [^{14}C] is a naturally occurring radioactive form of the element carbon. Adding a low dose of radiation to the study drug does not change how the drug works, but helps us to see how the drug appears in the blood, urine, and stool.

Who Can Be in This Study

Volunteers for this study must meet certain requirements. The study staff will ask you questions about your health, what kinds of medicines you take and what kinds of operations or diseases you may have had. It is important for you to answer all these questions honestly and accurately. If you would like to have a copy of the medical requirements for this study, please ask the study staff for a copy.

The study doctor will choose about 6 females to be in this study.

In case some people drop out of the study, extra people will be chosen at the start of the study. Not everyone may be chosen to stay in the study long enough to take the study drug. If you are not chosen to stay in the study, you will go home from the research unit the same day or the next morning. You will be paid for the time spent on the research unit. However, if you test positive for any unauthorized drugs or alcohol you will not be paid.

To be in this study, you must be a healthy female of non-childbearing potential between 30 and 55 years old. Use of certain products or medications may or may not be allowed in this study. It is your responsibility to comply with all the study restrictions and procedures if you are chosen to participate in this study. Please read the following chart carefully.

MAY I HAVE...?	**YES**	**NO**	**FOR HOW LONG?**
• Tobacco Products		**X**	6 months before and during the study
• Caffeine Products		**X**	1 day before each stay on the research unit
• Alcohol Products		**X**	1 day before each stay on the research unit
• Prescription Medicines		**X**	13 days before, and during the study, unless approved by the study doctor
• Over-the-Counter Medicines (Non-prescription including vitamins, herbal products, and dietary supplements)		**X**	2 days before, and during the study, unless approved by the study doctor
• St. John's Wort		**X**	13 days before, and during the study
• Grapefruit or grapefruit products		**X**	7 days before, and during the study
• Poppy Seeds		**X**	7 days before the Screening Visit - and during the study
• Donate(d) Blood		**X**	56 days before, and during the study
• Receive(d) excessive x-rays, or CT scans, or work with radiation		**X**	12 months before, and during the study or been exposed to or will be exposed (due to participation in this study) to > 5 milliSieverts of radiation exposure.
• Receive(d) other research drugs		**X**	At least 30 days before, and during the study, not to exceed 3 studies in the past 12 months
• Participate(d) in another radiolabeled research study		**X**	12 months before, and during the study

ABOUT SCREENING VISITS

The screening visit will tell us if you qualify to be in this study. If you are not completely truthful with the study doctor and study staff about your medical history and what medicines you take, you may harm yourself by participating in this study.

AT THE SCREENING VISIT YOU WILL:

FAST (no food) 8 hours before this visit

- Have a physical examination
- Review your medical history, provide your date of birth, race, sex, weight and height, and what medicines you take
- Have your vital signs recorded (blood pressure, heart rate, respiration and temperature)
- Have your blood drawn. About 3 tablespoons of blood will be taken from a vein in your arm.
- Give a urine sample
- Be tested for drugs of abuse, alcohol and nicotine
- Be tested for HIV and hepatitis B and C
- Have an ECG (electrocardiogram – a painless recording of heart action)
- Be given a hemoccult test to take home. The hemoccult test requires placing a small sample of your stool on a special card. You will mail the special card with the sample to the research unit from home.
- Receive information about the optional collection of a blood sample for storage for future testing
- Have your picture taken for study identification

ABOUT HEPATITIS AND HIV TESTS

Your blood will be tested for hepatitis viruses and HIV (the virus that causes AIDS). If you test positive for hepatitis viruses or HIV, we are required by state law to report it to the [redacted] Department of Health and Family Services.

The results of both tests are kept confidential and will not be shared except as required by state law. We will provide you with medical referrals and counseling if you test positive for HIV or hepatitis viruses. A separate consent form must also be signed before we can do the test for HIV.

ABOUT BLOOD SAMPLE STORAGE FOR FUTURE TESTING

You will be asked to give a sample of your blood to be frozen and stored for future testing. A separate consent form explaining more about this will be given to you. You do not have to agree to provide the sample for future testing in order to be in this study.

What Will Happen in This Study?

Your participation in this study will last over a period of up to 54 days.

You will stay on the research unit twice for up to 11 days/10 nights. You will have one outpatient visit at the end of the study that may last up to 3 hours.

During the stays on the research unit, it is possible that you may be discharged earlier than 11days if your body has gotten rid of the study drug before then. It is possible you may only need to stay 7 days/6 nights on the research unit. ***It is important that your schedule is flexible enough to adjust to shorter stays.***

You will be given a Study Calendar for this study.

IN THIS STUDY, YOU WILL:

- Have physical examinations
- Have vital signs recorded
- Review your medical history and what medicines you take
- Have your blood drawn
- Collect all your urine and stool
- Be tested for drugs of abuse and alcohol
- Have ECGs
- Fast up to 12 hours overnight and through breakfast
- Take study drug

ABOUT TAKING THE STUDY DRUG

Once during this study, you will receive 10 milligrams of [^{14}C]-GSK221149A through an intravenous catheter (a thin, flexible tube) placed in a vein in your arm.

Once during this study, you will drink a solution containing 100 milligrams of [^{14}C]-GSK221149A.

You will fast for 8 hours overnight both times before you take the study drug and for 4 hours afterwards. You will stay in bed for 4 hours after you take the study drug, and may not have anything to drink during that time.

OTHER PROCEDURES AND RESTRICTIONS

You must collect all your urine and stool while you are staying at the research clinic, unless otherwise directed by the staff. You must collect all toilet paper used for stool(s).

If you become nauseated and throw up while in this study, you must try to collect the vomit.

Collection containers for all samples will be provided.

Food and beverages will be provided during your stay on the research unit. You may not bring your own food or beverages.

If you should develop a visible side effect, such as a skin rash, we may need to take pictures of it for the study records.

You may not exercise strenuously during this study.

The information and any materials or items that you are given about (or during the study) - such as information regarding the study drug(s) or the type of study being performed - should be considered confidential business information of the study sponsor, GlaxoSmithKline. You are of course free to discuss such information under confidence with your doctor or with your friends and family while considering whether to participate in this study or at any time when discussing your present or future healthcare.

ABOUT BLOOD SAMPLES

During this study, up to 38 blood samples will be taken from a vein in your arm. Twice in this study your blood will be drawn up to 14 times over a 24 hour period (includes overnight).

The total amount of blood being drawn during this study is about 2½ cups. For comparison, you give about 2 cups of blood when you donate a unit at a blood collection center.

If you are discharged early from the research unit because your body has gotten rid of the study drug, the number of blood draws, and amount of blood drawn, will be less than the amounts stated above.

Additional blood samples of up to 3 teaspoons may be drawn during the study if the study doctor considers it necessary for monitoring your health.

You should not be in this study if you have a lot of problems having your blood drawn because of poor veins.

Side Effects and Risks of Being in This Study

Risks of Radiation: Radiation exposure is measured in millirems. The highest amount of radiation allowed by law in a single dose for research subjects is 3,000 millirems. In this study, you will receive about _____ millirems of radiation, depending on the calculation used. This is in comparison to the natural environmental radiation that you receive every year, which in the [redacted] area is 360 millirems. Environmental radiation includes cosmic radiation, radiation from the earth, radiation inside your body, and radiation from radon gas. The risk to your health from the radiation received on this study is too small to be detected.

Although there are no proven harmful effects from the radiation you will receive in this study, long term effects of this radiation on your health cannot be known for certain.

Risks of GSK221149A:

This will be the third study in which GSK221149A will be given to healthy volunteers. About 62 **healthy** female volunteers in total have received at least one dose of GSK221149A. In one of those studies, oral doses of up to 500 milligrams have been given 4 times daily for 14 days. In another study, single intravenous doses up to 20 milligrams of GSK221149A have been infused over 30 minutes, and single doses of 14 milligrams have been given over 5 minutes, followed by a constant infusion of 16 milligrams per hour for 48 hours. No serious side effects were reported.

The most common side effects reported by volunteers taking either GSK221149A or placebo (a tablet that does not contain any active medication) are listed below. You may experience some of these side effects with GSK221149A.

• Headache	• Nausea	• Pain at infusion site

Less common side effects reported include lightheadedness.

The most common side effect seen in **animal studies**, at intravenous and oral doses at least 360 times higher than you are being given intravenously or orally in this study, include vomiting.

Risks to Pregnancy: The effects of GSK221149A on the developing human fetus are unknown, and may cause physical or mental damage. Excessive radiation can cause harm to a developing human fetus.

In order to be in this study, you must have had a hysterectomy or no periods for at least two years.

THERE MAY BE… UNKNOWN RISKS, AND… UNKNOWN LONG TERM EFFECTS... FROM TAKING THE STUDY DRUG… OTHER THAN THE SIDE EFFECTS LISTED HERE.

The risks of having blood drawn include bruising, infection, bleeding, and blood clot formation. Sometimes having blood drawn can sting and be uncomfortable. Some people faint when they have their blood drawn. The amount of blood drawn in this study may or may not cause you to become anemic (low red blood count). If you become anemic, you may need to purchase and take over-the-counter iron supplements after the study.

Your skin may become itchy, red and sore under the patches used for ECGs.

Treatment for Side Effects or Injuries

Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for [redacted] is [redacted]

[redacted] will provide immediate medical treatment and follow-up care for side effects or injuries caused by being in this study. If, as part of participating in the study, you are injured (i) as result of your taking of the study drug or (ii) study-related procedures done to you in accordance with the study protocol, GlaxoSmithKline will pay for reasonable and necessary medical expenses to treat the injury. GlaxoSmithKline is not offering to compensate you for any other expenses, but you do not waive any legal rights by signing this consent form.

The costs for any other medical problems not caused by being in this study are your responsibility.

If You Have Questions

Please contact the study doctor (Dr. [redacted] or the study staff with any questions you may have. They can be reached at [redacted]

For questions about your rights as a research volunteer, please contact the Institutional Review Board (IRB) office [redacted] Letters may be sent to the attention of the IRB at [redacted]

The [redacted] is the review board that approved this study. The IRB reviews each research study to make sure that the known risks to research volunteers are adequately presented in this consent form. The IRB also makes sure that this study meets federal regulations for human subject research. Approval by the IRB is necessary before a study can begin, but only you can decide if you wish to be in the study.

Benefits of Being in This Study

This study will not improve your health or treat any medical problem you may have. If you have medical problems, you should see your own doctor about your care.

You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you. However, if you test positive for any unauthorized drugs or alcohol, all the tests may not be completed.

Alternative Treatment

You are not receiving the study drug as a treatment for a medical condition. Your only other choice is not to participate.

Payment for Your Time

Depending upon how long you need to stay on the research unit each time, you will receive between $2,500 and $5,500 if you complete all required study activities. A check should be mailed to your address within 10 working days after you have completed all required study activities.

NOTE: The amount of payment you will receive will be based on how many days you stay on the research unit. The number of days you will stay on the research unit will be based on when your body has gotten rid of the study drug.

The study doctor may decide that you need additional follow-up care, based on study test results. You may be asked to come to the research unit for extra blood or urine tests. You will be paid at a lesser rate for any follow-up visits you are asked to complete.

After you take the study drug, if you are released, or choose to stop, you will be paid for the time you spent on the study at a lesser rate.

No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes.

If you receive more than $600 in one calendar year from [redacted] you will receive a 1099 tax form the following January. [redacted] reports the money paid to you to the Internal Revenue Service.

Costs to You

There are no costs to volunteers. The study sponsor, GlaxoSmithKline, pays all the study costs.

Protecting Your Privacy

As much as possible, your name and identity will be kept private. You will be identified by your initials on many study records. Maintaining confidentiality is important to GlaxoSmithKline. Your personal information (for example your gender, age, and ethnicity) and data collected by GlaxoSmithKline as part of the study will be identified by a number only.

The people who are allowed to look at your study records include staff from GlaxoSmithKline, the U.S. Food and Drug Administration (FDA), and possibly other agencies as required by law. People from these organizations will be allowed to see and copy your study records. The study records will be checked to see that the study was conducted properly.

This study may be written about in medical or scientific journals, but your name will not be used in any public reports about this study.

Stopping the Study Early

The study sponsor and/or the study doctor can stop the study at any time. They can also require you to stop being in the study if there are risks to your health. You may also be required to stop being in the study if you do not follow the study directions, or do not meet the study requirements.

Leaving the Study

Your decision to be in this study is voluntary. You may leave the study at any time. If you decide to leave the study early, you will be asked to complete final laboratory tests, study procedures, and a physical examination for your safety. There are no penalties for leaving the study early. You will not lose any benefits for which you qualify. You will be told about any new information about the study or study drug that might make you change your mind about being in this study.

Volunteering to be in This Study

You may take as much time as you need to think about being in this study. Before you sign this form, please ask any questions you have about your part in this study or about the research. The staff will try to answer fully and clearly any questions you may have before, during and after this study. **You do not lose any of your legal rights by signing this form**. You will receive a signed copy of the Volunteer Information and Consent Form. You may request copies of your screening test results.

Please read the following paragraph out loud to the person obtaining the consent.

I have read the information in this study consent form. I have asked the staff any questions I have had at this time about my part in this study and about this research. I volunteer to take part in this study of my own free will.

_____

Your signature Date/Time

I have received a copy of this study consent form.

_____

Your Signature **Date**

[redacted] **STAFF ONLY**

_____

Signature of Person Obtaining Consent and Verification of Literacy Date/Scientific Time

[redacted]

Volunteer Information and Consent Form
Blood Sample Storage for Future Testing

Study Sponsor:	GlaxoSmithKline
[redacted] Study Doctor:	[redacted] M.D.
Study Title:	An open-label, two period, study to determine the excretion, balance and pharmacokinetics of [^{14}C]-GSK221149A, administered as single doses of an oral solution and an intravenous infusion to healthy female adults
Protocol No.:	OTA105101

Invitation

You are invited to provide a sample of blood for research purposes. The kind of testing that will be done with your sample is called gene analysis. Gene analysis is done by testing blood to determine if you have a specific gene type. Genes are located in the body inside of cells in the form of DNA. A gene is the material passed from parent to child that determines the make-up of the body and its function.

The Purpose of the Blood Sample Storage

The purpose of collecting a sample of your blood is to allow the sponsor to conduct gene analysis tests in the future. Your sample may be stored indefinitely. It is possible they may decide not to conduct testing with your sample at all. Your blood sample will be linked with your personal identity at the study site.

The gene analysis will not be shared with you because they are preliminary results intended for research purposes only. Results of your gene analysis will not provide a clinical diagnosis, and they are not intended to manage or improve your healthcare.

Who Can Volunteer for Blood Sample Storage

Only volunteers who are in the GlaxoSmithKline OTA105101 study can volunteer to have a blood sample stored for possible future testing.

How to Participate

After you have given your permission for the blood sample storage procedure, about 2 additional teaspoons of blood will be collected during a blood draw for the GlaxoSmithKline OTA105101 study. No additional blood draws will be done to obtain this sample.

Risks and Benefits

Your personal identity will be linked to your blood sample, making it possible to connect the genetic testing results to your name in the study records. Personal identity may include your initials, race, sex, age, ethnic origin, family history, and/or a special code number. Your name, initials, address, or social security number will never be sent to the sponsor. Every effort will be made to keep your personal identity confidential within your study records, however, possible risks always exist when genetic testing information is linked to your personal identity. These risks include, but are not limited to, loss of employment opportunities and denial of health insurance.

The risks of having blood drawn include bruising, infection, bleeding, and blood clot formation. Sometimes having blood drawn can sting and be uncomfortable. Some people faint when they have their blood drawn.

There is no personal benefit to you for agreeing to participate. Participation may help further medical knowledge.

Treatment for Injuries

[redacted] will provide immediate medical treatment and follow-up care for any injury caused by having your blood drawn. If you are injured as a result of the blood draw, done in accordance with the study protocol, GlaxoSmithKline will pay for reasonable and necessary medical expenses to treat the injury. GlaxoSmithKline is not offering to compensate you for any other expenses, but you do not waive any legal rights by signing this consent form.

Alternatives to Participation

You do not have to agree to participate in the blood sample storage for gene analysis to be a participant in the GlaxoSmithKline OTA105101 study.

The alternative to participating is to sign the last page under I DO NOT GIVE MY PERMISSION. If you do not give your permission for future gene analysis, no additional blood will be drawn for sample storage during the GlaxoSmithKline OTA105101 study.

Stopping Participation

If you decide to withdraw your consent after providing a blood sample, you do not have to give a reason and there will be no change to your medical treatment or to your participation in the OTA105101 study. If you withdraw consent, your sample will be destroyed and GSK will only keep any study information collected/generated up to that point.

Costs and Payment

There will be no costs to you for providing this sample. There will be no additional payment made to you for providing this sample, other than the amount paid for participating in the GlaxoSmithKline OTA105101 study.

Any information obtained from your gene analysis will belong to GlaxoSmithKline (and possibly other business associates of GlaxoSmithKline). They may use the research results and any developments or inventions resulting from this research for commercial and/or intellectual property purposes (for example, patents). You will not receive any payment for future commercial and/or intellectual property purposes.

Protecting Your Privacy

Your blood sample will be sent to the sponsor identified by a code number. The key to that code will be kept in a locked database at [redacted] and will never be shared with anyone but representatives from GlaxoSmithKline, except if required by law.

Results from the gene analysis may be written about in medical or scientific journals, but your name will not be used in any public reports about this study.

If You Have Questions

Please contact the study doctor or the study staff with any questions you may have. They can be reached at [redacted]

For questions about your rights as a research volunteer, please contact the Institutional Review Board (IRB) office [redacted] The [redacted] is the review board that approved this study. Letters may be sent to the attention of the IRB at [redacted]

Volunteering to Be in This Study

You may take as much time as you wish to think about taking part in the blood sample collection for future gene analysis. Before you sign this form, please ask any questions you have about your part in the sample collection. The staff will try to answer fully and clearly any questions you may have before, during, and after the sample collection**. You do not lose any of your legal rights by signing this form**. You will receive a signed copy of the Volunteer Information and Consent Form.

Please read the following paragraph aloud.

I have read the information in this consent form. I have asked the staff any questions I have had at this time about my part in the sample collection and about the blood sample storage. I volunteer to take part in this procedure of my own free will.

_____ _____

I GIVE MY PERMISSION: Date/Time
Your Signature

_____ _____

I DO NOT GIVE MY PERMISSION Date/Time
Your Signature

I have received a copy of this blood sample storage consent form.

_____

Your Signature **Date**

[redacted] **STAFF ONLY**

_____

Printed Name of Person Obtaining Consent and
Verification of Literacy

_____

Signature of Person Obtaining Consent and Verification of Literacy Date/Scientific Time

Master Schedule Report

StudyID: *OTA105101*
Description: *An open-label, two period, study to determine the excretion balance and pharmacokinetics of [14C]-GSK221149A, administered as single doses of an oral solution and an intravenous infusion to healthy female adults*

Treatments and Sequences defined for study

	Treatments		
Sequence	**Code**	**Description**	**Period**
A/B	B	Single Oral dose of GSK221149A	2
	A	Single IV dose of GSK221149A	1

Master Schedule Report

StudyID: *OTA105101*
Description: *An open-label, two period, study to determine the excretion balance and pharmacokinetics of [14C]-GSK221149A, administered as single doses of an oral solution and an intravenous infusion to healthy female adults*

Schedule No: 1
Stratum None

Randomisation Number	**Treatment / Sequence**
[redacted]	A/B
	A/B
	A/B
	A/B
	A/B
	A/B
	A/B
	A/B
	A/B
	A/B

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COA No.: 061126238-01

GlaxoSmithKline

Pharmaceutical Development
Drug Product Certificate of Analysis

GlaxoSmithKline Research & Development Limited
New Frontiers Science Park
Third Avenue
Harlow
Essex
CM19 5AW
Tel. [redacted]
Fax
www.gsk.com

Product: Radiolabelled GSK221149 [14C] Sterile Solution. 0.8mg/mL (1.6µCi/mL)

Strength / Dose Form: 0.8mg/mL (1.6µCi/mL) / Solution

Batch Number: 061126238

Date of Manufacture: 06-October-2006

Site of Manufacture: GSK, Harlow, UK

Test	Acceptance Criteria	Results
Description	A clear, colourless, solution, free of visible particulate matter.	Conforms
Identification of GSK221149 by HPLC	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the GSK221149A reference material chromatogram.	Conforms
GSK221149 content by HPLC (% stated content)	90.0 – 110.0	97.2, 97.1
Drug-related impurities content by HPLC (% a/a)		
Any unqualified impurity	Not greater than 0.5	Less than 0.05
Total Impurities	Not greater than 4.0	Less than 0.05
Volume in a container (mL)	Complies with the requirements of the USP <1>	Conforms, 20.9
Particulate matter in injections (counts per container)		Conforms
≥10µm	≤ 600	
≥25µm	≤ 6000	

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COA No.: 061126238-01

Test	Acceptance Criteria	Results
pH	4.3 – 4.7	4.5
Bacterial endotoxins (Eu/mL)	Not greater than 28	Less than 5.0
Sterility	Complies with the requirements of the USP <71>	Conforms
Radiochemical purity (% area) [1]	For information only	Greater than 99.8
This material conforms to Specification S0005446-01.		

1. This test does not form part of the specification.

This material was manufactured and tested in accordance with current Good Manufacturing Practices.

Approved by: [redacted] **Date:** [redacted]

[redacted]
Qualified person
R&D Quality Assurance
GSK, Harlow, UK

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COA No.: 051103515-01

GlaxoSmithKline

Pharmaceutical Development
Drug Product Certificate of Analysis

GlaxoSmithKline
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA
19426-0989

Tel. [redacted]
Fax
www.gsk.com

Product: GSK221149A Solution for IV Infusion 0.8mg/mL

Strength / Dose Form: 0.8mg/mL

Batch Number: 051103515

Date of Manufacture: 20 October 2005

Site of Manufacture: GSK, King of Prussia, USA

Test	Acceptance Criteria	Results
Description	A clear, colourless solution, free of visible particulate matter	Complies
Identification of GSK221149A by HPLC	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the GSK221149A reference material chromatogram.	Complies
GSK221149A content by HPLC (% stated content)	90.0 – 110.0	101.6
Drug related impurities by HPLC (%a/a)		
Any unqualified impurity	Not greater than 0.2	No unqualified impurity greater than 0.2
Total impurities	Not greater than 4.0	0.18
Volume in a container (mL)	Complies with the requirements of the USP	Complies, 20.5mL

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COA No.: 051103515-01

GlaxoSmithKline

GlaxoSmithKline
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA
19426-0989
Tel. [redacted]
Fax
www.gsk.com

Particulate matter in injections (counts per mL)		
≥10µm	≤25	0
≥25µm	≤3	0
pH (pH units)	4.3 - 4.7	4.5
Bacterial endotoxins (Eu/mL)	Not greater 2.8	<1.4
Sterility	Complies with the requirements of the USP	Complies
This material conforms to Specification S200404-02.		

This material was manufactured and tested in accordance with current Good Manufacturing Pract[redacted]

Approved by: [redacted] **Date:** 18 JAN 2006

Quality Assurance
GSK, Upper Provi[redacted]egeville, PA, USA

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COA No.: 061124266-01

GlaxoSmithKline

Pharmaceutical Development
Drug Product Certificate of Analysis

GlaxoSmithKline
709 Swedeland Road
P.O. Box 1539
King of Prussia, PA
19406-0939
Tel. [redacted]
Fax
www.gsk.com

Product: GSK221149A Solution for IV Infusion 0.8mg/mL

Strength / Dose Form: 0.8mg/mL / Solution for IV Infusion

Batch Number: 061124266

Date of Manufacture: 17-August-2006

Site of Manufacture: GSK, Upper Merion, King Of Prussia, PA, USA

Test	Acceptance Criteria	Results
Description	A clear, colourless, solution, free of visible particulate matter.	Conforms
Identification of GSK221149A by HPLC	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the GSK221149A reference material chromatogram.	Conforms
GSK221149A content by HPLC (% stated content)	90.0 – 110.0	98.6, 98.5
Drug-related impurities content by HPLC (% a/a)		
Any unqualified impurity	Not greater than 0.2	0.06
Total Impurities	Not greater than 4.0	0.06
Volume in a container (mL)	Complies with the requirements of the USP <1>	Conforms, 20.8

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COA No.: 061124266-01

Test	Acceptance Criteria	Results
Particulate matter in injections (counts per mL) ≥ 10µm ≥ 25µm	 ≤ 25 ≤ 3	Conforms
pH	4.3 – 4.7	4.5
Bacterial endotoxins (Eu/mL)	Not greater than 2.8	Less than 1.4
Sterility	Complies with the requirements of the USP <71>	Conforms
This material conforms to Specification S0005401-01.		

This material was manufactured and tested in accordance with current Good Manufacturing Prac[redacted]

Approved by: [redacted] **Date:** 26 Oct 2006

Quality Assurance
GSK, Upper Merion, King of Prussia, PA, USA

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GlaxoSmithKline

COA No.: 061126238-02

Pharmaceutical Development
Drug Product Certificate of Analysis

GlaxoSmithKline Research & Development Limited
New Frontiers Science Park
Third Avenue
Harlow
Essex
CM19 5AW
tel. [redacted]
Fax
www.gsk.com

Product: Radiolabelled GSK221149 [14C] Sterile Solution. 0.8mg/mL (1.6µCi/mL)

Strength / Dose Form: 0.8mg/mL (1.6µCi/mL) / Solution

Batch Number: 061126238

Date of Manufacture: 06-October-2006

Site of Manufacture: GSK, Harlow, UK

Test	Acceptance Criteria	Results	
Description	A clear, colourless, solution, free of visible particulate matter.	Conforms	
Identification of GSK221149 by HPLC	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the GSK221149A reference material chromatogram.	Conforms	
GSK221149 content by HPLC (% stated content)	90.0 – 110.0	97.2, 97.1	
Drug-related impurities content by HPLC (% a/a)		Release	Retest[1]
Any unqualified impurity	Not greater than 0.5	Less than 0.05	0.23
Total Impurities	Not greater than 4.0	Less than 0.05	0.64
Volume in a container (mL)	Complies with the requirements of the USP <1>	Conforms, 20.9	
Particulate matter in injections (counts per container)		Conforms	
≥ 10µm	≤ 600		
≥ 25µm	≤ 6000		

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COA No.: 061126238-02

Test	Acceptance Criteria	Results
pH	4.3 – 4.7	4.5
Bacterial endotoxins (Eu/mL)	Not greater than 28	Less than 5.0
Sterility	Complies with the requirements of the USP <71>	Conforms
Radiochemical purity (% area) [2]	For information only	Greater than 99.8
This material conforms to Specification S0005446-01.		

1. Retested on 7th November 2006 and CoA re-issued as 061126238-02, prior to 1st dosing period of Study OTA105101 (Covance Labs 643 8-480) due on 13th November 2006

2. This test does not form part of the specification.

This material was manufactured and tested in accordance with current Good Manufacturing Practices.

Approved by: [redacted] **Date:** [redacted]

Qualified person
R&D Quality Assurance
GSK, Harlow, UK

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COA No.: 061126238-03

GlaxoSmithKline

Pharmaceutical Development
Drug Product Certificate of Analysis

GlaxoSmithKline Research & Development Limited
New Frontiers Science Park
Third Avenue
Harlow
Essex
CM19 5AW
Tel. [redacted]
Fax
www.gsk.com

Product: Radiolabelled GSK221149 [14C] Sterile Solution. 0.8mg/mL (1.6µCi/mL)

Strength / Dose Form: 0.8mg/mL (1.6µCi/mL) / Solution

Batch Number: 061126238

Date of Manufacture: 06-October-2006

Site of Manufacture: GSK, Harlow, UK

Test	Acceptance Criteria	Results		
Description	A clear, colourless, solution, free of visible particulate matter.	Conforms		
Identification of GSK221149 by HPLC	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the GSK221149A reference material chromatogram.	Conforms		
GSK221149 content by HPLC (% stated content)	90.0 – 110.0	97.2, 97.1		
Drug-related impurities content by HPLC (% a/a)		Release	Retest[1]	Retest[2]
Any unqualified impurity	Not greater than 0.5	Less than 0.05	0.23	0.12
Total Impurities	Not greater than 4.0	Less than 0.05	0.64	0.38
Volume in a container (mL)	Complies with the requirements of the USP <1>	Conforms, 20.9		

gsk.0066a

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COA No.: 061126238-03

Test	Acceptance Criteria	Results
Particulate matter in injections (counts per container) ≥ 10µm ≥ 25µm	 ≤ 6000 ≤ 600	Conforms
pH	4.3 – 4.7	4.5
Bacterial endotoxins (Eu/mL)	Not greater than 28	Less than 5.0
Sterility	Complies with the requirements of the USP <71>	Conforms
Radiochemical purity (% area) [3]	For information only	Greater than 99.8
This material conforms to Specification S0005446-02.		

1. Retested on 7th November 2006 and CoA re-issued as 061126238-02, prior to 1st dosing period of Study OTA105101 (Covance Labs 643 8-480) due on 13th November 2006. (largest unqualified impurity reported)
2. Retested on 5th December 2006 and CoA re-issued as 061126238-03, prior to 2nd dosing period of Study OTA105101 (Covance Labs 643 8-480) due on 11th December 2006. (largest unqualified impurity reported)
3. This test does not form part of the specification.

This material was manufactured and tested in accordance with current Good Manufacturing Practices and is for Oral administration only.

Approved by: [redacted] **Date:** 11-DEC-2006

Qualified Person, Harlow, UK

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This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

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This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

Investigator Signature Page

STUDY TITLE: An open-label, two period, study to determine the excretion balance and pharmacokinetics of [^{14}C]-GSK221149A, administered as single doses of an oral solution and an intravenous infusion to healthy female adults

I have read this report and confirm that to the best of my knowledge Study OTA105101 was carried out as described in the GlaxoSmithKline Report EM2007/00008/00

Name of Investigator: [redacted] MD

Affiliation: [redacted]

Signature of Investigator: [redacted]

Date: 27 Feb 2008

Signatory Signature Page

STUDY TITLE: An open-label, two period, study to determine the excretion balance and pharmacokinetics of [^{14}C]-GSK221149A, administered as single doses of an oral solution and an intravenous infusion to healthy female adults

Study: OTA105101 Development Phase: I

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted] MD

Title of Sponsor Signatory: VP, Clinical Pharmacology and Discovery Medicine

Signature: [redacted]

Date: February 20, 2008