TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	An open label positron emission tomography (PET) imaging study using ^{89}Zirconium labelled GSK3128349 to investigate the biodistribution and clearance of an albumin binding domain antibody (AlbudAb) GSK3128349 following single dose intravenous administration in healthy male subjects.

Compound Number: GSK3128349

Development Phase I

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Author(s):

PPD

CPSSO, PCPS
Translational Medicine, PTS
Clinical Statistics, PCPS
PTS
Cell & Gene Therapy, PTS
Safety Assessment, PTS
Clinical Immunology, PTS
Translational Medicine, PTS
Clinical Pharmacology Modeling and Simulation, PCPS

SPONSOR SIGNATORY:

PPD

5/23/2016

John Toso
Head, Biopharm Translational Medicine, PTS, R&D

Date

PPD

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD PPD	PPD PPD	PPD PPD	PPD PPD	Upper Merion, US
Secondary Medical Monitor	PPD	PPD PPD	PPD PPD	PPD PPD	Upper Merion, US
SAE contact information	Medical Monitor as above				

Sponsor Legal Registered Address:

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

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Regulatory Agency Identifying Number(s): N/A

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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1. PROTOCOL SYNOPSIS FOR STUDY RES117169

Rationale

GSK3128349: GSK3128349 is a human domain antibody (dAb) that binds non-covalently to serum albumin with high affinity (also referred to as an 'AlbudAb™'). It contains a cysteine residue engineered at the C terminus of the molecule that can be used for the covalent attachment of a pharmacologically active entity As such, GSK3128349 is a scaffold that has of itself no pharmacological action, but has the potential to be conjugated with a pharmacologically active entity [O'Connor-Semmes, 2014].

GSK3128349 is a platform to extend half-life and alter biodistribution of therapeutics: Typically, dAbs are small (~15 kDa) and therefore are excreted renally in a matter of hours. Due to the combination of the high affinity of GSK3128349 for albumin and the high concentrations of albumin, it is expected that GSK3128349 will be bound to albumin the majority of the time. Therefore, AlbudAbs, like GSK3128349, form a complex too big to be subject to renal clearance. Furthermore, the binding of GSK3128349 to albumin confers some of the pharmacokinetic and biodistribution properties of albumin to GSK3128349; and hence any pharmacologically active entity conjugated to it. This includes AlbudAbs bound to albumin being subject to Neonatal Fc Receptor (FcRn) dependent albumin recycling enhancing the exposure half-life. As a result of these effects AlbudAbs can persist in the body for several days or even weeks. We expect the half life of GSK3128349 in humans to approach that of albumin (~19 days [Peters, 1985] [Peters, 1996(a)]). Therefore, GSK3128349 has the potential to significantly enhance the medicinal value of therapeutics conjugated to GSK3128349 by increasing their half-life and/or modulating their biodistribution [Kratz, 2008].

Study Objective: This study will determine the biodistribution and pharmacokinetics of the AlbudAb scaffold GSK3128349. The data will inform and validate a Physiologically Based Pharmacokinetics (PBPK) model, which will predict the distribution of future therapeutics conjugated to GSK3128349, as well as other AlbudAbs.

The validated PBPK modeling will improve our future clinical study designs by providing more accurate estimates of tissue exposures, which will lead to better: dose selection, timing of biomarker measurements, target engagement, and ultimately efficacy. This could potentially lead to a reduced number of assessments and/or subjects enrolled in future clinical trials. Furthermore, the PBPK modeling will be applied pre-clinically, yielding better selection of targets for discovery programs, and informing affinity requirements for discovery lead optimization efforts.

The data generated through this study will benefit all ongoing and future AlbudAb programs, and will provide generally applicable information to support understanding of biodistribution processes for all protein-based therapies.

Objective(s)/Endpoint(s)

	PRIMARY OBJECTIVE	END POINTS
1.1	Evaluate biodistribution of ^{89}Zr-GSK3128349 in regions of interest following IV administration to support future AlbudAb products and the development of a PBPK model.	• Quantitative parameters (including but not limited to ^{89}Zr-GSK3128349 concentration) derived from Positron Emission Tomography – Computed Tomography (PET-CT) data (e.g. Standardised Uptake Values (SUVs)[a], volume of Regions of Interest (ROI) to assess average and total uptake into regions of interest (*e.g.* liver, kidney, muscle, spleen, heart, lung, bladder, thymus – if feasible -, blood and bone).
	SECONDARY OBJECTIVES	**END POINTS**
2.1	Measure PK of ^{89}Zr-GSK3128349 by whole blood, plasma and urine radiolabel detection to support future AlbudAb products and the development of a PBPK model.	• Whole blood, plasma and urine radioactivity concentrations and derived pharmacokinetic parameters, as data allows, based on blood, plasma and urine scintillation counting.
2.2	Measure PK of GSK8128349 by mass spectroscopy to support the development of a PBPK model.	• Plasma concentrations and derived pharmacokinetic parameters. • Compare plasma exposure assessments via different GSK3128349 mass spectroscopy methods.
2.3	Measure dosimetry of ^{89}Zr-GSK3128349 from PET scans and blood radioactivity.	• Organ doses (mSv) • Effective dose (mSv)
2.4	Assess the safety and tolerability of ^{89}Zr-GSK3128349.	• Adverse events (AEs), serious adverse events (SAEs). • Safety laboratory values, proteinuria, electrocardiograms (ECGs) and vital signs.
2.5	Investigate the presence and levels of anti-GSK3128349 antibodies, including pre- and post-dose.	• Incidence of anti-GSK3128349 antibodies. • Serum titres of anti-GSK3128349 antibodies.

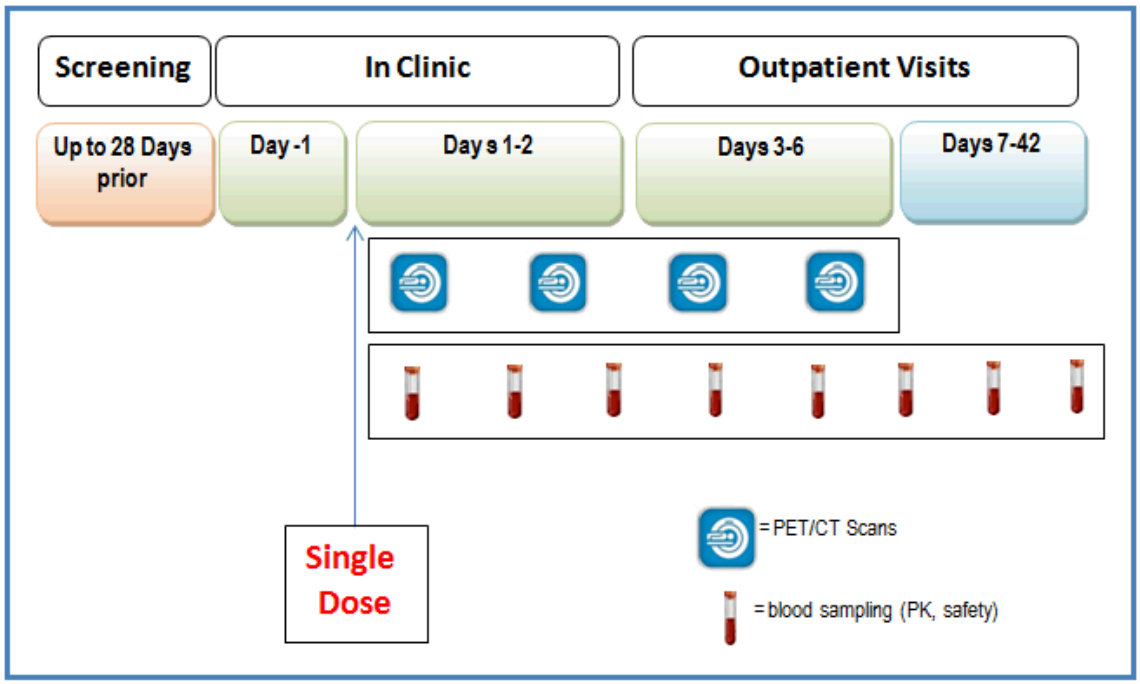
a SUV_{mean} for larger ROI (≥ 3 cm), SUV_{peak} for smaller ROI.

Overall Design

This open label single centre study will investigate the biodistribution and pharmacokinetics of the AlbudAb platform scaffold protein GSK3128349. Hence, GSK3128349 will be administered as a single drug product consisting of a mix of

unlabeled GSK3128349 and ^{89}Zr-GSK3128349 (GSK3128349 radiolabelled with zirconium).

Study Schematic



Study Overview

- On Day 1, enrolled subjects will receive one intravenous (IV) infusion of ^{89}Zr-GSK3128349 to deliver a dose of 1 mg and undergo PET/CT scans and blood sampling assessments prior to discharge at 24 hrs post-dose, on day 2.
- Subjects will be required to visit the clinic repeatedly over the subsequent 42 days and undergo further blood sampling and PET/CT scans up to 10-12 days after dosing. This will monitor ^{89}Zr-GSK3128349 concentrations in various regions of interest (ROI) over time.
- Blood samples will be taken for radioactivity, pharmacokinetic, immunogenicity, and safety assessments (
- After completion of the first 2 subjects, dosimetry assessments will be performed and used to refine the radiation dose administered to subsequent subjects.
- Urine will be collected during the first 24 hours and measured with respect to radioactivity and drug.
- The expected total duration of a subject's participation is approximately 10 weeks, including the screening period of up to 28 days.

Type and Number of Subjects

A single cohort of six to eight healthy male subjects will be enrolled into the study.

Analysis

Interim Analysis

There are no formal interim analyses planned. However, the following in-stream data review is planned:

Following completion of the first two subjects' PET scans, the study team will evaluate the emerging PET-CT scan data for:

- Dosimetry to potentially refine the radiation dose estimates, and to identify other ROI for further investigation, if required.
- Determine scan time points post dose of subsequent subjects.

Primary Analyses

The following analysis is planned for primary endpoints:

Analysis	**Details**
Endpoints	• Quantitative parameters (including but not limited to ^{89}Zr-GSK3128349 concentration) derived from PET-CT data (*e.g.* Standardised Uptake Values (SUVs)[a], volume of ROI) to assess average and total uptake into regions of interest (*e.g.* liver, kidney, muscle, spleen, heart, lung, bladder, thymus – if feasible -, blood and bone
Endpoint Definitions	• SUV: A simple way of determining activity in PET imaging for each region of interest, which is mathematically derived ratio of tissue radioactivity concentration at a point in time C(T) and the injected dose of radioactivity per kilogram of the patient's body weight: SUV = C(T)/[injection dose (MBq)/patient's weight (kg)] • Volume: The volume of specified organ as measured in PET or CT images.
Analysis (Raw Data)	• Descriptive statistics where appropriate, (*i.e.* n, arithmetic mean, geometric mean, standard deviation, minimum, median and maximum) will be calculated for all generated PET-CT imaging endpoints over time. • Graphical displays will be produced over time for applicable PET-CT imaging endpoints. • If analysed, all data will be listed.
Statistical Analysis (Modelled)	• If data permits, further statistical analyses (i.e. mixed effects models) will be performed to estimate quantitative parameters in ROI over time from PET-CT following IV administration. • Full details will be specified in the RAP.
a SUV_{mean} for larger ROI (≥ 3 cm), SUV_{peak} for smaller ROI	

Secondary Analyses

- **Pharmacokinetics (Concentration Data & Derived Parameters)**

PK	Details
Concentration	• Whole blood, plasma and urine concentrations of ^{89}Zr-GSK3128349 and plasma concentrations of GSK2138349 data will be graphically represented, descriptively summarised and listed appropriately.
Parameters	• Whole blood and plasma concentrations time data of ^{89}Zr-GSK3128349 and plasma concentrations time data of GSK3128349 will be analyzed by non-compartmental methods. • Calculations will be based on the nominal sampling times recorded during the study. • As data permits, from the plasma concentration-time data, the following PK parameters may be determined: o Maximum observed plasma concentration (Cmax) o Time to Cmax (Tmax) o Apparent terminal phase half-life (t1/2). o Area under the curve: AUC[0-t] for ^{89}Zr-GSK3128349 and GSK3128349, AUC[0-∞] only for GSK3128349 o Clearance o Volume of distribution • Additional PK parameters may be included as required. • Pharmacokinetic data will be presented in graphical and/or tabular form, summarized descriptively and listed.

- **Dosimetry**

Dosimetry results as organ radiation doses and subject effective dose will be listed.

- **Safety, Tolerability & Immunogenicity**

Safety, tolerability and immunogenicity data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

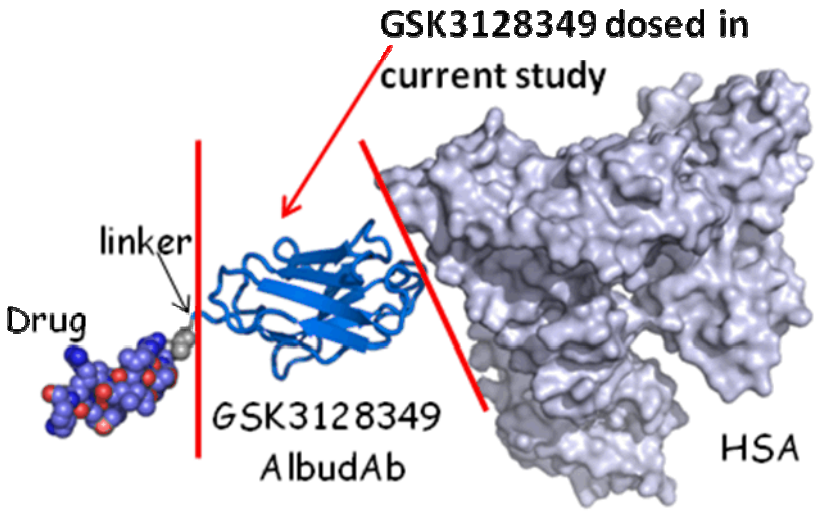
2. INTRODUCTION

2.1. Brief background

Albumin is the most prevalent protein in human plasma (35-54 g/L) and has a half-life in humans of approximately 19 days [Peters, 1985] [Peters, 1996(a)]. Total extravascular albumin is about twice that of the intravascular pool, and exchange occurs between these pools at a rate of 4-5% total albumin/hour [Peters, 1996(b)]. However, this is a simplification of a complex process. Certain organs (e.g. lungs, liver, kidney) show rapid exchange with intravascular albumin, and others (e.g. skin, muscle), that account for a large amount of extravascular albumin due to their size, show a much slower exchange [Peters, 1996(b)].

GSK3128349 is a human domain antibody (dAb) that binds non-covalently to serum albumin with high affinity (also referred to as an 'AlbudAb'). It contains a cysteine residue engineered at the C terminus of the molecule that can be used for the covalent attachment of a pharmacologically active entity (Figure 1). As such, GSK3128349 is a scaffold that has of itself no pharmacological action, but has the potential to be conjugated with a pharmacologically active entity [O'Connor-Semmes, 2014]. [The C-terminal cysteine of GSK3128349 used in the current study is blocked with N-ethyl-maleimide in order to avoid undesirable chemical reactivity towards serum proteins or covalent dimerization.]

Figure 1 Schematic of GSK3128349 AlbudAb, depicted binding to albumin (HSA) and with a conjugated therapeutic drug.



Typically, dAbs are small (~15 kDa) and therefore are excreted renally in a matter of hours. Due to the combination of the high affinity of GSK3128349 for albumin and the high concentrations of albumin, it is expected that GSK3128349 will be bound to albumin the majority of the time. Therefore, AlbudAbs, like GSK3128349, form a complex too big to be subject to renal clearance. Furthermore, the binding of

GSK3128349 to albumin confers some of the pharmacokinetic and biodistribution properties of albumin to GSK3128349; and hence any pharmacologically active entity conjugated to it. This includes AlbudAbs bound to albumin being subject to Neonatal Fc Receptor (FcRn) dependent albumin recycling enhancing the exposure half-life. As a result of these effects AlbudAbs can persist in the body for several days or even weeks. We expect the half life of GSK3128349 in humans to approach that of albumin (~19 days [Peters, 1985] [Peters, 1996(a)]). The medicinal value of therapeutics conjugated to GSK3128349 has the potential to be significantly enhanced by increasing their half-life and/or modulating their biodistribution [Kratz, 2008].

2.2. Study rationale

The study will determine the biodistribution and pharmacokinetics of the AlbudAb scaffold (GSK3128349). The data will inform and validate a Physiologically Based Pharmacokinetics (PBPK) model, which will predict the distribution of future therapeutics conjugated to GSK3128349, as well as other AlbudAbs.

The validated PBPK modeling will improve our future clinical study designs by providing more accurate estimates of tissue exposures, which will lead to better: dose selection, timing of biomarker measurements, target engagement, and ultimately efficacy. This could potentially lead to a reduced number of assessments and/or subjects enrolled in future clinical trials. Furthermore, the PBPK modeling will be applied pre-clinically yielding better selection of targets for discovery programs, and informing affinity requirements for discovery lead optimization efforts.

The data generated through this study will benefit all ongoing and future AlbudAb programs, and will provide generally applicable information to support understanding of biodistribution processes for all protein-based therapies.

3. OBJECTIVE(S) AND ENDPOINT(S)

	PRIMARY OBJECTIVE	END POINTS
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a SUV_{mean} for larger ROI (≥ 3 cm), SUV_{peak} for smaller ROI.		

4. STUDY DESIGN

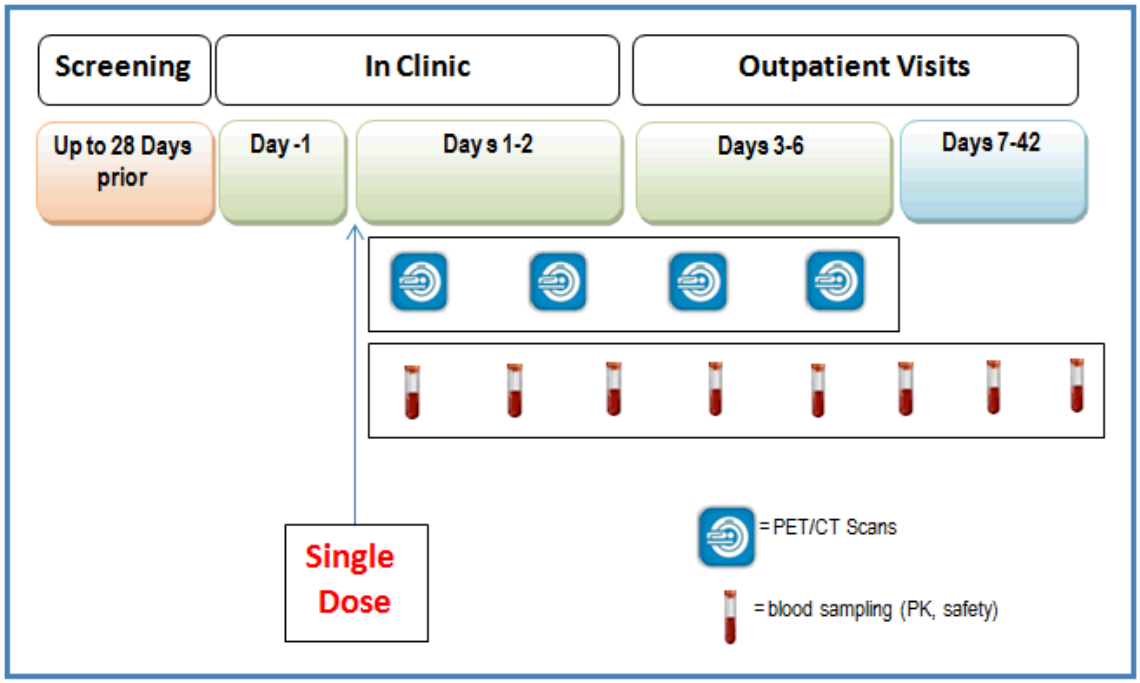
4.1. Overall Design

Using a single cohort of six to eight healthy male subjects, this open label single centre study will investigate the biodistribution and pharmacokinetics of the AlbudAb platform scaffold protein GSK3128349. Hence, GSK3128349 will be administered as a single drug product consisting of a mix of unlabeled GSK3128349 and ^{89}Zr-GSK3128349 (GSK3128349 radiolabelled with zirconium, see Section 6).

PET scanning, using ^{89}Zr labelling, is most optimal among available radioisotopes for monitoring longer half life therapies, such as antibodies, and is both quantitative and capable of assessing sites throughout the body, including within organs such as the kidneys and liver [Vugts, 2013]. This strategy has previously been used to monitor the distribution of the anti-HER2 antibody, Trastuzumab, among others [Dijkers, 2010]. Specifically, we have radiolabeled GSK3128349 with ^{89}Zr and have demonstrated that the rat radio-PK of ^{89}Zr-GSK3128349 is strikingly similar to the Pharmacokinetics (PK) of unlabeled GSK3128349, providing supportive data that the ^{89}Zr labelling of

GSK3128349 does not impact its functionality. Likewise, no difference in the albumin binding of ^{89}Zr-GSK3128349 was detected using an *in vitro* assay. Since the half-life of the radionuclide zirconium (^{89}Zr) is 3.3 days, labelling GSK3128349 with ^{89}Zr allows imaging to take place over a maximal time frame of up to about 10-12 days. This 10-12 day time frame encompasses the expected biodistribution phase and will allow gathering of biodistribution information for GSK3128349 via PET scanning and radio PK. The biodistribution is key information required to enhance our PBPK modelling ability. As ^{89}Zr signal will be limited during the elimination phase (beyond 12 days) and the anticipated half-life will approach that of albumin (approximately 19 days), measurement of plasma PK will be utilized to help inform upon GSK3128349 elimination.

Figure 2 Study Schematic



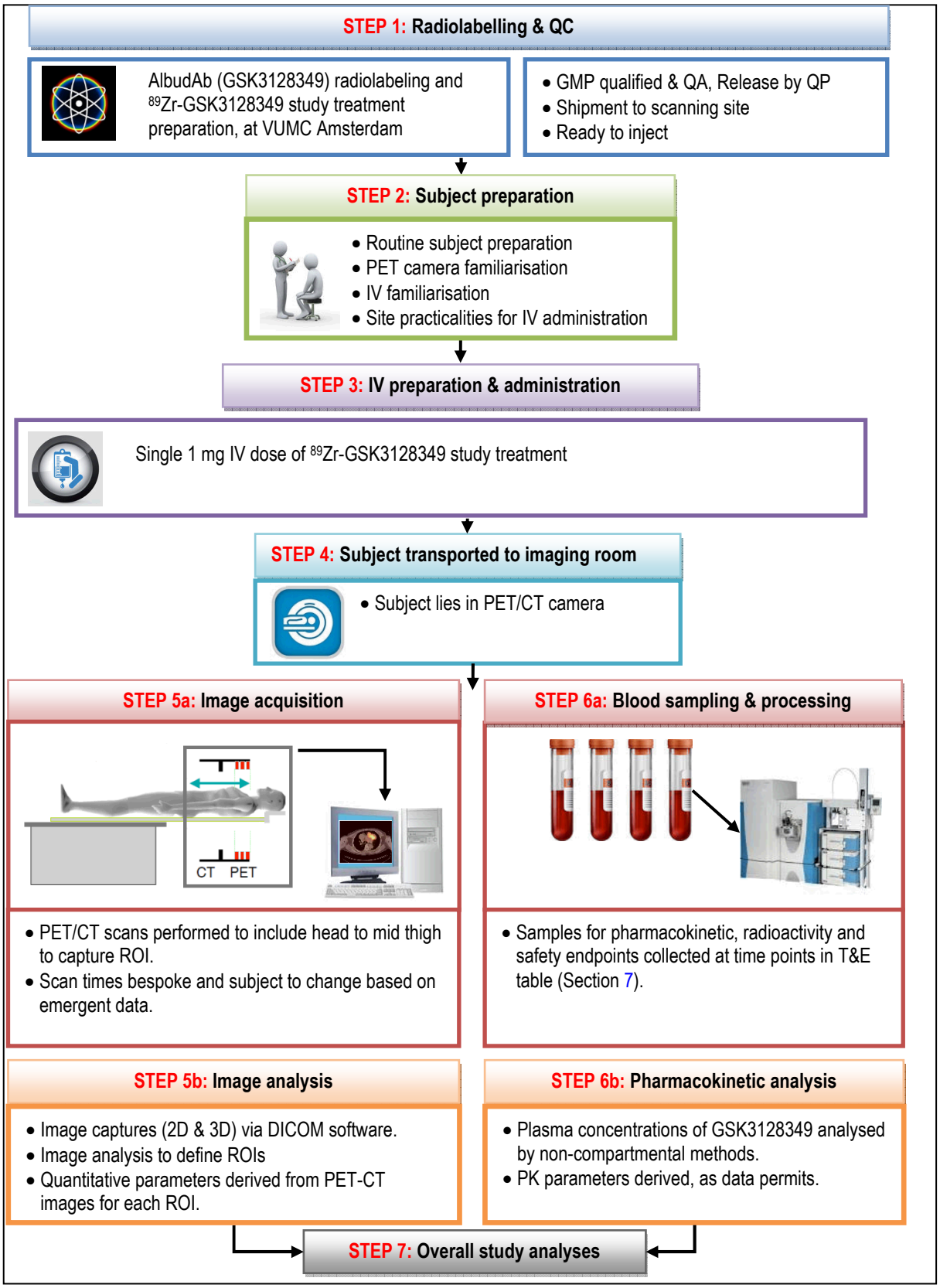
NOTE: Please refer to time and events table for PET and PK blood sampling timings

Study Overview

- On Day 1, enrolled subjects will receive one intravenous (IV) infusion of ^{89}Zr-GSK3128349 to deliver a dose of 1 mg (for further detail on dose see Section 4.3), and undergo PET/CT scans and blood sampling assessments prior to discharge at 24 hrs post-dose, on day 2.
- Subjects will be required to visit the clinic repeatedly over the subsequent 42 days and undergo further blood sampling and PET/CT scans up to 10 days after dosing. This will monitor ^{89}Zr-GSK3128349 concentrations in various regions of interest (ROI) over time.
- Blood samples will be taken for radioactivity, pharmacokinetic, immunogenicity, and safety assessments (see Time and Events table, Section 7.1.2).

- After completion of the first 2 subjects, dosimetry assessments will be performed and used to refine the radiation dose administered to subsequent subjects. This will ensure the total radiation exposure in subsequent subjects is kept below approximately 10 mSv. The data obtained with the first 2 subjects may also be used to adjust the time post dose for PET scans performed on subsequent subjects.
- Urine will be collected during the first 24 hours and measured with respect to radioactivity and drug.
- The expected total duration of a subject's participation is approximately 10 weeks, including the screening period of up to 28 days.

4.1.1. PET/CT Image Acquisition Workflow



4.1.2. PET scans

- Details of the procedures for the acquisition of PET scans and co-localisation low dose CT scans will be included in the Image Acquisition Guidelines. Each PET scan will have a typical duration of up to 60 minutes.
- PET scan data from the first two subjects will be analysed and used for a potential refinement of the radiation dose estimates and post dose scan time points for subsequent subjects.
- Radioactivity measurements from blood will also be used for dosimetry calculations in first 2 subjects (see Section 7.1 Time & Events Table).

Table 1 PET scanning times

Subject	Scan Times
1st Subject	Following completion of the IV infusion the subject will be scanned at the following times: 1 hr ± 30 min 6 hrs ± 1 hr 24 hrs ± 1 hr (Day 2) 5 days (Day 6)
2nd Subject	Following completion of the IV infusion the subject will be scanned at the following times: 3 hrs ± 30 min 8 hrs ± 1 hr 3 days (Day 4) 5 days (Day 6)
Remaining Subjects	Four to six additional subjects will undergo scanning, utilising modified scan timings such that the biodistribution is fully profiled over the time period of up to 10-12 days post dosing. A maximum of 4 PET/CT scans will be undergone by each subject.

4.2. Type and Number of Subjects

A total of six to eight healthy male volunteers will be enrolled. If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects at the discretion of the sponsor and in consultation with the investigator. Replacement subject numbers will be assigned to any additional subjects.

Volunteer ages will be limited from 50 to 65 years of age inclusive. The total radiation exposure in the current study is limited to below approximately 10 mSv, which is equivalent to about 3 years of average radiation exposure from normal living in Europe.

Even though the radiation exposure from this study is quite low, the purpose of the selected age range is to further limit the lifetime cancer risk resultant from radiation exposure (see GlaxoSmithKline Document Number POL-WWD-0019).

4.3. Dose Justification

The single dose of GSK3128349 administered in this study is a single drug product consisting of a mix of labelled and unlabeled GSK3128349 and is utilized in this study in order to facilitate the delivery of requisite data to support PBPK model development. The radiolabelled component is critical, as it will allow assessment of the biodistribution time course for GSK3128349 into various tissues. However, due to the relatively short half-life of the ^{89}Zr label the elimination phase for GSK3128349 will not be measurable via PET, and therefore the unlabeled GSK3128349 component is essential to assess elimination via plasma PK analysis. This measurement of unlabelled GSK3128349 plasma PK is complementary to the principal PET measurements performed in this study, and thereby delivers the greatest value from this study in informing and validating the PBPK model under development.

4.3.1. GSK3128349 dose selection and safety experience

Dose selection based on MS detection of GSK3128349 plasma exposures

The total dose of 1 mg has been determined as the minimum dose required in order to appropriately measure GSK3128349 PK concentrations by mass spectrometry (MS) assays. This was selected based on the lower limit of quantification of the MS assays and a need to measure exposure over a minimum of two half-lives. Anticipated plasma levels of the 1 mg dose were predicted by both albumin PBPK modelling and scaling of the available GSK3128349 rat PK data. The level of radiolabelled GSK3128349 included in this 1 mg of product is outlined in Section 4.3.2.

Preclinical safety

The safety profile of GSK3128349 has been evaluated in rodents, a relevant species based on albumin binding. GSK3128349 was well tolerated in a single IV (bolus) dose study in rats (males only) at a dose of 0.36 mg/kg (only dose tested) with no GSK3128349- related toxicological findings noted. This provides a 25 fold safety margin (based on dose) over the 1 mg clinical dose utilized in the current study. Predicted safety margins based on exposures are indicated in Table 2.

Table 2 Predicted safety margins based on modelling for proposed 1 mg dose in humans

Dose & frequency	Route	C_{max} µg/mL (at t=0)	$AUC_{0\text{-inf.}}$ µg.h/mL	Pre-clinical Safety Margin[a]	
				For Cmax	For AUC
1 mg single dose	Intravenous	0.322 (plasma)	83 (plasma)	26X	3.7X

a. Safety margin based on GSK3128349 rodent intravenous single dose (0.36 mg/kg) GLP toxicology study exposures at the No Observed Adverse Effect Level (NOAEL). (Cmax and AUC of 8.37 µg/mL and 310 µg.h/mL).

Further preclinical and clinical safety data generated with other AlbudAb variants provides additional support for the safety of the 1 mg single IV dose regime proposed in this study.

Other AlbudAbs have been generally well tolerated in preclinical toxicology. The only finding of note observed following repeat administration for greater that 4 weeks in duration was degeneration of the renal proximal tubule in mice, consistent with the exacerbation of a rodent specific chronic progressive nephropathy (CPN). This was observed following administration of various AlbudAb molecules (both conjugated and non-conjugated) when administered for 13 weeks, but NOT at 3 or 4 weeks in mice. There is not a strict counterpart for this lesion in nonhuman primates or human, and this is supported by the monkey toxicology studies in which there were no treatment-related findings in the kidneys of monkeys. Monkeys were administered conjugated or non-conjugated AlbudAbs, yielding plasma Area Under the Curve (AUC) values of up to 500–fold the projected AUC for the 1 mg GSK3128349 IV dose utilised in this clinical study.

Clinical safety
In healthy obese volunteers, single and repeat dose administration of exendin-4 AlbudAb GSK2374697 were generally well-tolerated [O'Connor-Semmes, 2014]. With the exception of the 4 mg single IV dose that resulted in exendin-4 related AEs including nausea, loss of appetite and constipation. Single and repeat doses of exendin-4 AlbudAb over the range of 0.1 mg to 6 mg (2+2+2) total dose administered by subcutaneous injection demonstrated sufficient safety and tolerability to be administered in future clinical trials. No impact on renal function was apparent based on an assessment of renal biomarkers (*e.g.* creatinine, KIM1).

Therefore, given the overall experience dosing AlbudAbs in preclinical safety studies and the exendin-4 AlbudAb First Time In Human (FTIH) clinical experience, the risk for the current clinical PET study with a 1 mg single administered dose of GSK3128349 is considered quite low.

4.3.2. Radioactivity dose

The study will be performed with strict consideration of the radiation limits as expressed by the Dutch authorities and Groningen local guidelines, as well as GSK guidance on exposure by radiation to healthy volunteers, which indicates that the effective radiation dose should be limited to approximately 10 mSv (average exposure for daily living in Europe is 3 mSv/year, and exposure for a diagnostic PET/CT performed with contrast agent is 10-30 mSv), and that subjects should be limited to those 50 years of age and above (see GlaxoSmithKline Document Number POL-WWD-0019).

The ionising radiation from a PET/CT study comes from two sources: the radionuclide injected for PET detection and the exposure to x-rays resultant from the CT scan. The 4 CT scans included in the protocol will contribute 2 mSv of exposure (0.5 mSv/scan x 4) to each subject, therefore providing a maximum exposure limit of approximately 8 mSv due to administration of ^{89}Zr-GSK3128349. The use of 4 PET scans was considered optimal, balancing the need to assess the time course of biodistribution in individual subjects and subject burden, while not significantly limiting the ^{89}Zr-GSK3128349 dose

that can be administered and hence the intensity of the PET signal detected. PBPK modelling and allometric scaling of available rat PK data for GSK3128349 supports that a reasonable PET signal will be measurable in the organs of interest and will inform and validate the PBPK model.

We have estimated that administering 15 MBq of ^{89}Zr-GSK3128349 as part of the 1 mg product should provide approximately 7.9 mSv of exposure and limit the total exposure when combined with the 4 CT scans in each subject to about 10 mSv. Although, we do not specifically have ^{89}Zr-GSK3128349 PET data from preclinical species to use for clinical dosimetry estimation, the radiation exposure attributed to the anticipated distribution and low clearance (based on other preclinical AlbudAb PET studies, historic AlbudAb PK (see GlaxoSmithKline Document Number 2014N199359_00. Investigator Brochure), and current albumin based PBPK modelling predictions) is expected to mimic that previously reported for a ^{89}Zr-radiolabelled monoclonal antibody (mAb) [Börjesson, 2009]. In the previous ^{89}Zr-mAb PET study the mean effective dose was reported to be 0.53 mSv/MBq. Hence 15 MBq of ^{89}Zr-GSK3128349 in this study would provide approximately 7.9 mSv (15 MBq X 0.53 mSv/MBq) of exposure.

After completion of the first 2 subjects in this study, dosimetry estimates will be performed. This data will be used to refine, if needed, the ^{89}Zr-GSK3128349 radiation dose included in the administered 1 mg of GSK3128349 product for subsequent subjects.

Overall, the estimates of radioactivity to be administered in the first 2 subjects (described above) and the refined dosimetry analyses based on data from these first 2 subjects, aim to ensure that the total radiation exposure (that from the radioactivity administration plus the associated low dose CT scans) is limited to approximately 10 mSv.

4.4. Risk Assessment and Management

Summaries of findings from non-clinical studies conducted with GSK3128349 can be found in the GlaxoSmithKline Document Number 2014N199359_00 Investigator Brochure. Although GSK3128349 was well tolerated in a rat toxicology study, it has not been tested in humans before therefore potential adverse affects may be encountered. The table below summarises the potential key risks and mitigation strategy for this protocol.

Table 3 Summary of protocol-specific risks and mitigation strategies

Potential risk	Summary of data	Impact- eligibility criteria	Strategy-monitoring/stopping criteria
Renal injury	The AlbudAb platform has been associated with degenerative changes in the proximal renal tubule in the mouse with repeat and long duration (greater than 4 weeks) dose regimen only. These observations appear reversible on washout and have not been observed in monkey safety studies (see summary Section 4.3 and IB for detailed information).	Subjects with history of renal disease and/or abnormalities are excluded, including proteinuria and reduced estimated Glomerular Filtration Rate (eGFR) (see exclusion criteria Section 5.2 points 3, 11 and 12 for more information).	Renal function and proteinuria will be closely monitored using standard serum and urine chemistry biomarkers.
Acute infusion reaction	Infusion / acute allergic reactions upon administration are a potential risk with all protein therapeutics.	Subjects are excluded with a history of sensitivity to any of the study treatment, or components thereof or a history of drug or other allergies.	Subjects will be monitored for symptoms of hypersensitivity or other potentially immune-mediated reactions post-infusion, and will be treated promptly as appropriate.
Immunogenicity	As is the case for all protein therapeutics, antibodies may develop against the agent administered.	None	Immunogenicity samples will be drawn at baseline and following dosing of GSK3128349 to monitor the immunogenicity potential of this molecule.
Radioactivity exposure	The total radioactivity exposure due to combined PET ligand	Subjects with previous involvement in a research	After completion of the first 2 subjects, dosimetry analysis will

Potential risk	**Summary of data**	**Impact- eligibility criteria**	**Strategy-monitoring/stopping criteria**
	administration and CT scanning will be limited to approximately 10 mSv.	and/or medical protocol involving nuclear medicine, PET or radiological investigations in which the total radiation burden in the last 3 years, including that which will be provided by the current study, is 10 mSv or greater will be excluded. Clinical exposure from which the subject receives a direct benefit (ex. diagnostic test) is not included in these calculations. Only male subjects between 50 and 65 year old will be included to limit the lifetime cancer risk resultant from radiation exposure.	be performed, and the radioactive dose may be adjusted for subsequent subjects (if required) in order to limit total exposure to approximately 10 mSv.

Overall the risk to the healthy volunteers following administration of GSK3128349 is considered low. This is based on the low dose of GSK3128349, preclinical safety assessment of GSK3128349 and other AlbudAb platform based molecules in pre-clinical and clinical studies. The benefit provided through the data generated in this small exploratory FTIH study of 6-8 healthy volunteers will be in the validation of our PBPK based modelling capabilities. Solidifying the PBPK model will enhance future clinical study designs for our AlbudAb based medicines: leading to more efficient dose selection and biomarker assessment. The risk benefit balance is considered positive and therefore supportive of progression of this proposed study to the clinic

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK product or other study treatment that may impact subject eligibility is provided in the GlaxoSmithKline Document Number 2014N199359_00 Investigator Brochure.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

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

AGE
1. Between 50 and 65 years of age inclusive at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS
2. Healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if the Investigator and the GSK Medical Monitor agree that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. 3. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and bilirubin ≤1.5x Upper Limit Normal (ULN) (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

WEIGHT
4. Body Mass Index (BMI) within the range 19.0 – 31.0 kg/m^2 (inclusive).

SEX
5. Male.

CONTRACEPTION
6. Subjects must agree to use one of the contraception methods listed in Section 6.8.1. This criterion must be followed from the time of the first dose of study treatment until 100 days post dose.

INFORMED CONSENT
7. Capable of giving written informed consent as described in Section 10.2, which includes compliance with the requirements and restrictions listed in the consent form.

CARDIOVASCULAR
8. Average Corrected QT interval (QTc) ≤450 msec NOTES: • The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. • The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial. • For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. Current evidence or history of an influenza-like illness as defined by fever (>38°C) and two or more of the following symptoms within 7 days before dosing: cough, sore throat, rhinorrhea, sneezing, limb/joint pain, headache, vomiting/diarrhea. 2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 3. History of, or current, acute renal failure, known renal disease, or a renal disorder or abnormality that may compromise renal function. This includes having one kidney. 4. Previous inclusion in a research and/or medical protocol involving nuclear medicine, PET or radiological investigations or occupational exposure that, together with the proposed study, will result in a total radiation exposure greater than 10 mSv over a 3 year period. Clinical exposure from which the subject receives a direct benefit (eg diagnostic test) is not included in these calculations.

RELEVANT HABITS
5. History of regular alcohol consumption within 6 months of the study defined as: a. An average weekly intake of >21 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits. 6. Unable to refrain from the use of prescription drugs within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study treatment, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety. 7. Subject is a smoker ≥5 cigarettes/day or with a smoking history of >5 pack years[a]. a. (Pack years = [cigarettes per day smoked/20] x [number of years smoked]).

CONTRAINDICATIONS
8. History of sensitivity to any of the study treatment or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation. 9. Subject suffers from claustrophobia that limits the ability to remain still in the PET/CT scanner for the required amount of time to complete the scanning protocol. 10. Subject has metal present in their body that will interfere with the PET/CT scanning.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
11. eGFR <60 mL/min/1.73 m^2 (utilising the Chronic Kidney Disease Epidemiology Collaboration (CKI-EPI) equation). 12. Urine mg protein/mg creatinine Urine Protein Creatinine Ratio (UPCR) >0.3. 13. Evidence of haematuria by urinalysis (1+ or greater dipstick test). 14. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C (Hep C) antibody result within 3 months of screening. 15. A positive test for Human Immunodeficiency Virus (HIV) antibody. 16. A positive pre-study drug/alcohol screen. 17. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). 18. Exposure to more than four new chemical entities within 12 months prior to the first dosing day. 19. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period.

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT)

publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

5.4. Study Withdrawal Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. The reason(s) for subjects not completing the study will be recorded in the Case Report Form (CRF).The investigator must document, if applicable, the reason (if specified by the subject) for withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

If any trends or unexpected increases in safety signals are observed, which in the Investigator's opinion, are of greater intensity, frequency, or duration than expected for the subject group under investigation, the GSK Medical Monitor should be notified as soon as possible. If the Investigator and GSK Medical Monitor consider that there is a reasonable possibility that the event was related to treatment with the product, the study may be put on-hold until all available safety data from the study has been reviewed.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.4.1. Liver Chemistry Management

Since this study is a single dose study, there are no liver-specific stopping criteria as such. In the event of liver parameters deviating from the thresholds described in Appendix 2, follow instructions in that section.

Liver chemistry increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the Food and Drug Administration (FDA) premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

5.4.2. QTc Evaluation Criteria

Further monitoring and/or evaluation should be considered in any subject who meets either of the bulleted criteria below:

- QTc >500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

For subjects with underlying **bundle-branch block**, follow the evaluation criteria listed below:

Baseline QTc with Bundle-Branch Block	**Criteria for Further Evaluation and Monitoring of QTc with Bundle-Branch Block**
<450 msec	>500 msec
450 to 480 msec	≥530 msec

- The enhanced monitoring criteria are based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, two additional ECGs must be obtained over a brief period, and then the averaged QTc values of the 3 ECGs will be used to determine whether the subject meets these criteria.
- The same QT correction formula must be used for each individual subject to determine eligibility for the study, and whether further evaluation and/or monitoring is/are necessary. This formula may not be changed or substituted once the subject has been enrolled.
  - For example, if a subject is eligible for the protocol based on QT interval corrected for heart rate according to Fridericia's formula (QTcF) then QTcF must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety electrocardiograms (ECGs) and other non-protocol-specified ECGs are an exception.
- Considerations for further monitoring and evaluation should include the following, as appropriate:
  - Assessment of any relevant symptoms (e.g., presyncope);
  - Follow-up ECGs to assess for resolution of QTc prolongation;
  - Review of concomitant or recently taken medications, including over the counter preparations and herbal supplements
  - Evaluation of electrolytes to include magnesium and potassium

- Referral to urgent care or to an emergency facility for further evaluation and monitoring
- Any other evaluation that may be necessary as determined by the investigator.

5.4.3. Renal Monitoring

If a subject develops any of the following signs:

i) haematuria (in the absence of urinary tract infection)
ii) demonstrates a UPCR>0.5
iii) demonstrates a >15% decline in eGFR

and findings are confirmed on a second assessment within 48 hours, then the subject should be referred for a nephrology consult.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

The term 'study treatment' or '^{89}Zr-GSK3128349' is used throughout the protocol to describe the drug product, which is a mix of ^{89}Zr labeled and unlabelled GSK3128349 received by the subjects as per the protocol design. Details of ^{89}Zr labelled GSK3128349 can be found in the relevant non Investigational Medicinal Product (IMP) document.

Product name:	^{89}Zr-GSK3128349
Formulation Description:	50 mM sodium acetate buffer and 200 mM sucrose at pH 5.20-5.80, associated with about 15 MBq of radioactivity.
Dosage Form:	Solution for IV administration
Unit Dose Strength	Approximately 10 mL of 0.1mg/mL ^{89}Zr-GSK312834
Dose level	1 mg
Route/ Administration/ Duration:	IV as a continuous infusion over 20 mins
Dosing Instructions:	Single dose
Physical Description:	Liquid in 50mL vial
Manufacturer/ Source of procurement:	VUMC, Amsterdam

6.1. Treatment Assignment

Subjects will be identified by a unique subject number at screening that will remain consistent for the duration of the study. Upon completion of screening subjects will be enrolled and will receive 1 mg of ^{89}Zr-GSK3128349. There will be no placebo in this study.

There are no randomisation requirements for the study. However, for internal study reporting, subjects will be assigned to randomisation numbers in accordance with the randomisation schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

6.2. Blinding

This will be an open-label study.

6.3. Packaging and Labeling

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

6.4. Preparation/Handling/Storage/Accountability

A full description of the method and materials required for administration of ^{89}Zr-GSK3128349 will be provided in the Study Reference Manual (SRM).

Study treatment must be dispensed or administered according to procedures described in the SRM. Only subjects enrolled in the study may receive study treatment. Only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure area with access limited to the investigator and authorized site staff. Storage instructions for all study treatments supplied by GSK (including study product as well as prepared solutions) are provided in the SRM. Maintenance of a temperature log (manual or automated) is required.

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

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.

6.5. Treatment of Study Treatment Overdose

For this study, any dose of ^{89}Zr-GSK3128349 over and above the dose specified in the protocol will be considered an overdose.

GSK does not recommend specific treatment for an overdose. The investigator or physician in charge of the subject at the time will use clinical judgment to treat any overdose.

6.6. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because only healthy volunteers are eligible for study participation.

6.7. Lifestyle and/or Dietary Restrictions

6.7.1. Contraception Requirements

Male subjects with female partners of child-bearing potential must use one of the following contraceptive methods for 100 days post dose of study treatment. Investigators are responsible for consulting with subjects on selection of contraceptive methods.

- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Condom plus partner use of a highly effective contraceptive (see list below).

Highly Effective Contraceptive Methods with a Failure Rate of < 1%

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of etonogestrel or levonorgestrel
- Percutaneous contraceptive patches

6.7.2. Caffeine, Alcohol, and Tobacco

Subjects will abstain from alcohol for 48hr before each visit to the clinic and during the in-house stay.

Subjects who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the Clinical Unit.

6.7.3. Activity

Subjects must refrain from strenuous exercise for approximately 72 hours before all study visits.

6.8. Concomitant Medications and Non-Drug Therapies

6.8.1. Permitted Medications and Non-Drug Therapies

Paracetamol or Acetaminophen, at doses of ≤ 2 grams/day is permitted for use. Other concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

6.8.2. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking prescription or non-prescription drugs, within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study treatment until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1. Detailed procedures for obtaining each assessment may be provided in the Study Reference Manual (SRM), where necessary. Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time.

The timing and number of planned study assessments, including: safety, pharmacokinetic or pharmacodynamic/biomarker assessments may be altered during the course of the study based on newly available data (*e.g.* to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. The timing of PET-CT scans may be changed but not the maximum number of four PET-CT sessions. The change in timing or addition of time points for any planned study assessments must be approved and documented by GSK, but this will not constitute a protocol amendment. The Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme. No more than 500 mL of blood will be collected within a 56 day period as per exclusion criteria 19 (Section 5.2), including any extra assessments that may be required.

7.1. Time and Events Table

7.1.1. Screening

Procedures	Screening up to 28 days prior to day 1
Informed Consent	X
Demographics	X
Eligibility	X
Full Physical Exam	X
Medical/Medication/Drug/Alcohol Hx	X
12-lead ECG (triplicate)	X
Vital Signs	X
Urine Drug/Alcohol	X
HIV, Hep B and Hep C Screen[1]	X
Haem/Chem/Urinalysis Tests/UPCR	X
Concomitant Medication Review	X
1 If test performed within 3 months prior to first dose of study treatment, testing at screening is not required	

7.1.2. Scanning & Dosing

Day of study	**Day -1**	**Day 1**						**Day 2**	**Day 4**	**Day 6**	**Day 13 ± 1 day**	**Day 20 ± 2 days**	**Day 31 ± 2 days**
Time post dosing		**Pre-dose**	**0**	**1 hour**	**3 hours**	**6 hours**	**8 hours**	**24 hours**					
Admission to Unit	X												
Brief Physical Exam	X							X[g]					
Medical/Medication/Drug/Alcohol Hx	X												
12-lead ECG		X[f]		X				X					
Vital Signs		X		X				X					
Urine Drug/Alcohol	X												
Urinalysis	X							X[i]		X	X	X	
Spot Urine Protein/Creatinine ratio	X							X[e]			X		
Haematology								X				X	
Clinical chemistry	X							X		X	X	X	X
Randomisation	X												
Immunogenicity Blood Sample		X											
IV Infusion Dosing			X										
PET imaging and co-localising CT (first subject)[a]				X		X		X		X			
PET imaging and co-localising CT (second subject)[a]					X		X		X	X			
PET imaging and co-localising CT (subsequent subjects)[a, b]			←----------						----------→				
PK Blood Sampling for MS		X		X	X	X	X	X	X	X	X	X	X
PK Blood Sampling for scintillation counting[h]		X		X	X	X	X	X	X	X	X		
Bladder Void[c]		X											
Urine Collection[d]			←----------					----------→					

Day of study	**Day -1**	**Day 1**						**Day 2**	**Day 4**	**Day 6**	**Day 13 ± 1 day**	**Day 20 ± 2 days**	**Day 31 ± 2 days**
Time post dosing		**Pre-dose**	**0**	**1 hour**	**3 hours**	**6 hours**	**8 hours**	**24 hours**					
Adverse Event Review			←----------→										
Concomitant Medication Review	←----------→												
Discharge								X					
Outpatient Visit									X	X	X	X	X

a. Each PET/CT scan must be preceded by heart rate and blood pressure assessments.
b. For subsequent subjects (3rd and beyond) timings of PET scans will be based on data analysis from subjects 1 and 2 and may be carried out anytime between 1 and 10-12 days post injection. A maximum of 4 PET scans will be conducted in each subject.
c. Pre-dose urine will not be retained.
d. 24 hour urine collection. Total volume will be measured. Part of urine sample will be used for scintillation counting. An aliquot will be utilized for UPCR assessment and another stored for later MS PK analysis if required. Based on data from first 2 subjects, urine may be collected for longer than 24 hrs post dose for subsequent subjects.
e. Aliquot from 24 hr collection sample, taken after 24 hr collection is complete.
f. Triplicate measurement
g. Prior to discharge
h. Aliquot from MS PK blood sample
i. Urine sample to be collected prior to discharge

Note: all time points are relative to <u>start</u> of infusion administration.

7.1.3. Follow-up

Procedure	Day 43 ±2 days
Brief Physical Exam	X
12-lead ECG	X
Vital Signs	X
Haem/Chem/Urinalysis Tests/UPCR	X
Immunogenicity Sample	X
PK Sample for MS	X
Concomitant medication review	X
Adverse Event Review	X
Outpatient Visit	X

7.2. Screening and Critical Baseline Assessments

The following demographic parameters will be captured: year of birth, race and ethnicity.

Medical/medication/alcohol history will be assessed as related to the eligibility criteria listed in Section 5.1 and Section 5.2.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Tables. Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up visit at the time points specified in the Time and Events Table (Section 7.1).
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the electronic Case Report Form (eCRF) page within 72 hours of submission of the SAE.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3.

7.3.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3.

7.3.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation 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 the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 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 a 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.

7.3.2. Pregnancy

Details of all pregnancies in female partners of male subjects will be collected after the start of dosing and until the follow-up visit.

If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

7.3.3. Physical Exams

- A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.
- A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- A full physical examination will be conducted at screening and a brief physical exam will be conducted on Day -1, at 24 hr post dose prior to discharge and at Follow-up.

7.3.4. Vital Signs

- Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, and temperature.
- All vital sign measurements will be made with the subject in a supine position having rested in this position for at least 5 minutes before each reading.

7.3.5. Electrocardiogram (ECG)

- ECG measurements will be made with the subject in a supine position having rested in this position for at least 5 minutes before each reading.
- Triplicate 12-lead ECGS will be obtained at screening and pre dose at Day 1 and single 12-lead ECGs will be obtained at other time points during the study.
- 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTcF intervals (if the machine does not automatically calculate QTcF, manual calculation is acceptable).
- Extreme changes in room temperature should be avoided as far as possible (the volunteers should be comfortable at all times in appropriate clothing). Hot and cold drinks and food should be avoided where possible 30 minutes before an ECG measurement.
- Care should be taken to ensure that the electrodes are placed in the positions dictated by standard ECG methodology.

If a subject's QTcF interval extends beyond 500msec on two or more ECG tracings separated by at least 5 minutes then the ECG tracing should be examined and manual measurement by a trained physician should be performed to confirm the accuracy of the equipment being used. If the reading is accurate the subject should be monitored closely and followed until the QT and QTcF interval returns to within 30msec of their baseline.

7.3.6. Clinical Safety Laboratory Assessments

Values for the laboratory parameters should be within the normal range for the relevant subject population as specified by the clinical laboratory, which will be an accredited facility. Subjects with screening laboratory values outside of the normal range will be accepted into the study only after the Investigator, or a qualified designee, and the GSK

Medical Monitor have determined that the out of range value(s) are not clinically significant and would not pose an increased risk to the subject.

At the Principal Investigator and GSK Medical Monitor's discretion, additional laboratory tests other than those outlined below may be included to further assess safety and tolerability.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes
Reticulocyte Count	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils
RBC- Red blood cell; WBC- White Blood Cell; MCV- Mean Corpuscular Volume; MCH- Mean Corpuscular Hemoglobin; MCHC- Mean Corpuscular Hemoglobin Concentration.		

Clinical Chemistry

BUN	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine (eGFR)	Chloride	ALT (SGPT)	Uric Acid
Glucose	Calcium	GGT	Albumin
Sodium		Alkaline phosphatase	Total Protein
BUN- Blood Urea Nitrogen; AST (SGOT)- Aspartate Aminotransferase (Serum Glutamic Oxaloacetate Transaminase); eGFR-ALT- Alanine Aminotransferase (SGPT)- (Serum Glutamic Pyruvic Transaminase); GGT- Gamma Glutamyl Transpeptidase.			

Routine Urinalysis

Specific gravity
pH, glucose, protein, blood and ketones by dipstick
Microscopic examination (if blood or protein is abnormal) includes RBC, WBC, casts and bacteria

Other tests

HIV
Hepatitis B (HBsAg)
Hepatitis C (Hep C antibody -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay (or other third generation immunoassay) should be reflexively performed **on the same sample** to confirm the result)
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).
Proteinuria (UPCR)
NOTE : Details of Liver Safety Required Actions and Follow-Up Assessments after a liver event are given in Appendix 2.

Additional drug screens may be performed at the discretion of site staff, if needed/required by local standard operating procedures.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.3.7. Urine protein/creatinine ratio

Urine samples will be collected as outlined in the Time and Events Table (Section 7.1) to assess the urine protein/creatinine ratio (mg/mg).

7.4. Pharmacokinetics

Samples for pharmacokinetic analysis of GSK3128349 will be collected at the time points indicated in the Time and Events Tables (Section 7.1).

7.4.1. Pharmacokinetic Blood Sample Collection

Sampling time points are defined in the Time and Events tables (Section 7.1).

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.4.2. Pharmacokinetic Urine Sample Collection for Scintillation Counting

Sampling time points are defined in the Time and Events tables (Section 7.1).

The actual start and end date and time of each urine sample collection will be recorded. The total volume collected will be recorded and an aliquot will be scintillation counted.

If the 24 hr urine sample contains > 3% of the administered radioactive dose, then a spot urine collection will be performed on Day 4 and Day 6 for scintillation counting and PK analysis by mass spectroscopy. Based on scintillation count data from Day 4 and Day 6, urine may be collected at subsequent visits for MS PK only.

Details of PK urine sample collection, processing and storage procedures are provided in the SRM.

7.4.3. Pharmacokinetic Sample Analysis

Plasma analysis will be performed under the management of Drug Metabolism and Pharmacokinetics (DMPK), GSK. Radioactivity counts of blood and plasma plus urine PK sample aliquots will be performed at the clinical site. Remaining samples will be retained for at least 10.5 half lives (test for radioactivity > 35 days) before shipping to GlaxoSmithKline for analysis. Concentrations of GSK3128349 will be determined in plasma samples using the currently approved analytical methodologies. Raw data will be stored in the Good Clinical Practice (GLP) Archives, GlaxoSmithKline.

Once the plasma has been analyzed for GSK3128349 any remaining plasma may be analyzed qualitatively for other circulating catabolites and the results reported under a separate DMPK protocol.

The urine samples may be analyzed for GSK3128349 (pending results of other endpoints) and the results will be reported under a separate DMPK protocol.

Details of the analysis procedures are provided in the SRM.

7.5. Immunogenicity

Blood samples for testing antibodies against GSK3128349 will be collected at the time points indicated in the Time and Events Tables (Section 7.1). The actual date and time of each blood sample collection will be recorded. The first blood sample will be taken pre-dose at baseline to determine the presence, if any, of pre-existing Anti Drug Antibodies (ADAs).

The presence of such antibodies will be assessed using an electrochemiluminescent (ECL) immuno assay. If sera contain anti-GSK3128349 antibodies, they will be further analyzed for the antibody specificity and titres. The results of anti-GSK3128349 antibody tests will be reported at the end of the study. The report will include the incidence of immunogenicity and titres.

Details on sample preparation, storage and analysis will be given in the SRM.

8. DATA MANAGEMENT

For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug. Subject initials will not be collected or transmitted to GSK according to GSK policy.

PET and CT images will be anonymized and transmitted to GSK in Digital Imaging and Communications in Medicine (DICOM) format to be stored in a GSK repository.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

There are no formal statistical hypotheses being tested, due to the exploratory nature of the study.

Where applicable, an estimation approach will be adopted to evaluate the primary objectives.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

There are no formal calculations of power or sample size for this exploratory study. A review of the literature was conducted and identified a number of PET studies using ^{89}Zr labelled mAbs [Dijkers, 2010] [Börjesson, 2009]. The majority of these were in oncology where the objective was to assess tumour uptake of mAbs. One study was identified [Börjesson, 2009] which examined biodistribution of ^{89}Zr labelled mAbs to organs over time. This paper provides some guidance in our study design with respect to dosimetry but provides very limited insight into variability and sample size requirements.

Sepp *et al* describes the PBPK model to be used for exploratory modelling in this study [Sepp, 2015]. This was developed in 18 animals using n=3 mice sacrificed at each of 6 time points. Sepp et al were able to demonstrate CV of approx ≤30% on estimated flow rate parameters for the majority of organs using n=3 for each post dose time point.

Therefore, based on the limited literature and novelty of this study, sample size has been primarily based on feasibility, but is also in the range of prior clinical immunoPET studies [Dijkers, 2010] [Börjesson, 2009]. Six to eight healthy male subjects will be recruited to complete this single dose level study protocol, and with conducting 4

PET/CT scans post dose per subject should provide the ability to assess the PET signal across a suitable range of post dose time points.

9.2.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Population	Definition / Criteria
Screen Failures	• Comprised of all potentially eligible subjects who have signed the ICF and subsequently fail screening.
Safety	• Comprised of all subjects who receive a dose of ^{89}Zr-GSK3128349.
PK	• Subjects in the 'Safety' population for whom a PK sample was obtained and analysed, and/or for which a PET scan was completed.

Additional analysis populations maybe defined in the Reporting and Analysis Plan (RAP).

9.3.2. Interim Analysis

There are no formal interim analyses planned. However, the following in-stream data review is planned:

Following completion of the first two subjects' PET scans, the study team will evaluate the emerging PET-CT scan data for:

- Dosimetry to potentially refine the radiation dose estimates, and to identify other ROI for further investigation, if required.
- Determine scan time points post dose of subsequent subjects.

9.4. Key Elements of Analysis Plan

Full details of the planned analyses will be specified in the Reporting and Analysis Plan (RAP).

9.4.1. Primary Analyses

The following analysis is planned for primary endpoints:

Analysis	**Details (Study Objective Section 3 (1.1))**
Endpoints	• Quantitative parameters (including but not limited to 89Zr-GSK3128349 concentration) derived from PET-CT data (e.g. Standardised Uptake Values (SUVs)a, volume of ROI) to assess average and total uptake into regions of interest (e.g. liver, kidney, muscle, spleen, heart, lung, bladder, thymus – if feasible -, blood and bone
Endpoint Definitions	• SUV: A simple way of determining activity in PET imaging for each region of interest, which is mathematically derived ratio of tissue radioactivity concentration at a point in time C(T) and the injected dose of radioactivity per kilogram of the patient's body weight: SUV = C(T)/[injection dose (MBq)/patient's weight (kg)] • Volume of ROI: The volume of specified organ as measured in PET or CT images.
Analysis (Raw Data)	• Descriptive statistics where appropriate, (i.e. n, arithmetic mean, geometric mean, standard deviation, minimum, median and maximum) will be calculated for all generated PET-CT imaging endpoints over time. • Graphical displays will be produced over time for applicable PET-CT imaging endpoints. • If analysed, all data will be listed, including unscheduled and/or repeat assessments.
Statistical Analysis (Modelled)	• If data permits, further statistical analyses (i.e. mixed effects models) will be performed to estimate quantitative parameters in ROI over time from PET-CT following IV administration. • Full details will be specified in the RAP.
a SUV_{mean} for larger ROI (≥3 cm), SUV_{peak} for smaller ROI	

9.4.2. Secondary Analyses

Pharmacokinetics (Concentration Data & Derived Parameters)

PK	Details (Study Objective Section 3 (2.1 & 2.2))
Concentration	• Whole blood, plasma and urine concentrations of ^{89}Zr-GSK3128349 and plasma concentrations of GSK2138349 data will be graphically represented, descriptively summarised and listed appropriately.
Parameters	• Whole blood and plasma concentrations time data of ^{89}Zr-GSK3128349 and plasma concentrations time data of GSK3128349 will be analyzed by non-compartmental methods. • Calculations will be based on the nominal sampling times recorded during the study. • As data permits, from the plasma concentration-time data, the following PK parameters may be determined as data permits: o Maximum observed plasma concentration (Cmax) o Time to achieve Cmax (Tmax) o Apparent terminal phase half-life (t1/2). o Area under the curve: Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject (AUC[0-t]) for ^{89}Zr-GSK3128349 and GSK3128349, Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time (AUC[0-∞]) only for GSK3128349 o Clearance o Volume of distribution • Additional PK parameters may be included as required. • Pharmacokinetic data will be presented in graphical and/or tabular form, summarized descriptively and listed.

Dosimetry

Dosimetry (objective Section 3 (2.3)) results as organ radiation doses and subject effective dose will be listed.

Safety, Tolerability & Immunogenicity

Safety, tolerability and immunogenicity data (study objectives Section 3 (2.4 and 2.5) respectively) will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

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

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable.
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable).
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC).
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, 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 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

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- 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 the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant 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 IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. 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 elsewhere), in a safe and secure location.

- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site 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 ensure 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, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ADA	Anti Drug Antibody
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
AUC[0-t]	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject
AUC[0-∞]	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CKI-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CPN	Chronic Progressive Nephropathy
CT	Computed Tomography
C(T)	Tissue radioactivity concentration at a point in time
CRF	Case Report Form
dAb	Domain antibody
DICOM	Digital Imaging and Communications in Medicine
DMPK	Drug Metabolism and Pharmacokinetics
ECG	Electrocardiogram
ECL	Electrocheluminescent
eCRF	Electronic Case Report Form
eGFR	estimated Glomerular Filtration rate
FcRn	Neonatal Fc Receptor
FDA	Food and Drug Administration
FTiH	First Time in Human
GCP	Good Clinical Practice
g/L	Gram/Litre
GMP	Good Manufacturing Practice
GGT	Gamma Glutamyl Transpeptidase
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
Hep	Hepatitis
HIV	Human Immunodeficiency Virus
hr	Hour
HSA	Human Serum Albumin
IB	Investigator Brochure

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intra Venous
kDa	kiloDalton
kg	kilogram
LE	Liver Event
mAb	Monoclonal antibody
MBq	MegaBecquerel (SI unit of radioactivity)
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedRA	Medical Dictionary for Regulatory Agencies
µg/mL	Microgram/milliltre
min	minute
mM	millimolar
MS	Mass Spectroscopy
MSDS	Material Safety Data Sheet
mSv	milliSievert
NOAEL	No Adverse Effect Level
PBPK	Physiologically Based Pharmacokinetic
PET	Positron Emission Tomography
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
QP	Quality Performance
QTc	Corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
ROI	Regions Of Interest
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetate Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SRM	Study Reference Manual
SUV	Standard Uptake Value
Tmax	Time at which maximum plasma concentration is observed
t 1/2	Apparent terminal phase half-life
ULN	Upper Limit Normal

UPCR	Urine Protein Creatinine Ratio
WBC	White Blood cell
^{89}Zr GSK3128349	GSK3128349 radiolabelled with zirconium

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
AlbudAb

Trademarks not owned by the GlaxoSmithKline group of companies
Chiron RIBA
InForm

12.2. Appendix 2: Liver Safety – Required Actions and Follow up Assessments

Phase I liver chemistry increased monitoring criteria have been designed to assure subject safety and to evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I liver chemistry increased monitoring criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Increased Monitoring Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following Liver Event</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)</td><td>• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 72 hrs of identified liver event.[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form</td></tr>
</table>

MONITORING: **<u>If</u> ALT≥3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> >1.5<u>:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **<u>If</u> ALT≥3xULN <u>AND bilirubin</u> < 2xULN <u>and INR</u> ≤1.5<u>:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**<u>If</u> ALT≥3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> >1.5<u>:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Assess history of acetaminophen usage in the past week. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**,indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. Record the date/time of the PK blood sample draw and the date/time of the dose of study treatment prior to blood sample draw on the CRF. Instructions for sample handling and shipping are in the SRM.

12.3. Appendix 3: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 study treatment 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 study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • 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. • 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.

12.3.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

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. Other situations:

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

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

- Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.3.3. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.3.4. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- 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. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.3.5. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.4. Appendix 4: Collection of Pregnancy Information

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study treatment.
- After obtaining the necessary signed informed consent from the female partner directly, 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
- 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 termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.