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: World Wide Development
Retention Category: GRS019
Information Type: Condensed Clinical Study Report

Title:	An open label study to determine the safety, tolerability, excretion balance and pharmacokinetics of [^{14}C]GW856553, administered as a single dose of an oral solution to healthy adult male subjects.

Phase: I

Compound Number: GW856553

Effective Date: 15-JAN-2009

Description: This was an open label study in six healthy male subjects. Each subject received a single 10 mg oral solution of GW856553 containing 50 μCi of [^{14}C] GW856553. Urine and faecal samples were collected until 216 h after dosing; blood and plasma were collected at various sample times after dosing to measure parent drug and total drug-related material. Safety was assessed by adverse event monitoring, vital signs, electrocardiography and clinical laboratory tests.

Following the administration of a single oral dose in solution, GW856553 was characterised by rapid absorption with the plasma concentration-time profile peaking at approximately 1.5 h and subsequently declining in a bi-exponential manner. Apparent t½ ranged from approximately 7 to 10 h.

The predominant route of elimination of GW856553 was via urine (approximately 65% of the dose), with approximately 29% of the dose eliminated via faeces. The total percentage of radioactivity recovered was 94.5%. In urine, 34% of the radioactivity was excreted from 0–6 h, 59% had been excreted by 24 h, and 64% had been excreted by 72 h. Increasing amounts of radioactivity were recovered in faeces up to a peak at 72 h. By 120 h post-dose, the amount recovered was 28%, out of the total recovered of 29%.

Single doses of GW856553 10 mg were well tolerated by healthy subjects. There were no clinically significant adverse events or laboratory, electrocardiography or vital sign results.

Subject: GW856553, ADME, radiolabel

Authors: [redacted]

Initiation Date:	17-JAN-2008
Completion Date:	18-FEB-2008
Date of Report:	15-JAN-2009

Sponsor Signatory: [redacted] PhD
(and Medical Officer) Director, Discovery Medicine, Respiratory CEDD
GlaxoSmithKline

This study was performed in compliance with Good Clinical Practices including the archiving of essential documents.

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Abbreviations

AE	Adverse event
AUC(0–∞)	Area under the concentration time curve from zero to infinity
AUC(0–t)	Area under the concentration time curve between zero and the time to the last measurable concentration
AUCR	Ratio of AUC(0–∞) of GW865663 over AUC(0–∞) of [^{14}C]-radioactivity
CL/F	Apparent oral clearance
Cmax	Maximum observed concentration
ECG	Electrocardiography
%AUCex	Percentage of AUC(0–∞) that is due to extrapolation from tlast to infinity
RAP	Reporting and Analysis Plan
t½	Terminal phase half-life
tlast	Time of last measurable concentration
tmax	First time of occurrence of maximum observed concentration

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
Captisol
WinNonlin

TITLE

An open label study to determine the safety, tolerability, excretion balance and pharmacokinetics of [^{14}C]GW856553, administered as a single dose of an oral solution to healthy adult male subjects.

INVESTIGATOR

Dr. [redacted]

STUDY CENTRE

[redacted]

PUBLICATIONS

None at the time of this report.

STUDY PERIOD

Initiation Date:	17 January 2008
Completion Date:	18 February 2008

PHASE OF DEVELOPMENT

I

OBJECTIVES

Primary

- To determine the rate and extent of excretion of total radioactivity in urine and faeces and total recovery of radioactivity, after a single oral dose of [^{14}C]GW856553 to healthy male subjects.
- To generate samples with which to characterise and quantify the metabolic profile of GW856553 in plasma, urine and faeces following administration of a single oral dose of [^{14}C]GW856553 to healthy male subjects.

Secondary

- To determine pharmacokinetic parameters of GW856553 and its major metabolite GSK198602 following a single oral administration of [^{14}C]GW856553.
- To further assess the tolerability of a single oral dose of GW856553 in healthy male subjects.

METHODOLOGY

This was an open-label study conducted in six male subjects: subjects were admitted to the Unit for 10 nights/11 days. Each subject received a single 10 mg (50 μCi) oral dose of [^{14}C]GW856553.

Urine and faecal samples were collected until 216 h after dosing but subjects may have been discharged after 168 h if 90% of the dose was recovered and/or <1% of the dose was recovered in a 24 h period. If recovery of radioactivity was incomplete at the end of the collection period, subjects may have been asked to collect samples of either urine and/or faeces for an extended period either within the clinical unit or at home.

Plasma and blood concentrations of total drug-related material (radioactivity) and plasma concentrations of unchanged GW856553 and its major metabolite GSK198602 were measured and used to determine pharmacokinetic parameters.

Safety was assessed by monitoring subjects for adverse events (AEs), vital signs, electrocardiography (ECG) and laboratory parameters.

See the Time and Events Table (Attachment 1) for more details.

NUMBER OF SUBJECTS

Number of Subjects	
Number of subjects planned, N:	6
Number of subjects randomised, N:	6
Number of subjects included in All subjects population, n(%):	6 (100)
Number of subjects included in Pharmacokinetic population, n(%):	6 (100)
Number of subjects completed as planned, n(%):	6 (100)
Number of subjects withdrawn (any reason), n(%):	0
Number of subjects withdrawn for SAE, n(%):	0
Number of subjects withdrawn for AE, n(%):	0
Demographics	
Age in Years, Mean (Range)	42.3 (35–52)
Sex, n(%)	
Female:	0
Male:	6 (100)
Body Mass Index (kg/m^2), Mean (Range)	25.03 (23.4–27.1)
Height (cm), Mean (Range)	170.0 (159–180)
Weight (kg), Mean (Range)	72.15 (68.2–77.5)
Ethnicity, n(%)	
Hispanic or Latino:	0
Not Hispanic or Latino:	6 (100)
Race, n(%)	
African American/African Heritage	1 (17)
American Indian or Alaskan Native	0
Asian – East Asian Heritage	0
Asian – Japanese Heritage	0
Asian – South East Asian Heritage	1 (17)
Native Hawaiian or Other Pacific Islander	0
White – Arabic/North African Heritage	0
White – White/Caucasian/European Heritage	4 (67)

Source Data: Table 9.1 and Table 9.2

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Healthy male volunteers aged 30 to 60 years, with a body weight ≥50 kg (110 lbs) and a body mass index within the range of 18.5 to 29.9 kg/m^2 inclusive.

TREATMENT ADMINISTRATION

A dose of 10 mg GW856553 containing 50 μCi of [^{14}C]GW856553 was delivered as 100 mL of a 0.1 mg/mL GW856553/0.5 μCi/mL oral solution. Bulk GW856553J (radiolabelled free base) powder was supplied by GlaxoSmithKline. This powder was made into a bulk oral solution (0.1 mg/mL/0.5 μCi/mL GW856553J) with an aqueous solution of sulfobutylether β-cyclodextrin (Captisol, Cydex, USA) on the day prior to dosing. Individual doses of 100 mL were then aliquoted for dosing. Water (100 mL) was added to the container and the contents rinsed and drunk by the subject.

CRITERIA FOR EVALUATION

- The primary endpoint of this study was to report the urinary and faecal cumulative excretion as a percentage of the total radioactive dose administered over time.

The secondary pharmacokinetic endpoints were:

- Area under the concentration time curve from zero to infinity (AUC(0–∞)), maximum observed concentration (Cmax), area under the concentration time curve between zero and the time to the last measurable concentration (AUC(0–t)), first time of occurrence of maximum observed concentration (tmax) and terminal phase half-life (t½) of total drug-related material (radioactivity) in plasma following oral dosing; and percentage of AUC(0–∞) that is due to extrapolation from tlast to infinity (%AUCex).
- AUC(0–∞), Cmax, AUC(0–t), %AUCex, ratio of AUC(0–∞) of GW865663 over AUC(0–∞) of [^{14}C]-radioactivity (AUCR), apparent oral clearance (CL/F), tmax and t½ of GW856553 and AUC(0–∞), Cmax, AUC(0–t), %AUCex, AUCR, tmax and t½ for its major metabolite GSK198602 in plasma following oral dosing.
- Adverse events, ECG, vital signs and clinical laboratory tests (including liver function tests).

Characterisation and quantification of metabolites in plasma, urine and faecal homogenates were performed under a separate protocol by Drug Metabolism and Pharmacokinetics, GlaxoSmithKline. Results will be reported in a separate report.

STATISTICAL METHODS

Full details of the analyses for this study are presented in the Reporting and Analysis Plan (RAP; Attachment 2).

Sample Size

The sample size was based on feasibility. Six healthy male volunteers were recruited in order to obtain four evaluable subjects. All data collected were analysed; however, data from four subjects would have been sufficient.

Analysis Populations

The All Subjects Population was defined as all subjects who received at least one dose of study medication. The Pharmacokinetic Population was defined as subjects in the All Subjects Population from whom a pharmacokinetic sample was obtained and analysed.

Interim Analyses

No interim analyses were planned or performed.

Final Analyses

Safety data were listed and summarised only. There was no formal statistical analysis of the safety data.

The derivation of pharmacokinetic parameters of GW856553, its major metabolite GSK198602 and [^{14}C]-radioactivity in plasma was conducted by SGS Aster (St Benoît, France), under the direction of Clinical Pharmacokinetics Modeling and Simulation, Clinical Pharmacology and Discovery Medicine, GlaxoSmithKline. Parameters were derived using non-compartmental methods with WinNonlin Version 4.1 or higher (Pharsight Corporation, Mountain View, CA, USA). The statistical analyses of pharmacokinetic data were the responsibility of Discovery Biometrics, GlaxoSmithKline.

The following plasma pharmacokinetic parameters were derived for GW856553, its major metabolite GSK198602 and [^{14}C]-radioactivity:

- Cmax.
- tmax.
- t½.
- AUC(0–t).
- AUC(0–∞).
- Time of last measurable concentration (tlast).
- Percentage of AUC(0–∞) that is due to extrapolation from tlast to infinity: (AUC(0–∞)- AUC(0–t))/AUC(0–∞))*100% (%AUCex).
- Apparent oral clearance (CL/F; derived for GW856553 only).
- AUCR.

The following pharmacokinetic parameters for [^{14}C]-radioactivity were calculated:

- Percentage of radioactivity excreted in urine.
- Percentage of radioactivity recovered in faeces.
- Cumulative percentage of radioactivity excreted in urine up to time t.
- Cumulative percentage of radioactivity recovered in faeces up to time t.
- Total percentage of radioactivity recovered.

Changes in the Conduct of the Study or Planned Analyses

There were no changes in the conduct of the study but there were two minor changes to the planned analyses.

1. Planned analyses to compute AUCR were adjusted from the methods described in the RAP to be consistent with WinNonlin.
2. Arithmetic means were plotted in Figure 11.2 instead of geometric means. The reason for this change was that non-quantifiable values were handled differently toward the end of the profile (an individual's non-quantifiable values were set to zero, therefore the geometric mean of all six subjects could not be computed).

SUMMARY

Safety

Adverse events

A summary of numbers of subjects (%) reporting AEs during the study is presented in Table 1. Four subjects reported eight AEs, which were all judged to be of mild intensity by the Investigator and all resolved during the study.

Table 1 Summary of All Adverse Events

	N=6
Any Event	4 (67)
Diarrhoea	2 (33)
Headache	2 (33)
Constipation	1 (17)
Haematochezia	1 (17)
Arthropod bite	1 (17)
Contusion	1 (17)

Source Data: Table 10.2

All AE episodes of diarrhoea and headache were judged to be drug-related by the Investigator (Table 10.3). The two episodes of diarrhoea lasted 3 days, 4 h and 50 minutes, and 2 days, 21 h and 46 minutes, respectively.

There is limited human experience with Captisol. Given the preclinical data with Captisol the gastrointestinal-related AEs (diarrhoea) seen in this study could be related to this rather than GW856553.

No serious AEs or AEs leading to withdrawal occurred during the study.

Laboratory Safety Tests

No subject had clinical chemistry or haematology results of potential clinical importance. No liver function test results were on or outside normal ranges (Table 10.5).

12-Lead Electrocardiography

No clinically significant ECG abnormalities were noted during the study (Table 10.4). Two subjects had ECG values of potential clinical importance during the study (Table 10.6):

- [redacted]
- [redacted]

Vital Signs

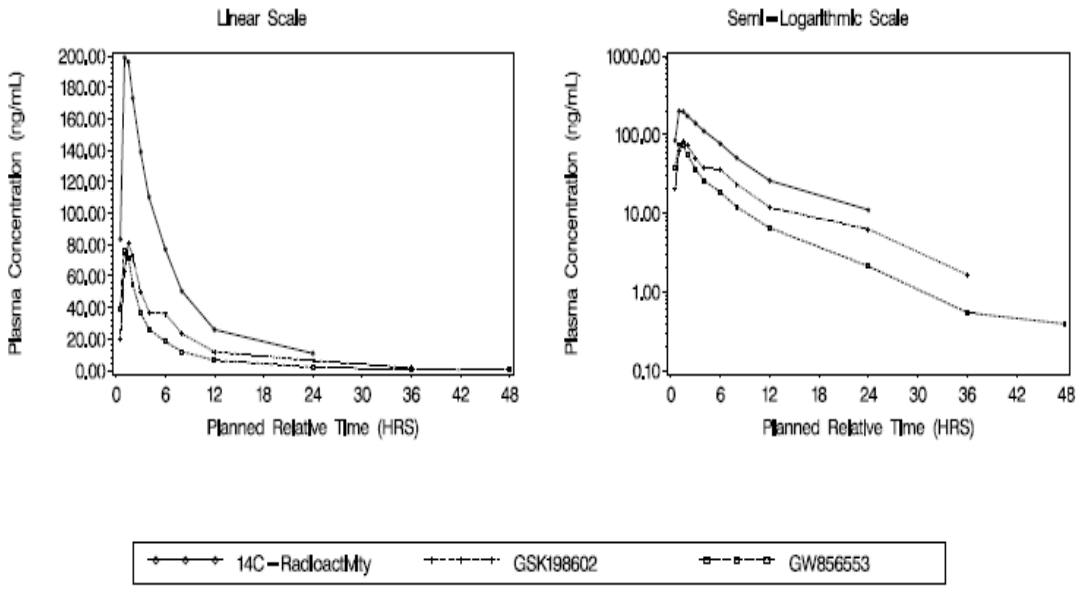
No subject had vital signs of potential clinical importance.

Pharmacokinetics

Summaries of GW856553 and GSK198602 plasma concentration-time data are presented in Table 11.1 and Table 11.2, respectively. A summary of plasma [^{14}C]-radioactivity levels over time is presented in Table 11.3.

A plot of median plasma GW856553 and GSK198602 concentrations and [^{14}C]-radioactivity levels over time, is presented in Figure 1. No plasma concentrations were excluded from the pharmacokinetic analysis.

Figure 1 Median Plasma GW856553 and GSK198602 Concentrations and [^{14}C]-Radioactivity Levels over Time



Source Figure: Figure 11.1

In plasma, GW856553 and GSK198602 were measurable in all subjects for 36 h post-dose. The concentration of drug-related material (radioactivity) was only measurable for up to 24 h post-dose. Following the administration of a single oral solution, GW856553 was absorbed rapidly with the plasma concentration-time profile peaking at approximately 1.5 h. Plasma GW856553 concentration level subsequently declined in a bi-exponential manner with apparent t½ ranging from approximately 7 to 10 h (see Table 2). Metabolite GSK198602 was formed rapidly.

A summary of derived plasma GW856553 pharmacokinetic parameters is presented in Table 2.

Table 2 Summary of Derived Plasma GW856553 Pharmacokinetic Parameters

Parameter	n	Geometric Mean	95% Confidence Interval of Geometric Mean	CVb(%)
AUC(0–∞) (ng.h/mL)	6	366.49	294.18, 456.57	21.2
Cmax (ng/mL)	6	81.18	62.61, 105.27	25.1
t½ (h)	6	8.25	7.08, 9.60	14.6
tmax (h)[1]	6	1.50	1.00–1.57	N/A
CL/F (L/h)	6	27.29	21.90, 33.99	21.2
AUCR	6	0.27	0.23, 0.32	16.1

Source Data: Table 11.4

1. Median (range).

AUC(0–∞)=area under the concentration time curve from zero to infinity; Cmax=maximum observed concentration; t½=terminal phase half-life; tmax=first time of occurrence of maximum observed concentration; CL/F=apparent oral clearance; AUCR=ratio of AUC(0–∞) of GW865663 over AUC(0–∞) of [^{14}C]-radioactivity.

A summary of derived plasma GSK198602 pharmacokinetic parameters is presented in Table 3.

Table 3 Summary of Derived Plasma GSK198602 Pharmacokinetic Parameters

Parameter	n	Geometric Mean	95% Confidence Interval of Geometric Mean	CVb(%)
AUC(0–∞) (ng.h/mL)	6	588.38	488.64, 708.46	17.8
Cmax (ng/mL)	6	91.71	64.72, 129.95	34.1
t½ (h)	6	8.87	7.44, 10.58	16.9
tmax (h)[1]	6	1.50	1.50–2.00	N/A
AUCR	6	0.43	0.39, 0.48	9.4

Source Data: Table 11.5

1. Median (range).

AUC(0–∞)=area under the concentration time curve from zero to infinity; Cmax=maximum observed concentration; t½=terminal phase half-life; tmax=first time of occurrence of maximum observed concentration; AUCR= ratio of AUC(0–∞) of GSK198602 over AUC(0–∞) of [^{14}C]-radioactivity.

A summary of derived plasma [^{14}C]-radioactivity pharmacokinetic parameters is presented in Table 4.

Table 4 Summary of Derived Plasma [^{14}C]-Radioactivity Pharmacokinetic Parameters

Parameter	n	Geometric Mean	95% Confidence Interval of Geometric Mean	CVb(%)
AUC(0–∞) (µg.h/mL)	6	1.36	1.22, 1.52	10.3
Cmax (µg/mL)	6	0.21	0.19, 0.24	12.5
t½ (h)	6	7.35	6.37, 8.49	13.8
tmax (h)[1]	6	1.50	1.00–1.57	N/A

Source Data: Table 11.6

1. Median (range).

AUC(0–∞)=area under the concentration time curve from zero to infinity; Cmax=maximum observed concentration; t½=terminal phase half-life; tmax=first time of occurrence of maximum observed concentration.

A summary of the percentage of derived urinary and faecal [^{14}C]-radioactivity parameters by time is presented in Table 11.7. Cumulative derived urinary and faecal [^{14}C]-radioactivity parameters by time are presented in Table 5.

Table 5 Summary of Cumulative Derived Urinary/Faecal [^{14}C]-Radioactivity Parameters (% Recovered) by Time

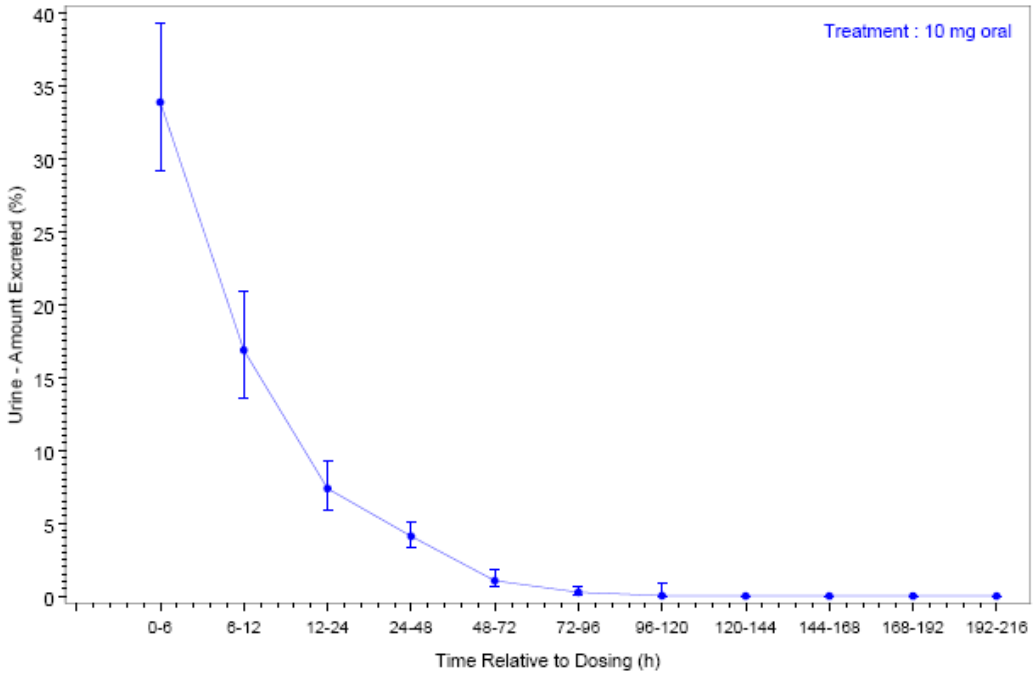
Parameter	Planned Relative Time (h)	N	n	Geometric Mean	95% Confidence Intervals of Geometric Mean	CVb(%)
Ae urine (0–t) (%)	0–6	6	6	33.89	(29.21, 39.33)	14.2
	6–12	6	6	51.27	(48.02, 54.74)	6.3
	12–24	6	6	58.76	(54.74, 63.09)	6.8
	24–48	6	6	62.94	(58.52, 67.68)	6.9
	48–72	6	6	64.13	(59.71, 68.87)	6.8
	72–96	6	6	64.48	(60.00, 69.29)	6.9
	96–120	6	6	64.59	(60.08, 69.44)	6.9
	120–144	6	6	64.64	(60.10, 69.53)	7.0
	144–168	6	6	64.66	(60.10, 69.57)	7.0
	168–192	6	6	64.67	(60.10, 69.59)	7.0
	192–216	6	6	64.68	(60.10, 69.61)	7.0
Ae faeces (0–t) (%)	0–24	6	3	1.29	(0.00, 2537.21)	10595.9
	24–48	6	6	5.59	(0.81, 38.58)	535.5
	48–72	6	6	20.01	(12.02, 33.33)	51.6
	72–96	6	6	24.56	(15.27, 39.48)	47.7
	96–120	6	6	28.09	(21.91, 36.02)	24.0
	120–144	6	6	28.45	(22.58, 35.83)	22.3
	144–168	6	6	29.05	(23.84, 35.40)	19.0
	168–192	6	6	29.14	(23.99, 35.40)	18.7
	192–216	6	6	29.35	(24.37, 35.36)	17.9

Source Data: Table 11.8

The predominant route of elimination of GW856553 in these healthy volunteers was via urine (approximately 65% of the dose), with less elimination through faeces (approximately 29% of the dose). The total percentage of radioactivity recovered was 94.45% (Table 11.9).

Plots of derived urinary and faecal [^{14}C[-radioactivity (% recovered) by time are presented in Figure 2 and Figure 3.

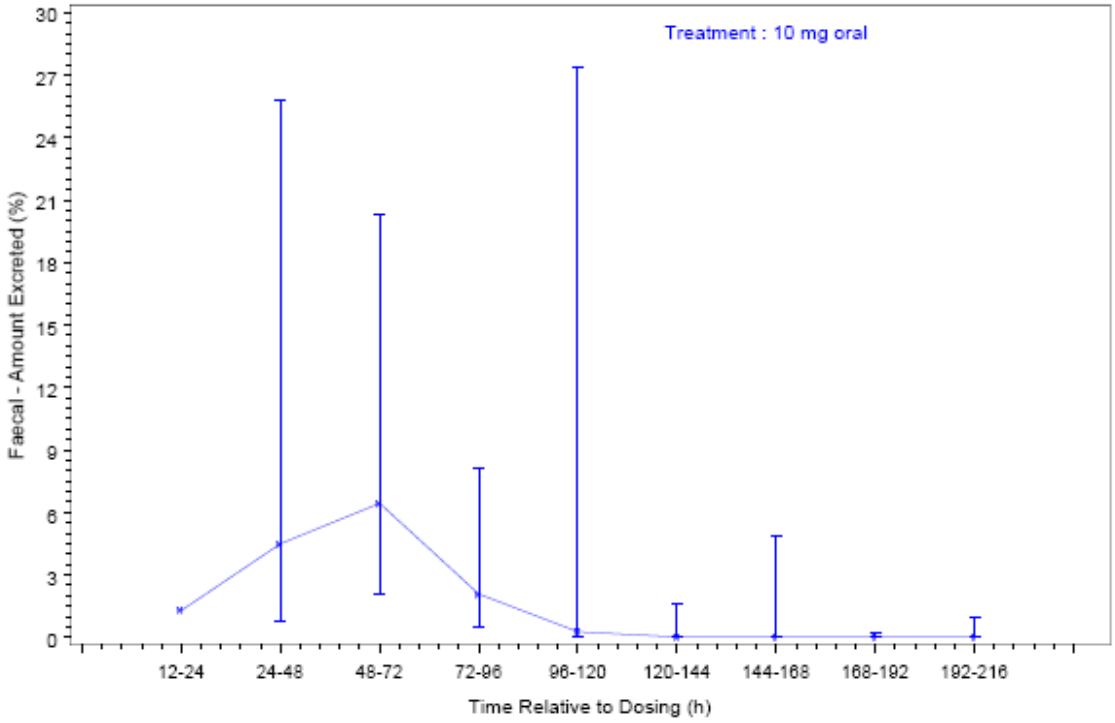
Figure 2 Plot of Derived Urinary [^{14}C]-Radioactivity (% Recovered) by Time



Source Figure: Figure 11.4

In urine, 34% of the radioactivity was excreted from 0–6 h, 59% had been excreted by 24 h, and a total of 64% had been excreted by 72 h.

Figure 3 Plot of Derived Faecal [^{14}C]-Radioactivity (% Recovered) by Time



Source Figure: Figure 11.5
As the 95% confidence intervals at 12–24 h post-dose were very wide due to the small sample size (n=3), these confidence intervals are not displayed.

Increasing amounts of radioactivity were recovered in faeces up to a peak at 72 h. By 120 h post-dose, the total amount recovered was 28%, out of the total recovered of 29%.

In plasma, the percentage of total radioactivity in the form of parent compound was approximately 27% and the percentage of total radioactivity in the form of GSK198602 was approximately 43%, suggesting the presence of other metabolites (30%). [^{14}C]-Radioactivity plasma concentration ratios for GW856553 and GSK198602 from the derived cold assay are summarised in Table 6.

Table 6 Summary of Derived Cold Assay: [^{14}C]-Radioactivity Plasma Concentration Ratios for GW856553 and GSK198602

Parameter	N	n	Geometric Mean	95% Confidence Interval of Geometric Mean	CVb%
AUC(0–∞) ratio GSK198602:[^{14}C]radioactivity	6	6	0.432	0.392, 0.477	9.4
AUC(0–∞) ratio GW856553:[^{14}C]radioactivity	6	6	0.269	0.228, 0.318	16.0

Source Data: Table 11.10
AUC(0–∞)=area under the concentration time curve from zero to infinity.

CONCLUSIONS

- Following the administration of a single oral dose in solution, GW856553 was rapidly absorbed with the plasma concentration-time profile peaking at approximately 1.5 h and subsequently declined in a bi-exponential manner. Apparent t½ ranged from approximately 7 to 10 h. Parent drug GW856553 was rapidly converted into the metabolite GSK198602.
- The predominant route of elimination of GW856553 was via urine (approximately 65% of the dose), with approximately 29% of the dose eliminated via faeces. The total percentage of radioactivity recovered was 94.45%.
- In urine, 34% of the radioactivity was excreted from 0–6 h, 59% had been excreted by 24 h, and a total of 64% had been excreted by 72 h.
- Increasing amounts of radioactivity were recovered in faeces up to a peak at 72 h. By 120 h post-dose, the amount recovered was 28%, out of the total recovered of 29%.
- Single doses of GW856553 10 mg were well tolerated by healthy subjects. There were no clinically significant adverse events or laboratory, electrocardiography or vital sign results.

DATE OF REPORT

January 2009.

Study Population Data Source Tables

Table 9.1
Summary of Subject Disposition

	10 mg oral (N=6)
Completion Status	
Completed	6 (100%)
Withdrawn	0

Table 9.2
Summary of Demographic Characteristics

		10 mg oral (N=6)
Age (yrs)	n	6
	Mean	42.3
	SD	5.68
	Median	41.5
	Min.	35
	Max.	52
Sex	n	6
	Female	0
	Male	6 (100%)
Ethnicity	n	6
	Hispanic/Latino	0
	Not Hispanic/Latino	6 (100%)
Height (cm)	n	6
	Mean	170.0
	SD	6.84
	Median	170.5
	Min.	159
	Max.	180
Weight (kg)	n	6
	Mean	72.15
	SD	3.768
	Median	71.50
	Min.	68.2
	Max.	77.5

Table 9.2
Summary of Demographic Characteristics

		10 mg oral (N=6)
Body mass index (kg/m^2)	n	6
	Mean	25.03
	SD	1.596
	Median	24.25
	Min.	23.4
	Max.	27.1

Safety Data Source Tables

Table 10.1
Summary of Exposure to Study Drug

		10 mg oral (N=6)
Dose	n	6
	Mean	10.0
	SD	0.00
	Median	10.0
	Min.	10
	Max.	10
Days on study drug	n	6
	Mean	1.0
	SD	0.00
	Median	1.0
	Min.	1
	Max.	1

Table 10.2
Summary of All Adverse Events

System Organ Class Preferred Term	10 mg oral (N=6)
ANY EVENT	4 (67%)
Gastrointestinal disorders	
Any event	2 (33%)
Diarrhoea	2 (33%)
Constipation	1 (17%)
Haematochezia	1 (17%)
Injury, poisoning and procedural complications	
Any event	2 (33%)
Arthropod bite	1 (17%)
Contusion	1 (17%)
Nervous system disorders	
Any event	2 (33%)
Headache	2 (33%)

Table 10.3
Summary of Drug Related Adverse Events

System Organ Class Preferred Term	10 mg oral (N=6)
ANY EVENT	4 (67%)
Gastrointestinal disorders	
Any event	2 (33%)
Diarrhoea	2 (33%)
Nervous system disorders	
Any event	2 (33%)
Headache	2 (33%)

Table 10.4
Summary of ECG Findings

	10 mg oral (N=6)
SCREENING 1	
n	6
Normal	5 (83%)
Abnormal - not clinically significant	1 (17%)
Abnormal - clinically significant	0
Not available	0
SCREENING 2	
n	6
Normal	4 (67%)
Abnormal - not clinically significant	2 (33%)
Abnormal - clinically significant	0
Not available	0
SCREENING 3	
n	6
Normal	4 (67%)
Abnormal - not clinically significant	2 (33%)
Abnormal - clinically significant	0
Not available	0
PRE-DOSE	
n	6
Normal	6 (100%)
Abnormal - not clinically significant	0
Abnormal - clinically significant	0
Not available	0

Table 10.4
Summary of ECG Findings

	10 mg oral (N=6)
0.5 H	
n	6
Normal	5 (83%)
Abnormal - not clinically significant	1 (17%)
Abnormal - clinically significant	0
Not available	0
1 H	
n	6
Normal	5 (83%)
Abnormal - not clinically significant	1 (17%)
Abnormal - clinically significant	0
Not available	0
2 H	
n	6
Normal	6 (100%)
Abnormal - not clinically significant	0
Abnormal - clinically significant	0
Not available	0
4 H	
n	6
Normal	5 (83%)
Abnormal - not clinically significant	1 (17%)
Abnormal - clinically significant	0
Not available	0

Table 10.4
Summary of ECG Findings

	10 mg oral (N=6)
6 H	
n	6
Normal	6 (100%)
Abnormal - not clinically significant	0
Abnormal - clinically significant	0
Not available	0
8 H	
n	6
Normal	6 (100%)
Abnormal - not clinically significant	0
Abnormal - clinically significant	0
Not available	0
24 H	
n	6
Normal	6 (100%)
Abnormal - not clinically significant	0
Abnormal - clinically significant	0
Not available	0
FOLLOW-UP	
n	6
Normal	6 (100%)
Abnormal - not clinically significant	0
Abnormal - clinically significant	0
Not available	0

Table 10.5
Summary of LFTs on or Outside Normal Ranges

No data to report

Population: All Subjects

Table 10.6
Listing of ECG Values of Potential Clinical Importance

Treatment: 10 mg oral

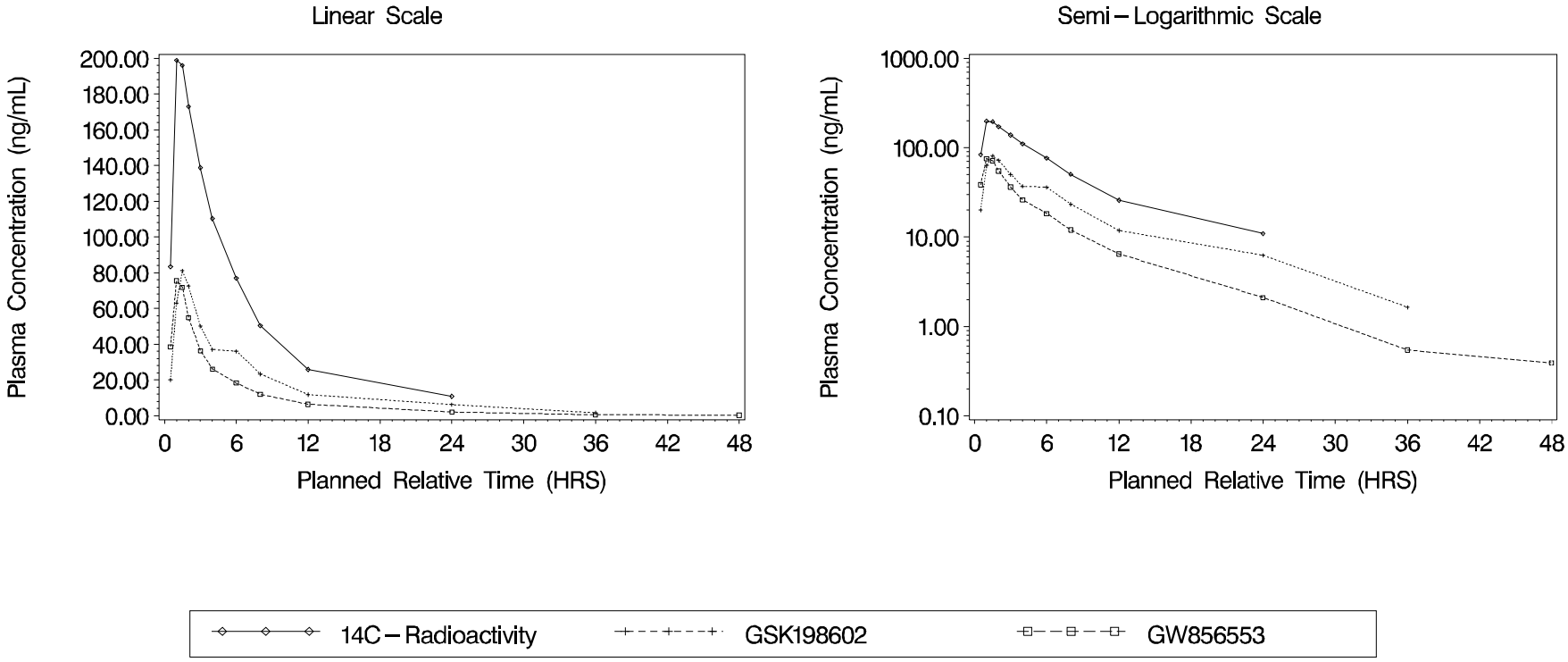
Inv./ Subj.	Age(y)/ Sex/ Race	Study Day	ECG Date/Time	Planned Relative Time	Actual Relative Time	Heart Rate (bpm)	PR Int. (msec)	QRS Dur. (msec)	RR Int. (msec)	QT Int. (msec)	QTcB (msec)	QTcF (msec)

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: H=High, L=Low.

Pharmacokinetic Data Source Figures and Tables

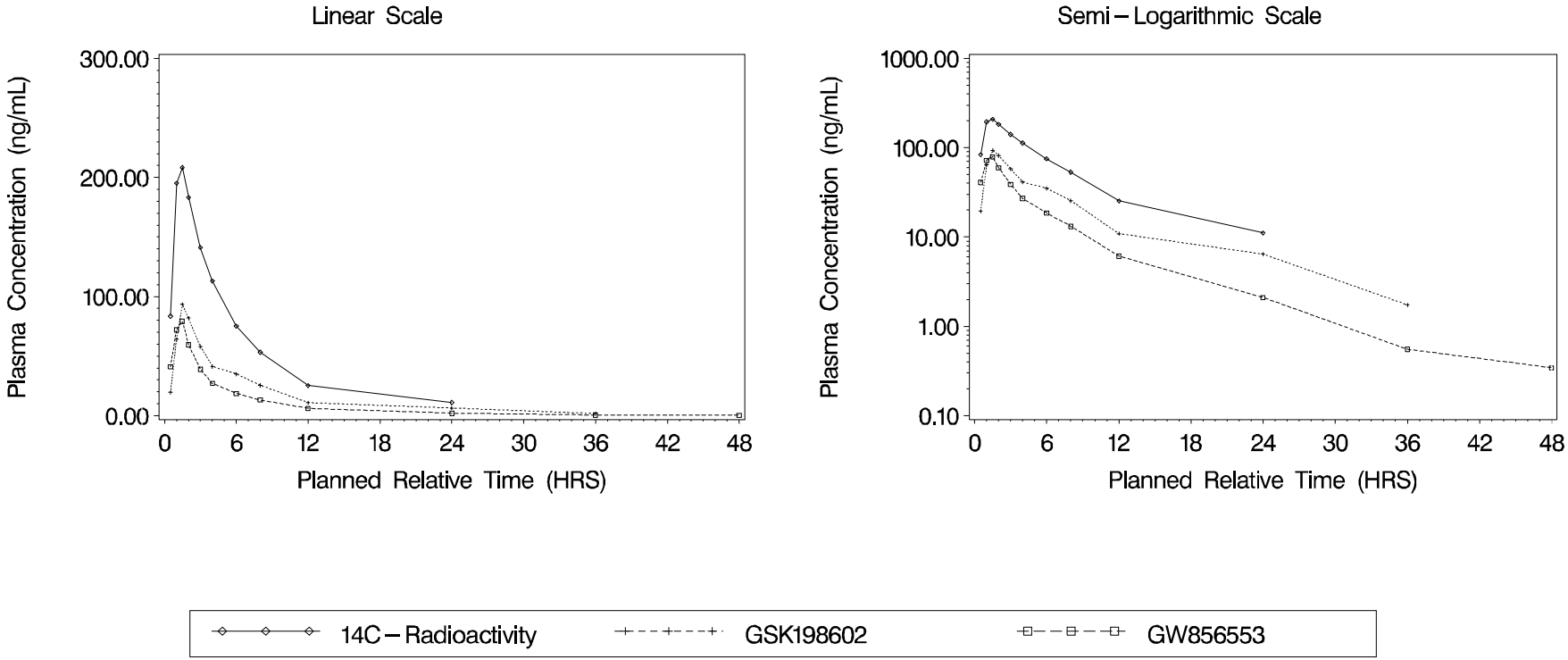
Figure 11.1
Plot of Median Plasma GW856553 Concentrations, GSK198602 Concentrations and 14C – Radioactivity Levels Over Time



Note : For display purposes 14C – Radioactivity Concentrations were converted from ug/mL to ng/mL

[redacted]

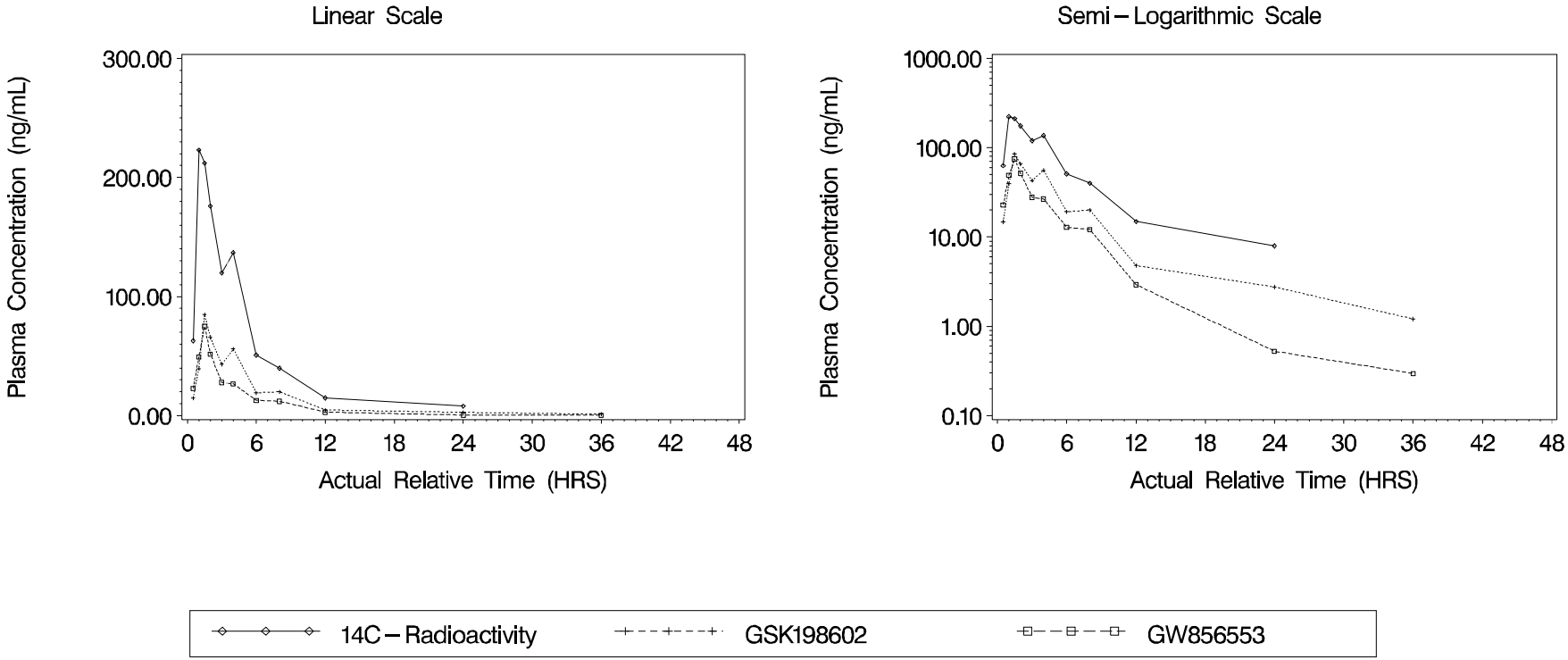
Figure 11.2
Plot of Mean Plasma GW856553 Concentrations, GSK198602 Concentrations and 14C−radioactivity Levels Over Time



Note : For display purposes 14C−Radioactivity Concentrations were converted from ug/mL to ng/mL

[redacted]

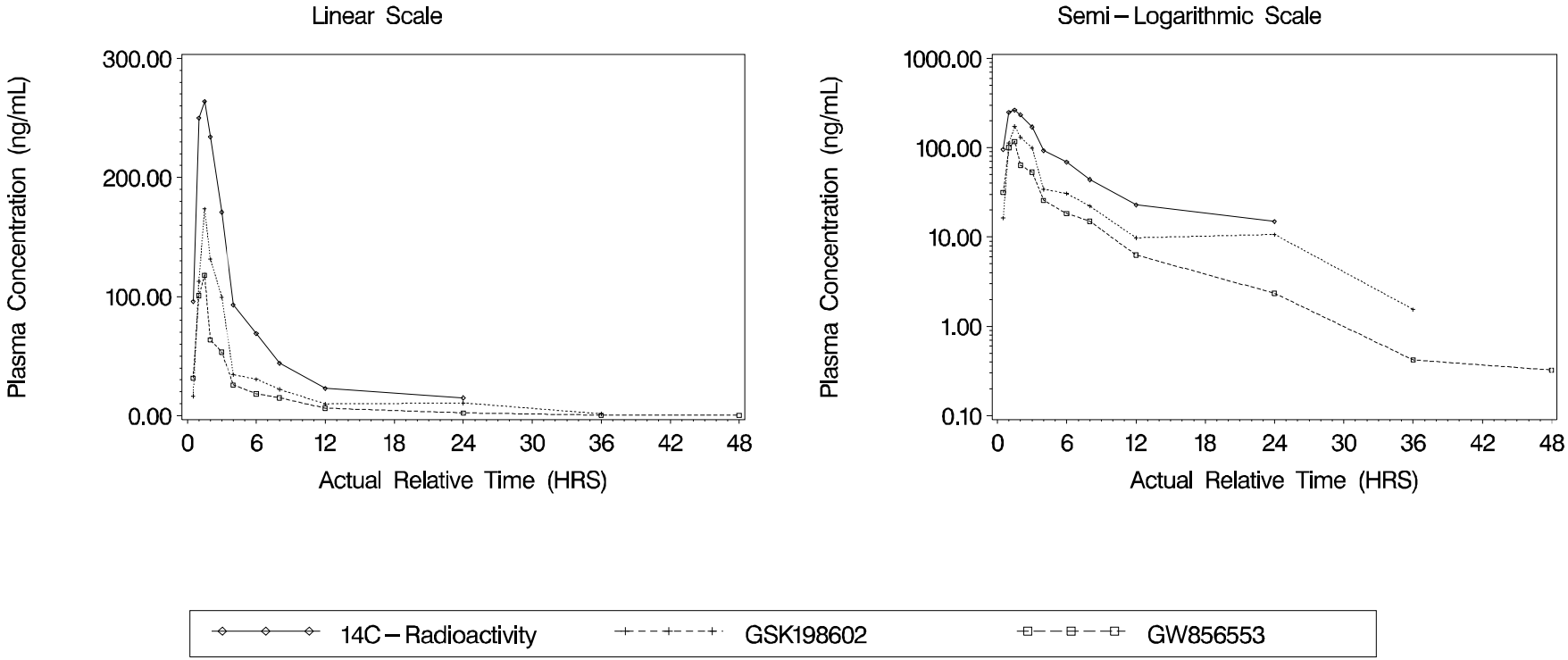
Figure 11.3
Plots of Individual Subject Plasma GW856553 Concentrations, GSK198602 Concentrations and 14C – Radioactivity Levels Over Time
Subject ID=[redacted]



Note : For display purposes 14C – Radioactivity Concentrations were converted from ug/mL to ng/mL

[redacted]

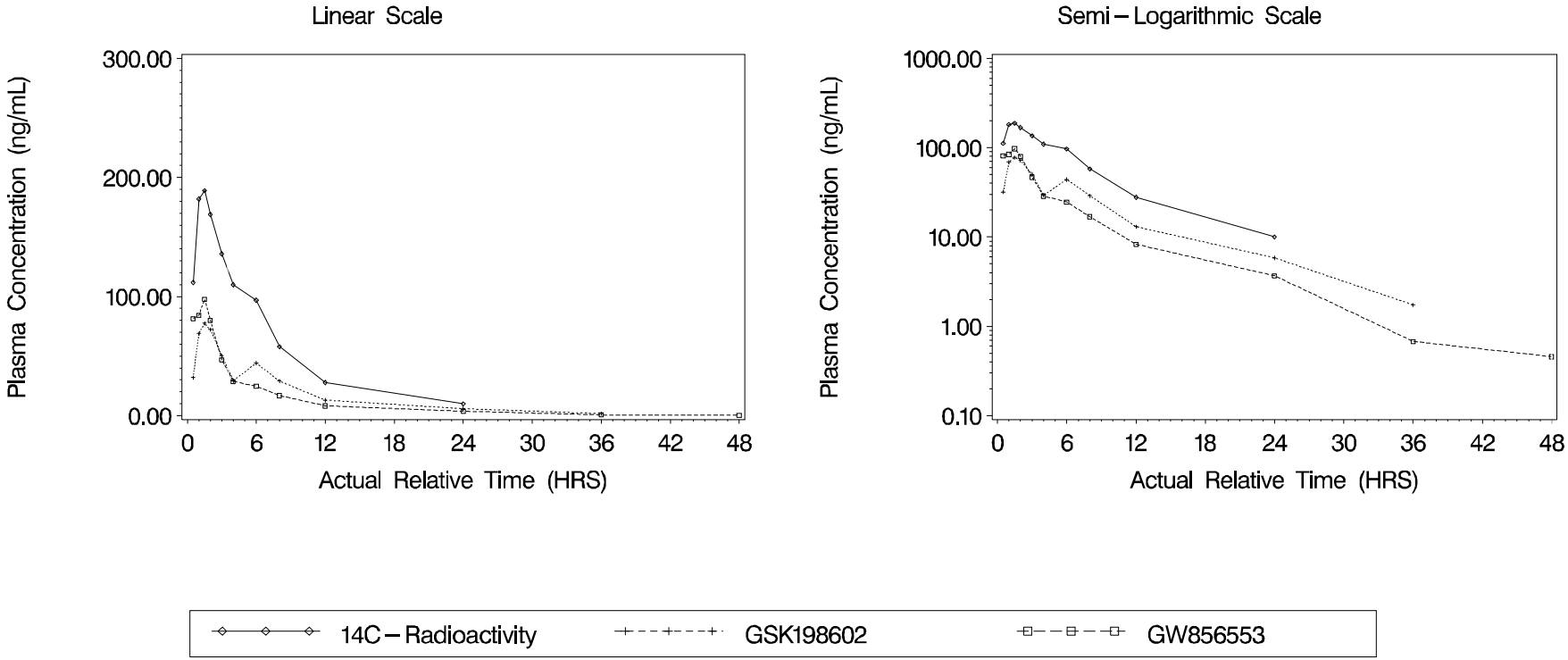
Figure 11.3
Plots of Individual Subject Plasma GW856553 Concentrations, GSK198602 Concentrations and 14C – Radioactivity Levels Over Time
Subject ID = [redacted]



Note : For display purposes 14C – Radioactivity Concentrations were converted from ug/mL to ng/mL

[redacted]

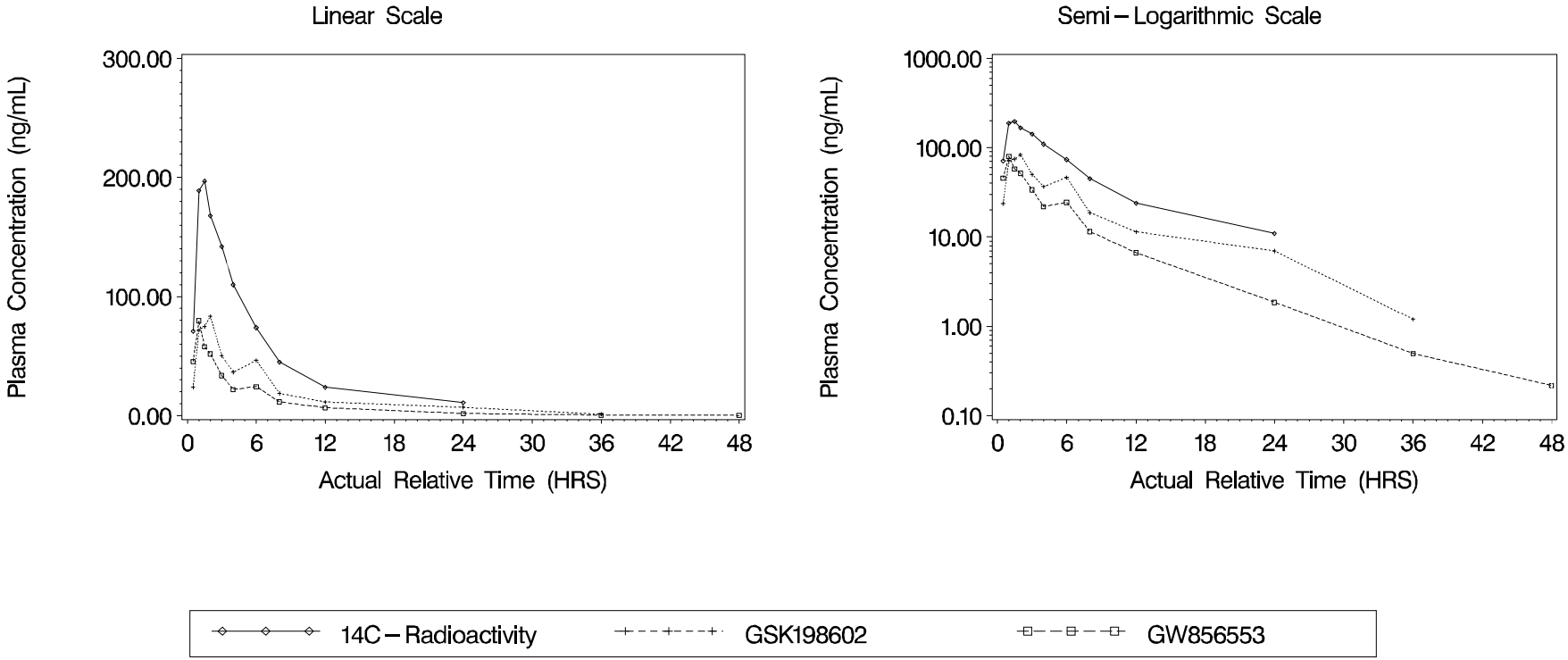
Figure 11.3
Plots of Individual Subject Plasma GW856553 Concentrations, GSK198602 Concentrations and 14C – Radioactivity Levels Over Time
Subject ID = [redacted]



Note : For display purposes 14C – Radioactivity Concentrations were converted from ug/mL to ng/mL

[redacted]

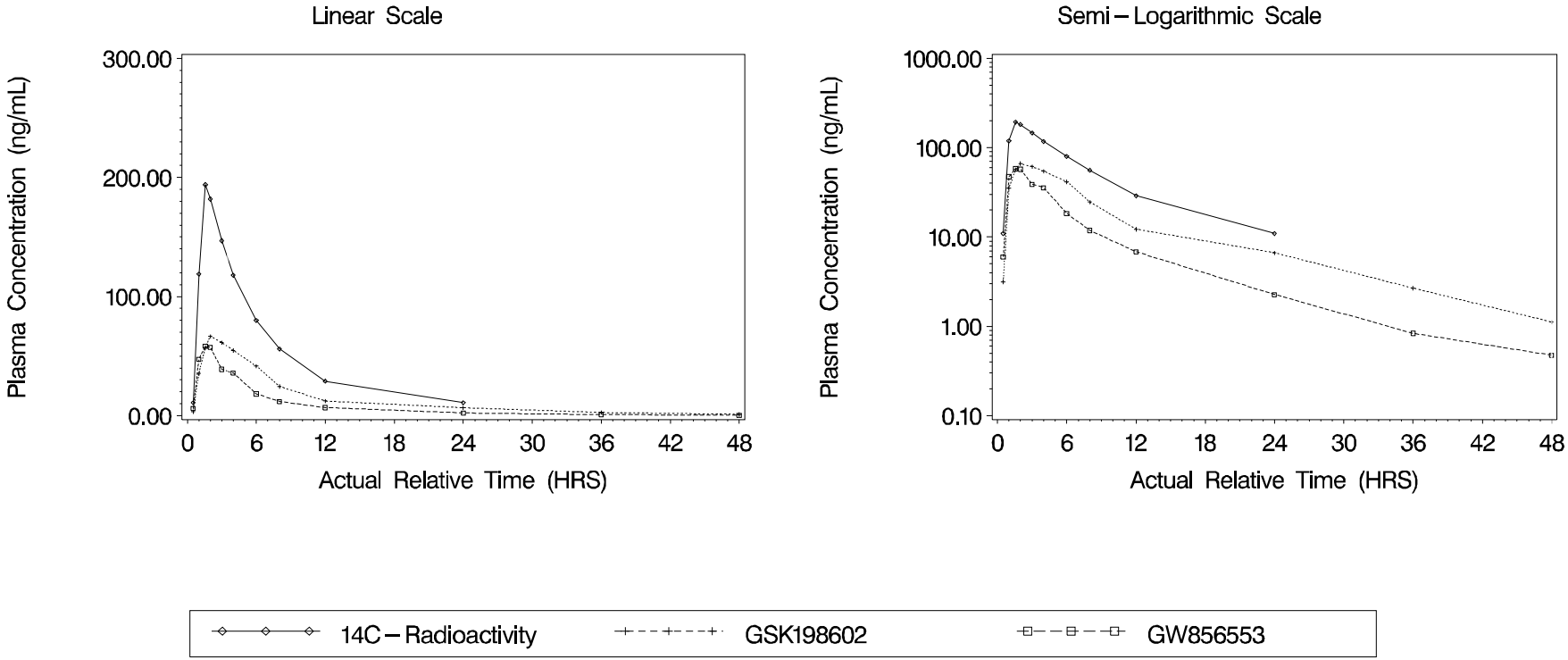
Figure 11.3
Plots of Individual Subject Plasma GW856553 Concentrations, GSK198602 Concentrations and 14C – Radioactivity Levels Over Time
Subject ID = [redacted]



Note : For display purposes 14C – Radioactivity Concentrations were converted from ug/mL to ng/mL

[redacted]

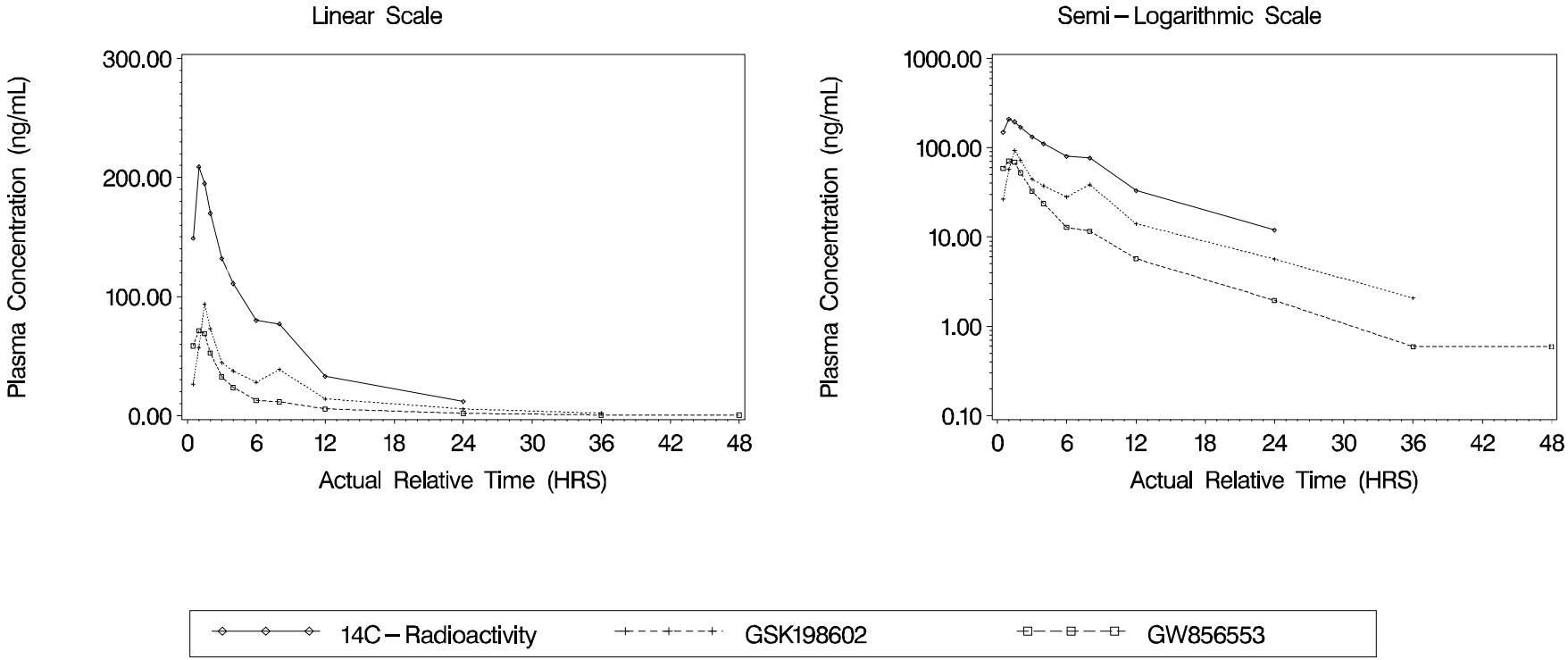
Figure 11.3
Plots of Individual Subject Plasma GW856553 Concentrations, GSK198602 Concentrations and 14C – Radioactivity Levels Over Time
Subject ID = [redacted]



Note : For display purposes 14C – Radioactivity Concentrations were converted from ug/mL to ng/mL

[redacted]

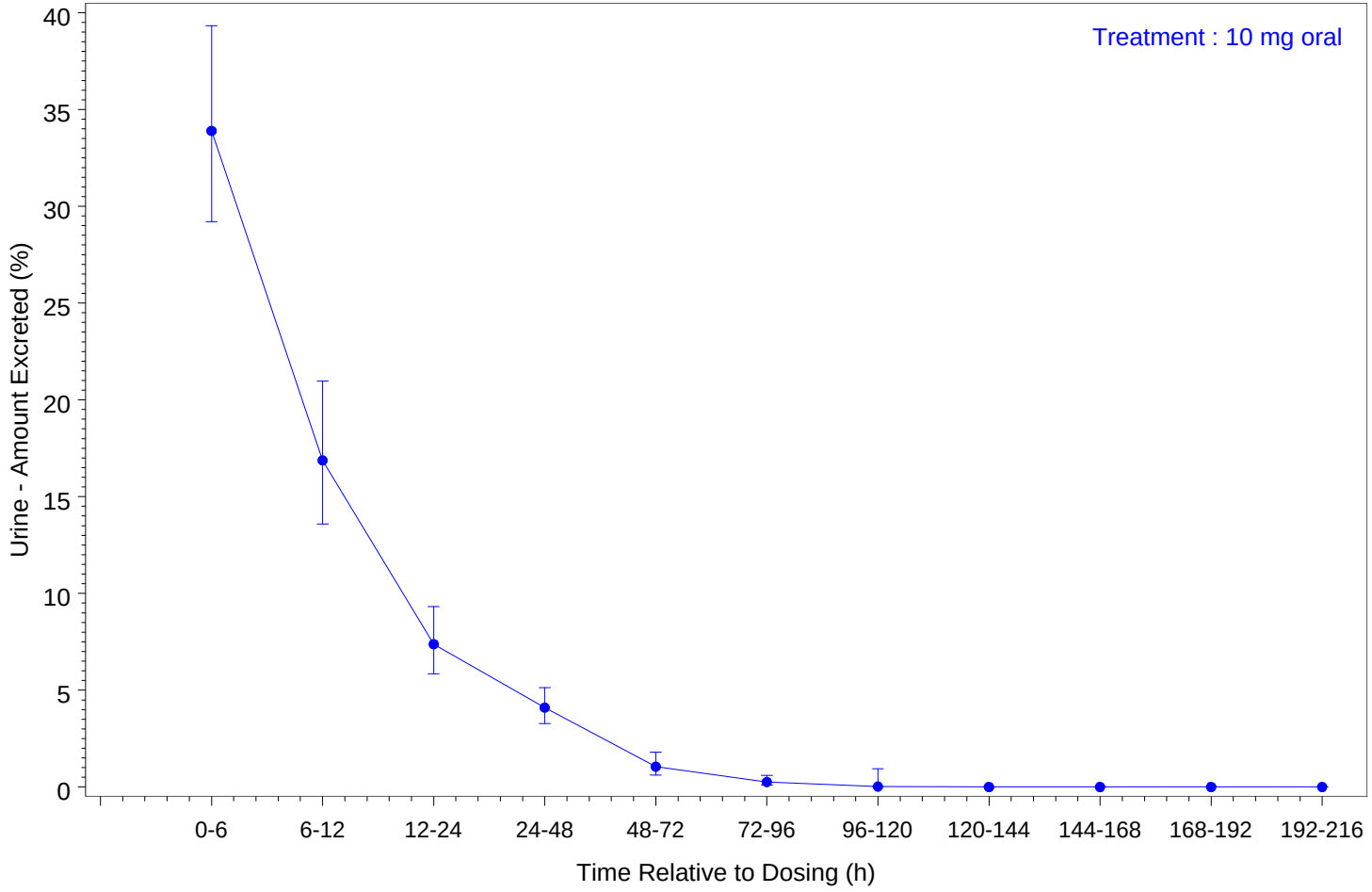
Figure 11.3
Plots of Individual Subject Plasma GW856553 Concentrations, GSK198602 Concentrations and 14C – Radioactivity Levels Over Time
Subject ID = [redacted]



Note : For display purposes 14C – Radioactivity Concentrations were converted from ug/mL to ng/mL

[redacted]

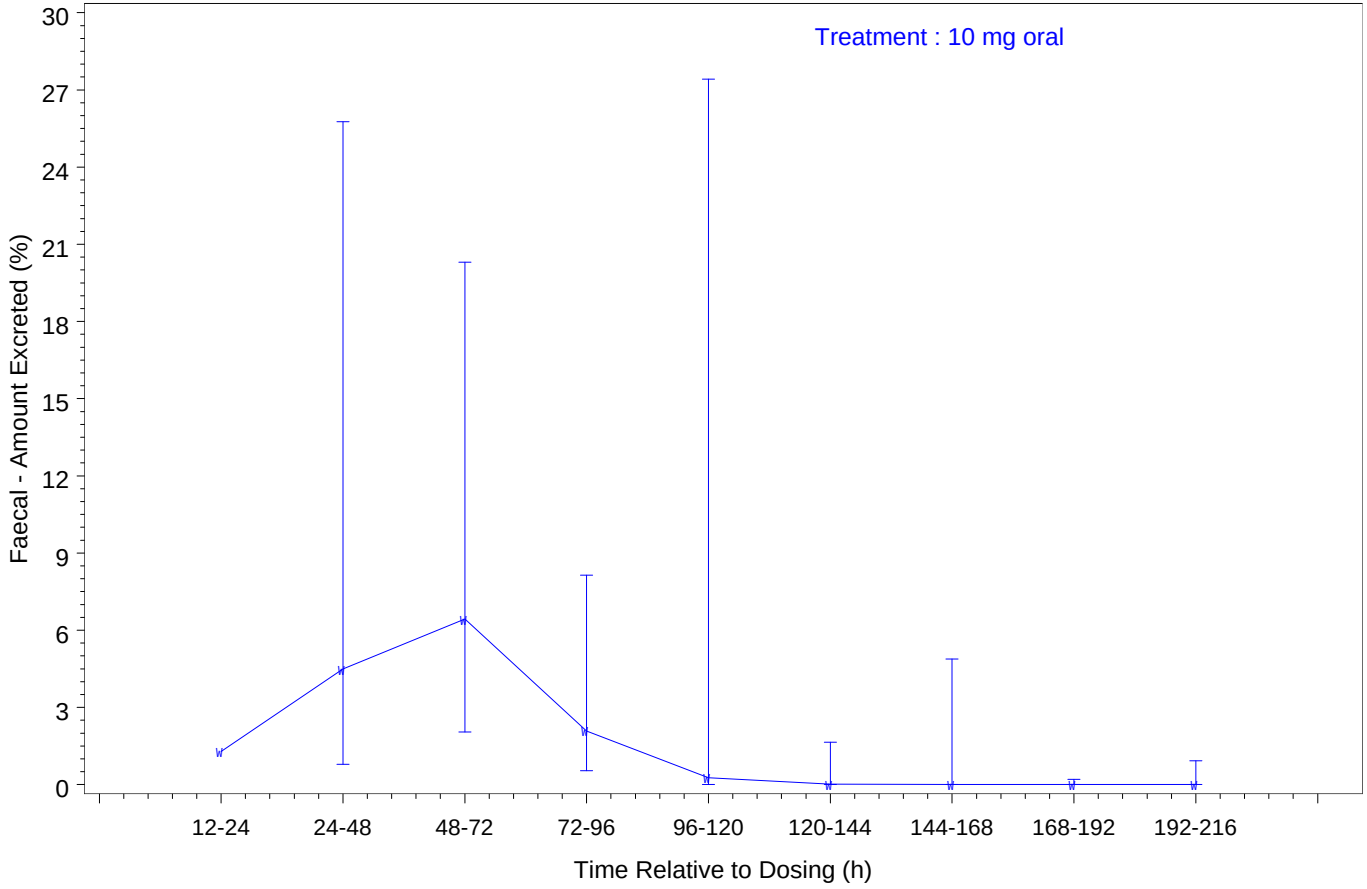
Figure 11.4
Plot of Derived Urinary 14C-Radioactivity Parameter (% Excreted) by Time



Note : Geometric Mean and 95% CI of Geometric Mean

[redacted]

Figure 11.5
Plot of Derived Faecal 14C-Radioactivity Parameter (% Excreted) by Time



Note1 : Geometric Mean and 95% CI of Geometric Mean
Note2 : For presentational purposes the 95% CI at 12-24 hours is not shown due to the small sample size (n=3).
The 95% CI at 12-24 hours is (0.000653,2537.20640).

[redacted]

Table 11.1
Summary of Plasma GW856553 Concentration (ng/mL) - Time Data

Treatment	N	Visit	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
10 mg oral	6	TREATMENT PERIOD	PRE-DOSE	6	6	NQ		NQ	NQ	NQ
			0.5 H	6	0	40.9990	26.85941	38.5615	5.992	81.367
			1 H	6	0	72.1513	20.79569	75.5375	47.375	100.828
			1.5 H	6	0	79.2563	23.90452	71.8715	57.885	117.943
			2 H	6	0	59.6203	11.06102	55.0270	51.853	80.142
			3 H	6	0	38.9205	9.55920	36.3645	27.931	53.299
			4 H	6	0	27.0987	4.86310	26.2180	21.921	35.756
			6 H	6	0	18.5958	5.24794	18.3855	12.834	24.677
			8 H	6	0	13.2058	2.24053	12.0380	11.550	16.924
			12 H	6	0	6.1287	1.78263	6.4890	2.933	8.288
			24 H	6	0	2.1067	1.01627	2.1115	0.526	3.687
			36 H	6	0	0.5537	0.19152	0.5450	0.297	0.836
			48 H	6	1	0.3445	0.21262	0.3910	NQ	0.591
			72 H	6	6	NQ		NQ	NQ	NQ

Table 11.2
Summary of Plasma GSK198602 Concentration (ng/mL) -Time Data

Treatment	N	Visit	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
10 mg oral	6	TREATMENT PERIOD	PRE-DOSE	6	6	NQ		NQ	NQ	NQ
			0.5 H	6	0	19.448	10.2290	20.065	3.15	32.01
			1 H	6	0	64.293	27.9625	63.185	35.44	112.65
			1.5 H	6	0	93.607	40.9747	81.155	57.24	173.52
			2 H	6	0	82.093	24.9829	72.500	65.92	131.46
			3 H	6	0	58.153	21.2643	50.240	42.98	99.52
			4 H	6	0	41.465	11.1690	37.090	29.42	56.01
			6 H	6	0	35.035	10.7478	36.160	19.16	46.47
			8 H	6	0	25.580	7.3761	23.430	18.77	38.66
			12 H	6	0	10.917	3.3365	11.865	4.79	14.11
			24 H	6	0	6.435	2.5654	6.260	2.76	10.69
			36 H	6	0	1.742	0.5659	1.645	1.20	2.68
			48 H	6	5	NQ		NQ	NQ	1.12
			72 H	6	6	NQ		NQ	NQ	NQ

Table 11.3
Summary of Plasma 14C-Radioactivity (ug/mL) Levels Over Time

Treatment	N	Visit	Planned Relative Time	n	No. Imputed	Mean	SD	Median	Min.	Max.
10 mg oral	6	TREATMENT PERIOD	0.5 H	6	0	0.0837	0.04710	0.0835	0.011	0.149
			1 H	6	0	0.1953	0.04469	0.1990	0.119	0.250
			1.5 H	6	0	0.2085	0.02828	0.1960	0.189	0.264
			2 H	6	0	0.1832	0.02546	0.1730	0.168	0.234
			3 H	6	0	0.1413	0.01722	0.1390	0.120	0.171
			4 H	6	0	0.1132	0.01430	0.1105	0.093	0.137
			6 H	6	0	0.0752	0.01514	0.0770	0.051	0.097
			8 H	6	0	0.0533	0.01359	0.0505	0.040	0.077
			12 H	6	0	0.0253	0.00622	0.0260	0.015	0.033
			24 H	6	0	0.0112	0.00232	0.0110	0.008	0.015
			36 H	6	6	NQ		NQ	NQ	NQ
			48 H	6	6	NQ		NQ	NQ	NQ
			72 H	6	6	NQ		NQ	NQ	NQ
			96 H	6	6	NQ		NQ	NQ	NQ
			120 H	6	6	NQ		NQ	NQ	NQ
			144 H	6	6	NQ		NQ	NQ	NQ
			168 H	6	6	NQ		NQ	NQ	NQ

Table 11.4
Summary of Derived Plasma GW856553 Pharmacokinetic Parameters

Parameter	Treatment	N	n	n*	Mean	SD	Median	Min.	Max.
AUC(0-t) (ng*hr/mL)	10 mg oral	6	6	0	368.279	77.5414	350.040	262.62	489.77
AUC(0-inf) (ng*hr/mL)	10 mg oral	6	6	0	373.201	77.7576	354.343	265.73	495.06
Cmax (ng/mL)	10 mg oral	6	6	0	83.317	21.2418	77.337	58.33	117.94
t1/2 (hr)	10 mg oral	6	6	0	8.321	1.2567	7.923	7.18	10.39
tlast (hr)	10 mg oral	6	6	0	46.000	4.8990	48.000	36.00	48.00
tmax (hr)	10 mg oral	6	6	0	1.345	0.2686	1.500	1.00	1.57
%AUCex (%)	10 mg oral	6	6	0	1.348	0.7061	1.120	0.64	2.55
CL/F (L/h)	10 mg oral	6	6	0	27.791	5.8809	28.221	20.20	37.63
AUCR	10 mg oral	6	6	0	0.272	0.0461	0.268	0.23	0.36

[1] CVb(%): Between subject CV = Sqrt(exp(SDLogs^2)-1) * 100
n* = Number of subjects with non calculable (NC) data for PK parameter

[redacted]

Table 11.4
Summary of Derived Plasma GW856553 Pharmacokinetic Parameters

Parameter	Treatment	N	n	n*	Geo. Mean	95% CI of Geo. Mean	SD Logs	CVb(%)[1]
AUC(0-t) (ng*hr/mL)	10 mg oral	6	6	0	361.541	(289.725,451.159)	0.211	21.3
AUC(0-inf) (ng*hr/mL)	10 mg oral	6	6	0	366.489	(294.180,456.572)	0.209	21.2
Cmax (ng/mL)	10 mg oral	6	6	0	81.180	(62.605,105.266)	0.248	25.1
t1/2 (hr)	10 mg oral	6	6	0	8.246	(7.081,9.603)	0.145	14.6
tlast (hr)	10 mg oral	6	6	0	45.753	(40.447,51.754)	0.117	11.8
tmax (hr)	10 mg oral	6	6	0	1.320	(1.053,1.656)	0.216	21.9
%AUCex (%)	10 mg oral	6	6	0	1.212	(0.717,2.047)	0.500	53.3
CL/F (L/h)	10 mg oral	6	6	0	27.286	(21.902,33.993)	0.209	21.2
AUCR	10 mg oral	6	6	0	0.269	(0.228,0.318)	0.160	16.1

[1] CVb(%): Between subject CV = Sqrt(exp(SDLogs^2)-1) * 100
n* = Number of subjects with non calculable (NC) data for PK parameter

[redacted]

Table 11.5
Summary of Derived Plasma GSK198602 Pharmacokinetic Parameters

Parameter	Treatment	N	n	n*	Mean	SD	Median	Min.	Max.
AUC(0-t) (ng*hr/mL)	10 mg oral	6	6	0	576.798	99.7382	584.777	406.40	717.63
AUC(0-inf) (ng*hr/mL)	10 mg oral	6	6	0	595.757	98.9189	608.078	427.51	735.52
Cmax (ng/mL)	10 mg oral	6	6	0	96.612	38.7139	84.115	66.73	173.52
t1/2 (hr)	10 mg oral	6	6	0	8.982	1.6370	8.460	7.56	12.09
tlast (hr)	10 mg oral	6	6	0	38.000	4.8990	36.000	36.00	48.00
tmax (hr)	10 mg oral	6	6	0	1.667	0.2582	1.500	1.50	2.00
%AUCex (%)	10 mg oral	6	6	0	3.288	1.1046	2.943	2.26	4.94
AUCR	10 mg oral	6	6	0	0.434	0.0399	0.437	0.37	0.49

[1] CVb(%): Between subject CV = Sqrt(exp(SDLogs^2)-1) * 100
n* = Number of subjects with non calculable (NC) data for PK parameter

[redacted]

Table 11.5
Summary of Derived Plasma GSK198602 Pharmacokinetic Parameters

Parameter	Treatment	N	n	n*	Geo. Mean	95% CI of Geo. Mean	SD Logs	CVb(%)[1]
AUC(0-t) (ng*hr/mL)	10 mg oral	6	6	0	568.996	(468.423,691.164)	0.185	18.7
AUC(0-inf) (ng*hr/mL)	10 mg oral	6	6	0	588.375	(488.643,708.461)	0.177	17.8
Cmax (ng/mL)	10 mg oral	6	6	0	91.707	(64.721,129.946)	0.332	34.1
t1/2 (hr)	10 mg oral	6	6	0	8.872	(7.441,10.578)	0.168	16.9
tlast (hr)	10 mg oral	6	6	0	37.768	(33.389,42.722)	0.117	11.8
tmax (hr)	10 mg oral	6	6	0	1.651	(1.413,1.930)	0.149	14.9
%AUCex (%)	10 mg oral	6	6	0	3.142	(2.228,4.430)	0.327	33.6
AUCR	10 mg oral	6	6	0	0.432	(0.392,0.477)	0.094	9.4

[1] CVb(%): Between subject CV = Sqrt(exp(SDLogs^2)-1) * 100
n* = Number of subjects with non calculable (NC) data for PK parameter

[redacted]

Table 11.6
Summary of Derived Plasma 14C-Radioactivity Pharmacokinetic Parameters

Parameter	Treatment	N	n	n*	Mean	SD	Median	Min.	Max.
AUC(0-t) (ug*hr/mL)	10 mg oral	6	6	0	1.245	0.1146	1.255	1.07	1.39
AUC(0-inf) (ug*hr/mL)	10 mg oral	6	6	0	1.366	0.1363	1.359	1.15	1.51
Cmax (ug/mL)	10 mg oral	6	6	0	0.213	0.0280	0.203	0.19	0.26
t1/2 (hr)	10 mg oral	6	6	0	7.413	1.0519	7.026	6.38	9.03
tlast (hr)	10 mg oral	6	6	0	24.000	0.0000	24.000	24.00	24.00
tmax (hr)	10 mg oral	6	6	0	1.345	0.2686	1.500	1.00	1.57
%AUCex (%)	10 mg oral	6	6	0	8.788	2.3578	7.933	6.91	12.90

[1] CVb(%): Between subject CV = Sqrt(exp(SDLogs^2)-1) * 100
n* = Number of subjects with non calculable (NC) data for PK parameter

[redacted]

Table 11.6
Summary of Derived Plasma 14C-Radioactivity Pharmacokinetic Parameters

Parameter	Treatment	N	n	n*	Geo. Mean	95% CI of Geo. Mean	SD Logs	CVb(%)[1]
AUC(0-t) (ug*hr/mL)	10 mg oral	6	6	0	1.241	(1.124,1.369)	0.094	9.4
AUC(0-inf) (ug*hr/mL)	10 mg oral	6	6	0	1.360	(1.222,1.515)	0.102	10.3
Cmax (ug/mL)	10 mg oral	6	6	0	0.211	(0.185,0.241)	0.124	12.5
t1/2 (hr)	10 mg oral	6	6	0	7.353	(6.365,8.494)	0.137	13.8
tlast (hr)	10 mg oral	6	6	0	24.000		0.000	0.0
tmax (hr)	10 mg oral	6	6	0	1.320	(1.053,1.656)	0.216	21.9
%AUCex (%)	10 mg oral	6	6	0	8.553	(6.587,11.106)	0.249	25.3

[1] CVb(%): Between subject CV = Sqrt(exp(SDLogs^2)-1) * 100
n* = Number of subjects with non calculable (NC) data for PK parameter

[redacted]

Table 11.7
Summary of Derived Urinary/Faecal 14C-Radioactivity Parameters(% Excreted) by Time

Parameter	Treatment	Planned Relative Time	N	n	Mean	SD	Median	Min.	Max.
Ae Urine (%)	10 mg oral	0-6 h	6	6	34.168333	4.605	34.340000	26.370000	40.170000
		6-12 h	6	6	17.185000	3.700	15.800000	13.380000	22.960000
		12-24 h	6	6	7.523333	1.538	7.575000	4.990000	9.370000
		24-48 h	6	6	4.180000	0.916	3.980000	3.150000	5.550000
		48-72 h	6	6	1.188333	0.736	0.965000	0.650000	2.610000
		72-96 h	6	6	0.355000	0.381	0.230000	0.110000	1.120000
		96-120 h	6	6	0.111669	0.158	0.060000	0.000015	0.430000
		120-144 h	6	6	0.051679	0.127	0.000015	0.000015	0.310000
		144-168 h	6	6	0.023346	0.057	0.000015	0.000015	0.140000
		168-192 h	6	6	0.011679	0.029	0.000015	0.000015	0.070000
		192-216 h	6	6	0.006679	0.016	0.000015	0.000015	0.040000
Ae Faeces (%)	10 mg oral	0-24 h	6	3	7.826667	11.829	1.990000	0.050000	21.440000
		24-48 h	6	6	8.830000	7.150	9.280000	0.260000	18.780000
		48-72 h	6	6	9.101667	6.494	7.925000	0.850000	19.400000
		72-96 h	6	6	4.471667	6.777	1.735000	0.410000	18.090000
		96-120 h	6	6	2.395008	3.367	1.585000	0.000045	9.060000
		120-144 h	6	6	0.280015	0.460	0.120000	0.000045	1.200000
		144-168 h	6	5	0.564018	1.129	0.100000	0.000045	2.580000
		168-192 h	6	6	0.076689	0.122	0.020023	0.000045	0.310000
		192-216 h	6	5	0.224027	0.399	0.000045	0.000045	0.920000

[1] CVb(%) : Between subject CV= Sqrt(exp(SDLogs^2)-1)*100
Note: NQ values were replaced with 1/2 LLQ prior to computing the above summary statistics.

[redacted]

Table 11.7
Summary of Derived Urinary/Faecal 14C-Radioactivity Parameters(% Excreted) by Time

Parameter	Treatment	Planned Relative Time	N	n	Geo. Mean	95% CI of Geo. Mean	SD Logs	CVb(%) [1]
Ae Urine (%)	10 mg oral	0-6 h	6	6	33.893291	(29.208940,39.328889)	0.142	14.2
		6-12 h	6	6	16.873469	(13.582812,20.961342)	0.207	20.9
		12-24 h	6	6	7.378880	(5.844908,9.315437)	0.222	22.5
		24-48 h	6	6	4.099229	(3.270908,5.137314)	0.215	21.8
		48-72 h	6	6	1.048491	(0.609248,1.804410)	0.517	55.4
		72-96 h	6	6	0.254490	(0.108203,0.598549)	0.815	97.1
		96-120 h	6	6	0.020715	(0.000458,0.937841)	3.633	73493.8
		120-144 h	6	6	0.000079	(0.000001,0.005547)	4.056	374234.4
		144-168 h	6	6	0.000069	(0.000001,0.003457)	3.732	105752.4
		168-192 h	6	6	0.000061	(0.000002,0.002288)	3.449	38286.0
		192-216 h	6	6	0.000056	(0.000002,0.001640)	3.221	17871.6
Ae Faeces (%)	10 mg oral	0-24 h	6	3	1.287308	(0.000653,2537.20640)	3.054	10595.9
		24-48 h	6	6	4.492380	(0.783196,25.768115)	1.664	386.9
		48-72 h	6	6	6.437002	(2.041318,20.298156)	1.094	152.1
		72-96 h	6	6	2.087294	(0.535634,8.133910)	1.296	208.9
		96-120 h	6	6	0.259427	(0.002455,27.418692)	4.441	1916945.7
		120-144 h	6	6	0.014105	(0.000121,1.646842)	4.536	2935228.5
		144-168 h	6	5	0.009394	(0.000018,4.886259)	5.037	32294054.8
		168-192 h	6	6	0.002234	(0.000024,0.209339)	4.326	1159652.4
		192-216 h	6	5	0.001757	(0.000003,0.926163)	5.047	34047410.5

[1] CVb(%) : Between subject CV= Sqrt(exp(SDLogs^2)-1)*100
Note: NQ values were replaced with 1/2 LLQ prior to computing the above summary statistics.

[redacted]

Table 11.8
Summary of Cum. Derived Urinary/Faecal 14C-Radioactivity Params.(% Excreted) by Time

Parameter	Treatment	Planned Relative Time	N	n	Mean	SD	Median	Min.	Max.
Ae Urine(0-t) (%)	10 mg oral	0-6 h	6	6	34.168	4.6055	34.340	26.37	40.17
		6-12 h	6	6	51.353	3.2589	50.390	48.36	56.52
		12-24 h	6	6	58.877	4.0183	57.865	54.32	64.28
		24-48 h	6	6	63.062	4.3916	62.220	57.78	68.38
		48-72 h	6	6	64.250	4.3666	63.970	59.06	69.19
		72-96 h	6	6	64.605	4.4194	64.640	59.35	69.44
		96-120 h	6	6	64.718	4.4454	64.880	59.42	69.51
		120-144 h	6	6	64.770	4.4806	65.035	59.42	69.51
		144-168 h	6	6	64.792	4.4963	65.100	59.42	69.51
		168-192 h	6	6	64.803	4.5050	65.135	59.42	69.51
		192-216 h	6	6	64.812	4.5113	65.160	59.42	69.51
Ae Faeces(0-t) (%)	10 mg oral	0-24 h	6	3	7.827	11.8293	1.990	0.05	21.44
		24-48 h	6	6	12.745	11.8423	12.220	0.26	31.53
		48-72 h	6	6	21.845	8.9495	23.995	9.21	32.38
		72-96 h	6	6	26.315	8.7321	30.280	10.18	32.79
		96-120 h	6	6	28.713	6.1912	31.570	19.25	33.75
		120-144 h	6	6	28.995	5.8862	31.690	20.45	33.91
		144-168 h	6	6	29.463	5.2327	31.690	22.75	34.05
		168-192 h	6	6	29.542	5.1667	31.745	22.75	34.09
		192-216 h	6	6	29.727	4.9795	31.840	22.75	34.09

[1] CVb(%) : Between subject CV= Sqrt(exp(SDLogs^2)-1)*100

[redacted]

Table 11.8
Summary of Cum. Derived Urinary/Faecal 14C-Radioactivity Params.(% Excreted) by Time

Parameter	Treatment	Planned Relative Time	N	n	Geo. Mean	95% CI of Geo. Mean	SD Logs	CVb(%) [1]
Ae Urine(0-t) (%)	10 mg oral	0-6 h	6	6	33.893	(29.209,39.329)	0.142	14.2
		6-12 h	6	6	51.269	(48.016,54.742)	0.062	6.3
		12-24 h	6	6	58.764	(54.738,63.085)	0.068	6.8
		24-48 h	6	6	62.935	(58.522,67.682)	0.069	6.9
		48-72 h	6	6	64.126	(59.712,68.868)	0.068	6.8
		72-96 h	6	6	64.479	(60.000,69.291)	0.069	6.9
		96-120 h	6	6	64.591	(60.083,69.437)	0.069	6.9
		120-144 h	6	6	64.640	(60.095,69.529)	0.069	7.0
		144-168 h	6	6	64.661	(60.099,69.569)	0.070	7.0
		168-192 h	6	6	64.672	(60.101,69.591)	0.070	7.0
		192-216 h	6	6	64.680	(60.103,69.606)	0.070	7.0
Ae Faeces(0-t) (%)	10 mg oral	0-24 h	6	3	1.287	(0.001,2537.206)	3.054	10595.9
		24-48 h	6	6	5.587	(0.809,38.578)	1.841	535.5
		48-72 h	6	6	20.012	(12.016,33.331)	0.486	51.6
		72-96 h	6	6	24.555	(15.274,39.476)	0.452	47.7
		96-120 h	6	6	28.089	(21.905,36.019)	0.237	24.0
		120-144 h	6	6	28.446	(22.584,35.829)	0.220	22.3
		144-168 h	6	6	29.047	(23.837,35.396)	0.188	19.0
		168-192 h	6	6	29.137	(23.985,35.396)	0.185	18.7
		192-216 h	6	6	29.354	(24.368,35.360)	0.177	17.9

[1] CVb(%) : Between subject CV= Sqrt(exp(SDLogs^2)-1)*100

[redacted]

Table 11.9
Summary of Total Urinary/Faecal 14C-Radioactivity Parameters (% Excreted)

Parameter	Treatment	N	n	Mean	SD	Median	Min.	Max.
Ae Urine (%)	10 mg oral	6	6	64.812	4.5113	65.160	59.42	69.51
Ae Faeces (%)	10 mg oral	6	6	29.727	4.9795	31.840	22.75	34.09
Ae Total (%)	10 mg oral	6	6	94.538	4.4903	93.170	91.90	103.60

[1] CVb(%) : Between subject CV= Sqrt(exp(SDLogs^2)-1)*100
Note: (i) All assessed time intervals were included in the derivation of the total amount excreted for urine and faeces.
(ii)Ae total (amount excreted) = Ae urine (total amount excreted) + Ae faeces (total amount excreted).

[redacted]

Table 11.9
Summary of Total Urinary/Faecal 14C-Radioactivity Parameters (% Excreted)

Parameter	Treatment	N	n	Geo. Mean	95% CI of Geo. Mean	SD Logs	CVb(%) [1]
Ae Urine (%)	10 mg oral	6	6	64.680	(60.103,69.606)	0.070	7.0
Ae Faeces (%)	10 mg oral	6	6	29.354	(24.368,35.360)	0.177	17.9
Ae Total (%)	10 mg oral	6	6	94.454	(90.015,99.111)	0.046	4.6

[1] CVb(%) : Between subject CV= Sqrt(exp(SDLogs^2)-1)*100
Note: (i) All assessed time intervals were included in the derivation of the total amount excreted for urine and faeces.
(ii)Ae total (amount excreted) = Ae urine (total amount excreted) + Ae faeces (total amount excreted).

[redacted]

Table 11.10
Summary of Derived 14C-Radioactivity Plasma Conc. Ratios for GW856553 and GSK198602

	Treatment	N	n	Mean	SD	Median	Min.	Max.
AUC(0-inf) ratio GSK198602:14C-Radioactivity	10 mg oral	6	6	0.4340	0.03994	0.4370	0.373	0.486
AUC(0-inf) ratio GW856553:14C-Radioactivity	10 mg oral	6	6	0.2723	0.04604	0.2675	0.231	0.357

[1] CVb(%): Between subject CV = Sqrt(exp(SDLogs^2)-1) * 100

Table 11.10
Summary of Derived 14C-Radioactivity Plasma Conc. Ratios for GW856553 and GSK198602

	Treatment	N	n	Geo. Mean	95% CI of Geo. Mean	SD Logs	CVb(%) [1]
AUC(0-inf) ratio GSK198602:14C-Radioactivity	10 mg oral	6	6	0.4324	(0.3920,0.4771)	0.093	9.4
AUC(0-inf) ratio GW856553:14C-Radioactivity	10 mg oral	6	6	0.2694	(0.2279,0.3183)	0.159	16.0

[1] CVb(%): Between subject CV = Sqrt(exp(SDLogs^2)-1) * 100

Time and Events Table

Assessment	Screening[1]	Pre-dose[2]	Day 1	Days 2-10	Follow-up[13]
Informed consent	X				
Medical history	X				
Demographics	X				
Physical examination	X				X
Serology (HbsAg, anti-HCV, anti-HIV)	X				
Urine drug screen and alcohol breath test	X	X			
12-lead electrocardiography	X	X	X[3]		X
Vital signs (blood pressure, pulse)	X	X	X[4]		X
Clinical laboratory including urinalysis	X	X		X[5]	X
Blood sampling for pharmacogenetics[6]					
Blood sample for plasma pharmacokinetics (cold analysis)		X	X[7]		
Blood sample for plasma radioactivity		X	X[8]		
Blood for metabolite analysis and radioactivity in whole blood		X	X[9]		
Drug administration			X		
Urine collection		X	X[10]	X[10]	
Faeces collection		X	X[11]	X[11]	
Serious adverse event/adverse event review and reporting[12]		X	X	X	X

Continued

Time and Events Table (Continued)

1. Screening assessments were carried out within 21 days prior to Day 1.
2. Assessments may have been on Day -1 or Day 1 pre-dose as appropriate.
3. Electrocardiography readings were taken at 30 minutes and 1, 2, 4, 6, 8 and 24 h post-dose.
4. Measurements were taken at 15 and 30 minutes and 1, 2, 4, 6, 8, 24 and 48 h post-dose.
5. Samples taken 48 h post dose (Day 3).
6. Pharmacogenetics sample was collected on Day -1 prior to dosing and after pharmacogenetics consent had been obtained.
7. Samples collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose.
8. Samples collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 h post-dose.
9. Samples collected at 1, 4 and 12 h post-dose.
10. Urine was collected for the periods 0–6 h, 6–12 h, 12–24 h and then at 24 h intervals up to 216 h post-dose (or until stopping criteria were reached).
11. Faeces was collected at 24 h intervals up to 216 h post-dose (or until stopping criteria were reached).
12. Only serious adverse events related to study participation were collected between screening and dosing.
13. Follow-up assessments were performed 7–14 days of the last sampling day.

Division: Worldwide Development
Retention Category: GRS019
Information Type: Clinical Pharmacology Reporting and Analysis Plan

Title:	Clinical Pharmacology Reporting and Analysis Plan for RA3107806: An open label study to determine the safety, tolerability, excretion balance and pharmacokinetics of [^{14}C] GW856553, administered as a single dose of an oral solution to healthy adult male subjects.

Compound Number: GW856553

Effective Date: 20-MAR-2008

Description:

The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Clinical Pharmacology Study Report for Protocol GM2007/00109/01 issued on 14-Nov-2007. This RAP describes the safety, tolerability, excretion and pharmacokinetic output that will be produced in this study. This document will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Identifier/Version Number: GM2007/00616/00

Subject: GW856553, ADME, radiolabel study

Author's Name and Functional Area:

[redacted]	BDSI, Bangalore (Statistician)

Approved by: Approved Electronically by RAP Headquarters system

[redacted]	BDSI Bangalore (Biostatistics and Programming Manager)

Approved by: Approved Electronically via RAP Headquarters system

[redacted]	Discovery Biometrics (Senior Statistician)

Approved by: Approved Electronically via RAP Headquarters system

[redacted]	Discovery Biometrics (Statistics & Programming Manager)

Approved by: Approved Electronically via RAP Headquarters system

[redacted]	CPDM (CMT Leader)

Approved by: Approved Electronically via RAP Headquarters system

[redacted]	CPK/M&S, CPDM (Senior Clinical Pharmacokineticist)

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LIST OF ABBREVIATIONS

^{14}C	Carbon 14 radioactive isotope
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ARSAC	Administration of Radioactive Substances Advisory Committee
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
AUC(0-t)	Area under the concentration time curve between zero and the time to the last measurable concentration
AUC(0-∞)	Area under the concentration time curve from zero to infinity
BDSI	Biomedical Data Sciences, India
BMI	Body Mass Index
BQL	Below Quantification Limit
CC	Critical Concern
CI	Confidence Interval
Cmax	Maximum observed plasma drug concentration
CPDM	Clinical Pharmacology and Discovery Medicine
CPDS	Clinical Pharmacology Data Sciences
CPK	Clinical Pharmacokinetics
CPK M&S	Clinical Pharmacokinetics, Modelling and Simulation
CPSR	Clinical Pharmacology Study Report
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of Variation
DB	Discovery Biometrics
DBF	Database Freeze
DMPK	Drug Metabolism and Pharmacokinetics
dp	Decimal Place
ECG	Electrocardiogram
F4PSP	Fit for Purpose Study Processess
Gamma-GT	gamma-glutamyl transpeptidase
Hb	haemoglobin
HCT	haematocrit
HDL	high density lipoprotein cholesterol
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IDSL TST	IDSL Therapeutic Standards Team
LDL	Low Density Lipoprotein cholesterol
LFT	Liver Function Test
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for Drug Regulatory Affairs
NC	Non Calculable
NQ	Concentrations below quantification limit
PGx	Pharmacogenetics

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QTc(B)	QT interval corrected (Bazett's formula)
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
t½	Terminal half-life
tmax	The time of the sample at which C_{max} was first measured
ULN	Upper Limit Normal
WBC	White Blood Cell

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1. INTRODUCTION

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

Revision Chronology:		
GM2007/00109/00	2007-OCT-17	Original
GM2007/00109/01	2007-NOV-14	Amendment No.: 01 Addition of information regarding the reporting of suspected serious unexpected adverse reactions at request of regulatory authority

All decisions regarding final analysis, as defined in this RAP document, have been made prior to Database Freeze (DBF) of the study data.

The tables, listings and figures described and listed in Section 14 will be reported in a Clinical Pharmacology Study Report (CPSR).

This clinical study is proposed to characterise the metabolic disposition of [^{14}C]GW856553 by analysing the radioactivity in whole blood, plasma, urine and faeces.

Qualified statisticians/programmers within BDSI, Bangalore will be responsible for the data displays. A pharmacokineticist in Clinical Pharmacokinetics, Modelling and Simulation (CPK M&S) will be responsible for the derivation of pharmacokinetic (PK) parameters.

Aside from subject accountability data, if any pharmacogenetic (PGx) data analysis is to be performed it will be described and reported at a later date.

The data for the study will be collected by paper Case Report Form (CRF).

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

2.1.1. Primary Objective(s)

- To determine the rate and extent of excretion of total radioactivity in urine and faeces and total recovery of radioactivity, after a single oral dose of [^{14}C] GW856553 to healthy male subjects.

- To generate samples with which to characterise and quantify the metabolic profile of GW856553 in plasma, urine and faeces following administration of a single oral dose of [^{14}C] GW856553 to healthy male subjects.

2.1.2. Secondary Objective(s)

- To determine pharmacokinetic parameters of GW856553 and its major metabolite GSK198602 following a single oral administration of [^{14}C] GW856553.
- To further assess the tolerability of a single oral dose of GW856553 in healthy male subjects.

2.2. Study Endpoint(s)

2.2.1. Primary Endpoint(s)

- The primary endpoint of this study is to report the urinary and faecal cumulative excretion as a percentage of the total radioactive dose administered over time.

2.2.2. Secondary Endpoints(s)

The secondary PK endpoints will consist of:

- AUC (0-∞), Cmax, AUC(0-t), tmax and t½ of total drug-related material (radioactivity) in plasma following oral dosing.
- AUC (0-∞), Cmax, AUC (0-t), tmax, t½ of GW856553 and its major metabolite GSK198602, and oral clearance of GW856553 in plasma following oral dosing.
- Adverse events, ECG, vital signs and clinical laboratory tests (including Liver Function Tests (LFTs)).

3. STUDY DESIGN

This will be an open-label study conducted in 6 male subjects. Each subject will receive a single 10mg (50 μCi) oral dose of [^{14}C]GW856553. This will involve a ten-night, eleven-day admission.

Urine and faecal samples will be collected until 216 h after dosing but subjects may be discharged after 168 h if 90% of the dose is recovered and/or <1% of the dose is excreted in a 24 h period. If recovery of radioactivity is incomplete at the end of the collection period, subjects may be asked to collect samples of either urine and/or faeces for an extended period either within the clinical unit or at home.

Plasma and blood concentrations of total drug-related material (radioactivity) and plasma concentrations of unchanged GW856553 and its major metabolite GSK198602 will be measured and will be used to determine the aforementioned PK parameters.

Safety will be assessed by monitoring subjects for adverse events, vital signs, ECGs and laboratory parameters.

4. PLANNED ANALYSES

4.1. Interim Analyses

No interim analyses are planned.

4.2. Final Analyses

The final planned analyses will be performed after all subjects have completed the study and after DBF. See Section 10 and Section 11 for all final planned analyses for this study.

5. ANALYSIS POPULATIONS

All Subjects Population

The All Subjects Population is defined as all subjects who receive at least one dose of study medication.

Pharmacokinetic (PK) Population

The PK Population is defined as subjects in the All Subjects Population for whom a pharmacokinetic sample was obtained and analysed.

6. HYPOTHESES AND TREATMENT COMPARISONS

This is an investigative study and no formal hypotheses will be tested with regard to the excretion and pharmacokinetics of GW856553.

7. TREATMENT AND OTHER SUB-GROUP DESCRIPTIONS FOR DATA DISPLAYS

There are no treatment comparisons. Summary statistics will be presented for both Safety and PK parameters of GW856553

7.1. Data Display Treatment and Other Subgroup Descriptors

For the purpose of all data displays the treatment group will be labelled as presented in Table 1:

Table 1 Data Display Treatment Labels

Randomisation		Final Data Display (i.e. in HARP)
Code	Treatment Description	Treatment Description
A	A 10mg oral solution dose of [^{14}C] GW856553	10mg oral

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

8.1. Reporting Conventions

All data displays will be presented according to the IDSL statistical display principles and all approved Integrated Data Standards Library Therapeutic Standards Team (IDSL TST) standards.

Note: this RAP has used the IDSL output standard available prior to F4PSP for the 'Listing of Laboratory Threshold (Reference) Ranges' (i.e. using a standard that is 'archived') since programs are still being developed for the revised standard.

All statistical analyses and reporting will be performed using the currently supported version of SAS on a validated computer platform.

Changes to Planned Displays

Any changes from the planned tables, listings and figures described in this RAP will be documented in the CPSR/Clinical Study Report (CSR), together with the reason for such changes.

General Considerations for Figures

Individual subject figures will be plotted by actual time. Summary figures will be plotted by planned relative time.

General Considerations for Listings

Any unplanned or unscheduled data will be presented in the subject listings. In all listings (except where otherwise stated) planned and actual time relative to the study drug dosing time will be included. All data will be listed by subject and planned relative time (hrs), unless otherwise stated. The treatment group will be included for completeness.

General Considerations for Summaries

Only planned (i.e. scheduled) data will be included in summaries according to the analysis populations defined in Section 5. Data collected at screening, unscheduled time points and follow-up will not be included in summary tables. In all summaries treatment group will be included for completeness and data will be sorted by planned relative time (hrs), where planned relative time is relative to the study dosing time.

The minimum set of descriptive statistics to be included in each summary table is described in Table 2.

Table 2 Minimum Descriptive Statistics with Specification of Decimal Places

Label	Description	No of Decimal Places (dp)
N	Number of subjects in treatment group	Always present to 0 dp
n	Number of subjects with non-missing values	Always present to 0 dp
Mean	Arithmetic mean	1 dp more than raw data
SD	Standard deviation	2 dp more than raw data
Median	Median	1 dp more than raw data
Min.	Minimum	Same as raw data
Max.	Maximum	Same as raw data
95% CI	95% Confidence Interval (CI)	1 dp more than raw data

If the data follows a log-normal distribution then an additional set of descriptive statistics will be displayed (Table 3). Note that in this case the 95% CI of the arithmetic mean will not be produced.

Table 3 Additional Descriptive Statistics with Specification of Decimal Places

Label	Description	No of Decimal Places (dp)
N	Number of subjects with non-missing and non-zero values	Always present to 0 dp
Geo. Mean	Geometric mean	1 dp more than raw data
95% CI of Geo. Mean	95% CI around the geometric mean	1 dp more than raw data
SD Logs	Standard deviation of the log-transformed data	Always present to 3 dp
CVb(%)	Coefficient of Variation (CV):- $CV_b(\%) = [\exp(sd^2) - 1]^{1/2} \times 100$, where sd is the standard deviation of the loge transformed data.	Always present to 1 dp

In the case where the number of decimal places in the raw data is so great that no additional information is being added, reporting will be to the number of decimal places considered appropriate.

Categorical data will be summarised in terms of frequencies and percentages (0 dp).

Note that for clinical laboratory evaluations the 95% CI of the mean or geometric mean will be excluded and the inter-quartile range reported instead.

CPK M&S will report all decimal places available.

8.2. Data Management

There is a relatively complex data process for the PK data in this study due to the "hot" plasma PK and excreta assays being performed by an external lab and the "cold" PK assays being performed in-house by DMPK. The aim of this section is to clarify what data will be supplied, to whom, in what format, and who will have overall responsibility for the reconciliation and merging of the "hot" and "cold" PK datasets with the CRF data for the subsequent (statistical and CPK M&S) analyses.

Note: The data transfer process described in this section has been included for guidance and, therefore, is not binding. It is not of concern if the actual data transfer process differs, provided the data used in analyses are accurate and reported in a timely manner.

Pertinent information relating to both the blood sampling for plasma PK and the excreta sampling (urine and faeces) will be recorded on the CRF (e.g. date, time and unique identification number of each sample). This information will be processed by CPDS and will be part of the basic SI PK dataset, which will be used in reconciliation. Note: The SI PK dataset will contain information relating to both types of samples (plasma and excreta).

8.2.1. Data process for PK plasma samples

The physical blood samples will be assayed by the external lab for ^{14}C-radioactivity in plasma (the "hot" assay; which only measures total radioactivity and does not distinguish between parent or metabolite). Once this is complete the external lab will send the physical samples onto DMPK where they will then be assayed for GW856553 and its major metabolite GSK198602 in plasma (the "cold" assay).

The external lab send the results of the "hot" plasma assay to DMPK via an Excel spreadsheet. DMPK will be responsible for entering this information into SMS2000. Once DMPK have completed the "cold" assay of the plasma samples they will record the results (for parent and metabolite) in SMS2000 and notify CPDS when all data have been entered into SMS2000.

A truncated version of the SMS2000 file(s) will be extracted by CPDS who will be responsible for reconciliation of the SI PK dataset and the (truncated) SMS2000 file to ensure that all samples and expected data are accounted for and to raise any necessary queries.

Once this reconciliation has taken place BDSI will be responsible for extracting the full SMS2000 dataset and then merging it with the SI PK dataset. BDSI will then send the result of the merge (i.e. the PKCNC dataset) onto CPK M&S (via a .CSV file that can be imported directly into Win Non-Lin). CPK M&S will derive the PK parameters for ^{14}C-radioactivity, GW856553 and its major metabolite GSK198602 (see Section 11) and send the results back to BDSI (as a .CSV file).

BDSI import the derived PK parameters from the CPK M&S .CSV file into SAS (and store as the PKPAR dataset) and perform appropriate statistical analyses (see Section 11).

8.2.2. Data process for Excreta samples (urine and faeces)

The urine/excreta samples will assayed by the external laboratory for ^{14}C-radioactivity. The results of the excreta assays will be sent to DMPK via an Excel spreadsheet, the structure of which can be found in Section 14.3.

DMPK will forward the excreta results onto CPDS, who will perform a (manual) reconciliation of the information in the SI PK dataset against the supplied Excel file to ensure that all excreta samples and expected data are accounted for and to raise any necessary queries.

Once this reconciliation has taken place BDSI will be responsible for merging the corresponding SI PK data with the results in the Excel file, and then implementing the required statistical analyses (see Section 11).

Note: The radioactivity will be supplied as a percentage of total dose administered (see Section 14.3). Prior to analysis the actual amounts of radioactivity will need to be derived from the supplied data for each subject (both cumulative totals and total at each sampling time).

8.3. Premature Withdrawal and Missing Data

All subjects who withdraw prematurely from the study/study drug will be documented and the reason for their withdrawal recorded in the final Clinical Pharmacology Study Report (CPSR). All available data from subjects who withdraw will be listed and all available planned data will be included in the summaries according to the populations defined in Section 5.

Any available planned on-treatment data that is excluded from summaries or statistical analyses will be documented along with the reason for exclusion in the CPSR.

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

8.4. Baseline Definition

The following table indicates the definition of baseline for laboratory, vital signs and ECG data:-

Table 4 Definition of Baseline

Parameter	Baseline (Predose) Day Used in Analysis[1]		
	Day -1	Day 1	
Safety :			
Laboratory	X	X	Day -1 or Day 1 (Predose)
Vital Signs	X	X	Day -1 or Day 1 (Predose)
ECG	X	X	Day -1 or Day 1 (Predose)

1. Baseline for each parameter will be subject specific and may be either of the possible days

The protocol allows the site flexibility in when they can take an individual subjects baseline. It could either be on Day -1 or on Day 1 (predose). Therefore the baseline measurement will be subject specific. For an individual subject there should not be measurements on both of the possible baseline days (for a given parameter). However, if there are multiple values databased then the most recent value should be used as baseline for that parameter for that subject.

8.5. Derived and Transformed Data

8.5.1. Pharmacokinetic Parameters

For the purposes of calculating summary statistics, all PK parameters with the exception of t_{max} will be log_e transformed.

For these log-transformed parameters, the between subject coefficient of variation (%CVb) will be calculated as follows:-

(%CVb) = 100 * (sqrt(exp(SD of log_e-transformed)^2-1))

(Also, see Table 3).

8.5.2. Multiple Measurements at One Time point

Where multiple measurements are recorded for a particular time point, the mean of the measurements will be calculated and used in any derivation of summary statistics. However all available data will be listed.

Where more than the specified number of measurements have been taken, the most recently recorded values will be used in the derivation of the appropriate summary measure (e.g. for the mean).

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8.5.3. Safety Data

Calculation of Body Mass Index

Body Mass Index (BMI) will be recalculated as follows:-

$$\boldsymbol{BMI} = \frac{Weight(kg)}{(Height(cm))^2} * 10{,}000$$

Calculation of corrected QT Interval

The following parameters will be derived for 12-lead ECG data:-

- $\boldsymbol{RR(msec)} = 1/\left[\left(Ventricular\ Rate/60\right)/1000\right]$

where ventricular rate is in bpm

- $\boldsymbol{QTc(F)\ (msec)} = \frac{QT}{(RR/1000)^{1/3}}$

where QT is in msec

8.6. Values of Potential Clinical Importance

Table 5 Laboratory Values of Potential Clinical Importance (Healthy Volunteers)

Hematology Analyte	Effect	Potential Clinical Importance (PCI) Range	Unit
White Blood Cell Count (WBC)	Low	< 3	$x10^9$/ L
	High	> 20	$x10^9$/ L
Neutrophil Count	Low	< 1.5	$x10^9$/ L
Hemoglobin	Low	> 25 change from baseline	g/L
	High	180	g/L
Hematocrit	Low	> 0.075 change from baseline	Ratio of 1
	High	0.54	Ratio of 1
Platelet Count	Low	< 100	$x10^9$/ L
	High	> 550	$x10^9$/ L
Lymphocytes	Low	< 0.8	$x10^9$/ L

Chemistry Analyte	Effect	Potential Clinical Importance (PCI) Range/Value	Unit
Albumin	Low	< 30	g/L
Calcium	Low	< 2.0	mmol/L
	High	> 2.75	mmol/L
Creatinine	High	> 1.3x ULN	mmol/L
	High	> 44 Change from baseline	µmol/L
Glucose	Low	< 3.0	mmol/L
	High	> 9	mmol/L
Magnesium	Low	< 0.5	mmol/L
	High	> 1.23	mmol/L
Phosphorus	Low	< 0.8	mmol/L
	High	> 1.6	mmol/L
Potassium	Low	< 3.0	mmol/L
	High	> 5.5	mmol/L
Sodium	Low	< 130	mmol/L
	High	> 150	mmol/L
Bicarbonate	Low	< 18	mmol/L
	High	> 32	mmol/L

Liver Function Test Analyte	Effect	Potential Clinical Importance (PCI) Range	Unit
ALT/SGPT	High	≥ 2x ULN	U/L
AST/SGOT	High	≥ 2x ULN	U/L
AlkPhos	High	≥ 2x ULN	U/L
T Bilirubin	High	≥ 1.5xULN	µmol/L
T. Bilirubin + ALT	High	≥ 1.5xULN T. Bilirubin + ≥ 2x ULN ALT	µmol/L U/L

Table 6 ECG Values of Potential Clinical Importance (Healthy Volunteers)

ECG Parameter	Potential Clinical Importance Range (PCI)	Unit
Absolute QTc interval	>450	msec
Increase from baseline QTc	>60	msec
PR interval	<110 and >220	msec
QRS interval	<75 and >110	msec

ECG Parameter	Potential Clinical Importance Range (PCI)	Unit
Absolute QTc interval	>450 to ≤479	msec
Absolute QTc interval	≥480 to ≤499	msec
Absolute QTc interval	≥500	msec
Increase from baseline QTc	>30 to ≤59	msec
Increase from baseline QTc	≥60	msec

Table 7 Vital Sign Values of Potential Clinical Importance (Healthy Volunteers)

Vital Sign Parameter	Potential Clinical Importance Range (PCI)	Unit
Systolic Blood Pressure	< 85 and > 160	mmHg
Diastolic Blood Pressure	< 45 and > 100	mmHg
Heart Rate	< 40 and > 110	bpm
Heart Rate	< 40 and > 110	bpm

9. STUDY POPULATION

All tables and listings in this section will use the All Subjects Population. The precise format and content of Study Population tables and listings are provided in Section 14.

9.1. Disposition of Subjects

A summary of the number and percentage of subjects who completed the study will be displayed (Table 9.1). A listing of reasons for withdrawal will also be produced (ICH Data Listing 1).

9.2. Protocol Deviations

The number of subjects who deviated from the inclusion or exclusion criteria will be listed (ICH Data Listing 2).

9.3. Demographic and Baseline Characteristics

Demographic characteristics

Demographic characteristics will be summarised and listed (Table 9.2 and ICH Data Listing 3). Age will be calculated as: date of screening assessment - date of birth. A listing of race will be presented (ICH Data Listing 4).

Concomitant Medications

A listing of all concomitant medications by generic term (i.e. according to GSK-Drug Anatomical Therapeutic Chemical (ATC) classification level 1) and ingredient will be produced (Other Listing 1).

10. SAFETY ANALYSES

All tables and listings in this section will use the All Subjects Population. Safety data will be listed and summarised. There will be no formal statistical analysis of the safety data.

The precise format and content of safety tables and listings are provided in Section 14.

10.1. Extent of Exposure

Treatment exposure will be summarised (Table 10.1) and listed (ICH Data Listing 5).

10.2. Adverse Events

Summaries, presenting the number and percentage of subjects reporting AEs, will be in terms of treatment-emergent AEs (i.e. AEs that start or worsen after the single oral dose is administered) and sorted by total incidence (Note: AEs will be grouped by system organ class and preferred term within class). AEs will be coded using the current Medical Dictionary for Regulatory Affairs (MedDRA) in order to provide the system organ class/body system and preferred term/group code.

The following will be summarised for treatment-emergent AEs:-

- All AEs by primary system organ class and preferred term (Table 10.2).
- All AEs considered as possibly drug-related by the investigator, by primary system organ class and preferred term (Table 10.3).

Both summary tables will present the number and percentage of subjects reporting AEs. The counting of events for subjects and the associated percentages will be based on the number of subjects on treatment.

AE listings will only include subjects reporting at least one AE. The following listings will be presented:-

- A by-subject listing of all AEs (Note: Non-treatment-emergent AEs will be presented first followed by treatment-emergent AEs). The listing will include both the preferred term and verbatim text (ICH Data Listing 6).
- A separate by-subject listing of subject numbers for individual AEs, including only subjects reporting at least one AE (ICH Data Listing 7).
- The association between the AE body system, preferred terms and the verbatim text (ICH Data Listing 8).

10.3. Serious Adverse Events

Serious AEs will be listed (ICH Data Listing 9).

10.4. Adverse Events of Special Interest

A separate listing will be produced for the following adverse events of special interest if such data is obtained (Other Listing 12):-

Liver Function

- Alanine transaminase (ALT) ≥ 3x ULN
- Aspartate transaminase (AST) ≥ 3x ULN
- Bilirubin ≥ 1.5x ULN
- Direct bilirubin ≥ 1.5x ULN
- Indirect bilirubin ≥ 1.5x ULN

Muscle Function

Clinically significant changes in creatine kinase.

Diarrhoea

Occurrence of diarrhea.

Red Blood Cells

Clinically significant changes in RBC.

10.5. Clinical Laboratory Evaluations

Laboratory data will be listed only.

The following parameters will be considered (as described in Appendix 3 of the Protocol):-

- Haematology: white blood cell count (WBC), red blood cell count (RBC), haemoglobin (Hb), haematocrit (HCT), mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), platelet count, neutrophil count, lymphocyte count, monocyte count, eosinophil count and basophil count.
- Biochemistry: alkaline phosphatase (ALP), ALT, AST, gamma-glutamyl transpeptidase (gamma-GT), glucose, cholesterol, triglycerides, albumin, total protein, total bilirubin, direct Bilirubin, indirect bilirubin, creatinine, creatine phosphokinase (CPK), sodium, potassium, calcium, urea, low density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol (HDL).
- Urinalysis: protein, glucose, ketones, nitrates, bilirubin, blood, urobilinogen and leucocytes.

If any of the multi-stick tests for a subject are abnormal the microscopy tests below will be performed:-

- Urinalysis (microscopy): RBC, WBC, hyaline casts, granular casts, and cellular casts

By-subject listings for haematology and clinical chemistry data will be provided (ICH Data Listing 10, Listing 11, 12 and Listing 13) as follows:-

- Listing of Haematology Abnormalities of Potential Clinical Importance.
- Listing of All Haematology Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance.
- Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance.
- Listing of All Clinical Chemistry Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance.

A listing of the laboratory threshold ranges will also be produced (Other Listing 14).

Liver function test (LFT) data will be summarised in a frequency table. For ALP, AST and ALT data, the summary table (Table 10.5) will depict the number and percentage of subjects with values >=1 x ULN (Upper Limit Normal), >=2 x ULN and >=3 x ULN. The table will also include Bilirubin (total, direct and indirect) depicting the number and percentage of subjects with values >=1.5 x ULN, >=2 x ULN and >=3 x ULN.

In addition, a by subject listing (Other Listing 13) of all available data on the six LFT parameters (i.e. those summarised in Table 10.5) will be produced for any subject with any of the LFT parameters >= 1 x ULN (>= 1.5 x ULN for Bilirubin (total, direct and indirect) LFT parameters).

10.6. Other Safety Measures

10.6.1. ECG Data

ECG interval findings will be summarised (Table 10.4).

ECG interval data [including ventricular rate, PR, QRS Duration, Uncorrected QT, and derived interval data RR, and QTc(F) (i.e. QT corrected using Fridericia's formula) as defined in Section 8.5.3] will be listed only. ECG values of potential clinical importance and abnormal ECG findings will also be listed (ICH Data Listing 14 and Listing 16 respectively). A listing of all ECG values for subjects with a value of potential clinical importance will be presented (ICH Data Listings 15).

Note: Since QTc is defined as Bazett's correction in the CRF and therefore QTc = QTc(B), QTc should be presented as QTc(B) in all outputs.

10.6.2. Vital Signs

A listing of vital signs of potential clinical importance only will be listed (ICH Data Listing 17). All vital signs data for subjects with values of potential clinical importance will also be listed (ICH Data Listing 18).

11. PHARMACOKINETIC ANALYSES

All tables, listings and figures in this section will use the PK Population. There will be no formal statistical analysis of the PK data.

The reconciliation of the CRF (PK) and SMS2000 data will be performed by, or under the direct guidance of, Clinical Pharmacology Data Sciences (CPDS).

BDSI, Bangalore will also perform a reconciliation of the Case Report Form (CRF) (PK) and SMS2000 data, and confirm with CPDS that from a Discovery Biometrics (DB) perspective the reconciliation is satisfactory. BDSI, Bangalore will then merge the PK concentration and CRF data. According to the Protocol [GlaxoSmithKline Document Number GM2007/00109/01] and CRF, SMS2000 data provided by DMPK should include the following:-

- PK - blood (plasma PK: cold analysis)
- PK - blood (plasma radioactivity)
- PK sampling urine interval collection data
- PK sampling faeces interval collection data

Derivation of PK parameters will be performed by, or under the direct guidance of, CPK M&S within Clinical Pharmacology and Discovery Medicine (CPDM).

11.1. Drug Concentration Measures

Plasma

Individual subject plasma GW856553 concentrations, its major metabolite GSK198602 and ^{14}C-radioactivity levels will be summarised (Table 11.1, Table 11.2 and Table 11.3) and listed (Other Listing 2, Listing 3 and Listing 4) by planned relative time.

Linear and log-linear plots of median and (geometric) mean plasma GW856553 concentrations, GSK198602 concentrations and ^{14}C-radioactivity levels will be plotted over time. Plots will contain a separate line for each analyte (Figure 11.1 and Figure 11.2). Individual subject linear and log-linear plots will also be produced (Figure 11.3).

11.2. Deriving and Summarising Pharmacokinetic (PK) Parameters

The derivation of PK parameters of GW856553, its major metabolite GSK198602 and ^{14}C-radioactivity in plasma will be the responsibility of CPK M&S within CPDM. Parameters will be derived using non-compartmental methods with WinNonlin Version 4.1 or higher (Pharsight Corporation, Mountain View, CA, USA). Actual sample collection times will be used in the analysis.

Plasma

The following plasma PK parameters will be derived for GW856553, its major metabolite GSK198602 and ^{14}C-radioactivity:-

C_{max}	=	maximum observed drug concentration
$_{max}$	=	time to attain maximum observed drug concentration
$t_{½}$	=	apparent terminal elimination phase half life
t_{last}	=	time of last measurable concentration
$AUC_{(0-t)}$	=	area under the drug concentration time curve between zero and the time of the last measurable drug concentration (linear up/log down)
$AUC_{(0-\infty)}$	=	area under the plasma concentration-time curve between zero and infinity
AUC%extrap	=	percentage of $AUC_{(0-\infty)}$ that is due to extrapolation from t_{last} to infinity: $((AUC_{(0-\infty)} - AUC_{(0-t)})/AUC_{(0-\infty)})*100\%)$
CL/F	=	apparent oral clearance (derived for GW856553 only).

The derived plasma PK parameters for GW856553 and its major metabolite GSK198602 will be summarised (Table 11.4 and Table 11.5) and listed by subject (Other Listing 5 and Listing 6). Similarly, the derived plasma PK parameters for ^{14}C-radioactivity will be summarised (Table 11.6) and listed by subject (Other Listing 7). If data permit i) the ratio of plasma $AUC_{(0-\infty)}$ of GW856553 and plasma $AUC_{(0-\infty)}$ of ^{14}C-radioactivity and ii) the ratio of plasma $AUC_{(0-\infty)}$ of GSK198602 and the plasma $AUC_{(0-\infty)}$ of ^{14}C-radioactivity will be calculated for each subject (all ratios will be computed using Log_e transformed $AUC_{(0-\infty)}$ and the results back transformed for display purposes). These ratios will be summarised (Table 11.10) and listed (Other Listing 11).

Urine/Faeces

The following PK parameters for ^{14}C-radioactivity will be calculated by BDSI, Bangalore (data to be provided via Excel as described in Section 8.2.2 above):-

$A^e_{urine\ (\%excreted)}$ =	percentage of radioactivity excreted in urine
$A^e_{faeces\ (\%excreted)}$ =	percentage of radioactivity excreted in faeces
$A^e_{urine\ 0\text{-}t\ (\%excreted)}$ =	cumulative percentage of radioactivity excreted up to time t
$A^e_{faeces\ 0\text{-}t\ (\%excreted)}$ =	cumulative percentage of radioactivity excreted up to time t
$A^e_{total\ (\%excreted)}$ =	total percentage of radioactivity excreted

Radioactivity data will be descriptively summarised. In particular, for derived urine and faecal ^{14}C-radioactivity parameters, both the % excretion, i.e. 'the amount excreted as a percentage of total radioactive dose', and cumulative % excretion (Table 11.7 and Table 11.8 respectively) will be presented by time. Urine and faecal total radioactivity parameters will also be presented (Table 11.9).

Derived urinary/faecal ^{14}C-radioactivity parameters (% excreted) by time will also be plotted (Figure 11.4 and Figure 11.5).

The following listings for radioactivity parameters will be presented:-

- Listing of nominal and actual dose & nominal and actual radioactive dose administered to subjects (Other Listing 8)
- Listing of derived urinary/faecal ^{14}C-radioactivity parameters (% excreted) by time (Other Listing 9)
- Listing of total derived urinary/faecal ^{14}C-radioactivity parameters (% excreted) (Other Listing 10)

12. PHARMACOGENETIC, VIRAL GENOTYPING AND PHENOTYPING ANALYSES

12.1. Pharmacogenetic Analyses

The PGx subject accountability data will be listed (Other Listing 15).

13. REFERENCES

GlaxoSmithKline Document Number GM2007/00109/01 Study ID RA3107806. An open label study to determine the safety, tolerability, excretion balance and pharmacokinetics of [14C]GW856553, administered as a single dose of an oral solution to healthy adult male subjects Effective Date: . 14th November 2007

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14. ATTACHMENTS

14.1. Table of Contents for Data Display Specifications

Listed below are the planned figures, tables and listings to be produced. The department responsible for each data display is listed. Table and Figure numbering reflects that to be used in the CPSR.

The 'Example Output' heading refers to the relevant example in the IDSL data standards.

Note: Links to example output are not available if accessing the IDSL data standards via the intranet:- i.e. via

http://kopsnwb003.corpnet1.com/I/IntgrtdDtv.nsf?OpenDatabase.

Please access IDSL examples via the Lotus Notes Database (see link in RAP-delivery email).

(CP) indicates where the user locates Clinical Pharmacology Options for Statistical Displays [here the link to the current IDSL standard (Core or ClinPharm specific) is obtained]:-

'Exemptions/Changes' → 'Supporting Documentation' → 'Clin Pharm' → 'All' → **Clin Pharm Options for Statistical Displays**.

(PK) refers to the Clinical Pharmacology data standards located under:-

'Data Standards' → 'By Therapeutic Component' → 'Clin Pharm' → '(Not Categorised)' → 'Statistical Displays' → 'PK' → **Standards for the Transfer and Reporting of PK Data for Implementation of PKOne**.

- Standard Parameter Nomenclature for Reports Containing Pharmacokinetic Data

Report Text Symbol(s)	SAS Report Format	SAS Variable Names
AUC(0-∞)	AUC(0-inf)	AUCINF
AUC(0-t)	AUC(0-t)	AUCLAST
%AUCex	%AUCex	AUCEXT
Cmax	Cmax	CMAX
Tmax	Tmax	TMAX
t1/2	t1/2	THALF
CL/F	CL/F	CLF
t	tlast	TLAST

14.1.1. Study Population

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
9.1	*All Subjects*	ES1 (CP)	Summary of Subject Disposition		BDSI	*SAC*
9.2	*All Subjects*	DM1 (CP)	Summary of Demographic Characteristics		BDSI	*SAC*

14.1.2. Safety Tables

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
10.1	*All Subjects*	EX1 (CP)	Summary of Exposure to study drug		BDSI	SAC
10.2	*All Subjects*	AE1 (CP)	Summary of All Adverse Events		BDSI	SAC
10.3	*All Subjects*	AE1 (CP)	Summary of Drug Related Adverse Events		BDSI	SAC
10.4	*All Subjects*	EG1 (CP)	Summary of ECG Findings		BDSI	SAC
10.5	*All subjects*	SST1	Summary of LFTs on or Outside Normal Ranges	See Table 10.8 in RAP for GW856553 study RA3109385 for an example	BDSI	SAC

14.1.3. Pharmacokinetic Source Figures and Tables

Figure No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
11.1	*PK*	PKCF3 (PK)	Plot of Median Plasma GW856553 Concentrations, GSK198602 Concentrations and 14C-radioactivity Levels Over Time		BDSI	SAC
11.2	*PK*	PKCF2 (PK)	Plot of Mean Plasma GW856553 Concentrations, GSK198602 Concentrations and 14C-radioactivity Levels Over Time	Please use Geo. Means	BDSI	SAC
11.3	*PK*	PKCF1 (PK)	Plots of Individual Subject Plasma GW856553 Concentrations, GSK198602 Concentrations and 14C-radioactivity Levels Over Time		BDSI	SAC
11.4	*PK*	PKSF1	Plot of Derived Urinary 14C-Radioactivity Parameter (% Excreted) by Time	Please use Geometric means and indicate with footnote what the bars are that surround the mean	BDSI	SAC
11.5	*PK*	PKSF2	Plot of Derived Faecal 14C-Radioactivity Parameter (% Excreted) by Time	Please use Geometric means and indicate with footnote what the bars are that surround the mean	BDSI	SAC

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
11.1	*PK*	PKCT1 (PK)	Summary of Plasma GW856553 Concentration-Time Data		BDSI	SAC
11.2	*PK*	PKCT1 (PK)	Summary of Plasma GSK198602 Concentration-Time Data (Major Metabolite of GW856553)		BDSI	SAC
11.3	*PK*	PKCT1 (PK)	Summary of Plasma 14C-Radioactivity Levels Over Time		BDSI	SAC
11.4	*PK*	PKST1a	Summary of Derived Plasma GW856553 Pharmacokinetic Parameters		BDSI	SAC
11.5	*PK*	PKST1b	Summary of Derived Plasma GSK198602 Pharmacokinetic Parameters (Major Metabolite of GW856553)		BDSI	SAC
11.6	*PK*	PKST2	Summary of Derived Plasma 14C-Radioactivity Pharmacokinetic Parameters		BDSI	SAC
11.7	*PK*	PKST4	Summary of Derived Urinary/Faecal 14C-Radioactivity Parameters (% Excreted) by Time Point	For the parameters Ae urine(%excreted) = percentage of radioactivity excreted in urine Ae faeces(%excreted) =percentage of radioactivity excreted in faeces	BDSI	SAC

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11.8	*PK*	PKST6	Summary of Cumulative Derived Urinary/Faecal 14C-Radioactivity Parameters (% Excreted) by Time	For the parameters Ae urine 0-t (%excreted) = Cumulative percentage of radioactivity excreted up to time t Ae faeces 0-t (%excreted) = cumulative percentage of radioactivity excreted up to time t	BDSI	SAC
11.9	*PK*	PKST8	Summary of Total Derived Urinary/Faecal 14C-Radioactivity Parameters (% Excreted)		BDSI	SAC
11.10	*PK*	PKST9	Summary of derived cold assay:14C-radioactivity plasma concentration ratios for GW856553 and its major metabolite GSK198602	Compute ratios using Loge transformed AUC	BDSI	SAC

14.1.4. ICH Data Listings

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
1	*All Subjects*	ES2 (CP)	Listing of Reasons for Withdrawal		BDSI	SAC
2	*All Subjects*	IE3 (CP)	Listing of Subjects With Inclusion/Exclusion Deviations		BDSI	SAC
3	*All Subjects*	DM2 (CP)	Listing of Demographic Characteristics		BDSI	SAC
4	*All Subjects*	DM9 (CP)	Listing of Race		BDSI	SAC
5	*All Subjects*	EX3 (CP)	Listing of Exposure Data		BDSI	SAC
6	*All Subject*	AE8 (CP)	Listing of All Adverse Events	Display includes both Fatal and Non-Fatal	BDSI	SAC
7	*All Subjects*	AE7 (CP)	Listing of Subject Numbers for Individual Adverse Events		BDSI	SAC
8	*All Subjects*	AE2 (CP)	Relationship of Adverse Event, System Organ Class, Preferred Terms and Verbatim Text		BDSI	SAC
9	*All Subjects*	AE8 (CP)	Listing of Serious Adverse Events		BDSI	SAC
10	*All Subjects*	LB5 (CP)	Listing of Haematology Abnormalities of Potential Clinical Importance	Only display PCI values in this listing	BDSI	SAC
11	*All Subjects*	LB5 (CP)	Listing of All Haematology Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance	Display ALL labs for a subject who experienced a value of potential clinical importance. As program is not in place for new standard CP_LB5, programmer will use this standard (and extract the correct data as determined by the title).	BDSI	SAC
12	*All Subjects*	LB5 (CP)	Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance	Only display PCI values in this listing	BDSI	SAC

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Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
13	*All Subjects*	LB5 (CP)	Listing of All Clinical Chemistry Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance	Display ALL labs for a subject who experienced a value of potential clinical importance. As program is not in place for new standard CP_LB5, programmer will use this standard (and extract the correct data as determined by the title).	BDSI	SAC
14	*All Subjects*	EG5 (CP)	Listing of ECG Values of Potential Clinical Importance		BDSI	SAC
15	*All Subjects*	CP_EG5a (CP)	Listing of All ECG Values for Subjects with a Value of Potential Clinical Importance		BDSI	SAC
16	*All Subjects*	EG5 (CP)	Listing of Abnormal ECG Findings		BDSI	SAC
17	*All Subjects*	VS4 (CP)	Listing of Vital Signs of Potential Clinical Importance		BDSI	SAC
18	*All Subjects*	VS4 (CP)	Listing of All Vital Signs for Subjects with Values of Potential Clinical Importance		BDSI	SAC

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14.1.5. Other Listings

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
1	*All Subjects*	CM3 (CP)	Listing of Concomitant Medications by Generic term		BDSI	SAC
2	*PK*	PKCL1P (PK)	Listing of Plasma GW856553 Concentration-Time Data		BDSI	SAC
3	*PK*	PKCL1P (PK)	Listing of Plasma GSK198602 Concentration-Time Data (Major Metabolite of GW856553)		BDSI	SAC
4	*PK*	PKCL1P (PK)	Listing of Plasma 14C -radioactivity Levels Over Time		BDSI	SAC
5	*PK*	PKPL1P (PK)	Listing of Derived Plasma GW856553 Pharmacokinetic Parameters		BDSI	SAC
6	*PK*	PKPL1P (PK)	Listing of Derived Plasma GSK198602 Pharmacokinetic Parameters (Major Metabolite of GW856553)		BDSI	SAC
7	*PK*	PKPL1P (PK)	Listing of Derived Plasma 14C-Radioactivity Pharmacokinetic Parameters		BDSI	SAC
8	*All Subjects*	NICHDL1	Listing of Nominal and Actual Doses & Radioactivity Administered to Subjects	The additional data for this listing should come in the same Excel spreadsheet as the other Urine/Faeces data	BDSI	SAC

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Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
9	*PK*	NICHDL2	Listing of Derived Urinary/Faecal 14C-Radioactivity Parameters (% Excreted) by Time	Utilise following parameters for this listing:- Ae urine (%excreted) = percentage of radioactivity excreted in urine Ae faeces (%excreted) = percentage of radioactivity excreted in faeces Ae urine 0-t (%excreted) = cumulative percentage of radioactivity excreted up to time t Ae faeces 0-t (%excreted) = cumulative percentage of radioactivity excreted up to time t Continue for all subjects for sample = urine. Then present for all subjects for sample = faeces	BDSI	SAC

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Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
10	*PK*	NICHDL3	Listing of Total Derived Urinary/Faecal 14C-radioactivity Parameters (% Excreted)	Final column corresponds to the parameter:- Ae total (%excreted) = total percentage of radioactivity excreted	BDSI	SAC
11	*PK*	NICHDL5	Listing of derived cold assay:14C-radioactivity plasma concentration ratios for GW856553 and its major metabolite GSK198602	Compute ratios using Loge transformed AUC but display back transformed values	BDSI	SAC
12	*All Subjects*	AE8 (CP)	Listing of Adverse Events of Special Interest		BDSI	SAC
13	*All Subjects*	NICHDL4	Listing of LFT Data	List all available LFT data for subjects with > 1 LFT parameter outside of normal range (footnote normal ranges). >=1.5 x ULN for the three Bilirubin parameters and >1 x ULN for the others. See Listing 4 of SB681323 RAP for Study MKC011 for an example.	BDSI	SAC
14	*All Subjects*	LB4 - Archive	Listing of Laboratory Threshold (Reference) Ranges		BDSI	SAC
15	*All Subjects*	GN8 (CP)	Listing of Genetics Subject Accountability		BDSI	SAC

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14.2. Data Display Specifications (Example Shells)

Available on request.

14.3. Structure of Excel spreadsheet for Excreta data transfer to DMPK

The following is a mock up of the excreta data structure that will be supplied by the external lab during the data transfer process. Note: for this study there will be six subjects (instead of the four shown below), so there will be an additional two columns in each data block, i.e. “005M” and “006M”.

Available on request.

Attachment 3: Study Administration

	Name and Address	Role/Responsibilities
Ethics Committee/ Institutional Review Board	[redacted]	

Attachment 4: [redacted] Report Number [redacted]

An Open label Study to Determine the Safety, Tolerability, Excretion Balance and Pharmacokinetics of [^{14}C]GW856553, Administered as a Single Dose of an Oral Solution to Healthy Adult Male Subjects

Author:

[redacted]

[redacted]

Sponsor:

GlaxoSmithKline

Park Road

Ware

Hertfordshire

SG12 0DP

UK

Contract Research Organisation:

[redacted]

[redacted]

[redacted]

[redacted]

UK

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Authentication

"I, the undersigned, hereby declare that the clinical aspects of this work were performed under my supervision and in accordance with the Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95). The study was conducted according to the procedures herein described and this report represents a true and accurate record of the results obtained."

[redacted] MBChB Date

Principal Investigator

"I, the undersigned, hereby declare that the analytical aspects of this study were performed under my direction and in accordance with the OECD Principles of Good Laboratory Practice, although no formal claim of compliance is made. The study was conducted according to the procedures herein described and this report represents a true and accurate record of the results obtained."

[redacted] BSc PhD Date

Principal Scientist

Quality Assurance Statement

The [redacted] Quality Assurance Unit conducted the following QA functions on this study. The dates of inspection are given below:

Date of QA Activity	Phase	Date of Report to Management
15 January 2008	Batch Production Record Review	16 January 2008
29 January 2008	Dose Manufacture	06 May 2008
30 January 2008	Dosing/Protocol Compliance	30 January 2008
14 February 2008	CRF Data Review	15 February 2008
04 March 2008	Analytical Data Review	06 March 2008
05 May 2008	Draft Report Audit	08 May 2008
24 July 2008	Final Report Audit	24 July 2008

The report has been audited by the Quality Assurance Personnel according to the appropriate Standard Operating Procedure(s). The report is considered to describe accurately the methods and procedures used in the study. The reported results accurately reflect the original data generated during the study.

[redacted] BSc — Date

Quality Assurance

Personnel Involved

Principal Scientist: [redacted] BSc (17 October 2007 - 11 July 2008)

[redacted] BSc PhD (11 July 2008 – present)

Manager, Clinical Metabolism: [redacted] BSc PhD

Principal Investigator: [redacted] MBChB

Co-Investigator: [redacted] MBChB

Project Manager: [redacted] RGN

Qualified Person: [redacted] BSc MSc MRPharms

Study Nurse: [redacted] RGN

[redacted] RGN

Scientific and Technical Staff: [redacted]

[redacted] BSc

[redacted] BSc

Quality Assurance: [redacted] BSc

SUMMARY

GW856553 is an inhibitor of p38 mitogen-activated protein kinase and is currently under development by GlaxoSmithKline. This study was conducted to investigate the absorption, distribution, metabolism and excretion of [^{14}C]GW856553 following a single oral administration (as the free base) to healthy male volunteers (aged 36-53 years) at a target dose of 10 mg per subject.

The highest mean concentration of total radioactivity was observed in plasma at 1.5 h post-dose (0.209 µg equivalents of GW856553/mL) and in whole blood at 1 h post-dose (0.144 µg equivalents of GW856553/g). Mean concentrations were below the limit of reliable measurement at 36 h post-dose for plasma and generally at 12 h post-dose for whole blood. The limits of reliable measurement were 0.005 µg equivalents of GW856553/mL for plasma and 0.009 µg equivalents of GW856553/g for whole blood.

Urinary and faecal elimination accounted for means of 64.8% (range: 59.4 to 69.5%) and 29.7% (range: 22.8 to 34.2%) of the administered dose, respectively. The mean total recovery was 94.5% (range: 91.9 to 103.6%) of the administered dose, recovered by the end of the collection period.

INTRODUCTION

GW856553 is an inhibitor of p38 mitogen-activated protein kinase. Further development of GW856553 requires a better knowledge of the absorption, metabolism and excretion in man. This was achieved by performing excretion balance, pharmacokinetic and metabolic profiling studies following administration of [^{14}C]GW856553 (also known as GW856553J; the radiolabelled free base) as an oral solution to 6 healthy male volunteers at a target dose of 10 mg per subject. Excreta samples were collected up to 216 h post-dose. Plasma samples were collected up to 168 h post-dose and samples for analysis of whole blood were collected up to 12 h post-dose. All of the samples were subjected to radioassay. In addition, key samples of urine, faeces and plasma were returned to the Sponsor for analysis of parent drug and GSK198602 (a metabolite of GW856553) concentrations (plasma only) and metabolite profiling investigations. The results of these analyses will be reported separately.

This Phase I clinical trial was performed by [redacted] (clinical phase) and [redacted] (analytical phase), a Contract Research Organisation (CRO) on behalf of GlaxoSmithKline.

The study was carried out according to Study No. [redacted] and the following time schedule:

ARSAC Approval:	13 December 2007
Ethics Approval:	18 December 2007
MHRA Approval:	25 January 2008
Volunteer Dosing:	30 January 2008

All data generated and recorded at [redacted] during this study, including a copy of the final report, will be stored in the Scientific Archives of [redacted] for 5 years after issue of the final report. After 5 years the Sponsor will be consulted regarding the disposition of continued storage.

EXPERIMENTAL PROCEDURE

Approval Procedure

The study was performed in accordance with Good Clinical Practice (GCP) and with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland (1964) as amended by the 29th WMA General Assembly, Tokyo, Japan (1975), the 35th WMA General Assembly, Venice, Italy (1983), the 41st WMA General Assembly, Hong Kong (1989), the 48th WMA General Assembly, Somerset West, Republic of South Africa (1996), the 52nd WMA General Assembly, Edinburgh, Scotland (2000), the 54th General Assembly, Washington (2002) revisions and the WMA Declaration of Helsinki, Tokyo (2004) revisions.

The European Clinical Trial Directive (2001/20/EC) requires authorisation from the competent authority (MHRA in the UK) prior to the conduct of clinical trials. The submission consists of a Clinical Trial Application (CTA) and an Investigational Medicinal Products dossier (IMPD). This Sponsor conducted the submission and a notice of acceptance from the MHRA was obtained on 16 February and 07 March 2007.

The proposed radioactive dose was subject to UK Department of Health Administration of Radioactive Substances Advisory Committee (ARSAC) approval.

The final protocol, the volunteer information, MHRA authorisation and ARSAC certificate were submitted to the [redacted] for consideration. The committee met on the 04 December 2007 and approval was granted on 18 December 2007 following the incorporation of their comments.

Volunteer Recruitment

Six healthy male subjects were selected from a panel of volunteers recruited by [redacted] on the basis of a satisfactory medical history, clinical examination and laboratory investigations.

Inclusion Criteria

Subjects were selected for study preparation if they met the following criteria:

- Male subjects, between 30-60 years of age, inclusive, at the time of screening.
- Body weight ≥ 50 kg (110 lbs).
- Body Mass Index between 18.5 and 29.9 kg/m^2, inclusive.
- Signed and dated informed consent prior to any screening activities for this study.
- The subject was able to understand and comply with protocol requirements, instructions and protocol stated restrictions.

Exclusion Criteria

A subject was excluded from the study if they met any of the following criteria:

- Any clinically relevant abnormality identified on the screening medical assessment, laboratory examination, or ECG (12-lead).
- Significant cardiac, pulmonary, metabolic, renal, hepatic, or gastro-intestinal conditions that in the opinion of the investigator and/or the Sponsor's medical monitor, placed the subject at an unacceptable risk as a participant in the trial.
- QTc(b) >450msecs.
- A definite or suspected personal or family history of adverse reactions or hypersensitivity to the trial drug or to drugs with similar chemical structure.
- History of regular alcohol consumption exceeding an average weekly intake of >21 units (or an average daily intake of greater than 3 units). One unit is equivalent to a half pint (284 mL) of beer/lager; 25 mL measure of spirits or 125 mL of wine.
- Subjects with a history of or presence of gastro-intestinal or renal disease or any other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
- Subjects who had consumed grapefruit or grapefruit juice within seven days of the first study day.
- Subjects who had exposure to more than three new chemical entities within 12 months prior to the start of the study.
- Subjects who had participated in a trial with a different new chemical entity within 90 days prior to the start of the study.
- If participation in the study would have resulted in the subject donating more than 400 mL of blood in the previous 56 days.
- Subjects who had received a total body radiation dose of greater than 5.0 mSv (upper limit of WHO Category II) or had been exposed to significant radiation (*eg* serial X-rays or CT scans, barium meals *etc*) in the 12 months prior to this study.

- History of elevated blood pressure or blood pressure persistently >140/90 mmHg at screening.
- An unwillingness to abstain from sexual intercourse with pregnant or lactating women; or an unwillingness of the subject to use a condom/spermicide in addition to having their female partner use another form of contraception such as an IUD, diaphragm with spermicide, oral contraceptives, injectable progesterone, sub-dermal implants or tube ligation if the women could become pregnant from the time of the first dose of the study medication until completion of the follow-up procedures.
- Lack of suitability for participation in this study, for any reason, in the opinion of the investigator.
- Any condition that could have interfered with the accurate assessment of recovery of ^{14}C.
- If the subject had taken any prescribed or over-the-counter medication within 5 days (or 5 half lives, whichever is longer) prior to the first dosing day, unless the investigator confirmed that it would not introduce additional risk or interfere with the study procedures or outcome.
- Liver function tests (ALT, AST, ALP, γGT and bilirubin) was greater than the upper limit of normal at screening.
- Positive urine drug screen.
- Positive HIV, Hepatitis B or C at screening.
- History of use of tobacco or nicotine-containing products within 6 months of screening or a positive urine cotinine screen (≥250 ng/mL).

Prestudy Procedures

Screening

The subjects attended the clinic for screening up to 21 days prior to the study commencement date. All subjects had a screening evaluation which consisted of the following:

1. Medical history
2. A record of detailed demographic data
3. Concurrent medication check
4. SAEs related to study participation
5. Physical examination (including assessment of height and weight)
6. Vital signs (heart rate (bpm), systolic and diastolic blood pressure (mmHg) in supine position)
7. 12-lead ECG measurement in supine position. Three readings conducted at least 5 min apart
8. Clinical laboratory testing (haematology, clinical chemistry, urinalysis)

9. Serology for hepatitis B, C and HIV
10. Alcohol breath test
11. Cotinine test
12. Urine drug test

Materials

[^{14}C]GW856553 (also known as GW856553J [Batch No. R16861/31/1]) was supplied by the Sponsor at a specific activity of 4.95 µCi/mg (183.2 kBq/mg) and with a stated radiochemical purity of 99.8%. [^{14}C]GW856553 was stored at ca -20°C in the dark until required for use. The Active Pharmaceutical Ingredient Release Document for [^{14}C]GW856553 is presented in Appendix 1.

Non-radiolabelled GW856553 reference standard (GW856553X Batch No. AA-013802-Batch-02-04) was supplied by the Sponsor and stored at ambient temperature. This material was used only as a chromatographic reference during the confirmation of the radiochemical purity of [^{14}C]GW856553. The certificate of analysis for GW856553X is shown in Appendix 2.

β-Cyclodextrin Sulfobutylether (Manufacturer's Batch No. CY-04A-05008, Sponsor Batch No 061125538) was supplied by the Sponsor and stored at ambient temperature until required for use. The certificate conformance for β-Cyclodextrin Sulfobutylether is represented in Appendix 3.

Aquasafe 500 Plus liquid scintillation fluid was obtained from Zinsser Analytic, Maidenhead, UK.

Carbo-Sorb® CO_2 absorbing solution and Permafluor® E^+ scintillation fluid were used in conjunction with the Packard Tri-Carb 307 Automatic Sample Oxidiser and were supplied by PerkinElmer Life Science and Analytical Instruments Inc, Sears Green, UK.

Spec-Check™-^{14}C used to estimate efficiencies of combustion and was also obtained from PerkinElmer.

All other materials and chemicals used were of analytical grade where available.

Radiochemical Purity

The radiochemical purity and chemical authenticity of [^{14}C]GW856553 was confirmed by High Performance Liquid Chromatography (HPLC) upon receipt at [redacted] Authentic, non-radiolabelled GW856553 reference standard was co-chromatographed with [^{14}C]GW856553. The HPLC equipment and conditions used are detailed in Appendix 4.

The supplied [^{14}C]GW856553 was shown to be chemically authentic with a radiochemical purity of 99.6%. Representative HPLC chromatograms are presented in Appendices 5 and 6.

Specific Activity

The specific activity of the supplied [^{14}C]GW856553 was not assessed at [redacted] The Sponsor supplied value of 4.95 μCi/mg (183.2 kBq/mg) was accepted and used in all calculations.

Admissions Procedures

The subjects were admitted to the clinic in the morning prior to dosing (Day -1). All subjects had an evaluation consisting of the following:

1. Medical history update
2. 12-lead ECG
3. Vital signs
4. Urine drug test
5. Clinical laboratory testing
6. Alcohol breath test

Prior to drug administration subjects were fasted for ca 10 h. A light standard lunch was provided ca 4 h after dosing. The pre-dose urine and faeces sample collection timepoint was started upon admission.

Subject Identification

Subjects were sequentially assigned unique subject numbers according to the code [redacted] on the morning of dosing. Demographic data is presented in Appendix 7.

Dosing Procedures

Dose Level

Each subject received a single oral administration of ca 10 mg of [^{14}C]GW856553 and a radioactive dose of ca 1.85 MBq. The radioactive dose received by each subject complied with the 'International Commission on Radiological Protection' (ICRP) Guidelines (1992) for a category IIa study (0.1-1 mSv).

Dose Manufacture

[^{14}C]GW856553 (91.07 mg, equivalent to 16.7 MBq) was weighed into a glass vial. This was transferred from the vial to a larger beaker with washings of β-Cyclodextrin Sulfobutylether solution. Further β-Cyclodextrin Sulfobutylether solution was added to the beaker to make up to target volume of 900 mL (total weight of β-Cyclodextrin Sulfobutylether solution added was 879.54 g). The beaker was then stirred for ca 4 h at ca 40ºC until a clear solution was confirmed by visual inspection.

The [^{14}C]GW856553 solution (target volume 100 mL, equivalent to 10 mg and 1.85 MBq) was weighed directly into labelled amber glass containers. Dose containers were transported to the clinical unit and stored overnight at ca 2-8°C.

The QP release certificate for the manufactured IMP (Batch 188003-002) is presented in Appendix 8.

Radioactive Concentration

The radioactive dose concentration of the [^{14}C]GW856553 oral dose formulation was determined as 0.49 µCi/mL (18.24 kBq/mL) prior to dosing.

Dose Administration

Each subject received a single oral administration of ca 10 mg of [^{14}C]GW856553. The subjects drank the solution (100 mL) directly from the dose container. Each dose container was rinsed with tap water (2 x 50 mL) and the water consumed.

Dose Determination

The actual dose received by each subject was calculated using the weight of dose in each individual dose container and the calculated radioactive concentration of [^{14}C]GW856553 solution. Any remaining dose in each container was accounted for. The actual dose received by each subject is presented in Appendix 7.

Safety Assessments

Vital signs (supine heart rate and supine systolic and diastolic blood pressure) were recorded at screening, Pre-dose (on the day of dosing), 15 min, 30 min, 1, 2, 4, 6, 8, 24 and 48 h after dosing and at the follow up visit.

Twelve lead ECGs were recorded at screening, pre-dose (on the day of dosing), 30 min, 1, 2, 4, 6, 8 and 24 h after dosing and at the follow up visit.

Blood samples were taken for haematology and clinical chemistry (including urinalysis) at screening, Day -1, 48 h post-dose and at the follow up visit.

A physical examination was performed at screening and at the follow up visit.

A urine drug screen was performed at screening and on Day -1.

An alcohol test was conducted at screening and on Day -1.

Adverse events were monitored and recorded throughout the study.

Collection of Biological Samples

Whole Blood and Plasma

Venous blood samples (ca 6 mL) were collected at the following time points from in situ venous cannulae or by venepuncture into tubes containing di-potassium EDTA for total radioactivity analysis:

Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 h post-dose.

An additional venous blood sample (ca 6 mL) was collected from each subject for analysis of the concentrations of parent drug and GSK198602 in plasma at the following time points:

Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose

An additional venous blood sample (3 x ca 10 mL) was collected from each subject for metabolite profiling analysis at the following time points:

Pre-dose, 1, 4 and 12 h post-dose

A ca 1 mL sample of blood was removed from each metabolite profiling sample, prior to centrifugation for total radioactivity analysis.

The remainder of each whole blood was subjected to centrifugation (1500 g for 15 min at ca 4^{o}C). Plasma samples were decanted into labelled polypropylene tubes for parent drug (ca 1 mL) and total radioactivity analysis (ca 1 mL). A reserve sample (ca 1 mL)

was also retained. Plasma for metabolite profiling analysis was decanted into labelled polypropylene tubes (3 x ca 5 mL).

A single ca 5 mL sample of pre-dose plasma from a single subject was retained and used to prepare a spiked sample storage control (see section 3.12).

Urine

Urine samples were collected as produced into pre-weighed, uniquely labelled containers pre-dose and for the following intervals:

0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192 and 192-216 h post-dose

A single sub-sample (ca 30 mL) was removed from the bulk sample for metabolite profiling analysis. An additional sub-sample (ca 5 mL) was retained for total radioactivity analysis and a further sub-sample (ca 1 L) was retained as a reserve sample.

Two ca 20 mL samples of pre-dose urine from a single subject were retained and used to prepare spiked sample storage controls (see section 3.12).

Any remaining bulk urine from each sample timepoint was discarded.

Faeces

Faeces samples were collected as produced into uniquely labelled, polypropylene containers pre-dose and at the following intervals:

0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192 and 192-216 h post-dose

At the end of each time point, faeces samples were defrosted, combined per subject and the bulk sample weight recorded.

Once homogeneity of the samples was confirmed, a sub-sample (ca 30 g) was removed and shipped to the Sponsor for metabolite profiling analysis. A further sub-sample (ca 30 g) was retained at [redacted] as a reserve sample. Any remaining bulk faeces homogenate was retained.

In addition, duplicate sub-samples (ca 20 g) were removed from a single subject's pre-dose faecal homogenate sample and were used to prepare spiked sample storage controls (see section 3.12).

Used toilet paper was retained but not analysed as it was deemed unnecessary.

Spiked Control Samples

Within 24 h of dosing, 2 aliquots of urine (ca 20 mL) were removed from a Day -1 urine sample from a single subject. They were spiked with [^{14}C]GW856553 solution at an appropriate concentration (ca 20000 dpm/mL). Two aliquots of pre-dose faecal homogenate from a single subject (ca 20 g) were spiked at ca 100,000 dpm/g, and a single aliquot of pre-dose plasma (ca 5 mL) from a single subject was spiked with ca 5000 dpm/mL). The spiked control samples were stored under the same conditions as the analytical samples and were subject to the same freeze/thaw regimen as other study samples.

Storage and Transportation of Biological Samples

Faeces for total radioactivity analysis were stored at ca -20^{o}C. Urine samples were stored at ca 4^{o}C prior to analysis. After analysis, samples were stored at ca -20^{o}C. Plasma samples for parent drug, metabolite and total radioactivity analysis were stored at ca -80^{o}C. Whole blood samples for total radioactivity analysis were stored at ca -20^{o}C.

Sub-samples of urine and faeces and plasma for metabolite profiling investigations and plasma samples for quantification of GW856553 and its metabolites, as well as spiked control samples for each matrix, were shipped to the Sponsor, Park Road, Ware, Hertfordshire, UK. The results of these analyses will be reported separately.

Preparation of Samples for Total Radioactivity Analysis

Liquid Samples

Duplicate aliquots of urine (ca 1 mL) and duplicate aliquots of plasma (0. 5 mL) were taken for Liquid Scintillation Counting (LSC) analysis. Samples were then mixed with Aquasafe 500 Plus scintillation fluid (10 mL). Plasma samples had an additional 1 mL of water added.

Solid Samples

Faeces samples were homogenised (using a Waring industrial blender) in approximately 3 times the weight of deionised water and the homogenate weight recorded. Duplicate aliquots of faeces homogenate (ca 0.3 g) and duplicate aliquots of whole blood (ca 0.3 g) were weighed into Combustocones® containing Combustopads® for combustion analysis. Samples were combusted using a Packard Tri-Carb 307 Automatic Sample Oxidiser. The resultant $^{14}CO_2$ generated was collected by absorption in Carbo-Sorb® (8 mL) to which Permafluor®E^+ (10 mL) was added.

Combustion of standards during sample combustion showed that recovery efficiencies were in excess of 97% throughout.

Quantification of Total Radioactivity

Radioactivity was quantified using a liquid scintillation analyser with automatic quench correction using an external standard method. Samples were allowed to heat and light stabilise and each sample was analysed for 5 min. Prior to calculation of individual results, a background count rate was determined and subtracted from each sample count rate.

A limit of reliable measurement of 30 d.p.m. above background has been instituted in these laboratories. At the specific activity used, this is equivalent to a limit of 0.005 µg equivalents of GW856553/mL for plasma (at a sample volume of 0.5 mL) and 0.009 µg equivalents of GW856553/g for whole blood (at a sample weight of ca 0.3 g).

Data Presentation

Radioactivity concentration data are quoted to three significant figures but to a maximum of three decimal places. Samples containing levels of radioactivity below the reliable limit of measurement are denoted as NQ (not quantifiable). For calculation of mean values and standard deviation (SD), NQ values are taken as zero. However, mean and SD values are not calculated if the results for at least half of the subjects are NQ and are reported as NC (not calculable). If all of the values in the subject group are NQ, the mean is reported as NQ and the SD as NC.

Blood:plasma ratios are quoted to one decimal place and are denoted as NC if either concentration is below the limit of reliable measurement. NC values are excluded from the calculation of the mean.

Excretion data are presented to one decimal place. Data below the limit of accurate determination are denoted as 0.0, and are taken as zero for calculation of the mean. Where a sample is not available, this is designated as NS (no sample) and taken as zero for calculation of the mean.

Data presented in Tables and Appendices are computer generated and rounded appropriately for inclusion in the report. As a consequence, calculations of values from data presented will, in some instances, yield minor variations.

RESULTS

Doses Administered

The actual doses received by the subjects were in the range 10.4 to 10.5 mg (Appendix 7).

Total Radioactivity Analysis in Plasma and Whole blood

The concentrations of total radioactivity in plasma and whole blood following a single oral administration of [^{14}C]GW856553 to healthy male volunteers at a target dose level of 10 mg per subject are shown in Tables 1 and 2, respectively, with mean results depicted graphically in Figure 1. Concentrations are expressed as µg equivalents of GW856553/mL (plasma) or µg equivalents of GW856553/g (whole blood). Whole blood:plasma concentration ratios are given in Table 3.

The highest observed mean concentration of total radioactivity in plasma occurs at 1.5 h post-dose, with a mean of 0.209 µg equivalents of GW856553/mL (range: 0.189 to 0.264 µg equivalents of GW856553/mL). The mean concentration decreased thereafter, and at 24 h post-dose was 0.011 µg equivalents of GW856553/mL (range: 0.008 to 0.015 µg equivalents of GW856553/mL). At 36 h post-dose and beyond, the concentrations were below the limit of reliable measurement (0.005 µg equivalents of GW856553/mL).

Concentrations of whole blood generally paralleled those in plasma, although at a lower level. The highest observed mean concentration occurred at the first sampling time (1 h post-dose), with a mean of 0.144 µg equivalents of GW856553/g (range: 0.093 to 0.179 µg equivalents of GW856553/g). The mean concentration decreased thereafter and was just above or below the limit of reliable measurement (0.009 µg equivalents of GW856553/g) at 12 h post-dose.

Mean whole blood:plasma ratios were 0.7 and 0.6 at 1 and 4 h post-dose, respectively.

Excretion Kinetics

The excretion of total radioactivity following a single oral administration of [^{14}C]GW856553 to healthy male volunteers at a target dose level of 10 mg per subject is shown in Table 4 with cumulative data given in Table 5. The mean cumulative excretion data is depicted graphically in Figure 2. Urine pH values are presented in Appendix 9. Individual sample and homogenate (faeces only) weights, together with the dpm/g values for urine and faeces are presented in Appendices 10 and 11, respectively.

The major route of elimination was via the urine, which accounted for a mean of 64.8% (range: 59.4 to 69.5%) of the administered dose by 216 h post-dose. Excretion via the faeces accounted for a mean 29.7% (range: 22.8 to 34.2%) of the administered dose. The mean total recovery was 94.5% (range: 91.9 to 103.6%) of the administered dose.

Urine pH values were shown to be within normal ranges with the majority of samples measured at pH 6.0 to 8.0.

CONCLUSIONS

Six male volunteers each received a single oral administration of [^{14}C]GW856553 at a target dose level of 10 mg per subject.

The highest mean concentration of total radioactivity was observed in plasma at 1.5 h post-dose (0.209 µg equivalents of GW856553/mL) and in whole blood at 1 h post-dose (0.144 µg equivalent of GW856553/g). Mean concentrations were below the limit of reliable measurement at 36 h post-dose for plasma and generally at 12 h post-dose for whole blood. The limits of reliable measurement were 0.005 µg equivalents of GW856553/mL for plasma and 0.009 µg equivalents of GW856553/g for whole blood.

Urinary and faecal elimination accounted for means of 64.8% (range: 59.4 to 69.5%) and 29.7% (range: 22.8 to 34.2%) of the administered dose, respectively. The mean total recovery was 94.5% (range: 91.9 to 103.6%) of the administered dose.

TABLES

Concentration of Total Radioactivity in Plasma Following Single Oral Administration of [^{14}C]GW856553 to Healthy Male Volunteers

Target Dose Level: 10 mg per subject

Results expressed as µg equivalents of GW856553/mL

Sample	Time point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Mean	SD

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.

NC – Not calculable

NQ – Below the limit of reliable measurement (0.005 µg equivalents of GW856553/mL)

SD – Standard deviation

Concentration of Total Radioactivity in Whole Blood Following Single Oral Administration of [^{14}C]GW856553 to Healthy Male Volunteers

Target Dose Level: 10 mg per subject

Results expressed as µg equivalents of GW856553/g

Sample	Time point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Mean	SD
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.									

NQ – Below the limit of reliable measurement (0.009 µg equivalents of GW856553/g, taken as zero for calculation of the mean and standard deviation, where applicable)

NC – Not calculable

NQ – Not quantifiable (taken as zero for calculation of the mean and standard deviation)

SD – Standard deviation

Whole Blood : Plasma Concentrations of Total Radioactivity; Concentration of Total Radioactivity Following Single Oral Administration of [^{14}C]GW856553 to Healthy Male Volunteers

Target Dose Level: 10 mg per subject

Whole Blood : Plasma Ratios								
Time point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Mean	SD
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.								

NC – Not calculable

NQ – Not quantifiable

SD – Standard deviation

Excretion of Total Radioactivity Following Single Oral Administration of [^{14}C]GW856553 to Healthy Male Volunteers

Target Dose Level: 10 mg per subject

Results Expressed as % of administered dose

Sample	Time point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Mean	SD
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.									

NC – Not calculable

NQ – Not quantifiable

NS – No sample (taken as zero for calculation of the mean and standard deviation, where applicable)

Cumulative Excretion of Total Radioactivity Following Single Oral Administration of [^{14}C]GW856553 to Healthy Male Volunteers

Target Dose Level: 10 mg per subject

Results Expressed as % of administered dose

Sample	Time point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Mean	SD
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.									

NC – Not calculable

NQ – Not quantifiable (taken as zero for calculation of the mean and standard deviation, where applicable)

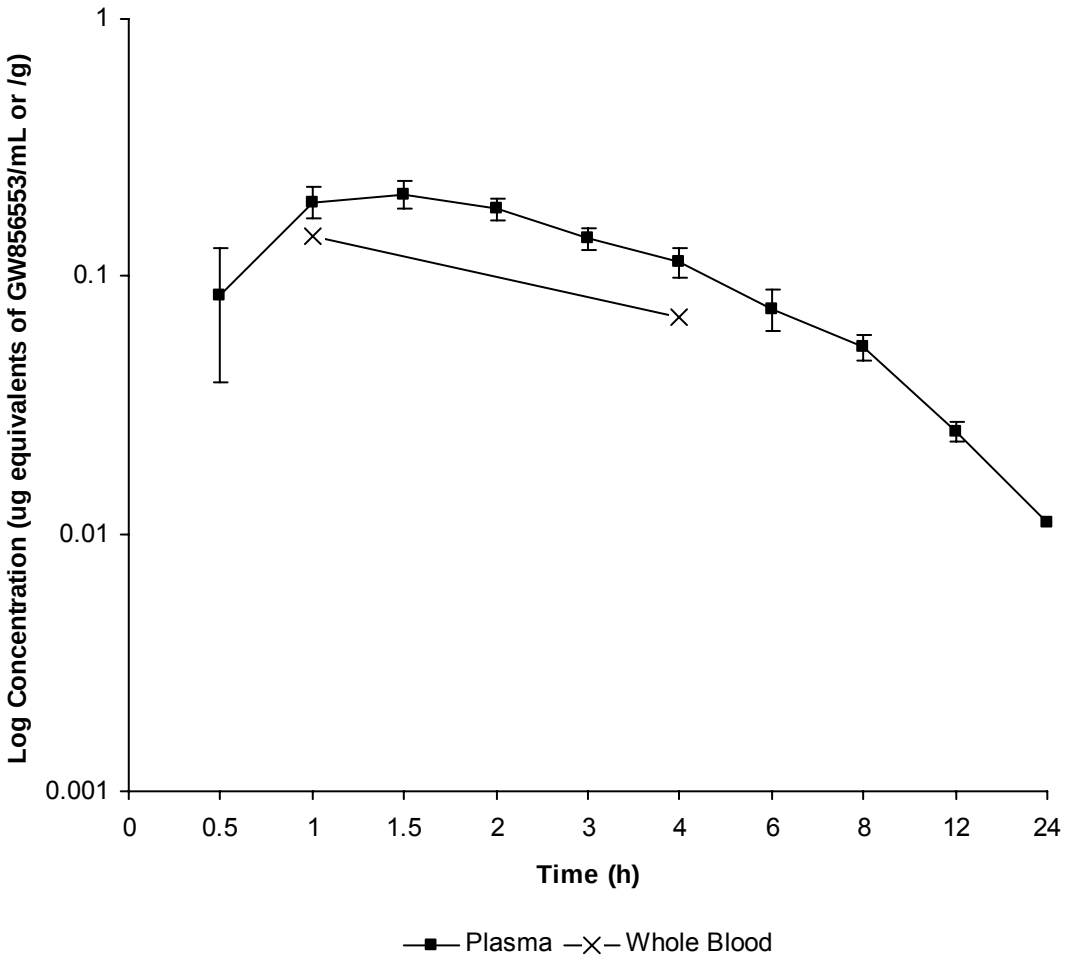
NS – No sample

FIGURES

Mean Concentration of Total Radioactivity in Plasma and Whole Blood Following Single Oral Administration of [^{14}C]GW856553 to Healthy Male Volunteers

Target Dose Level: 10 mg per subject

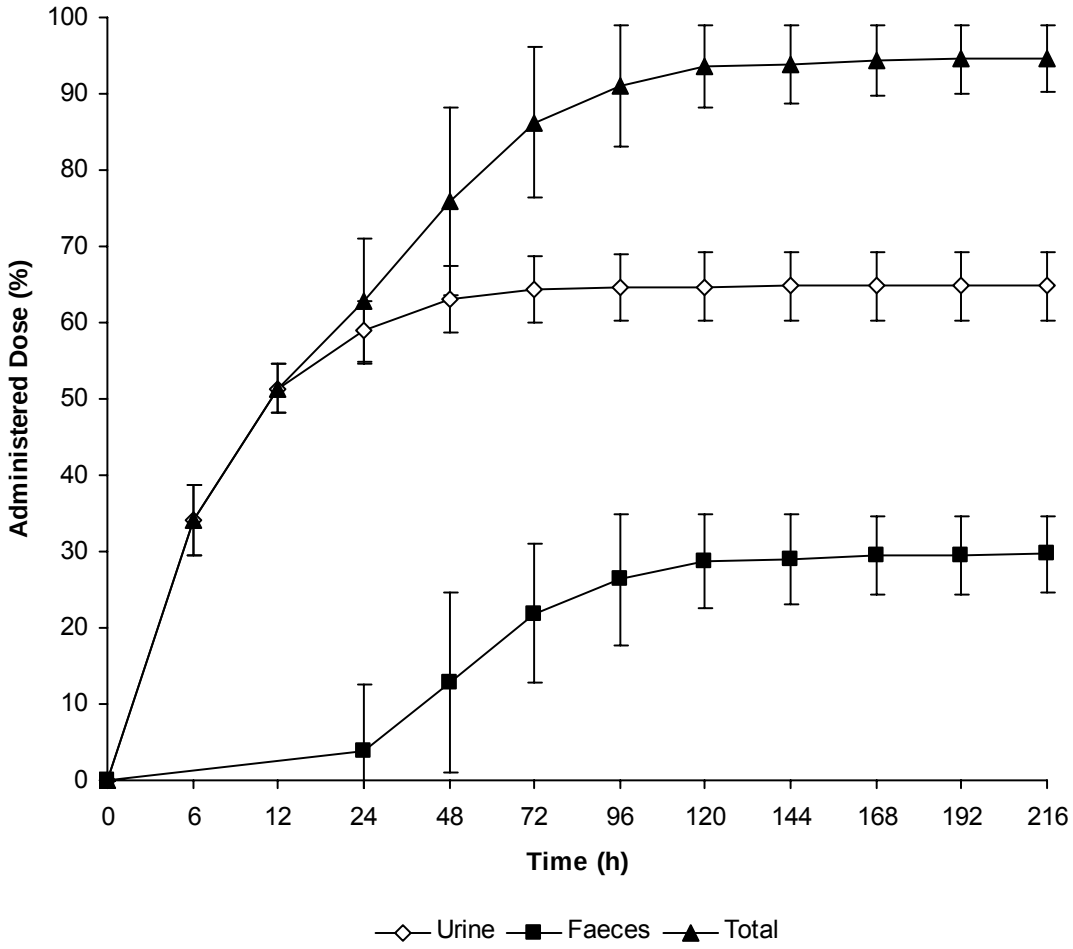
Results expressed as µg equivalents of GW856553/mL (plasma) or µg equivalents of GW856553/g (whole blood)



Mean Cumulative Excretion of Total Radioactivity Following Single Oral Administration of [^{14}C]GW856553 to Healthy Male Volunteers

Target Dose Level: 10 mg per subject

Results expressed as % of the administered dose



APPENDICES

Appendix 1 Active Pharmaceutical Ingredient Release Document for [^{14}C]GW856553

CHEMICAL DEVELOPMENT
ACTIVE PHARMACEUTICAL INGREDIENT RELEASE DOCUMENT
DNG# SD2008/00037/00

API Number:	GW856553J	Batch Number:	R16861/31/1
API Salt:	Free Base	Site of Manufacture:	Stevenage
Route/Process Number:	N/A	Site of Analysis:	Stevenage
Date of Manufacture:	11-Dec-2007	API Batch Report Ref:	N/A

APPROVED FOR: Clinical Studies

Summary of analytical data:-

Summary Analytical Reference:	EE305712 08-Jan-2008 16:08:44
Specification Reference:	S0010323v1
Identity Confirmed by:	1H NMR
Assigned Purity (%w/w)	100.8
Assigned Purity (as free base) (%w/w)	100.8
Weighing Factor	1.000g contains 1.000g of GW856553X as free base
Specific Activity (µCi/mg)	4.95
Radiochemical Purity (% area)	99.8
Retest Date	11-Mar-2008
Storage Conditions	Store in a freezer, -25 to -10°C
Ref. to stability data	eE305610

ANALYTICAL SCIENCES AUTHORISATION		
Analysis performed in compliance with cGMP		First Issue
Signature	[redacted]	Date 08- January 2008
Name	[redacted]	(Analytical Sciences)

CDQA AUTHORISATION FOR CLINICAL STUDIES		
This batch was manufactured and tested in compliance with cGMP The compliance of this batch with any regulatory dossier must be checked prior to release of the packed drug product.		
Materials of [redacted]	YES/NO	
Signature	[redacted]	Date 9 Jan 2008
Name	[redacted]	(Chemical Development Quality Assurance)

Received & accepted by [redacted] 30th Jan 08

Page 1 of 1

Appendix 2 Certificate of Analysis for Non-Radiolabelled GW856553 Reference Standard

CHEMICAL DEVELOPMENT

CERTIFICATE OF ANALYSIS

GW856553X

Page 1 of 1

Batch Number	AA-013802-Batch-02-04
Reference Number	SD2007/03088/00
Analytical Reference Number	200085402 (Carbogen data reference)
Date of Manufacture	21 April 2004
Storage Conditions	Store up to 30°C
Retest Date	12 December 2008

ANALYTICAL RESULTS	
Test	**Result**
Identity	Confirmed
Drug related impurities (%area)	0.122
Organic volatile impurities (%w/w)	0.043
Water content (%w/w)	0.017
Residue on ignition (%w/w)	< 0.1
Total impurities (%w/w)	0.182

Assigned Purity (%w/w)	99.8

[redacted]

Dr. [redacted]

12-Dec-2007

Date 12 Dec 2007

Copy 1

Appendix 3 Certificate of Conformance for β-Cyclodextrin Sulfbutylether

GlaxoSmithKline

Certificate of Conformance

GlaxoSmithKline Research & Development Limited
New Frontiers Science Park
Third Avenue
Harlow
Essex
CM19 5AW
Tel [redacted]
Fax
www.gsk.com

Product Name	B-Cyclodextrin Sulfobutylether (Captisol)
Batch Number	GSK Inventory Lot Number – 061125538
	Manfacturers Batch No - CY-04A-05008
Date of Manufacture	Mar 2005.
Re- Evaluation Date	Mar 2009
GSK Analytical Reference.	EE140872

This is to certify that the above Batch has been purchased by GSK from an approved supplier and tested / released for clinical use in accordance with GSK R&D Pharmaceutical Development procedures.

The use of Captisol with GW856553 is the subject of an agreement between GSK and Cydex.

Manufacturers Certificate of analysis and TSE statement are attached.

Approved by [redacted] 11 Dec 2007

Name [redacted] Date 11 Dec 2007

Job Title: Qualified Person.

Pharmaceutical Development Quality Assurance.

Harlow. UK.

Received & accepted by [redacted] 20th Jan 08

Page 1 of 1

Appendix 4 Radio-HPLC Conditions for the Determination of the Radiochemical Purity of [^{14}C]GW856553

Equipment

HPLC Model:	Waters Alliance 2695 Seperations Module Waters 2487 Dual Absorbance Detector
Radiodetector Model:	Radiomatic™ Flo-one®\Beta, Flow Scintillation Analyser (Model 150TR)
Data Handling:	Atlas 2002 (Thermo Labsystems) Product Version 6.18

Conditions

Column:	Phenomenex Luna C18 5 µm
Column Temperature:	30°C
Auto-sampler Temperature:	Ambient
Mobile Phase:	A: 50 mM ammonium acetate B: Acetonitrile

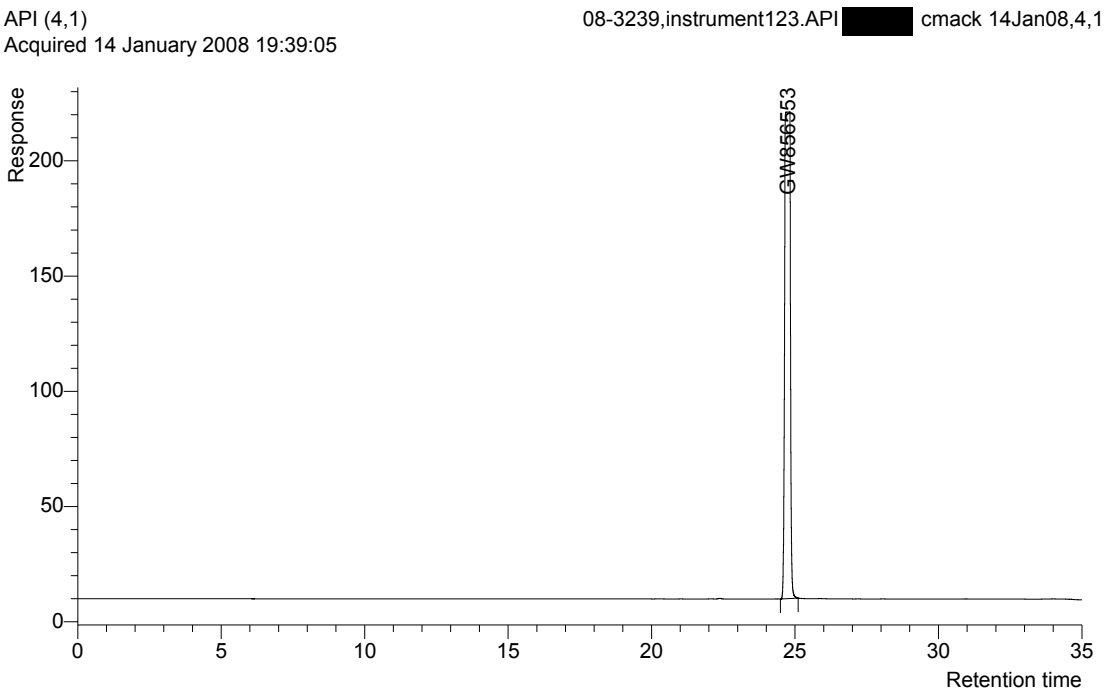
Gradient:

Time (min)	%A	%B
0	80	20
5	70	30
11	70	30
30	30	70
31	0	100
35	0	100
36	80	20
40	80	20

Flow rate 1.0°mL/min

U.V. Detector Wavelength: 220 nm

Appendix 5 Representative Radio-HPLC Chromatogram of the Radiochemical Purity of [^{14}C]GW856553



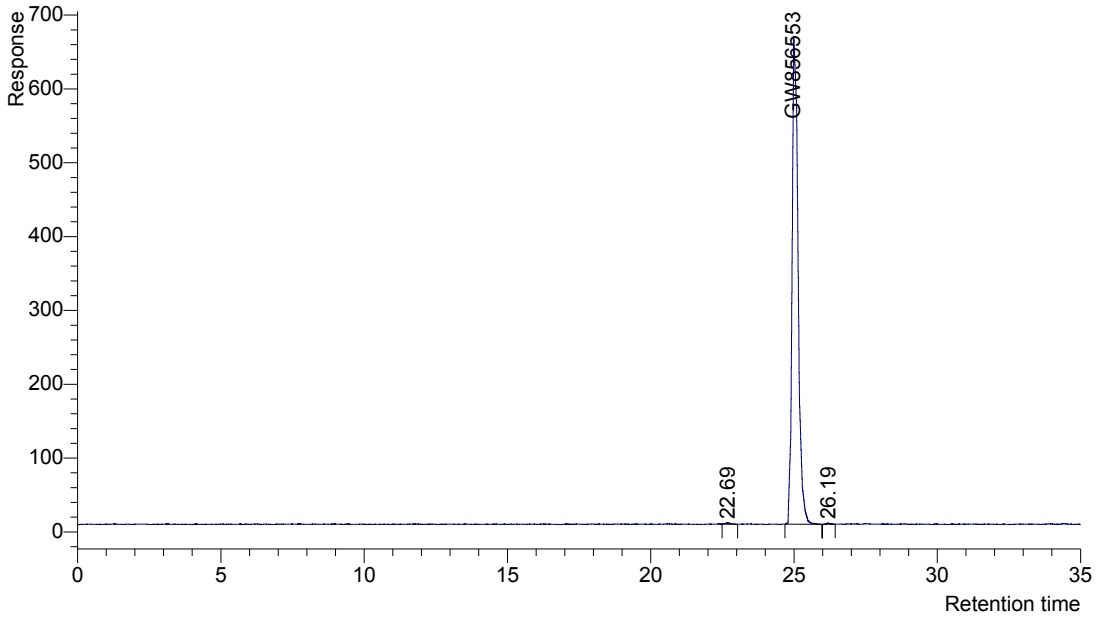
Peak Information

Peak No.	Retention Time (min)	Peak Name	Purity (%)
1	24.8	GW856553*	100

*assigned by co-chromatography with GW856553 reference standard

Appendix 6 Representative HPLC Chromatogram for Non-Radiolabelled GW856553 Reference Standard

API (4,1) 08-3239,instrument122.API [redacted] cmack 14Jan08,4,1
Acquired 14 January 2008 19:39:04



Peak Information

Peak No.	Retention Time (min)	Peak Name
1	22.7	-
2	25.0	GW856553
3	26.2	-

Appendix 7 Demographic and Dosing Data

Subject	Date of Birth	Age (year)	Height (cm)	Weight (kg)

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.

Subject	Date of Dosing	Dose Received		
		MBq	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.

Appendix 8 Qualified Person Certification of [^{14}C]GW856553 Investigational Medicinal Product (Batch No.: 188003-002)

[redacted]

Qualified Person Certification of a Batch of Investigational Medicinal Product

Manufacturer: Production Unit [redacted]

MIA IMP Licence No. : [redacted] **Site No. :** [redacted]

Schedule

Batch number: 188003 - 002 **Study Nos.:** [redacted] (Clinic)

Sponsor: GlaxoSmithKline

Eudract No.: 2007-000303-18

Product Description: A 250mL amber glass container with matching polypropylene screw cap closure, containing 100mL of *ca* 1.85 MBq and *ca* 10mg ^{14}[C] – GW856553 in a solution of β – cyclodextrin sulfobutylether. The glass container bears an open fixed and flag label

No. of units in batch: 7

Declaration
I have ensured that the batch of investigational product cited in the schedule above was manufactured and checked in accordance with the requirements of Commission Directive 2003/94/EC, the product specification file and the information notified in the clinical trial application.

[redacted] BSc MSc MRPharmS
Qualified Person (No. [redacted])

Date: 30th Jan 08

Appendix 9 Urinary pH Values

Subject	Collection Interval	pH
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.		

Subject	Collection Interval	pH
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.		

Appendix 10 Urinary Sample Weights and Mean dpm/g Values

Subject	Collection Interval	Total Weight (g)	Mean 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.

Subject	Collection Interval	Total Weight (g)	Mean 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.

Appendix 11 Faeces Sample and Homogenate Weights, and Mean dpm/g Values

Subject	Collection Interval	Sample Weight (g)	Homogenate Weight (g)	Mean 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.				

Subject	Collection Interval	Sample Weight (g)	Homogenate Weight (g)	Mean 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.				

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

Title:	An open label study to determine the safety, tolerability, excretion balance and pharmacokinetics of 14CGW856553, administered as a single dose of an oral solution to healthy adult male subjects

Compound Number: GW856553

Effective Date: 14-NOV-2007

Protocol Amendment Number: 01

Description:

GW856553 is a p38 MAP kinase inhibitor and is currently under development by GlaxoSmithKline.

This will be an open label study conducted at one site. Six healthy male subjects will be enrolled to ensure at least four fully evaluable subjects. Each subject will receive a single 10 mg oral dose of GW856553 containing 50 μCi of [^{14}C] GW856553. Urine and faecal samples will be collected until 216 h after dosing but subjects may be discharged after 168 h if 90% of the dose is recovered and/or <1% of the dose is excreted in a 24 h period. Blood and plasma will be collected at various sample times after dosing to measure parent drug and total drug-related material. Samples of urine, faeces and plasma will be transferred into a separate study to characterise and quantify metabolites in these matrices. Safety will be assessed by adverse event monitoring, vital signs, ECG and clinical laboratory tests

Subject: GW856553, ADME, radiolabel

Author(s):

[redacted] (CSSO, Greenford)
[redacted] (RDI CPDM, Stevenage)
[redacted] (DMPK, Ware)
[redacted] (CPK M&S, Greenford)
[redacted] (Discovery Biometrics, Greenford)
[redacted] (Pharm Dev, Ware)

Revision Chronology:

GM2007/00109/00	17-OCT-2007	Original
GM2007/00109/01	14-NOV-2007	Amendment No.: 01 Addition of information regarding the reporting of suspected serious unexpected adverse reactions at request of regulatory authority

SPONSOR SIGNATORY:

[redacted] MD, MSc, FFPM

14 Nov 2007
Date

Vice President
Head of Respiratory
Clinical Pharmacology and Discovery Medicine

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	Dr. [redacted]	[redacted]	[redacted]	[redacted]	Gunnells Wood Road Stevenage SG1 2NY Hertfordshire UK
Secondary Medical Monitor	Dr [redacted]	[redacted]	[redacted]	[redacted]	Gunnells Wood Road Stevenage SG1 2NY Hertfordshire UK
Tertiary Medical Monitor					

Sponsor Registered Address:

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

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): EudraCT 2007-005303-18

INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

Investigator Name:	Dr [redacted]
Investigator Address:	[redacted]
Investigator Phone Number:	[redacted]

Investigator Signature	Date

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
ALT	Alanine amino transferase
AP	Alkaline phosphatase
ARSAC	Administration of Radioactive Substances Advisory Committee
AST	Aspartate amino transferase
$AUC_{(0-t)}$	Area under the concentration time curve between zero and the time to the last measurable concentration
$AUC_{(0-\infty)}$	Area under the concentration time curve from zero to infinity
b.i.d.	Twice daily (*bis in die*)
BMI	Body Mass Index
CIB	Clinical Investigator's Brochure
CIC	Clinical information centre
Cmax	Maximum observed concentration
CPDS	Clinical Pharmacology Data Sciences
CPK	Creatine phosphokinase
CPU	Clinical Pharmacology Unit
CRF	Case Report Form
D	Dose
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra acetate
EFD	Embryofoetal development
e.g.	For example (exempli gratia)
EISR	Expedited investigator safety reports
FSH	Follicle stimulating hormone
Gamma-GT	Gamma glutamyl transferase
GCP	Good Clinical Practice
GI	Gastrointestinal
GSK	GlaxoSmithKline
h	Hour
Hb	Haemoglobin
HbsAG	Hepatitis B surface antigen
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
HDL	High Density Lipoprotein
HIV	Human immunodeficiency virus
HVD	Half value duration
IB	Investigator's Brochure
ICJ	Ileocaecal junction
i.e.	Id est
IEC	Independent Ethics Committee
IRB	Institutional Review Board
kg	Kilogram

LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
mg	Milligram
mL	Millilitre
MNLD	Maximum non-lethal dose
MSDS	Material Safety Data Sheet
ng	Nanogram
NOAEL	No observed adverse effect level
NRPB	National Radiation Protection Board
NSAIDs	Non-steroid anti-inflammatory drug
OTC	Over-the-counter
PGx	Pharmacogenetic(s)
pH	Potential of hydrogen
PK	Pharmacokinetic(s)
PR	Pulse rate
QC	Quality control
QRS, QT, QTc	ECG intervals
RBC	Red blood cell count
SAE	Serious adverse event
SNP	Single nucleotide polymorphism
SRM	Study reference manual
t1/2	Terminal phase half life
t.i.d.	Three times daily
tmax	First time of occurrence of maximum observed concentration
UK	United Kingdom
v/v	percent by volume in volume
v/w	volume per weight
WBC	White blood cell count

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Not applicable

Trademarks not owned by the GlaxoSmithKline group of companies
Captisol
Vfend
WinNonlin

PROTOCOL SUMMARY

Rationale

As part of the clinical development plan for GW856553, the absorption, metabolism and excretion in humans must be adequately characterised and described.

This clinical study is proposed to characterise the metabolic disposition of [^{14}C]GW856553 by analysing the radioactivity in whole blood, plasma, urine and faeces, and to provide samples for a separate study to characterise and quantify the metabolic profile of [^{14}C]GW856553 in each matrix.

Although some data on the disposition of GW856553 are available from *in vitro* and *in vivo* studies in animals, *in vitro* studies using human tissues and early Phase 1 clinical trials, the metabolic pathways and elimination routes for GW856553 in humans have not been fully explored.

The predominant route of elimination of drug-related material in rats and monkeys was via the faeces (78-89% of the dose), with urinary excretion representing a lesser amount of elimination (5-14% of the dose). In bile duct-cannulated rats and monkeys, elimination in bile accounted for approximately 19% and 10% of the dose, respectively. The combined biliary and urinary recoveries indicate that at least 37% and 19% of the oral dose was absorbed in the rat and monkey, respectively.

Objective(s)

- To determine the rate and extent of excretion of total radioactivity in urine and faeces and total recovery of radioactivity, after a single oral dose of [^{14}C]GW856553 to healthy male subjects.
- To generate samples (for a separate study) with which to characterise and quantify the metabolic profile of GW856553 in plasma, urine, and faeces following administration of a single oral dose of [^{14}C]GW856553 to healthy male subjects.
- To determine pharmacokinetic parameters of GW856553 and its major metabolite GSK198602 following a single oral administration of [^{14}C]GW856553.
- To further assess the tolerability of single oral doses of [^{14}C]GW856553 in healthy male subjects.

Endpoint(s)

The primary endpoint of this study is to report the urinary and faecal cumulative excretion as a percentage of the total radioactive dose administered over time.

The secondary pharmacokinetic endpoints will consist of:

- AUC(0-∞), Cmax, AUC(0-t), tmax and t½ of total drug-related material (radioactivity) in plasma following oral dosing.

- AUC(0-∞), Cmax, AUC(0-t), tmax, t½ of GW856553 and its major metabolite GSK198602 in plasma following oral dosing.
- Adverse events, ECG, vital signs and clinical laboratory tests (including LFTs).

Characterisation and quantification of metabolites in plasma, urine and faecal homogenates will be performed under a separate protocol by Drug Metabolism and Pharmacokinetics (DMPK), GSK and results will be reported in a separate report.

Study Design

This will be an open-label study conducted in 6 male subjects.

Each subject will receive a single 10mg (50 μCi) oral dose of [^{14}C]GW856553. This will involve a ten-night, eleven-day admission.

Urine and faecal samples will be collected until 216h after dosing but subjects may be discharged after 168h if 90% of the dose is recovered and/or <1% of the dose is excreted in a 24h period. If recovery of radioactivity is incomplete at the end of the collection period, subjects may be asked to collect samples of either urine and /or faeces for an extended period either within the clinical unit or at home.

Plasma and blood concentrations of total drug-related material (radioactivity) and plasma concentrations of unchanged GW856553 and its major metabolite GSK198602 will be measured and will be used to determine the aforementioned PK parameters.

Safety will be assessed by monitoring subjects for adverse events, vital signs, ECGs and laboratory parameters.

Study Population

Six healthy male volunteers aged 30-60 years will be recruited to obtain 4 evaluable 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 centre.

Study Assessments

Volunteers will undergo a medical examination within 21 days of the start of the study to confirm eligibility. On the day before dosing all subjects will attend the clinic and will fast from food and fluid from 11 pm. Subjects will have consented to a stay of 10 nights (216 hours) assuming average recovery across all subjects is >90% with <1% excreted in a 24 hour period.

An outline of the assessments is given below:

Pre-Study (within 21 days of dosing)

Medical history; physical examination; 12-lead ECG; vital signs (pulse rate, systolic and diastolic blood pressure) in a supine position; clinical safety laboratory (haematology, clinical chemistry, urinalysis); serology screening, alcohol breath test and a urine drug screen. Subjects do not need to be fasted for the pre-study assessments.

Treatment Phase

Safety will be assessed during the study period and follow-up by adverse event monitoring, laboratory safety tests, 12-lead ECG, supine vital signs and urine drug screen.

Blood samples will be collected to study the pharmacokinetics of GW856553 in plasma and to assess ^{14}C radioactivity. Further blood, urine and faeces collections will be made for metabolite identification.

Follow up

Follow-up (within 7 to 14 days of the last sampling day): a 12-lead ECG; vital signs (pulse rate, systolic and diastolic blood pressure) in supine position; adverse event reporting and clinical safety laboratory (haematology, clinical chemistry, urinalysis).

1. INTRODUCTION

1.1. Background

P38 MAP Kina25se in Inflammation

p38 mitogen-activated protein (MAP) kinase (p38, also known as CSBP) is a serine/threonine directed protein kinase identified in human monocytes as the target for a novel class of cytokine suppressive anti-inflammatory drugs (CSAIDS). p38 phosphorylates a number of intracellular proteins, including signal transduction molecules and transcription factors that are involved in regulating the biosynthesis of inflammatory cytokines such as interleukin (IL)-1 and tumour necrosis factor alpha (TNF-α). p38 also regulates many of the biological actions of these cytokines, such that p38 activation is involved in a cytokine amplification loop. Consequently, inhibitors of this kinase are expected to be effective in diseases such as rheumatoid arthritis (RA) where the pro-inflammatory mechanisms are particularly cytokine-dependent.

P38 MAP Kinase inhibitors in RA

Animal studies have demonstrated that p38 inhibitors have potent anti-inflammatory activity in the collagen induced arthritis model in mice, in the rat adjuvant-induced arthritis model, and in the PG-PS induced reactivation of arthritis in rats. Evidence of disease modifying, protective activity of p38 inhibitors has been demonstrated using radiographic assessment of joint destruction during the rat adjuvant-induced arthritis model.

An orally available treatment, which is able to simultaneously inhibit all three of the key cytokines implicated in the immunopathogenesis of RA (TNF-α, IL-1 and IL-6) would deliver a substantial benefit to the RA patients.

1.1.1. Pre-Clinical Information

Full details of the preclinical pharmacological, toxicological and pharmacokinetic profiles of GW856553 can be found in the Clinical Investigator's Brochure (CIB) [GlaxoSmithKline Document Number WM2004/00033/03].

1.2. Rationale

As part of the clinical development plan for GW856553, the absorption, metabolism and excretion in humans must be adequately characterised and described.

This clinical study is proposed to characterise the metabolic disposition of [^{14}C]GW856553 by analysing the radioactivity in whole blood, plasma, urine and faeces, and to provide samples for a separate study to characterise and quantify the metabolic profile of [^{14}C]GW856553 in each matrix.

Although some data on the disposition of GW856553 are available from *in vitro* and *in vivo* studies in animals, *in vitro* studies using human tissues and early Phase 1 clinical trials, the metabolic pathways and elimination routes for GW856553 in humans have not been fully explored.

The predominant route of elimination of drug-related material in rats and monkeys was via the faeces (78-89% of the dose), with urinary excretion representing a lesser amount of elimination (5-14% of the dose). In bile duct-cannulated rats, and monkeys, elimination in bile accounted for approximately 19% and 10% of the dose, respectively. The combined biliary and urinary recoveries indicate that at least 37% and 19% of the oral dose was absorbed in the rat, and monkey, respectively.

Bioavailability (F) is not known in humans, but oral bioavailability ranged from 71% in rats to 33% in monkeys. Plasma clearance ranged from 5.9 ml/min/kg in monkeys to 14 mL/min/kg in dogs.

A submission to the Administration of Radioactive Substances Advisory Committee (ARSAC) will be made. Once approval has been received, a copy of the approval will be submitted to the Ethics Committee.

2. OBJECTIVE(S)

2.1. Primary

- To determine the rate and extent of excretion of total radioactivity in urine and faeces and total recovery of radioactivity, after a single oral dose of [^{14}C]GW856553 to healthy male subjects.
- To generate samples with which to characterise and quantify the metabolic profile of GW856553 in plasma, urine and faeces following administration of a single oral dose of [^{14}C]GW856553 to healthy male subjects.

2.2. Secondary

- To determine pharmacokinetic parameters of GW856553 and its major metabolite GSK198602 following a single oral administration of [^{14}C]GW856553.
- To further assess the tolerability of a single oral dose of GW856553 in healthy male subjects.

3. ENDPOINT(S)

3.1. Primary

- The primary endpoint of this study is to report the urinary and faecal cumulative excretion as a percentage of the total radioactive dose administered over time.

3.2. Secondary

The secondary pharmacokinetic endpoints will consist of:

- AUC(0-∞), Cmax, AUC(0-t), tmax and t½ of total drug-related material (radioactivity) in plasma following oral dosing.
- AUC(0-∞), Cmax, AUC(0-t), tmax, t½ of GW856553 and its major metabolite GSK198602 in plasma following oral dosing.
- Adverse events, ECG, vital signs and clinical laboratory tests (including LFTs).

Characterisation and quantification of metabolites in plasma, urine and faecal homogenates will be performed under a separate protocol by Drug Metabolism and Pharmacokinetics (DMPK), GSK and results will be reported in a separate report.

4. STUDY DESIGN

This will be an open-label study conducted in 6 male subjects. Each subject will receive a single 10mg (50 μCi) oral dose of [^{14}C]GW856553. This will involve a ten-nights, eleven-day admission.

Urine and faecal samples will be collected until 216 h after dosing but subjects may be discharged after 168 h if 90% of the dose is recovered and/or <1% of the dose is excreted in a 24 h period. If recovery of radioactivity is incomplete at the end of the collection period, subjects may be asked to collect samples of either urine and /or faeces for an extended period either within the clinical unit or at home.

Plasma and blood concentrations of total drug-related material (radioactivity) and plasma concentrations of unchanged GW856553 and its major metabolite GSK198602 will be measured and will be used to determine the aforementioned PK parameters.

Safety will be assessed by monitoring subjects for adverse events, vital signs, ECGs and laboratory parameters.

5. STUDY POPULATION

5.1. Number of Subjects

Six healthy male volunteers aged between 30-60 years old will be recruited for this study, to obtain four evaluable subjects. Subjects will be recruited from a single site.

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. Healthy male aged between 30 and 60 years inclusive, at the time of screening.
2. Body weight ≥ 50 kg (110 lbs).
3. A body mass index (BMI) within the range of 18.5 to 29.9 kg/m2 inclusive.
4. Signed and dated written informed consent prior to admission to the study.

5. The subject is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions.

5.2.2. Exclusion Criteria

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

1. Any clinically relevant abnormality identified on the screening medical assessment, laboratory examination, or ECG (12-lead).
2. Significant cardiac, pulmonary, metabolic, renal, hepatic, or gastrointestinal conditions that in the opinion of the investigator and/or GSK medical monitor, places the subject at an unacceptable risk as participant in this trial.
3. QTc(b) > 450msecs
4. A definite or suspected personal or family history of adverse reactions or hypersensitivity to the trial drug or to drugs with a similar chemical structure.
5. History of regular alcohol consumption exceeding an average weekly intake of > 21 units (or an average daily intake of greater than 3 units). One unit is equivalent to a half-pint (284mL) of beer/lager; 25mL measure of spirits or 125mL of wine).
6. Subjects with a history or presence of gastro-intestinal or renal disease or any other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
7. Subjects who have consumed grapefruit or grapefruit juice within seven days of the first study day.
8. Subjects who have had exposure to more than three new chemical entities within 12 months prior to the first dosing period.
9. Subjects who have participated in a trial with a different new chemical entity within 90 days prior to the start of this study.
10. If participation in the study will result in the volunteer having donated more than 400mL of blood in the previous 56 days.
11. 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.
12. History of elevated blood pressure or blood pressure persistently >140/90 mmHg at screening.
13. An unwillingness to abstain from sexual intercourse with pregnant or lactating women; or an unwillingness of the subject to use a condom/spermicide in addition to having their female partner use another form of contraception such as an IUD, diaphragm with spermicide, oral contraceptives, injectable progesterone, sub dermal implants or a tubal ligation if the women could become pregnant from the time of the first dose of the study medication until completion of the follow-up procedures.
14. Lack of suitability for participation in this study, for any reason, in the opinion of the investigator.

15. Any condition that could interfere with the accurate assessment and recovery of ^{14}C.
16. Prescribed or over-the-counter medication within 5 days (or 5 half lives, whichever is longer) prior to the first dosing day, unless the investigator confirms that it will not introduce additional risk or interfere with the study procedures or outcome.
17. Liver function tests (ALT, AST, ALP, γGT and bilirubin) > upper limit of normal (ULN) at screening
18. Positive urine drug screen
19. Positive HIV, Hepatitis B or C result at screening.
20. History of use of tobacco- or nicotine-containing products within 6 months of screening or a positive urine cotinine screen (urine cotinine > 250ng/ml).

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 WM2004/00033/03].

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Demographic and Baseline Assessments

During the screening visit (within 21 days of the first dosing day) all volunteers will undergo a pre-study medical examination which will include:

- A record of detailed demographic data
- Full medical history
- Concurrent medication check
- SAEs related to study participation
- Physical examination
- Supine vital signs (blood pressure and heart rate)
- 12-lead ECG (supine) three readings to be conducted at least 5 min apart;
- clinical laboratory testing (haematology, clinical chemistry and urinalysis) (see Appendix 3)
- urine drugs of abuse screen
- serology for hepatitis B, C and HIV
- alcohol breath test.

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

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

6.2. Study Period

Subjects will attend the unit on Day-1 and will have a safety laboratory test screen (see Appendix 3) as well as their LFTs assessed (and results obtained).

Subjects will receive their dose of study medication (10mg of oral [^{14}C]-GW856553) on Day 1 and will be treated as in-patients for the duration of the radioactivity follow up period in the unit under supervised conditions.

Urine and faecal samples will be collected until 216 h after dosing but subjects may be discharged after 168 h if 90% of the dose is recovered and/or <1% of the dose is excreted in a 24 h period. If recovery of radioactivity is incomplete at the end of the collection period, subjects may be asked to collect samples of either urine and /or faeces for an extended period either within the clinical unit or at home.

See Appendix 1 for further information.

6.3. Follow-up

The following assessments will be performed at the follow-up visit within 7-14 days after the last sampling day (see Appendix 1).

- Adverse event monitoring
- Supine vital signs
- Physical examination
- 12-lead ECG
- Laboratory safety tests (haematology, biochemistry and urinalysis)

At the end of the follow-up period, subjects will be discharged from the unit without any further treatment with the study medication (as the subjects are all healthy subjects, who therefore require no continuation of treatment).

6.4. Safety

Safety will be assessed by adverse event monitoring, laboratory safety tests (haematology, biochemistry and urinalysis), 12-lead ECG, supine vital signs and a urine drug screen.

6.4.1. Adverse Events

Each subject will be monitored by the investigator and designated study personnel for the adverse events occurring throughout the study. Any subjects who withdraw from the study any time after screening should have any adverse events followed up.

6.4.2. Drugs of Abuse and Alcohol Screen

A urine sample to screen for drugs of abuse and an alcohol breath test will be obtained at the timepoints specified in Appendix 1. Samples will be analysed for the parameters described in Appendix 3. Random or repeat samples may be taken at any time.

6.4.3. Laboratory Safety Samples

Laboratory safety samples (haematology, biochemistry and urinalysis) (listed in Appendix 3) will be performed at the time points indicated in Appendix 1.

Any results falling outside the normal range may be repeated, at the discretion of the Principal Investigator. Additional blood or urine samples may also be taken for safety reasons, at the discretion of the Investigator.

Total blood draw in the study will be approximately 350mL (see Appendix 4), which is less than the volume that would be taken during a routine blood donation.

6.4.3.1. Liver Function Tests (LFTs)

Evidence of human hepatotoxicity, typified by increased concentrations of transaminases with or without hyperbilirubinemia, has been noted after repeat-dose administration of two other GSK p38 MAPK inhibitors as well as other competitor p38 MAPK inhibitors [Dominguez, 2005]. Although GW856553 (a different chemical class) has not demonstrated clinically apparent hepatotoxicity in studies to date, a few subjects receiving higher doses have demonstrated elevations of transaminases that were reversible.

In study MKI106295, a single dose 4 period crossover study followed by a 28 day repeat dose study, one subject had ALT values greater than ULN following single doses in Part 1. This subject (female) had an increase following dosing with GW856553 wet granulation 7.5mg (fasted) in period 1 (maximum ALT =47.3IU/L at 96hrs post dose). The ALT values remained elevated during period 2 following dosing with GW856553 direct compression 15.0mg (fasted), with maximum ALT 46.0IU/L at 72hrs post-dose. The ALT levels returned to normal during period 3 and 4. No others subjects had ALT values above the ULN following dosing with GW856553 in Part 1.

One male subject had ALT values >2 times the ULN and one female subject had ALT values >3 times the ULN following repeat dosing with GW856553. These subjects had a slow increase in ALT during 2 weeks dosing with 10 mg BID. Following withdrawal from treatment on Day 15 these values slowly returned to normal. AST increases were also seen in these subjects, although to a lesser extent. These changes followed a similar pattern to ALT (slow increase then decrease following withdrawal from treatment). Bilirubin levels were unaffected.

In study RA3103730, a parallel group single dose study in patients with rheumatoid arthritis, patients received doses of placebo, 7.5 mg, 20 mg or 60 mg of GW856553. Two subjects had treatment-emergent (i.e., first report was post-dose) liver function test values of potential clinical concern: one in the 20 mg group (from 48 h post-dose), and one in

the 60 mg group (from 120 h post-dose). Both had ALT > 3 x ULN, which subsequently normalized and both were clinically well. All total bilirubin values were within normal limits in both of these subjects. Please refer to the Investigator Brochure [GlaxoSmithKline Document Number WM2004/00033/03] for further information.

Liver function tests will be performed as detailed in Appendix 1. Subjects will not be dosed until the Day-1 safety results have been reviewed by the Investigator and confirmation has been obtained that LFT values are below the upper limit of the reference range.

6.4.4. Cardiac Monitoring

ECGs will be conducted at the time points detailed in Appendix 1.

Full 12-lead ECGs will be recorded using an ECG machine that automatically calculates the pulse rate and measures PR, QRS, QT, QTc(b) intervals (Bazett's correction will be applied to QTc measurements).

6.4.4.1. ECG recording procedures

ECGs will be recorded whilst the subject is in a supine position (subject lying flat with maximum one pillow) having rested in this position for at least 10 minutes before each reading.

Where the measurement of three ECGs has been specified, these should be taken at least 5 minutes apart. All ECGs must show sinus rhythm or sinus arrhythmia. Subjects must have a QTc(b) of less than 450msecs at screening. If the QTc(b) rises above these values during the study, this will be considered as abnormal and the ECG should be repeated.

6.4.4.2. QTc measurements

If a subject's QTc(b) interval extends beyond 500msec or is increased more than 70msec compared to baseline (mean of three screening values) on two or more ECG tracings separated by 5 minutes then:

The ECG tracing should be examined and manual measurement by a trained physician should be performed to assess the accuracy of the equipment being used. If the reading is accurate:

- The subject should be monitored closely and followed until the QT and QTc(b) interval returns to within 30msec of their baseline.
- The subject should be considered for withdrawal from treatment.

Consideration should be given to putting the study on hold until all subjects' data can be re-evaluated and confirmed.

6.4.5. Vital Signs

Vital signs (BP and HR) will be recorded whilst the subject is in a supine position (subject lying flat with maximum one pillow) having rested in this position for at least 10 minutes before each reading.

Vital signs will be measured at the time points detailed in Appendix 1.

Measurements that deviate substantially from previous readings will be repeated immediately.

The Investigator (or deputee) will review all vital signs on an ongoing basis on each study day when a measurement has been made.

6.4.6. Pregnancy

As only male subjects are eligible to participate in this study, pregnancy testing will not be required.

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

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

6.5. Pharmacokinetics

During this study a series of blood, urine and faeces samples will be taken for the analysis of GW856553, GSK198602 and for determination of ^{14}C-radioactivity levels. These samples will be collected as the time points specified in Appendix 1.

GW856553 and GSK198602 will be quantified by HPLC-MSMS. Total radioactivity will be quantified by liquid scintillation counting.

6.5.1. Blood and Plasma Samples

6.5.1.1. Plasma Pharmacokinetics (cold assay) and Determination of ^{14}C Radioactivity in Plasma

During the study period, blood samples will be collected via an indwelling catheter or by direct venepuncture into EDTA containing tubes at the time points specified in Appendix 1.

Please refer to the Study Reference Manual (SRM) for further details on collection, processing and shipment of these samples.

6.5.1.2. Samples for Metabolite Profiling in Plasma and ^{14}C Radioactivity in Blood

Blood samples will be drawn following dosing for metabolic profiling and blood concentrations of radioactivity at the time points specified in Appendix 1.

Please refer to the SRM for further details on collection, processing and shipment of these samples.

6.5.2. Urine Collection

Urine samples to measure total radiocarbon excreted in urine and for metabolite profiling will be collected at the time points specified in Appendix 1. Urine collection will continue for an individual subject until 216 h after dosing but subjects may be discharged after 168 h if 90% of the dose is recovered and/or <1% of the dose is excreted in a 24 h period . If recovery of radioactivity is incomplete at the end of the collection period, subjects may be asked to collect samples of urine for an extended period either within the clinical unit or at home.

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.

Please refer to the SRM for further details on collection, processing and shipment of urine samples.

6.5.3. Faeces Collection

Subjects will be asked to bring a faecal sample to the unit. Stool samples will also be collected from each subject prior to dosing (if available) and at the time points specified in Appendix 1. The pre-dose sample will be the last sample obtained before dosing. Faeces collection will continue for an individual subject until 216 h after dosing but subjects may be discharged after 168 h if 90% of the dose is recovered and/or <1% of the dose is excreted in a 24 h period . If recovery of radioactivity is incomplete at the end of the collection period, subjects may be asked to collect samples of faeces for an extended period either within the clinical unit or at home.

Please refer to the SRM for further details on collection, processing and shipment of faeces samples.

6.6. 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

- Subjects should avoid the consumption of grapefruit or grapefruit juice from 7 days prior to dosing until they leave the unit.
- There is no requirement for subjects to fast prior to attending for blood sampling for clinical laboratory monitoring at screening and follow-up.
- Subjects will fast from food and fluids from 11p.m. the night before dosing, with the exception of small amounts of water which may be taken until 1 hour before dosing.
- Subjects will fast from food until 4h after dosing. Water (100 mL) will be given at 1 and 3 hours. Fluids will be unrestricted after lunch. Lunch will be provided at approximately 4 hours after dosing and dinner will be provided at approximately 9 to 11 hours after dosing.
- Subjects must refrain from all recreational drugs from screening until follow-up.
- Subjects must refrain from alcohol from 24 hours before admission until discharge from the clinic and for 48 hours before returning for the follow-up visit.
- Subjects must abstain from caffeine-containing drinks (tea, coffee, cocoa, cola) from 24 hours prior to dosing until they leave the unit.

8. INVESTIGATIONAL PRODUCT(S)

8.1. Description of Investigational Product

A dose of 10mg GW856553 containing 50µCi of [^{14}C]GW856553 will be delivered as 100mL of a 0.1mg/mL GW856553/0.5 µCi/mL oral solution. Bulk GW856553J (radiolabelled free base) powder will be supplied by GSK. This will be made into a bulk oral solution (0.1mg/mL/0.5 µCi/mL GW856553J) with an aqueous solution of sulfobutylether β-cyclodextrin on the day prior to dosing. Individual doses of 100mL will then be aliquoted for dosing.

A worksheet for preparation of the investigational product will be supplied in the SRM.

A small amount of additional radioactive material will be shipped in a separate container so that the radiochemical purities can be determined on arrival and a non-radiolabelled authentic reference standard (with Certificate of Analysis) will also be supplied to facilitate analysis. Additional GW856553J bulk powder will be supplied for a mock dose preparation and to check radiochemical purity and stability and radioactive concentrations, as required.

8.1.1. Non-Radiolabelled Test Item

Non-radiolabelled test item will be supplied (in suitable containers and under the appropriate conditions) by GSK. The test item will be used as a means of establishing the specific activity and authenticity of [^{14}C]GW856553.

Prior to the commencement of the study, GSK will supply an Active Product Ingredient Release Document (APIRD) and Technical Terms of Supply Document (TTS) indicating identity, purity, stability, appearance, handling and safety instructions. These documents may cross-refer to GSK's Certificate of Analysis.

The non-radiolabelled test item will be stored at up 30°C.

GSK will supply written instructions regarding disposal or return of unused test item on completion of the study.

8.2. Dosage and Administration

Individual oral dose solutions will be 10mg of GW856553 containing 50 μCi of [^{14}C]-GW856553 in 100 mL of Sulfobutylether β-Cyclodextrin solution.

Oral doses (one for each subject to be dosed) will be prepared the day prior to dosing at the clinical site (see SRM for further information) in a pre-weighed vessel. An aliquot will be removed to determine the radiochemical purity and the radioactivity concentration in each dose. The full vessel will be re-weighed and administered to each subject. A further 100 mL (2 x 50 mL) of water will be added to the container and the contents rinsed and drunk by the subject. The glass container 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.

8.3. Dose Rationale

8.3.1. GW856553

A 10 mg oral solution dose of [^{14}C]GW856553 will be administered.

In the First Time in Human (FTIH) study, MKI101678 [GlaxoSmithKline Document Number GM2005/00538/00], it was found that single oral doses of GW856553 up to 60mg (fast and fed) were well tolerated in healthy subjects. Exposure to GW856553 was approximately dose proportional up to 20mg, however, the systemic exposure of GW856553 (Cmax and AUC0-∞) was only marginally increased with 60mg dose compared to 20mg due to the saturation of absorption in fasted state. There was an increase in exposure (31% in AUC0-∞ and 163% in Cmax) when GW856553 was administered with food. The maximum human AUC0-∞ and Cmax following a single dose of GW856553 (60mg, fed) was 1682 ng.h/mL and 226 ng/mL, respectively. These observations were used as references when selecting doses for this study.

The formulation used in the FTIH study was a tablet made of micronised GW856553. The micronisation process is predicted to improve the dissolution of the drug such that it is no longer rate limiting. Consequently, absorption of this formulation would be similar to the solution formulation. This is supported by the preclinical data obtained from a pharmacokinetic study in the monkey. In this study, GW856553 was administered orally at a dose of 0.5 mg/kg as a solution in β-cyclodextrin or as a micronised suspension in hydroxymethylcellulose (HPMC) containing Tween 80 (the same vehicle as was used in the toxicology studies). Mean pharmacokinetic parameters indicated no difference between the solution and micronised suspension groups [GlaxoSmithKline Document Number WD2004/00140/00]. Therefore, it is considered likely that an oral dose of 10mg [^{14}C]GW856553 in solution will result in exposures similar to those achieved at 10mg GW856553 tablet, and is unlikely to exceed the levels observed in the FTIH study. In addition, exposures would be expected to be >10 fold and >18 fold (AUC and Cmax) below the no adverse effects levels seen in rat and monkey 13 and 26 week toxicology studies, respectively.

The maximum exposure and Cmax observed in the FTIH study (60mg, fed) and the expected values after a 10mg dose (fasted) are shown in Table 1.

Table 1 Exposure to GW856553 Following 60mg (Fed) (FTIH study MKI101678) and Predicted for 10mg (Fasted)

	Observed in FTIH after 60mg (Fed)	Expected after 10mg fasted	Fold cover
AUC (0-inf)	1682[1]	349[2]	4.8
Cmax	226[1]	36[2]	6.2

1. Geometric mean [GlaxoSmithKline Document Number GM2005/00538/00]
2. Geometric mean observed from 10mg OD in MKI102422 study [GlaxoSmithKline Document Number GM2005/00543/00]

8.3.2. Sulfobutylether β-Cyclodextrin

The [^{14}C]GW856553 formulation will contain 0.067M sulfobutylether β-cyclodextrin (14.49g) in a 100 mL solution. β-Cyclodextrins have been widely administered to humans by various routes including oral [Challa, 2005]. The specific β-cyclodextrin to be administered in this study, sulfobutylether β-cyclodextrin, is also known as Captisol (Cydex, USA).

Captisol is used in the formulation of an active antimycotic substance voriconazole for infusion. This licensed formulation of Vfend (Pfizer) contains Captisol at 160mg/ml and voricoanazole at 10mg/ml. The therapeutic dose of voriconazole is 6mg/kg BID. Assuming a 70kg subject receiving 420mg of voriconazole this equates to an intravenous dose of 6.72g BID of Captisol. Given the fact that β-cyclodextrins are bucket-shaped oligosaccharides produced from starch, it is reasonable to expect that this exposure will provide adequate systemic cover for the oral delivery route intended for this study.

Captisol has also been used in a solution formulation in a previous GSK ADME study [GlaxoSmithKline Document Number HM2003/00574/00]. This was administered as both an oral solution and an intravenous infusion. The oral dose of Captisol was 18.16g

and the IV dose 10.38g. In that study 6 subjects received both oral and IV doses and tolerability was good. One of the 6 subjects reported adverse events including loose stools and abdominal pain these being reported after both routes of administration [GlaxoSmithKline Document Number HM2004/00248/00]. Based on these data the proposed oral administration of 14.49g of Captisol is considered to be appropriate.

8.3.3. [^{14}C]GW856553

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. Effective doses for intravenous and oral administrations of [^{14}C]GW856553 have been calculated by the Health Protection Agency (HPA), [Reference RPB-RE-2-2005]. A dose of 50 μCi corresponds to an effective dose of approximately 0.4 mSv which is below the upper limit for an ICRP category IIa exposure of 1 mSv. The proposed radioactive dose for this study will not be administered without prior approval by ARSAC (Administration of Radioactive Substances Advisory Committee). Category IIa covers doses to the public from controlled sources with minor risk level.

8.4. Blinding

This study will be performed in an open label manner.

8.5. Treatment Assignment

All subjects will be assigned to the same treatment schedule of a single 10mg (50 μCi) oral dose of [^{14}C]-GW856553.

8.6. Packaging and Labeling

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

8.7. Preparation

Please refer to the SRM for details of drug preparation

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 authorised 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

Study medication will be administered under the supervision of study personnel. The study personnel will be required to have documented 100% compliance with the administration of study medication. Each subject's oral cavity will be checked after the oral dosing to confirm that the dose has been taken by the subject.

8.11. Treatment of Investigational Product Overdose

An overdose for this study will be considered as any dose of study drug more than the planned dose on the single dosing occasion. In the event of an overdose, there are no recommended medications or non-drug therapies for treatment. Management should be supportive and the investigator should use his/her clinical judgment in treating any overdose situation.

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.

Paracetamol will be allowed as a mild analgesic at a dose of 2 single doses of 1000mg per day during the study period, though a higher dose may be administered if deemed essential and safe by the clinical investigator.

9.2. Prohibited Medications

Subjects taking a regular (or course of) medication, whether prescribed or not, will be excluded from the study.

Use of prescription or non-prescription drugs, including paracetamol (at doses > 2000mg per day), thyroid replacement therapy, vitamins, herbal and dietary supplements (including St John'sWort), aspirin or other NSAIDs, will not be permitted for 7 days prior to the first dose of study medication, until the end of the study. Subjects must also refrain from using any aspirin-containing products.

10. SUBJECT COMPLETION AND WITHDRAWAL

10.1. Subject Completion

Subjects who participate in all study sessions (screening, dosing session and follow-up) will be considered as having completed the study.

10.2. Subject Withdrawal

10.2.1. Subject Withdrawal from Study

A subject may withdraw from the study at any time at their own request, or they may be withdrawn at any time based on general safety and tolerability.

If a subject is prematurely withdrawn, the Investigator must make every effort to perform the following evaluations:

- Follow-up visit
- Follow-up of any outstanding adverse events/concurrent medications

10.2.2. Subject Withdrawal from Investigational Product

A subject may be withdrawn from the investigational product at any time at the discretion of the investigator for safety, behavioural, or administrative reasons. Withdrawal due to AEs (see Section 11) will be distinguished from withdrawal for other reasons.

10.3. Treatment After the End of the Study

At the end of the follow-up period, subjects will be discharged from the unit without any further treatment with the study medication (as the subjects are all healthy volunteers, who therefore require no continuation of treatment).

10.4. Screen and Baseline Failures

Any subject, who is screened for the study and then is withdrawn before taking the investigational product, for any reason, will be considered a screen failure. Data from these subjects will not be collected (except for SAE data), however the information will be kept at the study site where the study monitor can review it if required.

If a blood sample for Pharmacogenetic (PGx) research has been collected and it is determined that the subject does not meet the inclusion and exclusion 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 investigator study files.

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 unfavourable 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 conditions 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 concurrent 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.

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 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 hospitalization or fulfills 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, 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 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.

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

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., 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.

Liver chemistry threshold stopping criteria have been designed to assure subject safety. When subjects meet the following liver chemistry threshold criteria, additional follow-up testing must be performed, and the subject monitored until liver chemistries resolve, stabilize, or return to baseline values.

- ALT ≥ 3xULN and bilirubin ≥ 1.5xULN (>35% direct).
- ALT ≥ 3xULN.

For subjects with ALT ≥ 3xULN **and** bilirubin ≥ 1.5xULN (>35% direct bilirubin; bilirubin fractionation required) every attempt must be made to have the subject return to clinic (within 24 hours) for repeat liver chemistries and additional testing, and monitored closely (with specialist or hepatology consultation recommended). This event must be reported to GSK within 24 hours of learning of its occurrence. Subjects must be monitored twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Subjects with ALT ≥3xULN must be monitored weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values. This event must be reported to GSK within 24 hours of learning of its occurrence.

In all the above situations, every attempt must be made to obtain the following:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody.
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
  - Hepatitis C RNA.
  - Cytomegalovirus IgM antibody.
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  - Hepatitis E IgM antibody (if subject resides outside the USA or Canada, or has traveled outside USA or Canada in past 3 months).
- Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if bilirubin≥1.5xULN.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, putative hepatotoxins, or alcohol on the concomitant medications report form.

The following are required for subjects with ALT ≥3xULN **and** bilirubin ≥1.5xULN but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

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

From the time a subject consents to participate in the study until he 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.

The time period for collecting and recording all AEs and SAEs will begin at receipt of investigational product and will end at the follow-up visit.

11.4. Prompt Reporting of SAEs to GSK

Regulatory Reporting Requirements For SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

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 Reports of SAEs/AEs of special interest to GSK

	Initial SAE Reports		Follow-up Information on a Previously Reported SAE	
Type of SAE/AE of Special Interest	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hrs	"SAE" data collection tool	24 hrs	Updated "SAE" data collection tool
Male Subject Partner Pregnancy	2 Weeks	Pregnancy Form	2 Weeks	Updated Pregnancy Form
ALT≥3xULN	24 hrs	Liver Chemistry Report Form	24 hrs	Updated Liver Chemistry Report Form
ALT≥3xULN PLUS Bilirubin≥1.5x ULN)	24 hrs	Liver Chemistry Report Form	24 hrs	Updated Liver Chemistry Report Form

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

This is an investigative study and no formal hypotheses will be tested with regard to the excretion/balance, pharmacokinetics and biotransformation of GW856553.

12.2. Study Design Considerations

12.2.1. Sample Size Assumptions

The sample size is based on feasibility. Six healthy male volunteers aged 30-60 years will be recruited in order to obtain four evaluable subjects. All data collected will be analysed (e.g. should all six subjects complete), however, data from four subjects will be sufficient.).

12.2.2. Sample Size Sensitivity

No sample size sensitivity calculations will be conducted.

12.2.3. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

12.3. Data Analysis Considerations

12.3.1. Analysis Populations

The Safety Population will be defined as all subjects who receive at least one dose of study drug. This population will be used for all safety summaries.

The Pharmacokinetic Population will be defined as all subjects in the Safety Population for whom a PK sample was obtained and analysed. This population will be used for all summaries of pharmacokinetic concentration and parameters.

12.3.2. General Considerations for Data Analysis

Data will be entered into a computer database system by Clinical Pharmacology Data Sciences (CPDS), GlaxoSmithKline. Appropriate checks and validations, including a 100% audit of adverse events, will be performed. The database file and all associated documentation will be retained as permanent records of the study.

Statistical analysis will be performed by, or under the direct guidance of Discovery Biometrics, GlaxoSmithKline.

Only planned (i.e. scheduled) data will be included in data summaries. Any unplanned or unscheduled data will be presented in the subject listings only. If the actual time of an assessment is collected this will be included in the relevant listing along with the planned time relative to dosing.

Full details of the general considerations for data analysis will be outlined in the RAP. Any changes from the data analysis described within this protocol will be stated in the RAP and/or the Clinical Pharmacology Study Report (CPSR).

12.3.2.1. Withdrawal

All subjects who withdraw prematurely from the study will be documented and the reason for their withdrawal recorded in the final CPSR. All available data from subjects who withdraw will be listed and all available planned data will be included in the summaries according to the populations defined in Section 12.3.1.

12.3.2.2. Missing Data

All missing data will be listed. No data imputation techniques will be used.

12.3.2.3. Derived and Transformed Data

Only planned (i.e. scheduled) data will be included in the calculation of any derived parameters; see Section 12.3.5.2 for further details

12.3.3. Treatment Comparisons

12.3.3.1. Primary Comparisons of Interest

No statistical evaluations will be performed. Summary statistics will be presented for the pharmacokinetic parameters of GW856553.

12.3.3.2. Other Comparisons of Interest

There are no other comparisons of interest.

12.3.4. Interim Analysis

No interim analysis is planned.

12.3.5. Key Elements of Analysis Plan

12.3.5.1. Safety Analyses

All subjects who receive at least one dose of study drug will be included in the evaluation of clinical safety and tolerability. Clinical monitoring and laboratory data will be reviewed by the study physician but will not be formally analysed.

12.3.5.1.1. Extent of Exposure

The extent of exposure will be listed by subject, dosing date and dosing time.

12.3.5.1.2. Adverse Events

Elected adverse events and spontaneous reporting by subjects (i.e. 'events') will be summarised. This data will also be listed with verbatim text used to describe the 'event' occurrences.

A more formal reporting of adverse events will be undertaken using the current Medical Dictionary for Regulatory Affairs (MedDRA) in order to provide the body system/system organ class and preferred term/group code. All adverse event summaries will be in terms of treatment-emergent adverse events (i.e. adverse events that start or worsen on or after the date when the study drug is first taken).

All adverse events (regardless of causality) will be summarised by body system and preferred term. For both body system and preferred term, summaries will be sorted in terms of total incidence. Preferred terms of adverse events will not be presented when the total incidence for a preferred term within a body system is zero. If the total incidence for two or more adverse events is equal, the events will be presented in alphabetical order.

Adverse events regarded as serious by the investigator will be summarised similarly.

The association between the adverse event body system, preferred term and the verbatim text will also be presented.

All adverse events will be listed.

12.3.5.1.3. Clinical Laboratory Evaluations

Absolute values for each item of laboratory data for each of the three categories: haematology, biochemistry and urinalysis (as defined in Appendix 3), will be summarised by planned time-point relative to dosing. All laboratory data will be listed. Listings will include change from baseline, where the baseline assessment will be defined as either the value provided at pre-dose (Day -1) or the value provided at screening; this will be clarified in the RAP.

For Liver Function Tests (LFTs), a summary table depicting the number of subjects having values in the intervals 1 x ULN (Upper Limit Normal) $\leq$ LFT $<$ 2, 2 x ULN $\leq$ LFT $<$ 3 and $\geq$ 3 x ULN will be produced for ALT and AST.

All laboratory data will be listed.

Other Safety Measures

All vital signs and ECG data (systolic and diastolic blood pressure, and heart rate measurements – collected as described in Section 6) will be summarised by planned time point relative to dosing. Vital signs and ECG data will be listed. Listings will include change from baseline, where the baseline assessment will be defined as the value provided at pre-dose (Day -1) or pre-dose (Day 1). Further clarification of baseline will be given in the RAP.

12.3.5.2. Pharmacokinetic Analyses

Concentration of GW856553 and its major metabolite GSK198602 in plasma and total drug-related material (radioactivity) in plasma will be evaluated by standard non-compartmental analysis using WinNonlin 4.1 or higher (Pharsight Corporation, Mountain View, CA, USA).

The pharmacokinetic parameters to be determined or calculated for GW856553, GSK198602 and ^{14}C-radioactivity in plasma are:

- Cmax (maximum drug concentration)
- Tmax (time to attain maximum drug concentration)
- t½ (terminal phase half life)
- AUC(0-t) (area under the drug concentration time curve between zero and the time of the last measurable drug concentration)
- AUC(0-∞) (area under the plasma concentration-time curve between zero and infinity)
- %AUC(0-∞) (percentage of estimated part for the calculation of AUC(0-∞))

The pharmacokinetic parameters to be determined or calculated for ^{14}C-radioactivity in urine and faeces are:

- Ae urine (amount of radioactivity excreted in urine)
- Ae faeces (amount of radioactivity excreted in faeces)
- Ae urine (%excreted) (percentage of radioactivity excreted in urine)
- Ae faeces (%excreted) (percentage of radioactivity excreted in faeces)
- Ae urine 0-t (cumulative amount of drug excreted up to time t)
- Ae faeces 0-t (cumulative amount of drug excreted up to time t)
- Ae urine 0-t (%excreted) (cumulative percentage of drug excreted up to time t)
- Ae faeces 0-t (%excreted) (cumulative percentage of drug excreted up to time t)
- Ae total (total amount of radioactivity excreted)

- Ae total (%excreted) (total percentage of radioactivity excreted)

Individual subject plasma concentration-time data, as well as derived PK parameters, will be listed and summarised. The descriptive statistics will include the mean, standard deviation, median, minimum, maximum, and for all data except Tmax, the standard deviation of log-transformed values, geometric mean and corresponding 95% confidence interval.

Individual (for each subject for whom concentrations are quantifiable), median and mean plasma concentration-time data will be plotted. Where appropriate, the range and SD may be included on the median and mean plot.

Individual subject blood radioactivity will be summarised by planned time point relative to dosing and individual subject radioactivity levels will be listed for both urine and faeces.

Radioactivity results will be expressed as ng-GW856553-equivalents/mL (or g). For derived urine and faecal radioactivity parameters, the cumulative amount excreted and cumulative percent of the radiocarbon dose recovered will be listed for each subject and collection interval.

Radioactivity data will be descriptively summarised. In particular, for derived urine and faecal ^{14}C-radioactivity parameters, both the excretion and cumulative excretion will be presented by time point (for responses the amount excreted and the amount excreted as a percentage of total radioactive dose). Urine and faecal total radioactivity parameters will also be presented (i.e. data will be summarised over all time points).

Pharmacokinetic analyses will be conducted under the guidance of the CPK/M&S – CPDM and DMPK at GSK.

13. STUDY CONDUCT CONSIDERATIONS

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

GSK will obtain favourable 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.

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 favourable 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 multicenter 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 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

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GlaxoSmithKline Document Number WD2004/00140/00. A Study to Investigate the Relative Systemic Exposure to GW856553X Following Oral Administration of Three Formulations of GW856553X to the Cynomolgus Monkey at a Target Dose Level of 0.5 mg/kg.

Appendices

Appendix 1: Time and Events Table

Assessment	Screening[1]	Pre-dose[2]	Day 1	Days 2-10	Follow-up[13]
Informed consent	X				
Medical history	X				
Demographics	X				
Physical examination	X				X
Serology (HbsAg, anti-HCV, anti-HIV)	X				
Urine drug screen & alcohol breath test	X	X			
12-lead ECG	X	X	X[3]		X
Vital signs (blood pressure, pulse)	X	X	X[4]		X
Clinical laboratory incl. urinalysis	X	X		X[5]	X
Blood sampling for pharmacogenetics[6]					
Blood sample for plasma PK (cold analysis)		X	X[7]		
Blood sample for plasma radioactivity		X	X[8]		
Blood for metabolite analysis and radioactivity in whole blood		X	X[9]		
Drug Administration			X		

Continued

Assessment	Screening[1]	Pre-dose[2]	Day 1	Days 2-10	Follow-up[13]
Urine collection		X	X[10]	X[10]	
Faeces collection		X	X[11]	X[11]	
SAE/AE review and reporting[12]		X	X	X	X

1. Screening assessments to be carried out within 21 days prior to Day 1.
2. Assessments may be on Day-1 or Day 1 pre-dose as appropriate
3. ECG readings to be taken at 30mins, 1h, 2, 4, 6, 8 and 24 h post dose
4. Measurements to be taken at 15mins, 30mins, 1h, 2, 4, 6, 8, 24 and 48 h post dose
5. Samples taken 48 h post dose (Day 3).
6. Pharmacogenetics sample will be collected on Day -1 prior to dosing and after PGx consent has been obtained
7. Samples collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours post-dose.
8. Samples collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose.
9. Samples at 1, 4 and 12 hrs post dose
10. Urine will be collected for the periods 0-6 h, 6-12 h, 12-24 h and then at 24 h intervals up to 216 h post dose (or until stopping criteria are reached)
11. Faeces will be collected at 24 h intervals up to 216 h post dose (or until stopping criteria are reached)
12. Only SAEs related to study participation are collected between screening and dosing
13. Follow-up assessments to be performed 7-14 days of the last sampling day

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 [Roses, 2002]	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 GW856553.

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 GW856553. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with GW856553 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 GW856553 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 GW856553. 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 GW856553 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 GW856553.

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 GW856553. 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 [Roses, 2002] 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.

References

Cardon LR, Idury RM, Harris TJR, Witte JS, Elston RC. Testing drug response in the presence of genetic information: sampling issues for clinical trials. *Pharmacogenetics*. 2000; 10:503-10.

Drazen JM, Yandava CN, Dube L, Szcerback N, Hippensteel R, Pillari A, Israel E, Schork N, Silverman ES, Katz DA, Drajesk J. Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. *Nature Genet*. 1999; 22:168-70.

Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, Lai E, Davies K, Handley A, Dow DJ, Fling ME, Stocum M, Bowman C, Thurmond LM, Roses AD. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet*. 2002; 359:1121-2.

Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002; 359:727-32.

McCarthy JJ, Hilfiker R. The use of single-nucleotide polymorphism maps in pharmacogenomics. *Nat Biotechnol*. 2000; 18:505-8.

Palmer LJ, Cookson WO. Using single nucleotide polymorphisms as a means to understanding the pathophysiology of asthma. *Respir Res*. 2001; 2:102-12.

Roses AD. Genome-based pharmacogenetics and the pharmaceutical industry. *Nat Rev Drug Discov*. 2002; 1:541-9.

Appendix 3: Clinical Laboratory Safety Assessments

Haematology

Blood will be collected according to local procedures for analysis of the following:

- White blood cell count (WBC)
- Red blood cell count (RBC)
- Haemoglobin (Hb)
- Haematocrit (HCT)
- Mean cell volume (MCV)
- Mean cell haemoglobin (MCH)
- Mean cell haemoglobin concentration (MCHC)
- Platelet count
- Neutrophil count
- Lymphocyte count
- Monocyte count
- Eosinophil count
- Basophil count
- LUC

Biochemistry

Blood will be collected according to local procedures for analysis of the following:

- Alkaline phosphatase (ALP)
- Alanine transaminase (ALT)
- Aspartate transaminase (AST)
- Gamma-glutamyl transpeptidase (gamma-GT)
- Glucose
- Cholesterol
- Triglycerides
- Albumin
- Total protein
- Bilirubin (total, direct and indirect if >1.5x ULN')
- Creatinine

- Creatine phosphokinase (CPK)
- Sodium
- Potassium
- Calcium
- Urea
- LDL and HDL

Urinalysis

Approximately 10-20 mL mid-stream urine will be collected into a sterile container and will be screened for:

- Protein
- Glucose
- Ketones
- Nitrates
- Bilirubin
- Blood
- Urobilinogen
- Leucocytes

Sediment microscopy is required at screening. For other timepoints, sediment microscopy will be performed only if any of the above tests are abnormal. In such cases, microscopy will be performed for:

- White blood cells
- Red blood cells
- Hyaline casts
- Granular casts
- Cellular casts

Recreational Drug Screen

Approximately 10-20 mL mid-stream urine will be collected into a sterile container and screened for:

- Cannabinoids
- Amphetamines
- Benzodiazepines
- Cocaine

- Opiates
- Barbiturates
- Methadone

Alcohol Screen

Alcohol breath test.

Serology

Blood will be collected according to local procedures for analysis of the following: HIV I & II, Hepatitis B surface antigen and Hepatitis C antibody.

Appendix 4: Blood Volumes

Screening Visit		
Haematology	1 x 3.0 mL	3.0 mL
Biochemistry	1 x 4.0 mL	4.0 mL
Serology	1 x 3.0 mL	3.0 mL
	Total	10.0 mL
Study Period		
Haematology	2 x 3.0 mL	6.0 mL
Biochemistry	2 x 4.0 mL	8.0 mL
PGx	1 x 10.0 mL	10.0 mL
PK analysis (cold)	14 x 6.0 mL	84.0 mL
PK analysis (^{14}C)	18 x 6.0 mL	108.0 mL
Metabolite and radioactivity in whole blood	4 x 30.0 mL	120.0 mL
	Total	336.0 mL
Follow-up		
Haematology	1 x 3.0 mL	3.0 mL
Biochemistry	1 x 4.0 mL	4.0 mL
	Total	7.0 mL
TOTAL STUDY BLOOD DRAW	Total	353.0 mL

NB. At the discretion of the Investigator additional samples may be taken for safety reasons

Appendix 5: Protocol Amendment Changes

Amendment 1

Summary of Amendment Changes with Rationale

List of Specific Changes

Section 11.4 Prompt Reporting of SAEs to GSK

Previous Text

None

Added Text

Regulatory Reporting Requirements For SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Case Report Form

Confidential

Volunteer Identifier	Subject Identifier

RA3107806

An open label study to determine the safety, tolerability, excretion balance and pharmacokinetics of [14C]GW856553, administered as a single dose of an oral solution to healthy adult male subjects.

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 are placed at the correct visit and on the correct CRF page.

Protocol Identifier	Subject Identifier		Visit Description
RA3107806		WORKSHEET	Screening

CONCOMITANT MEDICATIONS PROMPT

Record details of the subject's ongoing concomitant medications in the appropriate Concomitant Medications section.

SAE PROMPT

From the time a subject consents to participate in the study until he 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.

PGx SAMPLE PROMPT

Pharmacogenetics sample will be collected on Day -1 prior to dosing and after PGx consent has been obtained.

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

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Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
RA3107806			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

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Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Screening

VITAL SIGNS

Height ☐☐☐ cm Weight ☐☐☐.☐ kg

Body mass index ☐☐.☐ kg/m²

Date Day Month Year	Planned Relative Time	Actual Time Hr : Min (00:00 - 23:59)	Blood Pressure Supine mmHg Systolic	 Diastolic	Heart Rate beats/min
e.g., 01 JAN 03	*15 min*	*13:02*	*110*	*80*	*75*
1.	Screening	:			
2.	Unscheduled	:			
3.	Unscheduled	:			

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Screening

12-LEAD ECG

ECG Number	ECG1	ECG2	ECG3	ECG4	ECG5	ECG6
Start Date of ECG Day Month Year						
Planned Relative Time	Screening	Screening	Screening	Unscheduled	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:	:	:	:
Heart 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 additional ECG Abnormalities page if clinically significant abnormalities are present.*

Note: Bazett's correction will be applied to QTc measurements.

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.

Protocol Identifier	Subject Identifier		Visit Description
RA3107806		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.		
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22.		
23.		
24.		
25.		
26.		
27.		
28.		

Protocol Identifier	Subject Identifier		Visit Description
RA3107806		WORKSHEET	Screening

PHYSICAL EXAMINATION

Date of Assessment ☐☐ ☐☐☐ ☐☐ Day Month Year

Indicate current physical findings by ✓ the appropriate box(es) below and if ABNORMAL, describe concisely: [different findings should be separated by either a (;) or a (/)].

	Normal	Abnormal	Not Done	
1. Hair and skin	☐	☐		_____
2. Lymph nodes	☐	☐		_____
3. Eyes	☐	☐		_____
4. Ears, Nose and Throat	☐	☐		_____
5. Breasts	☐	☐	☑	_____
6. Respiratory	☐	☐		_____
7. Cardiovascular	☐	☐		_____
8. Abdomen	☐	☐		_____
9. Urogenital	☐	☐	☑	_____
10. Pelvic	☐	☐	☑	_____
11. Rectal	☐	☐	☑	_____
12. Musculoskeletal	☐	☐		_____
13. Neurological	☐	☐		_____
14. Mental Status	☐	☐		_____

ALCOHOL INTAKE
INVESTIGATOR INSTRUCTIONS

ALCOHOL CONVERTER
1 unit of alcohol in UK = 1 measure of spirits, 1/2 pint beer, 1 small glass of wine (125ml)

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Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
RA3107806			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.*

ALCOHOL BREATH TEST

Date sample taken ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Results ✓*one:* ☐ Positive
If positive, exclude subject from the study.

☐ Negative

DRUG SCREEN

Date and time of sample taken ☐☐ ☐☐☐ ☐☐ ☐☐:☐☐ (Day Month Year Hr:Min (00:00-23:59))

✓*appropriate box(es)*	Positive	Negative
Cocaine	☐	☐
Amphetamines	☐	☐
Benzodiazepines	☐	☐
Cannabinoids	☐	☐
Opiates	☐	☐
Barbiturates	☐	☐
Methadone	☐	☐
Cotinine	☐	☐

If any of the above are positive, exclude subject from the study.

HISTORY OF TOBACCO USE
INVESTIGATOR INSTRUCTIONS

DEFINITIONS

- **Never smoked** Never smoked
- **Current smoker** Currently smoking or has smoked within 6 months of screening visit
- **Former smoker** Previously smoked and has not smoked for at least 6 months prior to screening visit

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Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
RA3107806			Screening

HISTORY OF TOBACCO USE

What is the subject's history of smoking use (includes all tobacco products)?

☐ Never smoked

☐ Current smoker → *Exclude subject from study.*

☐ Former smoker → When did the subject last smoke? ☐☐ Day ☐☐☐ Month ☐☐ Year

SEROLOGY - HIV SCREEN

Date sample taken ☐☐ Day ☐☐☐ Month ☐☐ Year

✓*appropriate box(es)*

	Positive	Negative
HIV antibody	☐	☐
Hepatitis B surface antigen	☐	☐
Hepatitis C antibody	☐	☐

If any of the above are positive, ***exclude*** *subject from the study.*

ELECTRONICALLY TRANSFERRED LABORATORY DATA - CLINICAL CHEMISTRY

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - HAEMATOLOGY

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - URINALYSIS

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Screening

LIVER EVENTS ASSESSMENT

If a liver event has occurred, complete the Liver Events Assessment page in the End of Study section of the CRF.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - CLINICAL CHEMISTRY

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

ELECTRONICALLY TRANSFERRED LABORATORY DATA - HAEMATOLOGY

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

ELECTRONICALLY TRANSFERRED LABORATORY DATA - URINALYSIS

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

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 Description
RA3107806			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.

*Do **not** enter the subject into the study if they failed any inclusion or exclusion criteria below.*

INCLUSION CRITERIA

✓ the boxes corresponding to any of the inclusion criteria the subject failed.

1. ☐ Healthy male aged between 30 and 60 years inclusive, at the time of screening.
2. ☐ Body weight ≥ 50 kg (110 lbs).
3. ☐ A body mass index (BMI) within the range of 18.5 to 29.9 kg/m2 inclusive.
4. ☐ Signed and dated written informed consent prior to admission to the study.
5. ☐ The subject is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions.

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			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 ECG (12-lead).
2. ☐ Significant cardiac, pulmonary, metabolic, renal, hepatic, or gastrointestinal conditions that in the opinion of the investigator and/or GSK medical monitor, places the subject at an unacceptable risk as participant in this trial.
3. ☐ QTc(b) > 450msccs
4. ☐ A definite or suspected personal or family history of adverse reactions or hypersensitivity to the trial drug or to drugs with a similar chemical structure.
5. ☐ History of regular alcohol consumption exceeding an average weekly intake of > 21 units (or an average daily intake of greater than 3 units). One unit is equivalent to a half-pint (284mL) of beer/ lager; 25mL measure of spirits or 125mL of wine).
6. ☐ Subjects with a history or presence of gastro-intestinal or renal disease or any other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
7. ☐ Subjects who have consumed grapefruit or grapefruit juice within seven days of the first study day.
8. ☐ Subjects who have had exposure to more than three new chemical entities within 12 months prior to the first dosing period.
9. ☐ Subjects who have participated in a trial with a different new chemical entity within 90 days prior to the start of this study.
10. ☐ If participation in the study will result in the volunteer having donated more than 400mL of blood in the previous 56 days.
11. ☐ 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 Xray or CT scans, barium meal etc) in the 12 months prior to this study.
12. ☐ History of elevated blood pressure or blood pressure persistently >140/90 mmHg at screening.
13. ☐ An unwillingness to abstain from sexual intercourse with pregnant or lactatingwomen; or an unwillingness of the subject to use a condom/spermicide in addition to having their female partner use another form of contraception such as an IUD, diaphragm with spermicide, oral contraceptives, injectable progesterone, sub dermal implants or a tubal ligation if the women could become pregnant from the time of the first dose of the study medication until completion of the follow-up procedures.
14. ☐ Lack of suitability for participation in this study, for any reason, in the opinion of the investigator.
15. ☐ Any condition that could interfere with the accurate assessment and recovery of ^{14}C.

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Screening

EXCLUSION CRITERIA (Continued)

✓ *the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.*

16. ☐ Prescribed or over-the-counter medication within 5 days (or 5 half lives, whichever is longer) prior to the first dosing day, unless the investigator confirms that it will not introduce additional risk or interfere with the study procedures or outcome.

17. ☐ Liver function tests (ALT, AST, ALP, γGT and bilirubin) > upper limit of normal (ULN) at screening

18. ☐ Positive urine drug screen

19. ☐ Positive HIV, Hepatitis B or C result at screening.

20. ☐ History of use of tobacco- or nicotine-containing products within 6 months ofscreening or a positive urine cotinine screen (urine cotinine > 250ng/ml).

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Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Screening

12-LEAD ECG ABNORMALITIES

ECG Number ☐☐

Transcribe from the 12 Lead ECG result page.

Date of ECG ☐☐ Day ☐☐☐ Month ☐☐ Year Time of ECG ☐☐:☐☐ Hr:Min (00:00-23:59)

Complete additional ECG abnormalities pages if clinically significant abnormalities are present.

✓ *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		Visit Description
RA3107806			Screening

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
[D96] ☐ ST segment abnormality, not specified
[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
[D97] ☐ T wave abnormality, not specified
[D99] ☐ Other depolarisation/repolarisation

Comment _____

Other Abnormalities

[E99] ☐ Other abnormalities

Comment _____

Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
RA3107806			Study Visit

CONCOMITANT MEDICATIONS PROMPT

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 PROMPT

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.

ALCOHOL BREATH TEST

Date sample taken ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Results ✓*one:*

☐ Positive
If positive, exclude subject from the study.

☐ Negative

DRUG SCREEN

Date and time of sample taken ☐☐ ☐☐☐ ☐☐ ☐☐:☐☐ (Day Month Year Hr:Min (00:00-23:59))

✓*appropriate box(es)*	Positive	Negative
Cocaine	☐	☐
Amphetamines	☐	☐
Benzodiazepines	☐	☐
Cannabinoids	☐	☐
Opiates	☐	☐
Barbiturates	☐	☐
Methadone	☐	☐
Cotinine	☐	☐

If any of the above are positive, exclude subject from the study.

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Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
RA3107806			**Study Visit**

INVESTIGATIONAL PRODUCT

Date of Dose Day Month Year	Time of Dose Hr : Min 00:00-23:59	
05 JUN 03	***10:54***	
	:	

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)

_____

_____

_____

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Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Study Visit

VITAL SIGNS

Date Day Month Year	Planned Relative Time	Actual Time Hr : Min (00:00 - 23:59)	Blood Pressure Supine mmHg Systolic	 Diastolic	Heart Rate beats/min
e.g., 01 JAN 03	*15 min*	*13:02*	*110*	*80*	*75*
1.	Pre-dose	:			
2.	15 mins	:			
3.	30 mins	:			
4.	1 hr	:			
5.	2 hrs	:			
6.	4 hrs	:			
7.	6 hrs	:			
8.	8 hrs	:			
9.	24 hrs	:			
10.	48 hrs	:			
11.	Unscheduled	:			
12.	Unscheduled	:			
13.	Unscheduled	:			

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Study Visit

12-LEAD ECG

ECG Number	ECG1	ECG2	ECG3	ECG4	ECG5	ECG6	ECG7	ECG8
Start Date of ECG Day Month Year								
Planned Relative Time	Pre-dose	30 mins	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	24 hrs
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:	:	:	:	:	:
Heart 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.*

Note: Bazett's correction will be applied to QTc measurements.

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Study Visit

12-LEAD ECG (Continued)

ECG Number	ECG1	ECG2	ECG3	ECG4	ECG5	ECG6
Start Date of ECG Day Month Year						
Planned Relative Time	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:	:	:	:
Heart 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.*

Note: Bazett's correction will be applied to QTc measurements.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - CLINICAL CHEMISTRY

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - HAEMATOLOGY

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - URINALYSIS

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Study Visit

LIVER EVENTS ASSESSMENT

If a liver event has occurred, complete the Liver Events Assessment page in the End of Study section of the CRF.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - CLINICAL CHEMISTRY

PRE-DOSE

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

If the laboratory results meet the protocol definition of an adverse event, record the details in the Non-Serious Adverse Events or Serious Adverse Event section(s).

ELECTRONICALLY TRANSFERRED LABORATORY DATA - HAEMATOLOGY

PRE-DOSE

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

If the laboratory results meet the protocol definition of an adverse event, record the details in the Non-Serious Adverse Events or Serious Adverse Event section(s).

ELECTRONICALLY TRANSFERRED LABORATORY DATA - URINALYSIS

PRE-DOSE

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

If the laboratory results meet the protocol definition of an adverse event, record the details in the Non-Serious Adverse Events or Serious Adverse Event section(s).

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Study Visit

PHARMACOKINETICS - BLOOD (COLD ANALYSIS)

Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample ✓ if Taken	Sample Number
1. Pre-dose		:		**101**
2. 0.5 hrs		:		**102**
3. 1 hr		:		**103**
4. 1.5 hrs		:		**104**
5. 2 hrs		:		**105**
6. 3 hrs		:		**106**
7. 4 hrs		:		**107**
8. 6 hrs		:		**108**
9. 8 hrs		:		**109**
10. 12 hrs		:		**110**
11. 24 hrs		:		**111**
12. 36 hrs		:		**112**
13. 48 hrs		:		**113**
14. 72 hrs		:		**114**

PHARMACOKINETICS - BLOOD (METABOLITES)

Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample ✓ if Taken	Sample Number
1. Pre-dose		:		**115**
2. 1 hr		:		**116**
3. 4 hrs		:		**117**
4. 12 hrs		:		**118**

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Study Visit

PHARMACOKINETICS - BLOOD (PLASMA RADIOACTIVITY)

Planned Relative Time Time Relative to Dosing	Date Sample Taken Day Month Year	Actual Time Hr : Min (00:00 - 23:59)	Sample ✓ if Taken	Sample Number
1. Pre-dose		:		**119**
2. 0.5 hrs		:		**120**
3. 1 hr		:		**121**
4. 1.5 hrs		:		**122**
5. 2 hrs		:		**123**
6. 3 hrs		:		**124**
7. 4 hrs		:		**125**
8. 6 hrs		:		**126**
9. 8 hrs		:		**127**
10. 12 hrs		:		**128**
11. 24 hrs		:		**129**
12. 36 hrs		:		**130**
13. 48 hrs		:		**131**
14. 72 hrs		:		**132**
15. 96 hrs		:		**133**
16. 120 hrs		:		**134**
17. 144 hrs		:		**135**
18. 168 hrs		:		**136**

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Study Visit

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)	Was all of the sample collected for this interval? Y=Yes N=No	Sample ✓if Taken	Sample Number
1. Pre-dose		:		:			137
2. 0-6 hrs		:		:			138
3. 6-12 hrs		:		:			139
4. 12-24 hrs		:		:			140
5. 24-48 hrs		:		:			141
6. 48-72 hrs		:		:			142
7. 72-96 hrs		:		:			143
8. 96-120 hrs		:		:			144
9. 120-144 hrs		:		:			145
10. 144-168 hrs		:		:			146
11. 168-192 hrs		:		:			147
12. 192-216 hrs		:		:			148

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Study Visit

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)	Was all of the sample collected for this interval? Y=Yes N=No	Sample ✓if Taken	Sample Number
1. Pre-dose		:		:			**149**
2. 0-24 hrs		:		:			**150**
3. 24-48 hrs		:		:			**151**
4. 48-72 hrs		:		:			**152**
5. 72-96 hrs		:		:			**153**
6. 96-120 hrs		:		:			**154**
7. 120-144 hrs		:		:			**155**
8. 144-168 hrs		:		:			**156**
9. 168-192 hrs		:		:			**157**
10. 192-216 hrs		:		:			**158**

ELECTRONICALLY TRANSFERRED LABORATORY DATA - CLINICAL CHEMISTRY

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - HAEMATOLOGY

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - URINALYSIS

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Study Visit

LIVER EVENTS ASSESSMENT

If a liver event has occurred, complete the Liver Events Assessment page in the End of Study section of the CRF.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - CLINICAL CHEMISTRY

48HRS POST-DOSE

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

If the laboratory results meet the protocol definition of an adverse event, record the details in the Non-Serious Adverse Events or Serious Adverse Event section(s).

ELECTRONICALLY TRANSFERRED LABORATORY DATA - HAEMATOLOGY

48HRS POST-DOSE

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

If the laboratory results meet the protocol definition of an adverse event, record the details in the Non-Serious Adverse Events or Serious Adverse Event section(s).

ELECTRONICALLY TRANSFERRED LABORATORY DATA - URINALYSIS

48HRS POST-DOSE

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

If the laboratory results meet the protocol definition of an adverse event, record the details in the Non-Serious Adverse Events or Serious Adverse Event section(s).

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Protocol Identifier	Subject Identifier	WORKSHEET	Visit Description
RA3107806			Follow-up

PHYSICAL EXAMINATION

Date of Assessment ☐☐ ☐☐☐ ☐☐ Day Month Year

Indicate current physical findings by ✓ the appropriate box(es) below and if ABNORMAL, describe concisely: [different findings should be separated by either a (;) or a (/)].

	Normal	Abnormal	Not Done	
1. Hair and skin	☐	☐		_____
2. Lymph nodes	☐	☐		_____
3. Eyes	☐	☐		_____
4. Ears, Nose and Throat	☐	☐		_____
5. Breasts	☐	☐	☑	_____
6. Respiratory	☐	☐		_____
7. Cardiovascular	☐	☐		_____
8. Abdomen	☐	☐		_____
9. Urogenital	☐	☐	☑	_____
10. Pelvic	☐	☐	☑	_____
11. Rectal	☐	☐	☑	_____
12. Musculoskeletal	☐	☐		_____
13. Neurological	☐	☐		_____
14. Mental Status	☐	☐		_____

Protocol Identifier	Subject Identifier	Visit Date (Day Month Year)	Visit Description
RA3107806			Follow-up

VITAL SIGNS

Date (Day Month Year)	Planned Relative Time	Actual Time (Hr : Min (00:00 - 23:59))	Blood Pressure Supine mmHg		Heart Rate (beats/min)
			Systolic	Diastolic	
e.g., 01 JAN 03	*15 min*	*13:02*	*110*	*80*	*75*
1.	Follow-up	:			
2.	Unscheduled	:			
3.	Unscheduled	:			

12-LEAD ECG

ECG Number	ECG1	ECG2	ECG3
Start Date of ECG Day Month Year			
Planned Relative Time	Follow-up	Unscheduled	Unscheduled
Start Time of ECG Hr : Min (00:00-23:59)	:	:	:
Heart 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.*

ELECTRONICALLY TRANSFERRED LABORATORY DATA - CLINICAL CHEMISTRY

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - HAEMATOLOGY

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - URINALYSIS

MONITOR DATA VALIDATION CHECK

- Ensure that the appropriate lab samples have been sent for processing.

Protocol Identifier	Subject Identifier		Visit Description
RA3107806			Follow-up

LIVER EVENTS ASSESSMENT

If a liver event has occurred, complete the Liver Events Assessment page in the End of Study section of the CRF.

ELECTRONICALLY TRANSFERRED LABORATORY DATA - CLINICAL CHEMISTRY

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

If the laboratory results meet the protocol definition of an adverse event, record the details in the Non-Serious Adverse Events or Serious Adverse Event section(s).

ELECTRONICALLY TRANSFERRED LABORATORY DATA - HAEMATOLOGY

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

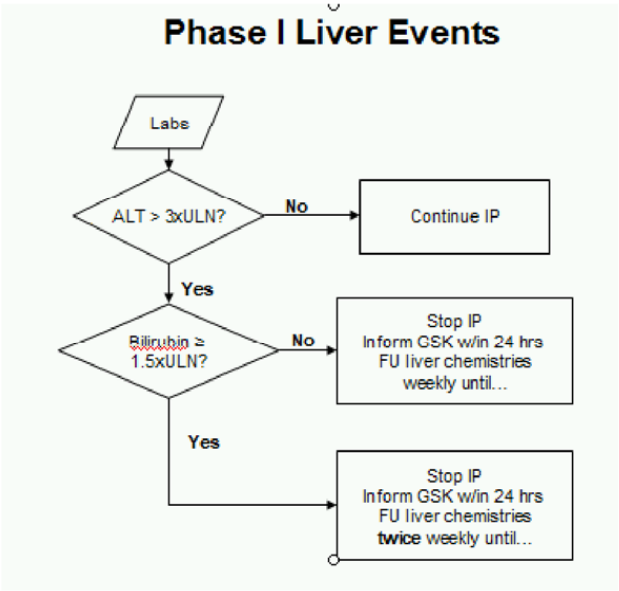
If the laboratory results meet the protocol definition of an adverse event, record the details in the Non-Serious Adverse Events or Serious Adverse Event section(s).

ELECTRONICALLY TRANSFERRED LABORATORY DATA - URINALYSIS

Date Sample Taken Day Month Year	Actual Time Hr : Min 00:00-23:59	
	:	

If the laboratory results meet the protocol definition of an adverse event, record the details in the Non-Serious Adverse Events or Serious Adverse Event section(s).

LIVER EVENTS ASSESSMENT
DECISION TREE FOR LIVER EVENTS



LIVER EVENTS ASSESSMENT
INVESTIGATOR INSTRUCTIONS

- **If subject exhibits** ALT ≥3xULN, stop investigational product, complete date stopped on Investigational Product form and contact GSK within 24 hours of occurrence. Follow-up liver chemistry (ALT, AST, alkaline phosphatase, bilirubin) should be obtained at weekly intervals until values resolve, stabilize or return to within baseline values.
- **If subject exhibits** concomitant ALT ≥3xULN **and** bilirubin ≥1.5xULN, stop investigational product, complete date stopped on Investigational Product form and contact GSK within 24 hours of occurrence. Follow-up liver chemistries should be obtained at twice weekly intervals until values normalise, substantively improve, or stabilise.

Protocol Identifier	Subject Identifier	
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LIVER EVENTS ASSESSMENT

Have liver chemistry results reached or exceeded protocol-defined investigational product stopping criteria?

[Y] ☐ Yes [N] ☐ No

If Yes, stop investigational product, complete date stopped on Investigational Product form, contact GSK within 24 hours of occurrence, complete Liver Events Form and obtain the following tests:

- *PK blood sample within 24 hours of last dose (or 3x the investigational product half-life or t1/2).*
- *Hepatitis A: Hepatitis A IgM antibody.*
- *Hepatitis B: Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).*
- *Hepatitis C: Hepatitis C RNA.*
- *Hepatitis E IgM antibody (if subject resides or has travelled in past 3 months outside the USA or Canada).*
- *Cytomegalovirus IgM antibody (CMV)*
- *EBV (Epstein Barr viral capsid antigen IgM antibody) or if unavailable, obtain heterophile antibody or monospot testing.*
- *CPK (serum creatine phosphokinase)*
- LDH *(lactate dehydrogenase)*
- *Bilirubin fractionation, if bilirubin ≥1.5xULN*

The following are only needed when ALT ≥3xULN and bilirubin ≥1.5xULN (>35% direct)

- *Anti-nuclear antibody*
- *Anti-smooth muscle antibody*
- *Type 1 anti-liver kidney microsomal antibodies (if available)*
- *Liver Imaging (ultrasound, magnetic resonance, or computerised tomography)*

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PHARMACOGENETIC (PGx) RESEARCH
INVESTIGATOR INSTRUCTIONS

CONSENT FOR PGx RESEARCH

The question "Has informed consent been obtained for PGx research?" should be completed on Day -1 prior to dosing and after PGx consent has been obtained

- 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 subject withdrawn consent for PGx 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 pharmacogenetic (PGx) 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 destruction and retain form in the clinical study file and, where appropriate, the designated laboratory 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 blood 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 pharmacogenetic (PGx) research.

- If the question is answered Yes, ✓one box for reason.

Protocol Identifier	Subject Identifier	
RA3107806		

PHARMACOGENETIC (PGx) RESEARCH

CONSENT FOR PGx RESEARCH (DNA)

Has informed consent been obtained for PGx research?

[Y] ☐ Yes [N] ☐ No

If Yes, record the date informed consent obtained for PGx research ☐☐ Day ☐☐☐ Month ☐☐ Year

If No, ✓ one reason:

[1] ☐ Subject declined
[2] ☐ Subject not asked by Investigator
[Z] ☐ Other, *specify* _____

BLOOD SAMPLE COLLECTION

Has a blood sample been collected for PGx research?

[Y] ☐ Yes [N] ☐ No

If Yes, record the date sample taken ☐☐ Day ☐☐☐ Month ☐☐ Year

WITHDRAWAL OF CONSENT

Has subject withdrawn consent for PGx research?

[Y] ☐ Yes [N] ☐ No

If Yes, record the date informed consent withdrawn for PGx research ☐☐ Day ☐☐☐ Month ☐☐ Year

BLOOD SAMPLE DESTRUCTION

Has a request been made for blood sample destruction?

[Y] ☐ Yes [N] ☐ No

If Yes, ✓ one reason:

[3] ☐ Subject withdrew consent for PGx
[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 start date is completed **or** 'Taken Prior to Study?' is 'Yes'.
  - It is acceptable for start date to be missing if 'Taken Prior to Study?' is 'Yes'.
  - It is acceptable if 'Taken Prior to Study?' is 'Yes' and a start date is present, as long as the start date is prior to the date of the subject's initial visit.
- 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	
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CONCOMITANT MEDICATIONS

Were any concomitant medications taken by the subject during the study?

[Y] ☐ Yes [N] ☐ No

If Yes, record each medication on a separate line using Trade Names where possible.

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.							:			:	

[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).
ActionTaken 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.

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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.*

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.

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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	Withdrawal	Relationship 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 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 investigational 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?

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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.

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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

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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) _____

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PREGNANCY INFORMATION
MONITOR DATA VALIDATION CHECK

- Check that responses provided correspond with the sex of the subject.
- If the answer to the female partner of the male subject pregnancy question is 'Yes', ensure that a Pregnancy Notification Form has been completed for the subject's partner.

Protocol Identifier	Subject Identifier	
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PREGNANCY INFORMATION

Did a female partner of the male subject become pregnant during the study?

[Y] ☐ Yes [N] ☐ No [X] ☐ Not Applicable (subject is female, female partner not of childbearing potential or no female partner)

If Yes, complete Pregnancy Notification form.

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STUDY CONCLUSION
INVESTIGATOR INSTRUCTIONS

Date of subject completion or withdrawal

- Refer to protocol section(s) to evaluate subject completion or withdrawal from the study.
- If subject completed the study
  'Date of subject completion (or withdrawal)' must match the last scheduled study visit date.
- If the subject withdrew from the study
  'Date of subject completion or withdrawal' is the date at which the investigator agreed, or determined, that the subject's participation in the study was over. Typically, this will be the date of the subject's last visit to the investigator but an alternative date of withdrawal may be used in the circumstances described below.
  - In the event that the contact between subject and investigator is conducted remotely during the planned study period (as defined in the protocol, i.e., by phone, by mail or electronic e-mail) and the subject is deemed to have withdrawn or been withdrawn, the date of withdrawal is considered to be the date on which the investigator is made aware of the withdrawal or makes the decision to withdraw the subject.
  - In the event that the subject is lost to follow-up, the date of withdrawal is considered to be the last point at which the investigator had contact with the subject **during** the study period (as defined in the protocol).

Primary reason for withdrawal

- You must only tick **ONE** Primary reason for withdrawal
- If the subject is withdrawn from the study, only tick 'Investigator discretion' or 'Withdrew consent' if the reason for withdrawal does not fit into any of the other primary reason categories.

Adverse event

- Use this primary reason only if the subject discontinues medication and is withdrawn from the study due to an adverse event

Protocol deviation

Study closed/terminated

- Use this primary reason only if the site is closed or the study is terminated by the sponsor.

Lost to follow-up

- In the event that the subject is lost to follow-up, the date of withdrawal is considered to be the last point at which the investigator had contact with the subject.

Investigator discretion

- Use this primary reason only if the subject discontinues from the study at the investigator's discretion and none of the other reasons apply.

Withdrew consent

- Use this primary reason only if the subject discontinues from the study because consent has been withdrawn and none of the other reasons apply (e.g., subject found the travel time to the clinic too long and does not want to continue in the study). Only use 'specify' to provide detailed information which is not covered by predefined sub-reasons provided.

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, telephone contacts or electronic e-mail.

STUDY CONCLUSION

MONITOR DATA VALIDATION CHECKS

- Check that 'Date of subject completion or withdrawal' has been provided.
- Check that either the 'Yes' or 'No' box at the top of the page has been completed. If 'Yes' is ticked, ensure **AT LEAST ONE** box is ticked for primary reason withdrawn from the study.
- If the subject was withdrawn due to an adverse event, confirm that details recorded correspond with details on the appropriate Adverse Event page.
  - "Withdrawal" on the AE/SAE page is recorded as 'Yes'.
  - "Action Taken with Investigational Product(s)" is recorded as 'Investigational Product Withdrawn'
- If any 'specify' comments have been written (for primary reason Investigator discretion or Withdrew consent), ensure that the information provided would not be more appropriately captured under any of the other primary reason categories.

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STUDY CONCLUSION

Date of subject completion or withdrawal ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Was the subject withdrawn from the study?

[Y] ☐ Yes [N] ☐ No

*If Yes, ✓ one **primary** reason for withdrawal:*

[1] ☐ Adverse event → *Record details on the Non-Serious Adverse Events or Serious Adverse Event pages as appropriate.*

[3] ☐ Protocol deviation

[4] ☐ Subject reached protocol defined stopping criteria

[5] ☐ Study closed/terminated

[6] ☐ Lost to follow-up

[7] ☐ Investigator discretion *(Only ✓ if none of the other primary reasons are appropriate)*

Specify: _____

[8] ☐ Withdrew consent *(Only ✓ if none of the other primary reasons are appropriate)*

Protocol Identifier	Subject Identifier	
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INVESTIGATOR COMMENT LOG

Only use this form to record explanatory information on anomalies such as missing data, 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).

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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) _____

000019P

RA3107806

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Protocol Identifier	Subject Identifier	
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12-LEAD ECG ABNORMALITIES

ECG Number ☐☐

Transcribe from the 12 Lead ECG result page.

Date of ECG ☐☐ Day ☐☐☐ Month ☐☐ Year Time of ECG ☐☐:☐☐ Hr:Min (00:00-23:59)

Complete additional ECG abnormalities pages if clinically significant abnormalities are present.

✓ *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 _____

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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
[D96] ☐ ST segment abnormality, not specified
[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
[D97] ☐ T wave abnormality, not specified
[D99] ☐ Other depolarisation/repolarisation

Comment _____

Other Abnormalities

[E99] ☐ Other abnormalities

Comment _____

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LIVER BIOPSY

Complete a separate form for each liver biopsy performed.

Date of liver biopsy ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Approximate size of liver biopsy ☐☐ mm *(number from 0 - 50)*

A. Final Diagnosis ✓*all that apply:*

- [A0] ☐ Normal
- [A1] ☐ Acute hepatitis
- [A2] ☐ Chronic hepatitis
- [A3] ☐ Cholestatic hepatitis
- [A4] ☐ Drug-induced cholestasis
- [A5] ☐ Acute viral hepatitis
- [A6] ☐ Chronic viral hepatitis
- [A7] ☐ Drug-induced hepatitis
- [A8] ☐ Autoimmune hepatitis
- [A9] ☐ Bridging necrosis
- [A10] ☐ Submassive hepatic necrosis
- [A11] ☐ Massive hepatic necrosis
- [A12] ☐ Steatosis - microvesicular
- [A13] ☐ Steatosis - macrovesicular
- [A14] ☐ Steatosis - mixed
- [A15] ☐ Non-alcoholic steatohepatitis
- [A16] ☐ Alcoholic hepatitis
- [A17] ☐ Hepatic granulomas
- [A18] ☐ Sarcoidosis
- [A19] ☐ Fibrosis
- [A20] ☐ Cirrhosis
- [A21] ☐ Primary biliary cirrhosis
- [A22] ☐ Primary sclerosing cholangitis
- [A23] ☐ Autoimmune overlap syndrome
- [A24] ☐ Hemochromatosis
- [A25] ☐ Alpha-1-antitrypsin deficiency
- [A26] ☐ Wilson's disease
- [A27] ☐ Veno-occlusive disease
- [A28] ☐ Budd-Chiari syndrome
- [A29] ☐ Neoplasia
- [A99] ☐ Other, *specify*: _____

B. Liver Architecture ✓*all that apply:*

- [B1] ☐ Normal
- [B2] ☐ Bridging fibrosis
- [B3] ☐ Diffuse fibrosis
- [B4] ☐ Nodular regenerative hyperplasia
- [B5] ☐ Congenital hepatic fibrosis
- [B6] ☐ Cirrhosis
- [B7] ☐ Centrilobular congestion
- [B8] ☐ Endophlebitis
- [B9] ☐ Veno-occlusive disease
- [B10] ☐ Canalicular cholestasis
- [B11] ☐ Apoptosis
- [B12] ☐ Focal (or spotty or mild) hepatocellular necrosis
- [B13] ☐ Interface hepatitis (periportal hepatitis or piecemeal necrosis)
- [B14] ☐ Ischaemic necrosis
- [B15] ☐ Centrolobular (Zone 3) necrosis
- [B16] ☐ Focal coagulative necrosis
- [B17] ☐ Centrolobular (Zone 3) coagulative necrosis
- [B18] ☐ Bridging hepatocellular necrosis
- [B19] ☐ Massive or panlobular hepatocellular necrosis
- [B20] ☐ Dysplasia
- [B21] ☐ Neoplasia
- [B99] ☐ Other, *specify*: _____

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LIVER BIOPSY (Continued)

C. Description of Liver Cells or Hepatocytes ✓*all that apply:*

- [C0] ☐ Normal
- [C1] ☐ Ballooning
- [C2] ☐ Acidophilic
- [C3] ☐ Pseudoxanthomatous
- [C4] ☐ Multinucleated giant hepatocytes
- [C99] ☐ Other, *specify*: _____

D. Liver Cell or Hepatocyte Inclusions or Vacuoles ✓*all that apply:*

- [D0] ☐ No inclusions
- [D1] ☐ Macrovesicular steatosis
- [D2] ☐ Microvesicular steatosis
- [D3] ☐ Bile accumulation
- [D4] ☐ Diastase-resistant, PAS-positive cytoplasmic inclusions
- [D5] ☐ Alpha-1-antitrypsin inclusions
- [D6] ☐ Megamitochondria
- [D7] ☐ Mallory bodies
- [D8] ☐ "Ground Glass" inclusions
- [D9] ☐ Lipofuscin pigment
- [D10] ☐ Hemosiderin granules
- [D11] ☐ Orcein-positive cytoplasmin granules
- [D12] ☐ Protoporphyrin crystals (birefringent under polarised light)
- [D13] ☐ Uroporphyrin crystals (red fluorescence under ultraviolet light)
- [D99] ☐ Other, *specify*: _____

E. Hepatocyte or Liver Cell Nuclear Abnormalities ✓*all that apply:*

- [E0] ☐ None
- [E1] ☐ Hepatocellular mitoses
- [E2] ☐ Binucleated or multinucleated hepatocytes
- [E3] ☐ CMV inclusion bodies
- [E4] ☐ HSV inclusions
- [E5] ☐ Varicella inclusions
- [E99] ☐ Other, *specify*: _____

F. Liver or Lobular Infiltrates ✓*all that apply:*

- [F0] ☐ None
- [F1] ☐ Eosinophils
- [F2] ☐ Lymphocytes
- [F3] ☐ Plasma cells
- [F4] ☐ Neutrophils
- [F5] ☐ Macrophages and proliferating Kupffer cells
- [F6] ☐ Granulomas
- [F99] ☐ Other, *specify*: _____

G. Portal Tract Inflammation ✓*all that apply:*

- [G0] ☐ None
- [G1] ☐ Eosinophils
- [G2] ☐ Lymphoid aggregates and/or follicles
- [G3] ☐ Plasma cells
- [G4] ☐ Neutrophils
- [G5] ☐ Histocytes and macrophages
- [G99] ☐ Other, *specify*: _____

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LIVER BIOPSY (Continued)

H. Bile Ducts ✓*all that apply:*

- [H0] ☐ Normal
- [H1] ☐ Proliferation of bile ducts (bile ductular reaction)
- [H2] ☐ Dilation, degeneration or disruption of portal bile ducts
- [H3] ☐ Paucity of bile ducts
- [H4] ☐ Periductal fibrosis
- [H99] ☐ Other, *specify*: _____

I. Portal Veins ✓*all that apply:*

- [I0] ☐ Normal
- [I1] ☐ Pyelophlebitis
- [I2] ☐ Thrombosis, sclerosis or occlusion of portal vein
- [I3] ☐ Neoplastic invasion of portal vein
- [I4] ☐ Granulomatous compression of portal vein
- [I99] ☐ Other, *specify*: _____

J. Liver Infections ✓*all that apply:*

- [J0] ☐ Normal
- [J1] ☐ Leishmaniasis donovani
- [J2] ☐ Plasmodium falciparum
- [J3] ☐ Toxoplasmosis
- [J4] ☐ Cryptococcus neoformans
- [J5] ☐ Histoplasma capsulatum
- [J6] ☐ Mycobacterium tuberculosis
- [J7] ☐ Other mycobacterial species
- [J99] ☐ Other, *specify*: _____

K. Parasites or Ova ✓*all that apply:*

- [K0] ☐ None
- [K1] ☐ Schistosome and/or ova
- [K2] ☐ Ascaris and/or ova
- [K3] ☐ Toxocara and/or ova
- [K4] ☐ Echinococcus cysts
- [K5] ☐ Hepatic capillariasis worms and/or ova
- [K99] ☐ Other, *specify*: _____

L. Histologic Staining or Additional Studies Obtained ✓*all that apply:*

- [L1] ☐ Haematoxylin and eosin (or H & E)
- [L2] ☐ Masson
- [L3] ☐ Toluidine blue or Giemsa
- [L4] ☐ Prussian blue
- [L5] ☐ Periodic Acidic Schiff (PAS), with or without diastase
- [L6] ☐ Oil red O
- [L7] ☐ Congo red
- [L8] ☐ Hall's stain
- [L9] ☐ Gridley's stain
- [L10] ☐ Rhodanine (copper)
- [L11] ☐ Rubeanic acid (copper)
- [L12] ☐ Orcein, aldehyde fuchsin or Victoria blue
- [L13] ☐ Electron microscopy
- [L14] ☐ Hepatitis A immunostains positive
- [L15] ☐ Hepatitis B core antigen or hepatitis B surface antibody immunostains positive
- [L16] ☐ Hepatitis D immunostains
- [L17] ☐ Other immunostains
- [L99] ☐ Other, *specify*: _____

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LIVER EVENTS

Date of assessment Day Month Year

Which liver chemistry result reached or exceeded protocol-defined investigational product stopping criteria?
✓ *all that apply*

[1] ☐ ALT (alanine aminotransferase)

[2] ☐ AST (aspartate aminotransferase)

[3] ☐ Total bilirubin

[4] ☐ Alkaline phosphatase

[OT] ☐ Other

Time period to the onset of ALT ≥2x Upper Limit Normal (ULN).

Note: Although stopping criteria is ALT ≥3x ULN, GSK are interested in capturing ALT ≥2x ULN to assess the probability of drug relatedness of liver event.

Note: Only complete dates for the treatment period applicable to the onset of ALT ≥2x ULN.	Start Date Investigational Product	End Date Investigational Product
If the liver event occurred during treatment period record start and stop date of investigational product for that treatment period.	Day Month Year	Day Month Year
If the liver event occurred after treatment period record start and stop date of investigational product for the most recent period prior to the liver event.	Day Month Year	Day Month Year

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LIVER EVENTS (Continued)

Record the details of any Adverse Events or exacerbations of Adverse Events on the Non-Serious Adverse Event Form OR the Serious Adverse Event Form. Exacerbations of Adverse Events include increases in frequency and severity.

It is particularly important to record any significant hypotension immediately prior to or concomitant with ALT elevation.
It is particularly important to record any gallbladder or biliary disease, or pancreatitis, that occurred during the study.

Is the subject age 55 or older?

[Y] ☐ Yes [N] ☐ No

If female, is the subject pregnant?

[Y] ☐ Yes [N] ☐ No [X] ☐ Not applicable

If Yes, ensure Pregnancy Notification Form has been completed.

Were any diagnostic imaging tests of the liver or hepatobiliary system performed (such as a liver ultrasound, computerized tomography or CAT scan, magnetic resonance imaging or MRI, or endoscopic retrograde cholangiopancreatography, or other)?

[Y] ☐ Yes [N] ☐ No

If Yes, were the results normal?

[Y] ☐ Yes [N] ☐ No

If No, record the details on the Non-Serious Adverse Events form or Serious Adverse Event form.

Were any liver biopsies performed?

[Y] ☐ Yes [N] ☐ No

If Yes, complete Liver Biopsy form.

Does the subject use herbals, complementary or alternative medicines, food supplements (vitamins) or illicit drugs?

[Y] ☐ Yes [N] ☐ No

If Yes, record on the appropriate Concomitant Medication form.

Did the subject fast or undergo significant dietary change in the past week?

[Y] ☐ Yes [N] ☐ No

ALCOHOL INTAKE
INVESTIGATOR INSTRUCTIONS

ALCOHOL CONVERTER
1 unit of alcohol in UK = 1 measure of spirits, 1/2 pint beer, 1 small glass of wine (125ml)

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LIVER EVENTS (Continued)

An unscheduled PK blood sample must be obtained within 24 hours of last dose (or 3x the investigational product half-life or t1/2).

Was a pharmacokinetic blood sample obtained?

[Y] ☐ Yes [N] ☐ No

If Yes, date and time sample taken — Day / Month / Year / Hr:Min (00:00-23:59)

If Yes, date and time of last investigational product dose prior to PK sample — Day / Month / Year / Hr:Min (00:00-23:59)

Sample Identifier Label	*Attach Sample Identifier Label Here*
Sample Number	

ALCOHOL INTAKE

Record the average number of units of alcohol[1] consumed per week ☐☐☐ units per week

[1] *See facing page for conversion guidelines.*

LIVER EVENTS
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.

NO MEDICAL CONDITION

No current or past condition.

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LIVER EVENTS (Continued)

LIVER DISEASE MEDICAL CONDITIONS

Specific Condition ✓ *only one response for each condition*	Current [1]	Past [2]	No Medical Condition [5]
1. Acute Viral Hepatitis A			
2. Chronic Hepatitis B			
3. Chronic Hepatitis C			
4. Cytomegalovirus Hepatitis			
5. Epstein Barr Virus Infectious Mononucleosis			
6. Herpes Simplex Hepatitis			
7. Alcoholic Liver Disease			
8. Non-alcoholic Steatohepatitis			
9. Fatty Liver			
10. Hepatic Cirrhosis			
11. Hemochromatosis			
12. Autoimmune Hepatitis			
13. Gallbladder disease			

DRUG RELATED LIVER DISEASE CONDITIONS (All drugs including Investigational Product)

14. Drug related liver disease			

OTHER LIVER DISEASE CONDITIONS

Specific Condition *Record only one per line for each condition and* ✓ *only one response for each condition*	Current [1]	Past [2]
15.		
16.		

OTHER MEDICAL CONDITIONS

Specific Condition ✓ *only one response for each condition*	Current [1]	Past [2]	No Medical Condition [5]
17. Drug Allergies			
18. Rheumatoid Arthritis			
19. Psoriasis			
20. Thyroid Disease			
21. Inflammatory Bowel Disease			
22. Lupus			
23. Sjogren's Syndrome			
24. Vitiligo			

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LIVER IMAGING

Complete a separate form for each individual imaging test performed.

Date of hepatic or liver imaging test Day Month Year

What method was used for this imaging test? ✓*one: (If more than one imaging test was performed, complete a separate form for each test).*

- [1] ☐ Ultrasound - transabdominal
- [2] ☐ Ultrasound - endoscopic
- [3] ☐ Magnetic Resonance Imaging (MRI)
- [4] ☐ Computerised Tomography (CT)
- [5] ☐ Endoscopic Retrograde Cholangiopancreatography (ERCP)
- [6] ☐ Positron Emission Tomography (PET)
- [7] ☐ Positron Emission Tomography/Computed Tomography (PET/CT)
- [OT] ☐ Other, *specify:* _____

Are images technically adequate? ✓*one:*

- [1] ☐ Optimal
- [2] ☐ Readable, but not optimal
- [3] ☐ Not readable
- [OT] ☐ Other, *specify:* _____

A. Indicate the liver size ✓*one:*

- [A1] ☐ Normal size
- [A2] ☐ Hypertrophy (or enlarged)
- [A3] ☐ Atrophy (or smaller than normal)
- [A4] ☐ Segmental hypertrophy
- [A99] ☐ Other, *specify:* _____

B. Indicate the liver texture ✓*one:*

- [B1] ☐ Normal
- [B2] ☐ Heterogeneous
- [B3] ☐ Suggestive of fibrosis
- [B4] ☐ Nodular or suggestive of cirrhosis
- [B99] ☐ Other, *specify:* _____

C. Grade the diffuse and/or geographic fatty infiltrate of the liver ✓*one:*

- [C1] ☐ Not applicable - no fatty infiltration
- [C2] ☐ Mild (≤25%)
- [C3] ☐ Moderate (>25% to <75%)
- [C4] ☐ Severe (≥75%)
- [C99] ☐ Other, *specify:* _____

D. Ascites present ✓*one:*

- [D1] ☐ None present
- [D2] ☐ Yes - small amount
- [D3] ☐ Yes - moderate or severe amount
- [D99] ☐ Other, *specify:* _____

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LIVER IMAGING (Continued)

E. Are Focal Hepatic Lesions characterisable? ✓*all that apply:*

- [E0] ☐ Not applicable - no hepatic lesions
- [E1] ☐ Solid
- [E2] ☐ Cystic
- [E3] ☐ Hemangioma
- [E4] ☐ Focal Nodular Hyperplasia
- [E99] ☐ Other, *specify:* _____

F. Gallstones or gallbladder lesions? ✓*all that apply:*

- [F0] ☐ None
- [F1] ☐ Gallstones
- [F2] ☐ Gallbladder polyp(s)
- [F3] ☐ Sludge
- [F4] ☐ Gallbladder wall thickening/oedema
- [F5] ☐ Gallbladder wall gas
- [F6] ☐ Cholecystitis
- [F7] ☐ Gallbladder wall calcification
- [F8] ☐ Gallbladder mass
- [F99] ☐ Other, *specify:* _____

G. Biliary ductal lesions? ✓*all that apply:*

- [G0] ☐ None
- [G1] ☐ Intrahepatic ductal dilation (focal involving the right hepatic lobe)
- [G2] ☐ Intrahepatic dutal dilation (focal involving the left hepatic lobe)
- [G3] ☐ Intrahepatic ductal dilation (involving both right and left hepatic lobes)
- [G4] ☐ Extrahepatic ductal dilation
- [G5] ☐ Diffuse ductal dilation (involving both intrahepatic and extrahepatic ducts)
- [G6] ☐ Acute Cholangitis
- [G7] ☐ Primary sclerosing cholangitis
- [G8] ☐ Choledocholithiasis (gallstone in duct)
- [G9] ☐ Ductal filling defect(s), other than gallstone
- [G10] ☐ Ductal wall thickening or oedema
- [G11] ☐ Choledochal cyst
- [G12] ☐ Ductal mass
- [G13] ☐ Extrinsic mass compressing bile duct(s)
- [G99] ☐ Other, *specify:* _____

H. Portal/Hepatic vein abnormalities? ✓*all that apply:*

- [H0] ☐ None
- [H1] ☐ Portal vein enlargement
- [H2] ☐ Hepatic vein enlargement
- [H3] ☐ Nonocclusive portal vein thrombosis
- [H4] ☐ Occlusive portal vein thrombosis - bland
- [H5] ☐ Hepatic vein thrombosis - bland
- [H6] ☐ Occlusive portal vein thrombosis - malignant
- [H7] ☐ Hepatic vein thrombosis - malignant
- [H8] ☐ Involvement of the main portal vein
- [H9] ☐ Involvement of the right portal vein
- [H10] ☐ Involvement of the left portal vein
- [H11] ☐ Budd-Chiari syndrome
- [H99] ☐ Other, *specify:* _____

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PREGNANCY NOTIFICATION FORM (SUBJECT'S PARTNER)

This form should be completed according to the protocol reporting requirements.

Complete this form for each subject's partner who becomes pregnant during the study period. Send a copy of the form to GlaxoSmithKline (GSK will provide separately a list of contact names and information) by mail or fax (fax preferred) within two weeks of learning of the pregnancy. Original pages should remain with the subject's Case Report Form.

Note: This form does not routinely need to be completed for subject's partner pregnancy unless there is specific instruction to do so stated in the protocol.

MOTHER'S RELEVANT MEDI

Mother's date of birth

Date of last menstrual period

Day Month Year

Estimated date of delivery

Day Month Year

Was the mother using a method of contraception?

☐ Yes ☐ No

If Yes, specify _____

Type of conception, ✓*one:*

☐ Normal (includes use of fertility drugs)

☐ IVF (in vitro fertilisation)

Relevant laboratory tests and procedures (e.g., ultrasound, amniocentesis and chorionic villi sampling, including dates of tests and procedures).

_____

_____

Number of previous pregnancies ☐☐ Pre-term ☐☐ Full-term

If applicable, record the number in the appropriate categories below:

☐☐ Normal births

☐☐ Stillbirths

☐☐ Children born with defects

☐☐ Spontaneous abortion

☐☐ Elective abortion

☐☐ Other

Record details of children born with defects _____

Are there any additional factors that may have an impact on the outcome of this pregnancy?

☐ Yes ☐ No

If Yes, specify _____

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PREGNANCY NOTIFICATION FORM (SUBJECT'S PARTNER) (Continued)

FATHER'S RELEVANT MEDICAL/FAMILY HISTORY

(Include habitual exposures such as alcohol/substance abuse, chronic illnesses, familial birth defects/genetic/ chromosomal disorders and medication use)

_____

_____

DRUG EXPOSURES

*In the following table, list **all** medications (including study medications) the subject received during the study period (e.g. prescription, OTC, vaccines, recreational, alcohol, etc.). **Enter the investigational product details on the first line** (if the investigational product is blinded, enter 'Investigational Product' on this line). If there are extensive concomitant medications, attach a copy of the Concomitant Medications CRF page.*

Drug Name *(Trade Name preferred)*	Route of Admin. or For-mulation	Total Daily Dose	Units	Started Pre-Study	Start Date	Stop Date	Ongoing Med-ication	Reason for Medication
				Y=Yes N=No	Day Month Year	Day Month Year	Y=Yes N=No	

Was the subject withdrawn from the study as a result of this pregnancy?

☐ Yes ☐ No

REPORTING INVESTIGATOR INFORMATION *(Forward to a more appropriate physician if needed)*

Name _____Title ___ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code _____

Telephone No _____

Fax No _____ ☐☐☐☐☐☐☐☐

Investigator's signature _____ Date
(confirming that the data on these pages are accurate and complete) Day Month Year

Investigator's name (print) _____

INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EVENT FORMS (SAE)

SECTION 12 **SAE Additional/Follow-up Information**	On receipt of follow-up information, the appropriate section(s) on the SAE form must be amended/updated with any changes (i.e., diagnosis, end date or death, change in intensity, or causality). These changes must be initialled and dated with confirmation by the investigator with his/her re-signing the form and forwarded to GSK within 24 hours. The investigator and others responsible for subject care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors. This may include seeking a further opinion from a specialist in the field of the AE. GSK may also request extra tests or extra follow-up information. If a subject dies, any post-mortem/autopsy findings, including histopathology, must be provided to GSK.

Protocol Identifier	Subject Identifier	Centre Number	Randomisation Number	
RA3107806				

SERIOUS ADVERSE EVENT (SAE) - ADDITIONAL/FOLLOW-UP INFORMATION (Continued)

SECTION 12 SAE Additional/Follow-up Information *(use this page to provide any additional details on the SAE not already captured on the previous pages)*

Investigator's signature _____
(confirming that the data on this page is accurate and complete)

Investigator's name (print) _____

Date ☐☐ Day ☐☐☐ Month ☐☐ Year

LIST OF INVESTIGATORS AND IECS/IRBS FOR RA3107806 (GM2008/00162/00)

Investigator	Investigator/ Site no.	Hospital/Institution and Address	IEC/IRB Committee Chair and Name of Committee
[redacted]	[redacted]	[redacted]	Dr. [redacted]

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

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[redacted]

VOLUNTEER INFORMATION

STUDY TITLE **An open label study to determine the *safety, tolerability,* excretion balance and pharmacokinetics of [^{14}C]GW856553, administered as a single dose of an oral solution to healthy adult male subjects.**

SPONSOR **GlaxoSmithKline**

EudraCT Number: **2007-005303-18**

Introduction

You are invited to take part in a research study that [redacted] is conducting on behalf of the Sponsor identified above. Before you decide to take part in the study it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and ask questions if anything is unclear.

This study has been approved by the [redacted] (a committee that reviews the rights of volunteers and the safety of the study) and the UK regulatory authority. [redacted] will comply with all applicable ethical and regulatory standards including the Declaration of Helsinki, which ensures that the rights of volunteers taking part in clinical studies are protected.

Taking part in this study is voluntary and if you decide not to take part this will not affect your inclusion in future studies at [redacted] If you choose to take part in the study, you will be free to withdraw at any time without giving any reason. However, if you do withdraw from the study early, you are encouraged to talk to the study doctor or nursing staff first, and you may be asked to return to the clinic for a follow-up visit to check your health. After your last visit to the clinic no new information will be collected from you. If you have taken the test drug, the doctor may advise you to remain in the clinic for a period of time for your own safety. If you do not

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follow the doctor's advice you will be asked to sign a "Discharge against medical advice" form. Before you leave the clinic a check will be performed to confirm your well-being.

Test drug information

The drug that is under investigation in this study is [^{14}C]GW856553. GW856553 is an experimental medicine being developed for a range of medical conditions including rheumatoid arthritis. GW856553 works by partially stopping the inflammation process associated with rheumatoid arthritis.

So far, GW856553 has been tested in 5 completed clinical trials throughout the world in 95 healthy volunteers, including an elderly population over 65 years old, 24 patients with chronic obstructive pulmonary disease (COPD – which is a disease which causes coughing and shortness of breath) and 50 patients with rheumatoid arthritis. Overall doses of up to 60 mg as a single dose and repeated doses of 7.5mg twice a day for 14 days have been well tolerated in all subjects studied so far. In one study, 9 healthy volunteers received 10mg of GW856553 twice a day for 14 days followed by 20mg of GW856553 once a day for 14 days. Two of the subjects had minor changes in liver function blood tests whilst receiving 10 mg GW856553 twice a day. GW856553 was stopped after 2 weeks in these subjects and their liver function blood tests returned to normal. There were no significant changes in liver function blood tests for the other 7 subjects in the study.

What is the purpose of the study?

The purpose of this study is to find out how a single dose of radiolabelled GW856553 and its breakdown products are absorbed, broken down and excreted by the body by measuring their concentration in blood, urine and faeces over one 10 day period. "Radiolabelled" means that the test drug has a radioactive component (identified as [^{14}C] before the drug number) to help us track the drug. The safety and tolerability of the test drug will also be assessed.

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Subject selection

A maximum of 6 healthy male volunteers between 30 and 60 years of age who meet the inclusion criteria will be enrolled in this study.

Study duration

This study consists of a screening visit, one dosing/in-patient observation period and a follow-up visit. The duration of your participation in this study from admission to final follow-up visit is approximately 5 weeks. During the in-patient observation period, volunteers are required to stay in the clinic. This will be for 10 nights on 1 occasion. Final study evaluations will be conducted during the follow-up visit, approximately 10 days after you have been discharged from the clinic.

Table 1: Study Schedule

Group	Admission (Day Before Dosing)	Dosing Day	Discharge*	Follow-up visit	Total No. of Nights in Clinic
1	Day -1	Day 1	Day 10 (216 hours)	10 Days after discharge from clinic	10

*****You will be discharged from the clinic approximately 216 hours after dosing (Day 10). If enough of the radioactivity is recovered by 168 hours (Day 8) after dosing you may be discharged, but not any earlier than this time.

Study design and dosing

You will be admitted for one ten day period. The group will consist of 6 subjects. The dose of [^{14}C]GW856553 to be studied is listed below in Table 2. On the day after admission to the clinic (Day 1) subjects will receive the test drug. The test drug [^{14}C]GW856553 will be in liquid form to be drunk. Dosing will be at approximately 08.30 h on Day 1.

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Table 2: Dose level to be studied

Group	Dose Level	Number of Administrations
1	10 mg [^{14}C]GW856553	1

GW856553 has been administered at this dose and higher doses in tablet form to volunteers and patients in previous studies.

The 10 mg dose of [^{14}C]GW856553 liquid you receive ***is expected to be*** absorbed at a ***similar*** rate ***to*** 10 mg of GW856553 in tablet form.

What does the radioactive dose mean?

The radioactivity you will receive is a radioactive carbon (Carbon-14 also written as ^{14}C).

The radiation received from the small amount of radioactive ^{14}C you will be given is equivalent to 0.4 milliSiverts (mSv the units used to express radiation).

All of us are exposed to radiation sources every day, for example from the rocks that are present in the area we live and from the sun. Some things we do increase the amount of radiation we are exposed to, for example flying in an aeroplane or having an X-ray. The table below lists the average radiation dose received in a number of situations.

Table 3: Radiation exposure

Type of Exposure		mSv
Single Exposure	Chest X-Ray	0.02
	This Study (approximately)	0.4
	Abdominal X-Ray	0.6
Annual Exposure	Aircraft Crew	2.0
	Natural Radiation (UK Average)	2.2
	Natural Radiation (Cornwall)	7.4

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From the table, you can see that the amount of radioactivity you will receive from this study is slightly less than the radiation dose that would result from one abdominal X-ray. This amount of radioactivity has been administered to a large number of volunteers and patients in other studies/procedures with no short or long-term problems.

What are the side effects of taking part?

GW856553 is a new drug that is early in its development and there is therefore limited information about its safety profile in man. In clinical trials to date, GW856553 has been well tolerated and most side effects have been mild in intensity.

GW856553 has been administered to over 150 subjects in five clinical trials. Overall doses of up to 60 mg as a single dose and repeated doses of 7.5mg twice a day for 14 days have been well tolerated. The most common side effects ***in taking part in*** these clinical trials were headache (14% of the subjects), common cold (4% of the subjects), and nausea (2% of the subjects). Skin effects (including acne, rash and dry skin) were seen more frequently in healthy volunteers who received GW856553 10 mg twice a day for 14 days followed by 20 mg once a day for 14 days than in healthy volunteers who received placebo (dummy drug) during the same study. All the side effects lasted only a short time and resolved fully.

Some previous examples of drugs from the family of drugs that GW856553 belongs to, have in some cases caused significant problems with liver function blood tests. This has not been observed with GW856553 in studies to date. Two healthy volunteers had minor changes in liver function blood tests whilst receiving 10 mg GW856553 twice a day. GW856553 was stopped after 2 weeks in these subjects and their liver function blood tests returned to normal.

When investigating new drugs, there is a risk of unexpected side effects and occasionally allergic reactions. You will be closely monitored during the study for any sign of side effects. In the unlikely event that these occur treatment will be available in the clinic.

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Possible effects of study procedures

On Day 1 (day of dosing) a cannula (a small plastic tube) will be inserted into a vein in your arm to allow blood samples to be obtained at frequent intervals throughout the day (a separate needle and syringe may be used on each occasion to obtain a blood sample if you prefer). Repeated blood tests and cannula insertion can cause soreness and bruising of arms or rarely blockage of a vein, but these problems usually clear up within a few days to a few weeks.

The cannula for blood sampling will be removed approximately 24 hours after dosing. Blood samples will be taken for the remainder of the study using a needle and syringe.

What will happen to me if I take part?

You will attend [redacted] for screening within 21 days before the first day of dosing. The screening examination will consist of:

- Medical history
- Physical examination (including height and weight)
- Blood pressure, pulse and oral temperature
- ECG (electrical heart tracing)
- Blood sampling for various tests (e.g. for anaemia, liver and kidney function)
- Blood sampling to test for Hepatitis B and Hepatitis C
- Blood sampling to test for HIV (the virus that can cause AIDS)
- Urine will be tested, including a test for drugs of abuse (which will include cannabis)
- Urine will be tested to confirm you are a non-smoker
- Alcohol breath test

Your general practitioner (GP) will be contacted regarding your past medical history.

In the event of a positive test for HIV we will inform you of the result and with your consent refer you to your local Genitourinary Medicine clinic or your GP for counselling. **Please note that**

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signing this consent form allows [redacted] **to inform your GP of any significant abnormal result.** In the event of a positive HIV, Hepatitis B or Hepatitis C result or if any of the other examinations and tests show any important abnormality we would discuss these with you and you would not be allowed to take part in the study.

You have the option to give a blood sample that, if used will help assess how quickly your body is able to breakdown GW856553 or how well it works in your blood. There is a separate information and consent form for this (Informed Consent Form and Information for Pharmacogenetic Research). Your decision whether or not to take part will not affect whether you can take part in this study or not. You will not receive an additional payment for this blood sample.

Future private healthcare or life insurance may be affected if an unsuspected problem is found at screening.

Once you have successfully completed screening, your co-operation with the following will be required:

1. On the day before you are scheduled to receive the test drug (Day -1) you will be admitted to the clinic at 10.00 h. The admission tests will include:

    - Blood pressure and pulse
    - ECG
    - Blood sampling for various tests (e.g. for anaemia, liver and kidney function)
    - Urine will be tested, including a test for drugs of abuse (which will include cannabis)
    - Urine will be tested to confirm you are a non-smoker
    - Alcohol breath test
    - You will be asked for details of any medication taken since the screening visit
    - You will be asked if you have been unwell since the screening visit.

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The results from these tests will determine whether you are eligible to enter the study or continue with the study.

2. You will be asked to provide a faecal sample before you receive the test drug. You will be given a container at screening to collect this sample at home or on the day of admission, if necessary. ***If possible a faecal sample will be obtained before dosing on Day 1.***

3. On the day of admission you will be fasted from 11.00pm. Water only will be available on request up to one hour before dosing.

4. On the morning of dosing (Day 1) you will not have breakfast.

5. Before you receive the test drug you will empty your bladder completely.

6. On the morning of dosing (Day 1) you will be given the test drug ***at approximately 08:30*** as a 100 mL solution to drink. A further 100 mL of water will be used to rinse the dose container and drunk.

7. You will be seated in bed for dosing and you must remain sitting upright for 1 hour and in bed for 2 hours after dosing. During this time you will only be allowed out of bed to go to the toilet. Approximately 2 hours after dosing you may walk about in the ward.

8. You will be given 100 mL of water to drink at 1 and 3 hours after dosing. Lunch will be provided 4 hours after dosing.

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9. **You must remain in the ward for 24 hours after dosing**. During that time you will not be allowed visitors as there will be a lot of study procedures being carried out.

10. You may shower on the morning of dosing before you receive the test drug. You will not be allowed to shower again for 24 hours after dosing. This is to ensure that all urine samples during this period are collected.

11. During the course of the study approximately 353 mL of blood will be taken compared to 480 mL which is a standard blood donation. If you have donated or lost more than 400 mL of blood in the previous 56 days you will not be permitted to take part. You must not donate blood for 12 weeks before the start of the study or following the completion of this study.

12. The following procedures will be performed at various intervals during your stay in the clinic:
    - Blood pressure and pulse
    - ECG
    - Blood sampling
    - Urine testing
    - Physical examination

    If you have an adverse event during the study it may be appropriate to perform additional safety measurements which have not been scheduled.

13. You will collect ***all*** the urine and faeces you produce throughout your stay in the clinic. You may be asked to collect urine and/or faeces at home if the radioactivity has not been fully recovered within the 10 days after dosing.

14. You will take part in a supervised walk every day weather, staff and study procedures permitting.

15. The following procedures will be performed at the follow up visit:
    - Blood pressure and pulse
    - ECG

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- Blood sampling
- Urine testing
- Physical examination

16. [redacted] confirms that:

You will receive the sum of £1070 for completing the study, and if you are withdrawn from the study for medical reasons associated with taking part you will receive this sum in full. If you withdraw from the study for medical reasons not associated with the study, a payment will be made to you proportional to the length of the period of taking part. If you withdraw for any other reason, the payment to be made shall be at the discretion of the supervising doctor.

If you do not comply with all the requirements of the study and the rules of the clinic you may forfeit a proportion of the fee at the discretion of the supervising doctor.

Your travelling allowance to and from the clinic will be reimbursed separately.

What is required of me for this study?

1. You must not have taken part in a study with any drug within 90 days before the start of the study. ***You must not have taken part in more than 3 studies involving new chemical drugs within the last 12 months.***

2. You should not have taken part in a radiolabelled study or have been exposed to additional radiation within the last 12 months. Sources of radiation include X-rays ***(including dental X-rays)*** and CT scans.

3. You must adhere to the following restrictions before and during the study. This is for your safety and to ensure an accurate assessment of the data collected from you during the study.

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Restricted Item / Activity	**Interval of Restriction**
Prescription medication	5 days before dosing until follow-up visit
Grapefruit, grapefruit juice and cranberry juice (a chemical in these fruits can slow down the elimination of certain drugs from your body by affecting their breakdown).	7 days before admission until discharge
Over-the-counter medication including paracetamol	5 days before dosing until follow-up visit
Alcohol	24 hours before admission until discharge and from 48 hours before returning for the follow-up visit.
Caffeine and caffeine containing products (e.g. chocolate, tea, coffee, carbonated drinks)	24 hours before admission to discharge

4. You must only take food and drinks that are provided by clinic staff. All food and drinks provided in the clinic will be caffeine free. Your calorie intake will be limited to no more than 2,500 per day to avoid excessive weight gain. You will be shown an example of a typical menu which will be provided during your stay in the clinic.

5. ***You must not be in the habit of drinking more than 21 units of alcohol per week (or an average 3 units of alcohol per day). A unit of alcohol is equivalent to: half a pint of average strength beer (280 mL), a glass (125 mL) of wine or a standard measure (25 mL) of spirits, sherry or port.***

6. You must be a non smoker (for a minimum of 6 months).

7. It is important that you use an adequate method of contraception during the study and until completion of the follow up visit. As GW856553 is a new drug its effects on sperm production and pregnancy are unknown, therefore pregnancy should be avoided in partners of male volunteers taking the test drug. ***All volunteers must agree to use a condom with spermicide. In addition your partner must use*** another form of contraception ***unless she has been surgically sterilised*** such as diaphragm with spermicide, coil (intra-uterine device), oral contraceptive pill, depot progesterone injections, sub-dermal implant or tubal

ligation. If you are usually not sexually active (using abstinence as a form of contraception) but become sexually active ***you and your partner should follow this advice.***

8. You must not have sexual intercourse with women who are pregnant or breastfeeding during the course of the study.

9. With your approval and the approval of your partner the investigator will collect where possible information on the pregnancy of any female partner who becomes pregnant during the study.

10. You must comply with any instruction given during the study and co-operate fully with the clinic staff. If you do not comply you may be removed from the study.

11. You should inform the supervising doctor of any symptoms you have or medicines you take during the study period. You must tell them immediately if you notice any change in your health, or if any symptoms occur. You will be given a card with a 24 h telephone number to call if you have any questions or worries. You should keep this card with you at all times for one month after you leave the clinic following your last visit.

12. You must agree that you will not seek to restrict the use of your results and accept that they may be disclosed to regulatory authorities for medicines in the UK and elsewhere.

Reasons why you may be withdrawn from the study

If you want to leave the study at any time, you will be allowed to do so. In addition, you may be withdrawn from the study for any of the following reasons:

1. If you experience a serious or severe adverse event
2. If you do not comply with the study instructions
3. If the sponsor terminates the study

What are the possible benefits of taking part?

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This is a research study and you will not obtain any medical benefit from taking part.

What if new information becomes available?

You will be advised if any information becomes available during the course of the study, which may affect your willingness to continue.

If you develop any significant side effects, including any major changes in laboratory results, you may be withdrawn from the study. The sponsor company may also stop the study.

What if something goes wrong?

If your health or wellbeing deteriorates significantly as a result of taking part in the study the Sponsor will compensate you in accordance with the Association of the British Pharmaceutical Industry "Guidelines for Phase I Clinical Trials (2007 Edition)".

The amount of compensation shall be calculated by reference to the amount of damages that would commonly have been awarded for similar injuries by a [redacted] court had liability been admitted. The amount of compensation will be reduced if you are partly responsible for the injury or if you have been compensated under another insurance policy of the Sponsor.

You and the Sponsor shall refer to an arbitrator any dispute or disagreement about the compensation undertaking. If you and the Sponsor cannot agree on the identity of an arbitrator, the President of the [redacted] will be invited to appoint an arbitrator with the power to consult an advocate of not less than 10 years standing on any issue of law including the amount of damages to be paid.

The contractual undertaking to compensate you shall follow the law in [redacted] and, subject to the provisions above, the [redacted] courts shall have sole jurisdiction over any dispute that may arise out of it.

If you would like an explanation of these legal terms please feel free to ask.

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Will my taking part in this study be kept confidential?

[redacted] will use its best endeavours to keep confidential any personal details about you it obtains during the study. However, please note the following:

The medical history and personal details [redacted] collected about you before the study began are held in a database controlled by [redacted] That database is password protected and only accessible by certain authorised personnel of [redacted] The information about you so collected and stored will remain on [redacted] database as previously notified to you in either the application form or the Data Protection Act Notice that you have already signed.

The samples and the study records collected from you throughout the study by study doctors, nurses and other [redacted] personnel (the "Study Data") will, unless otherwise required by law, be anonymised so that you are identified by your initials and a subject number ("identification data"), not your full name. Your identification data will also include information about your health and your demographic details (such as your date of birth, your sex and your ethnic origin). You will not be personally identified in any scientific reports or presentations or clinical publications that may result from the study.

The Study Data collected about you during the study including medical and health data relating to you, will be held by [redacted] and the Sponsor in their records for such period of time as may be required for the Sponsor to obtain regulatory approval of the test drug in the UK and elsewhere. However, neither [redacted] nor the Sponsor will retain personal data about you or the study for any longer than required. [redacted] will hold the Study Data in a paper file on its premises. The paper file will be kept in a secure area, which is only accessible to a limited number of authorised personnel (such as the doctors who are conducting the study) who require access to the file.

The Sponsor is responsible for controlling the use of your personal information in accordance with applicable laws and the terms of this consent form. The Study Data will be used and/or processed (including being disclosed) for the following purposes: the study; certain additional

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scientific research; registration of the test drug as a product; research purposes in general; and ensuring compliance with medical, ethical and pharmaceutical laws and regulations. By signing the attached consent form, you agree to and expressly authorise such processing.

Representatives from regulatory agencies, the local ethics committee, and the Sponsor or its designees, will also have access to and may inspect, review and copy the Study Data for the purpose of verifying clinical and scientific research procedures and/or data collected for the study to the extent permitted by applicable laws and regulations, subject always to obligations of confidentiality. By signing the attached consent form, you authorise such access to your study records. Even if you withdraw your consent, your personal information may still be processed by the Sponsor if so permitted or required by law.

During the study, you have the right, on producing sufficient identification evidence, to access the data relating to your taking part in the study via a member of [redacted] staff and, in the event of any inaccuracies about you recorded in the Study Data, you have the right to request that such data be corrected.

For your own safety and to fulfil the objectives of the study it is essential that you observe any instructions you are given by the doctors and/or medical staff who are carrying out the Study, and all the requirements referred to in this document. The supervising doctor will be pleased to supply to you further information about the Study at any time.

You may contact the impartial third party listed below with any questions you have about the research and your rights as a research subject.

It is essential that you observe any instructions you are given by the doctors and/or medical staff who are carrying out the Study, and all the requirements referred to in this document. The supervising doctor will be pleased to supply to you further information about the Study at any time.

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You may contact the impartial third party listed below with any questions you have regarding the study, your rights as a research subject or if you have any symptoms or side effects.

Thank you for reading this.

Supervising Doctors

Dr [redacted] / Dr [redacted]
[redacted]

Tel: [redacted]

Impartial Third Party

Ethics Committee Chairperson
Contact via Ethics Committee Administrator
[redacted]

Tel: [redacted]

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Volunteer Screening Consent Form **Volunteer Panel Number** ☐☐☐☐☐

This agreement is between the volunteer and [redacted]

(FIRST) (MIDDLE) (LAST)

(To be completed by the Volunteer) Initial box

1. I confirm that I have read and understand the attached Volunteer Information Form for the study. I have been given the opportunity to ask questions about the study and understand the advice and information given. ☐
2. I have been given a full explanation of the nature, purpose and likely duration of the study and what I will be expected to do. I have been advised about any discomfort and possible side effects. ☐
3. I agree to have all of the screening procedures performed for this study. ☐
4. I agree to Dr [redacted] contacting my General Practitioner (GP) to make known my participation in the study and I authorise my GP to report details of my relevant medical and drug history to [redacted] in confidence. ☐
5. I agree to have my blood taken to test for HIV, Hepatitis B and Hepatitis C. I authorise [redacted] to inform my GP of any positive result and any other significant abnormality. ☐
6. I understand that I am free to withdraw from the study at any time without needing to justify my decision. ☐

Signed by the volunteer: _____

Name of the volunteer (printed): _____

(FIRST) (MIDDLE) (LAST)

Dated by the volunteer: _____/_____/_____ Time of consent **(to be completed by the volunteer)** ☐☐.☐☐ hh mm

I confirm that the nature, purpose and possible hazards of this study have been explained to:
Name of the volunteer (printed): _____

(FIRST) (MIDDLE) (LAST)

Signed by the person giving explanation: _____

Name of person giving explanation (printed): _____ Date: _____/_____/_____

I confirm that I have witnessed the above explanation:
Signed by the witness : _____

Name of the witness (printed): _____ Date: _____/_____/_____

Signed by an Investigator: _____
(signed on behalf of [redacted] as its authorised representative)
Name of Investigator (printed): _____ Date: _____/_____/_____

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Volunteer On-Study Consent Form

Volunteer Panel Number ☐☐☐☐☐

This agreement is between the volunteer and [redacted]

(FIRST) (MIDDLE) (LAST)

(To be completed by the Volunteer) Initial box

1. I confirm that I have read and understand the attached Volunteer Information Form for the study. I have been given the opportunity to ask questions about the study and understand the advice and information given. ☐
2. I have been given a full explanation of the nature, purpose and likely duration of the study and what I will be expected to do. I have been advised about any discomfort and possible side effects. ☐
3. I agree to comply with all the requirements of the study and the rules of the clinic. ☐
4. I understand that the study will involve the administration of [^{14}C]GW856553. ☐
5. I understand that I am free to withdraw from the study at any time without needing to justify my decision. ☐
6. I understand that my personal and medical data collected by [redacted] staff will be retained by [redacted] and the Sponsor and may be used by, disclosed to or reviewed by certain authorised individuals from GlaxoSmithKline *(*Sponsor*)*, the regulatory authorities and the Ethics Committee where relevant. I give permission to [redacted] and the Sponsor to hold and retain my personal data and for the individuals and/or organisations listed herein to have access to my Study Data for the purposes set out above and also as detailed in the attached Patient Information Form. I also agree to my anonymised personal information being transferred outside the European Economic Area (EEA), if so required. ☐
7. I, the undersigned, voluntarily agree to take part in the study. ☐

[redacted] **STUDY NUMBER:** [redacted]
[redacted] **CLINIC REFERENCE NUMBER:** [redacted]
SPONSOR REFERENCE NUMBER: RA3107806
VERSION 2 – 14 DECEMBER 2007

Volunteer On-Study Consent Form **Volunteer Panel Number** ☐☐☐☐☐

Signed by the volunteer: _____

Name of the volunteer (printed): _____
(FIRST) (MIDDLE) (LAST)

Dated by the volunteer: _____/_____/_____ Time of consent **(to be completed by the volunteer)** ☐☐.☐☐
hh mm

I confirm that the nature, purpose and possible hazards of this study have been explained to:

Name of the volunteer (printed): _____
(FIRST) (MIDDLE) (LAST)

Signed by the person giving explanation: _____

Name of person giving explanation (printed): _____ Date: _____/_____/_____

I confirm that I have witnessed the above explanation:

Signed by the witness : _____

Name of the witness (printed): _____ Date: _____/_____/_____

Signed by an investigator:

(signed on behalf of [redacted] as its authorised representative) _____

Name of Investigator (printed): _____ Date: _____/_____/_____

[redacted] **STUDY NUMBER:** [redacted]
[redacted] **CLINIC REFERENCE NUMBER:** [redacted]
SPONSOR REFERENCE NUMBER: RA3107806
VERSION 2 – 14 DECEMBER 2007

APPENDIX 1

Summary of Study Procedures

Procedure	**Time**
Physical examinations	Screen and follow-up
Hepatitis B and C and HIV test	Screen
Drugs of abuse screen	Screen and Day-1
Alcohol breath test	Screen and Day-1
Safety blood tests	Screen, Day-1, 48 hours post dose and follow-up visit
Urine test	Screen, Day-1, 48 hours post dose and follow-up visit
Vital signs recording	Screen, Day 1, predose, 0.25, 0.5, 1, 2, 4, 6, 8, 24 and 48 hours post dose and follow-up visit
ECG	Screen, Day 1, pre-dose, 0.5, 1, 2, 4, 6, 8 and 24 hours post dose and follow-up visit
Side effect monitoring	Throughout study from Day 1 until follow-up visit
Blood samples for GW856553	At frequent intervals from pre dose until the end of the study
Urine collections for GW856553	From pre dose until you are discharged from the clinic
Faecal and urine collections for radioactivity	From pre dose to discharge (216 hours). Possibly at home if required and agreed with volunteer
Blood sample for pharmacogenetic research	Pre dose Day 1 but not compulsory

Additional procedures may be performed or blood samples collected for your safety or to provide more information about the study drug.

[redacted] Study No. [redacted]
Clinic Reference No. [redacted]
GSK Protocol No. RA3107806
Version 2 – 14 December 2007

[redacted]

Informed Consent Form and Information Sheet for Pharmacogenetic Research

Protocol Title: **An open label study to determine the *safety, tolerability,* excretion balance and pharmacokinetics of [^{14}C]GW856553, administered as a single dose of an oral solution to healthy adult male subjects.**

EudraCT Number: 2007-005303-18
Principal Investigator: Dr [redacted]
Site Address: [redacted]

Site Phone Number: [redacted]

This form is in addition to the consent form you have already signed for the clinical study [redacted] for drug GW856553.

Purpose and Description of the Research
The purpose of this information sheet 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 the sponsor in this consent]. [redacted] is paid by the sponsor to conduct this research. This study is expected to have six subjects at only this site in the UK.

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 GW856553, the sponsor may study these differences using your genes or genetic material taken from your blood sample. Your sample will only be used in relation to data collected about GW856553.

What are the benefits of participating in this research study?
You may help scientists understand why people react to or handle GW856553 differently. This may help identify who is more likely to respond to GW856553 and who may experience side effects.

[redacted] Study No. [redacted]
Clinic Reference No. [redacted]
GSK Protocol No. RA3107806
Version 2 – 14 December 2007

[redacted]

What will happen to me if I take part?
If you agree to take part in this research, a trained person will take about 10 ml (or 2 teaspoons) of your blood. The blood sample will be taken on the morning of the day you receive the study drug. In the unlikely case that there is a problem processing your sample, then we may ask you to give a second sample.

Do I have to take part?
It is up to you to choose whether or not to take part. You can take your time to decide if you want to participate. If you decide to take part you are still free to withdraw at any time if you change your mind. The sponsor may store your sample for up to 15 years after the last subject completes the study or the sponsor may destroy your sample before then. If you decide not to take part 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 GW856553 study. If you withdraw from this research, your sample will be destroyed and the sponsor will only keep and study information collected/generated up to that point.

In some circumstances your sample may not be used, for example if there are not enough subjects in the study, if the study is stopped for any reason, or if there are not any differences in the way people respond to or handle GW856553. If your sample is not used, it will be destroyed.

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 ***when the blood sample is being drawn***. ***You may also*** experience mild pain, bruising, irritation or redness at the site where the blood sample was taken, but these problems usually clear up within a few days to a few weeks.

What if something goes wrong?
You are insured for this research study by the same insurance and under the conditions as described for the main study (refer to Section entitled “What if something goes wrong”).

What are the alternatives?
You have the choice not to take part in this research but this does not affect your participation in the main study.

How are privacy, data protection and confidentiality protected?
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. The sponsor 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.

The sponsor or those working with the sponsor (for example, other researchers) will only work with your sample for the use stated in this consent. Samples will be stored securely. The sponsor will require anyone who works with your sample to agree to hold the research information and any individual results in confidence.

[redacted] Study No. [redacted]
Clinic Reference No. [redacted]
GSK Protocol No. RA3107806
Version 2 – 14 December 2007

[redacted]

If your sample is analysed, you may request, through your study doctor, that GSK makes your personal results available to you. Under no circumstances will GSK provide your personal results to a third party. Your test results are not used for diagnosis or treatment of a disease. These results serve only scientific purposes.

Medical information, samples and research results from you and other research participants may be studied by the sponsor to make medicines or tests to determine the body's response to or handling of GW856553. Your information, sample and results (labelled only with your subject number, not your name) could be sent to other researchers working with GSK for analysis purposes. GSK or those working with GSK (for example other researchers) will only work with your sample for the use stated in this consent. The Data Protection Act will be complied.

By agreeing to take part in this research, you will allow your ***anonymised*** pharmacogenetic results to be reviewed as part of collecting and analyzing study results. The people who may check this research include the sponsor, people working with the sponsor on this research, ethics committees and regulatory authorities such as the European Medicines Evaluation Agency (EMEA) in Europe. These persons are required to maintain the confidentiality of the information.

Will there be compensation for participation in the research?
You will not receive any additional payment for taking part in this pharmacogenetic research.

What will happen to the results of this study?
The sponsor 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 the sponsor can apply for patents and you understand that you will not receive any financial benefit that might come from the research.

Who should I contact if I have any questions?
You may contact Dr [redacted] or Dr [redacted] at telephone number [redacted] 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.

[redacted] Study No. [redacted]
Clinic Reference No. [redacted]
GSK Protocol No. RA3107806
Version 2 – 14 December 2007

[redacted]

CONSENT FOR PHARMACOGENETIC RESEARCH

A copy of this Consent Form (signed and dated) will be given to you

---

If you agree with each sentence below, please INITIAL **the box:**		**INITIALS**
1)	I have read and understood this information sheet Version 1, 06 November 2007 for the above study and I confirm that the study procedures and information have been explained to me. I have had the opportunity to ask questions and I am satisfied with the answers and explanations provided.	☐
2)	I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to take part in the study.	☐
3)	I have been given the time to consider participation and understand that my participation in this study is voluntary and that I am free to withdraw from the study at any time, without giving any reason, without my medical care or legal rights being affected.	☐
4)	I agree that my data and sample can be transferred outside the EU.	☐
5)	I agree to take part in this research study.	☐
6)	I have received a copy of this volunteer's information and consent form.	☐

[redacted] Study No. [redacted]
Clinic Reference No. [redacted]
GSK Protocol No. RA3107806
Version 2 – 14 December 2007

[redacted]

Signed by the volunteer: .....

Name of the volunteer (printed): ….....
(FIRST) (MIDDLE) (LAST)

Dated by the volunteer: .....
dd/mmm/yyyy

I confirm that the nature, purpose and possible hazards of this study have been explained to:

Name of the volunteer (printed): .....
(FIRST) (MIDDLE) (LAST)

Signed by the person giving explanation: .....

Name of person giving explanation (printed): .....

Dated : .....
dd/mmm/yyyy

I confirm that I have witnessed the above explanation:

Signed by the witness : .....

Name of the witness (printed)*:* .....

Dated : .....
dd/mmm/yyyy

Signed by the physician : .....
(signed on behalf of [redacted] as its authorised representative)

Name of physician (printed): .....

Dated : .....
dd/mmm/yyyy

CHEMICAL DEVELOPMENT
ACTIVE PHARMACEUTICAL INGREDIENT RELEASE DOCUMENT

DNG# SD2008/00037/00

API Number:	GW856553J	**Batch Number:**	R16861/31/1
API Salt:	Free Base	**Site of Manufacture:**	Stevenage
Route/Process Number:	N/A	**Site of Analysis:**	Stevenage
Date of Manufacture:	11-Dec-2007	**API Batch Report Ref:**	N/A

APPROVED FOR: Clinical Studies

Summary of analytical data:-

Summary Analytical Reference:	EE305712 08-Jan-2008 16:08:44
Specification Reference:	S0010323v1
Identity Confirmed by:	1H NMR
Assigned Purity (%w/w)	100.8
Assigned Purity (as free base) (%w/w)	100.8
Weighing Factor	1.000g contains 1.000g of GW856553X as free base
Specific Activity (µCi/mg)	4.95
Radiochemical Purity (% area)	99.8
Retest Date	11-Mar-2008
Storage Conditions	Store in a freezer, -25 to -10°C
Ref. to stability data	eE305610

ANALYTICAL SCIENCES AUTHORISATION	
Analysis performed in compliance with cGMP	**First Issue**
Signature [redacted]	Date 08- January 2008
Name [redacted]	(Analytical Sciences)

CDQA AUTHORISATION FOR CLINICAL STUDIES	
This batch was manufactured and tested in compliance with cGMP The compliance of this batch with any regulatory dossier must be checked prior to release of the packed drug product.	
Materials of Animal Origin used: ~~YES~~/NO	
Signature [redacted]	Date 9 Jan 2008.
Name [redacted]	(Chemical Development Quality Assurance)

ICH Data Listings

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****.*

Other Data Listings

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 study to determine the safety, tolerability, excretion balance and pharmacokinetics of [^{14}C]GW856553, administered as a single dose of an oral solution to healthy adult male subjects.

I have read this report and confirm that to the best of my knowledge Study RA3107806 was carried out as described in the GlaxoSmithKline Report GM2008/00162/00

Name of Principal Investigator: Dr. [redacted]

Affiliation: [redacted]

Signature of Investigator: [redacted]

Date: 04 Jul 2008

Sponsor Signatory Signature Page

STUDY TITLE: An open label study to determine the safety, tolerability, excretion balance and pharmacokinetics of [^{14}C]GW856553, administered as a single dose of an oral solution to healthy adult male subjects.

Study: RA3107806 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] PhD

Title of Sponsor Signatory: Director, Discovery Medicine, Respiratory CEDD

Signature: [redacted]

Date: 15th Jan 2009.