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Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

The GlaxoSmithKline group of companies

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Protocol No.: 207440

A Phase I, First Time in Human, Two Part, Randomized, Placebo-Controlled, Double-Blind (Sponsor Unblind), Single and Repeat Dose Escalating Study to Evaluate the Safety, Tolerability and Pharmacokinetics of GSK3352589, a REarranged during Transfection (RET) Growth Factor Receptor Tyrosine Kinase Inhibitor, in Normal Healthy Volunteers

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Explanation
%CVb	Between-subject Coefficient of Variation
AE	Adverse Event
ALT	Alanine Transferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUC_{24h}	Area Under the Curve from Time 0 to 24 hr post-dose (AUC over 24 hr=2 doses for BID dosing)
AUC_{inf}	Area Under the Curve from Time 0 extrapolated to infinity
$AUC_{extrap\%}$	Area Under the Curve from last measured concentration extrapolated to infinity, %
AUC_{PD4h}	Area Under the Curve from Time 0 to the 4h Post-dose for PD Biomarkers
AUC_{PDlast}	Area Under the Curve from Time 0 to the Last Measured Concentration for PD Biomarkers
AUC_{t}	Area Under the Curve from Time 0 to the Last Measured Concentration
AUC_{tau}	Area Under the Curve from Time 0 to the End of the Dosing interval (10 hr for BID morning dose)
BID	Twice Daily
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BSFS	Bristol Stool Form Scale
CI	Confidence Interval
C_{max}	Maximum Observed Plasma GSK3352589 PK Concentration
C_{last}	Last Measured Concentration
C_{PDmax}	Maximum Observed Plasma for PD Biomarkers
CPSR	Clinical Pharmacology Study Report
CRF	Case Report Form
CV	Coefficient of Variation

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Abbreviation	Explanation
MRT	Mean Residence Time for GSK3352589
ECG	Electrocardiogram
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Total GLP-1	Total Glucagon Like Peptide-1 or GLP-1 Total
GMR	Geometric Mean Ratio
GSK	GlaxoSmithKline
HBsAG	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
ITT	Intent to Treat
LLQ	Lower Limit of Quantification for Bioassay Methods
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No Observed Adverse Effect Level
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PT	Preferred Term
Total PYY	Total Peptide YY or PYY Total
QD	Once Daily
R_{2adj}	Correlation coefficient for log-linear regression to calculate terminal elimination rate for PK
R_{AUCt}	Accumulation Ratio (R) for AUC_t at Steady State compared to first dose interval
R_{AUCtau}	Accumulation Ratio (R) for AUC_{tau} at Steady State compared to first dose interval
R_{Cmax}	Accumulation Ratio (R) for C_{max} at Steady State compared to first dose interval
RET	REarranged during Transfection
SAE	Serious Adverse Event

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Abbreviation	Explanation
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error
SoA	Schedule of Activities
SOC	System Organ Class
$t_{1/2,terminal}$	Terminal plasma half-life
T_{max}	Time to Maximum Observed Plasma GSK3352589 PK Concentration
T_{last}	Time to Last Observed Plasma GSK3352589 PK Concentration
T_{PDmax}	Time to Maximum Observed Plasma for PD Biomarkers
TEAE	Treatment Emergent Adverse Events
ULN	Upper Limit of Normal

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1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the handling of the data and planned statistical analyses for the GlaxoSmithKline (GSK) group of companies, study 207440. This will include the planned analyses that will be undertaken at the time of the final analysis.

This SAP is based on the following study documents:

- Final Protocol, dated 31 March 2017;
- Case Report Form (CRF) v2.0, dated 09 June 2017.

1.1. Responsibilities

INC Research will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings. The safety laboratory database will be handled by CMAX and transferred to INC data management. The pharmacokinetics (PK) database will be handled by GSK and transferred to INC data management. The PK concentration time and actual time merge will be the responsibility of INC. The PK parameter derivation and statistical analysis will be the responsibility of INC, including the tables, figures and listings for both drug concentrations and PK parameters under the auspices of GSK.

The pharmacodynamics (PD) database will be handled by BioAgilytix and transferred to INC data management. The PD concentration time and actual time merge will be the responsibility of INC. The PD parameter derivation and statistical analysis will be the responsibility of INC, including the tables, figures and listings for the PD biomarker concentrations and derived PD parameters under the auspices of GSK.

Data permitting, exploratory dose response graphical relationships will be the responsibility of INC.

Quality assurance and oversight of all statistics, programming and data management activities performed by INC will be performed by GSK in line with the oversight plan.

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2. OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objectives for the Part A Single Dose section of this study are:

- To evaluate the safety and tolerability of single escalating oral doses of GSK3352589 administered in the fasted state and a single dose of GSK3352589 administered in the fed state in healthy adult subjects.
- To evaluate the pharmacokinetic parameters of escalating single oral doses of GSK3352589 under fasting and fed (for one dose only) conditions in healthy adult subjects.

The primary objectives for the Part B Repeat Dose section of this study are:

- To evaluate the safety and tolerability of repeat escalating oral doses of GSK3352589 administered once or twice daily in the fasted or fed state.
- To characterize the PK of GSK3352589 of repeat escalating oral doses administered once or twice daily in the fasted or fed state.

2.1.2. Exploratory Objectives

The exploratory objectives for Part B of this study are:

- To explore the effect of GSK3352589 on the postprandial plasma profiles of total glucagon like peptide-1 (GLP-1) and total peptide YY (PYY) following repeat oral doses of GSK3352589 administered once or twice daily.
- To investigate the biotransformation of GSK3352589 in plasma and urine.

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary endpoints for this study will consist of clinical safety and tolerability data including:

- Spontaneous Adverse Event (AE) reporting;
- Clinical Observations;
- Physical Examination findings;
- 12-Lead Electrocardiograms (ECG);

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- Vital Signs;
- Bristol Stool Form Scale (BSFS) Scores;
- Clinical Laboratory tests.

They shall also consist of the PK parameters obtained following the administration of both single and multiple doses of GSK3352589.

- PK parameters obtained following administration of single dose of GSK3353589:

AUC_{inf}	Area under the concentration-time curve from the time of dosing extrapolated to infinity
AUC_t	Area under the concentration-time curve from the time of dosing up to the last quantifiable concentration
C_{last}	Last observed quantifiable concentration
C_{max}	Maximum observed PK concentration
MRT	Mean residence time MRT (0-infinity)
$t_{1/2, terminal}$	Terminal elimination half- life
T_{last}	Time of the last observed quantifiable concentration
T_{max}	Time to Maximum Observed Plasma GSK3352589 PK Concentration

- PK parameters obtained following administration of multiple doses of GSK3353589 over 14 days in BID dosing regimen:

AUC_t	Area under the concentration-time curve from the time of dosing to T_{last} for Days 1 and 14 for BID 1st dosing interval and BID dosing (i.e., 24h day)
AUC_{tau}	Area under the concentration-time curve from the time of dosing during dosing interval for Days 1 and 14, 0-10 hrs for BID morning dose
C_{max}	Maximum observed concentration after dose on Days 1 and 14 separately for 1st dosing interval only (0-10) for BID
T_{last}	Time of the last observed quantifiable concentration after dose on Days 1 and 14 separately for 1st dosing interval only (0-10) for BID

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T_{max}	Time of maximum concentration after dose on Days 1 and 14 separately for 1st dosing interval only (0-10) for BID
R_{AUCt}	Accumulation Ratio (R) for AUC_t at Steady State compared to first dose interval
R_{AUCtau}	Accumulation Ratio (R) for AUC_{tau} at Steady State compared to first dose interval
R_{Cmax}	Accumulation Ratio (R) for C_{max} at Steady State compared to first dose interval

2.2.2. Exploratory Endpoints

The exploratory endpoints of the study will consist of:

- Postprandial challenge (mixed-meal) profiles of total GLP-1 and total PYY: Ave Pre-meal concentrations of biomarkers on each Days -1, 1 and 14 separately, AUC_{PDlast}, AUC_{PD4h}, C_{PDMAX} and T_{PDMAX} over the sampling interval.
- Samples of plasma and urine for the identification of any compound-derived metabolite(s).

2.3. Hypotheses

There are no formal hypotheses being tested. An estimation approach will be taken to provide a plausible range of values. For the PK endpoints, where appropriate, point estimates and 90% Confidence Intervals (CIs) will be provided.

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3. STUDY DESIGN

This is a randomized, double-blind (sponsor unblind), placebo-controlled, dose escalation study that will be divided in to two parts: Part A is a single dose escalating, four period crossover (Cohort 1) with a two period, single sequence pilot food effect (Cohort 2) and a two period crossover (Cohort 3) study, and Part B is a 14 day repeat dose escalating, ascending cohort study.

The study will be composed of 3 periods for all subjects (Screening, Treatment and Follow-up). Subjects will participate in either Part A or Part B, and also subjects participating in Part A Cohorts 1 or 2 are will not be permitted to participate in Part A Cohort 3. A subject's total time involved in the study will be approximately 10 weeks for subjects enrolled in Part A, Cohort 1 and approximately 8 weeks for subjects enrolled in Part A, Cohort 2 or Cohort 3. Subjects enrolled in Part B will be involved in the study for a total time of approximately 7 weeks.

All dosing periods for subjects participating in Part A will be completed before beginning enrollment in Part B.

For Part A, the planned dose range for Cohort 1 is single doses of 2 to 400 mg in the fasted state, whilst a single dose of GSK3352589 will be administered in the fasted and fed states in Cohort 2 and the planned dose range for Cohort 3 is 150 to 400 mg in the fasted state. For Part B, up to six (6) cohorts are planned and will be conducted sequentially. The selection of the starting dose for Part B, along with requirements for fasted or fed state study drug administration, will occur after review of the safety, tolerability and PK data of all subjects enrolled in Part A. For Part A Cohort 1, Part A Cohort 3 and Part B, the actual doses to be administered may be adjusted based on safety, tolerability and PK data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose. For Part A Cohort 2, the dose selected to evaluate the food effect will allow for a 2X increase in bioavailability and predicted exposures will not exceed the highest observed exposures at prior doses.

3.1. Number of Centers

This is a single center study, conducted at one site in Australia.

3.2. Number of Subjects

A sufficient number of healthy volunteers will be screened to randomize 24 subjects (8 subjects/cohort) for Part A and 48 subjects (8 subjects/cohort; 6 subjects will be randomized to GSK3352589 and 2 subjects will be randomized to placebo) for Part B for a total of 64 randomized subjects. If subjects prematurely discontinue the study, additional replacement subjects may be randomized and assigned to the same treatment at the discretion of the Sponsor and in consultation with the Investigator.

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3.3. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to define any investigational treatment or placebo intended to be administered to a study participant according to the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

3.4. Treatment Assignment

The randomization schedule will be computer generated by GSK. On Day 1, subjects will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to one of the four treatment arms of the study in accordance to the randomization schedule generated prior to the start of the study, using validated software. Each participant will be dispensed blinded study treatment, labelled with his/her unique randomization number, throughout the study.

3.5. Planned Dose Adjustments

3.5.1. Part A Single Dose

Single dose, dose escalating, four period, crossover (Cohort 1) with a two period, single sequence pilot food effect (Cohort 2) and a two period crossover (Cohort 3) study.

Subjects assigned to Cohort 1 will participate in 4 dosing periods: 1 placebo and 3 dose escalating periods. The planned dose range for Cohort 1 is 2 to 400 mg. Each dosing period during Cohort 1 will be staggered so that only 2 of the 8 subjects will be administered study drug initially. Once 24 hours have elapsed, and provided there are no safety concerns, the remainder of subjects scheduled for that dosing period may be dosed. A review of safety and tolerability will occur prior to administration of the next dose level. This same procedure will be followed for each escalating dosing period. Within each cohort, subjects will return for their next scheduled dosing period approximately 14 days after administration of the study drug during the prior dosing period.

Cohort 2 will proceed after completion of the treatment periods in Cohort 1. Subjects assigned to Cohort 2 will participate in a pilot food effect in Periods 1 and 2 (see Table 1 below). A single dose of GSK3352589 will be administered in the fasted and fed states in Cohort 2. The dose selected to evaluate the food effect will allow for a 2X increase in bioavailability and predicted exposures will not exceed the highest observed exposures at prior doses.

Subjects assigned to Cohort 3 will participate in 2 periods where subjects will receive escalating (increasing) doses of GSK3352589 and/or placebo. Cohort 3 will be staggered so that only 2 of the 8 subjects will be administered study drug initially (1 subject will receive GSK3352589 and 1 will receive placebo). This is referred to as a sentinel dosing. Once 24 hours have elapsed, and provided there are no safety concerns, the remainder of the subjects scheduled for that dosing period may be dosed. This same procedure will be followed for both periods of Cohort 3. For each dosing period, 2 subjects will be randomized

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to placebo and 6 subjects will be randomized to GSK3352589, thus 4 subjects will be treated with placebo during the 2 dosing periods and all 8 enrolled subjects will receive at least one dose of GSK3352589.

The decision to proceed to the next dose level of GSK3352589 will be made by the GSK Medical Monitor and the investigator based on safety, tolerability and available PK data. The actual doses to be administered may be adjusted based on safety, tolerability and preliminary PK data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose for Cohort 1. Dose escalation will occur only if mean systemic exposures are projected not to exceed the defined plasma toxicokinetic (TK) limits. Preliminary safety and PK data from all subjects will be reviewed prior to the next Dosing Period.

Table 1: Part A Treatment Sequence

Cohort 1 (Single Dose Escalation[1])

Treatment Sequence	Subjects	Period 1	Period 2	Period 3	Period 4
A	PPD and PPD	Placebo	D2	D3	D4
B	and	D1	Placebo	D3	D4
C	and	D1	D2	Placebo	D4
D	and	D1	D2	D3	Placebo

1 Dose escalation will occur only if mean systemic exposures are projected not to exceed the defined plasma toxicokinetic (TK) limits.

Cohort 2 (Pilot Food Effect)

Treatment Sequence	Subjects	Period 1	Period 2
E	PPD	D5	D5 + food
F	PPD and PPD	Placebo	Placebo + food

Cohort 3 (Single Dose Escalation[1])

Treatment Sequence	Subjects	Period 1	Period 2
G	PPD and PPD	D6	Placebo
H	and	Placebo	D7
I	PPD	D6	D7

1 Dose escalation will occur only if mean systemic exposures are projected not to exceed the defined plasma toxicokinetic (TK) limits.

3.5.2. Part B Repeat Dose

The planned dose range is 2 mg once daily to 200 mg twice daily. The starting dose for Part B will be selected after review of the safety, tolerability and PK data of subjects enrolled in Part A and completing all dosing periods.

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An example dose escalation plan is shown in Table 2 below. The actual doses to be administered may be adjusted based on safety, tolerability and PK data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose. Dose escalation will occur only if mean systemic exposures are projected not to exceed the defined plasma toxicokinetic (TK) limits.

Subjects will undergo pretreatment pharmacodynamic (PD) testing after administration of a breakfast mixed-meal challenge on Day -1 prior to receiving the first dose of study drug, on Day 1, and at the end of the treatment period on Day 14.

The decision to proceed to the next dose level will be made by the GSK Medical Monitor and the investigator based on safety, tolerability and available PK data. Preliminary safety and tolerability from 14 days of dosing and PK data from 7 days of dosing for each cohort will be reviewed prior to dose escalation and will be used to determine the dose to be administered in the subsequent cohort.

Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels or dosing regimens.

Table 2: Planned Dose Escalation for Part B

	Regimen Descriptions	Number of Subjects
Cohort 1	2 mg of GSK3352589 administered QD or matching placebo administered QD	GSK3352589 n=6 Placebo n=2
Cohort 2	10 mg of GSK3352589 administered QD or matching placebo administered QD	GSK3352589 n=6 Placebo n=2
Cohort 3	25 mg of GSK3352589 administered BID or matching placebo administered BID	GSK3352589 n=6 Placebo n=2
Cohort 4	50 mg of GSK3352589 administered BID or matching placebo administered BID	GSK3352589 n=6 Placebo n=2
Cohort 5	100 mg of GSK3352589 administered BID or matching placebo administered BID	GSK3352589 n=6 Placebo n=2
Cohort 6	200 mg of GSK3352589 administered BID Or matching placebo administered BID	GSK3352589 n=6 Placebo n=2

3.5.3. Dose Modification

The protocol allows some alteration from the currently outlined dosing regimen, but the (predicted) maximum/cumulative exposure will not exceed a CMAX=26.6 ng/mL or AUC = 40.4 ng.h/mL.

The decision to proceed to the next dose level of GSK3352589 (either an increase or a decrease) will be made by the Medical Monitor and the investigator based on safety, tolerability and preliminary PK data obtained in at least 4 GSK3352589-treated subjects at the prior dose level.

The dosing regimen may also be adjusted to expand a dosing cohort to further evaluate safety or PK findings at a given dose level or to add cohorts to evaluate up to 2 additional dose levels or dosing regimens. The study procedures for these additional participant(s) or cohort(s) will be the same as that described for other study participants/cohorts.

If adverse events (AEs), which are of moderate or severe intensity and are consistently observed across subjects in a cohort, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with GSK3352589 are observed in more than 1 subject in a cohort, the dose escalation will be temporarily halted and no further subject will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with Medical Monitor, relevant GSK personnel, and with the Ethics Committee will take place prior to any resumption of dosing.

3.6. Randomization and Blinding

Subjects will be randomized to one of the four treatment arms of the study in accordance with the randomization schedule generated prior to the start of the study by GSK, using validated software.

This will be a double blind (sponsor unblind) study and the following will apply. GSK staff will be considered unblinded to treatments, though the number with access to treatment information will be minimized.

4. PLANNED ANALYSES

4.1. Interim Analyses

No formal statistical interim analysis is planned for this study. Safety, tolerability and pharmacokinetic data will be reviewed prior to each dose-escalation and prior to all within subject escalations.

4.2. Final Analysis

The final analysis for both Part A and Part B of the study will be conducted once all subjects have completed the study.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

Sample sizes are based on feasibility; no formal power calculations were performed, and no statistical sample size re-estimation or adjustment will be used.

5.2. Sample Size Sensitivity

Not applicable for this study.

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6. ANALYSIS POPULATIONS

6.1. All Screened Population

The All Screened population will include all subjects who consented to participate in the clinical trial. The All Screened Population will be used for the listing of subject enrolment and eligibility.

6.2. Safety Population

The Safety population will comprise all randomized subjects who receive at least one dose of study medication and will be based on the actual treatment received, if this differs from that to which the subject was randomized to. This population will be used for the listing and summarization of subject disposition, all baseline and demographic data and for all general and safety analyses. With the exception of subject enrolment and eligibility, PD and PK outputs, all listings will be produced for the Safety Population.

6.3. PK Concentration Population

The PK Concentration population will comprise all randomized subjects who receive at least one dose of active treatment (GSK3352589) and for whom a pharmacokinetic sample was obtained and analysed. This population will be used for the listing of all PK concentrations.

The PK data will be evaluated for significant protocol violations or deviations that would significantly affect the PK evaluation of the drug, and will be flagged and may be excluded from the summary statistics and PK parameters derivation.

6.4. PK Parameter Population

The PK Parameter population will comprise all randomized subjects who receive at least one dose of active treatment and who have GSK3352589 PK parameter estimates from any portion of the study. This population will be used for the summaries and listings of PK parameters and tables for statistical models involving PK parameters, figures and analysis of all PK data.

6.5. Pharmacodynamic Concentration Population

The Pharmacodynamic Concentration population will include all randomized subjects who receive at least one dose of the study medication or placebo and who have at least one concentration of any PD biomarker (GLP-1 or total PYY) available. PD Biomarker concentrations will be listed for all subjects in PD Concentration population.

6.6. Pharmacodynamic Parameter Population

The Pharmacodynamic Parameter population will include all randomized subjects who receive at least one dose of the study medication or placebo and who have at least two pre-meal values and all four postprandial concentrations of any PD biomarker (GLP-1 or total PYY)

available on Days -1, 1 and 14. This population will only include subjects who completed at least 75% of the mixed meal breakfast on Days -1, 1 and 14.

Though no subjects with available PD data will be excluded, the PD data will be evaluated for protocol violations or deviations that would significantly affect the PD evaluation of the drug and may be flagged and excluded from summary statistics and/or PD parameters derivation.

7. TREATMENT COMPARISONS

7.1. Data Display Treatment and Other Subgroup Descriptors

For both Parts A and B, the actual doses may be adjusted based on safety, tolerability and PK data at previous dose levels.

For the purposes of the summary tables, all subjects randomized to placebo in Part A in the fasted state (Cohorts 1 and 3) will be grouped and in addition all subjects randomized to placebo in Part A in the fed state (Cohort 2) will be grouped and all subjects randomized to placebo in Part A in the fasted state (Cohort 2) will be grouped. In Part B, subjects (all cohorts) will be combined into a single placebo BID group.

7.1.1. Part A Single Dose

Cohorts

The following labels for cohorts in Part A of the study will be used on all tabulations where the results are displayed by cohort, in the following order:

- Cohort 1 and 3;
- Cohort 2;

The actual dose levels (rather than planned/generic descriptions) will be used for relevant outputs:

Treatments

- Placebo;
- GSK3352589 Dose 1 mg;
- GSK3352589 Dose 2 mg;
- GSK3352589 Dose 3 mg;
- GSK3352589 Dose 4 mg;
- Fed Placebo;
- Fasted Placebo;
- GSK3352589 Dose 5 mg;

- Fed GSK3352589 Dose 5 mg;
- GSK3352589 Dose 6 mg;
- GSK3352589 Dose 7 mg.

Where:

- Placebo will be Cohorts 1 and 3 combined;
- Doses 1-4 in Cohort 1 will take values from 2 to 400 (mg);
- Dose 5 in Cohort 2 will be selected to allow for a 2X increase in bioavailability and predicted exposures will not exceed the highest observed exposures at prior doses;
- Fed Placebo will be from Cohort 2;
- Fasted Placebo will be from Cohort 2;
- Dose 6 and Dose 7 in Cohort 3 will take values from 150 to 400 (mg).

7.1.2. Part B Repeat Dose

The following labels for treatment groups in Part B of the study will be used on all tabulations, in the following order. The actual dose levels (rather than planned/generic descriptions) will be used:

- Placebo;
- GSK3352589 Dose 1 mg;
- GSK3352589 Dose 2 mg;
- GSK3352589 Dose 3 mg;
- GSK3352589 Dose 4 mg;
- GSK3352589 Dose 5 mg;
- GSK3352589 Dose 6 mg;
- Overall.

Where:

- Doses 1-6 in Part B are different to Doses 1-6 in Part A;
- The starting dose will be selected after a review of the safety, tolerability and PK data of subjects enrolled in Part A and completing all dosing period;

- The example dose levels from the protocol are Dose 1 = 2 mg QD, Dose 2 = 10 mg QD, Dose 3 = 25 mg BID, Dose 4 = 50 mg BID, Dose 5 = 100 mg BID and Dose 6 = 200 mg BID.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The currently supported version of SAS software will be used to perform all data analyses. The actual SAS version used will be presented in the Clinical Study Report.

INC Research will be responsible for reporting the demographic and safety data, including the listings of the administration information for the collection of PK samples. INC Research is responsible for the PK analyses and the reporting of the PK analysis results, as well as the PD analysis and reporting of results.

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be presented by study part and sorted by treatment group, subject number and assessment date/time. Summaries presented by study part and treatment will be displayed for Part A followed by Part B and then as follows: placebo first, then ascending dose levels of GSK3352589. Part A and Part B will be displayed on a separate page for all listings and summaries. Similarly, each treatment group will be displayed on a separate page for by treatment summaries.

Unless otherwise stated, continuous variables will be summarized using the statistics mean, median, standard deviation, minimum and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the CRF, mean, median and standard deviation will be presented to one more decimal place than the raw data. Categorical variables will be summarized with frequency counts and percentages. Percentages will be rounded to one decimal place, with the denominator being the number of subjects in the relevant population, unless otherwise stated.

Summary tables will indicate the number of subjects with complete data for each measurement, event or outcome. With the exception of the calculation of the PD parameters, no substitutions will be made for missing data unless otherwise stated (PK analysis considerations). All analysis will be based on available data, unless otherwise stated.

8.1. Multicenter Studies

Not applicable for this study.

8.2. Examination of Subgroups

Not applicable for this study.

8.3. Multiple Comparisons and Multiplicity

Not applicable for this study.

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9. DATA HANDLING CONVENTIONS

9.1. Premature Withdrawal and Missing Data

For subjects who are withdrawn from the study prior to study completion, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal.

Subjects who are withdrawn prematurely from study treatment will be included in all analyses regardless of the duration of treatment.

- A participant 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, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA (Section 2 of the Protocol) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

There will be no imputation for missing data, unless otherwise stated.

9.2. Partial Dates

For the purposes of assigning AEs and concomitant medications to study periods the following algorithm will be used for partial start dates (AE start dates and concomitant medication start dates):

- Should the full date be missing then the start date will be assumed to be the date of the first administration of study drug.
- Should the day and month be missing and the year is the same as the year of the first administration of study drug then the date will be assumed to be the date of the first administration of study drug.
- Should the day and month be missing and the year is not the same as the year of the first administration of study drug then the day and month will be assumed to be 1 January.
- Should the day be missing and the month and year are the same as the month and year of the first administration of study drug then the date will be assumed to be the date of the first administration of study drug.

- Should the day be missing and the month and year are not the same as the month and year of the first administration of study drug then the day will be assumed to be first of the given month.

9.3. Derived and Transformed Data

Baseline

In general, baseline will be defined for each subject and will be defined as the last available, non-missing assessment prior to the first administration of study assigned treatment. 'Unknown', 'Not Done', 'Not Applicable' and other classifications of missing data will not be considered when calculating baseline observations. However, valid categorical observations will be considered for baseline calculations. Unscheduled assessments will also be included for the derivation of baseline.

Baseline will be considered to occur at the following time points for the following parameters:

Table 3: Part A Baseline Values

Safety End Point	Baseline Value is Captured on/at
Physical Examinations	Day -1 or Screening if the Day -1 data are not available/ Unscheduled time point
Laboratory Assessments	Day -1 or Screening if the Day -1 data are not available/ Unscheduled time point
ECG	Day 1 pre-dose or Screening if the Day 1 data are not available/ Unscheduled time point
Vital Signs	Day 1 pre-dose or Day -1 if Day 1 pre-dose data are not available/ Unscheduled time point
PD for Mixed Meal Profiles	Not applicable

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Table 4: Part B Baseline Values

Safety End Point	Baseline Value is Captured on/at
Physical Examinations	Day -2 or Screening if the Day -2 data are not available/ Unscheduled time point
Laboratory Assessments	Day -2 or Screening if the Day -2 data are not available/ Unscheduled time point
ECG	Day 1 pre-dose or Screening if the Day 1 data are not available/Unscheduled time point
Vital Signs	Day 1 pre-dose or Day -1/ or Day -2 if Day 1 pre-dose data are not available/ Unscheduled time point
PD Parameters for Mixed Meal Profiles	Day -1 (see section 14.5)

Age

Age, in completed years, at screening will be calculated for each subject and will be defined as:

- Age (years) = year informed consent signed - year of birth.

Body Mass Index (BMI)

BMI, in kg/m^2, at screening will be calculated for each subject and will be defined as:

- BMI (kg/m^2) = weight at screening (kg) / (height at screening (m))^2.

Study Day

Study day will be calculated using the first study drug administration date as the reference date. If the date of interest occurs on or after the first study drug administration date, study day will be calculated as (date of interest – start of first study drug administration date) + 1. If the date of interest occurs prior to the start of first study drug administration date, study day will be calculated as (date of interest – start of first study drug administration date). There will be no study day 0.

Time on Study

Time on study will be calculated as follows and displayed in the following format day, hour, minute. Date/Time (min) = (day x 1440) + (hour x 24) + minute

Time since first dose will be calculated as follows:

- Day = Integer[(Onset Date/Time (min) - First Admin Date/Time (min))/1440].
- Hour = Integer[{(Onset Date/Time (min) - First Admin Date/Time (min) - (Day x 1440)}/60].
- Minute = Integer[{(Onset Date/Time (min) - First Admin Date/Time (min) - (Day x 1440) – (Hour x 60)].

Time since last dose will be calculated as follows:

- Day = Integer[{Onset Date/Time (min) - Last Admin Date/Time (min)}/1440].
- Hour = Integer[{(Onset Date/Time (min) - Last Admin Date/Time (min) - (Day x 1440)}/60].
- Minute = Integer[{(Onset Date/Time (min) - Last Admin Date/Time (min) - (Day x 1440) – (Hour x 60)].

Missing resolution date/time will not be imputed, and AE duration will not be calculated in those cases.

AE Duration

AE duration will be calculated as follows and displayed in the following format day, hour, minute.

- Day = Integer[{Resolution Date/Time (min) - Onset Date/Time (min)}/1440].
- Hour = Integer[{(Resolution Date/Time (min) - Onset Date /Time (min) - (Day x 1440)}/60].
- Minute = Integer[{(Resolution Date/Time (min) - Onset Date/Time (min) - (Day x 1440) – (Hour x 60)].

Missing data will not be imputed.

9.4. Assessment Windows

All assessments will be included in the listings. No visit windows will be applied to assessments.

9.5. Coding Dictionaries

Concomitant medications will be coded using the latest version of the GSK Drug dictionary.

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The actual dictionary versions used will be presented in the Clinical Study Report.

9.6. Values of Clinical Significance

Reference ranges for all laboratory parameters collected throughout the study are provided by the respective laboratory. A laboratory value that is outside of the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical significance.

The laboratory reference ranges will be provided on the listings of standardized laboratory data with out of range values flagged (low or high).

10. STUDY POPULATION

10.1. Disposition of Subjects

The total number of subjects randomized to the study and in each population will be summarized, by study part, treatment group and overall for all subjects.

A listing of subject enrolment will include the date informed consent was signed, the version date of protocol effective at informed consent, the date and time of first treatment and whether included in each population.

The number of subjects prematurely terminated from the study along with the reason for early study termination will be both summarized and listed.

10.2. Protocol Deviations

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Subject data will be examined for evidence of protocol deviations in order to assess how well the protocol was followed. These will be assessed before unblinding for the final analysis and according to data available on the CRF. Possible protocol deviations will be independently reviewed and approved by GlaxoSmithKline.

All protocol deviations will be detailed in a listing.

Protocol deviations are defined as follows:

- Noncompliance with the clinical trial protocol (including intake of any prohibited medications, as detailed in Section 7.7 of the protocol), Good Clinical Practice (GCP), or Manual of Procedure requirements. The noncompliance may be either on the part of the subject, the site PI, or the study site staff. Any subject enrolled who does not meet eligibility criteria will be considered an enrollment deviation. Additional important protocol deviations include noncompliance with the informed consent procedure, concomitant medication use, Serious Adverse Event (SAE) reporting, and study drug dosing.

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Protocol deviations will be listed including a classification of minor or major, as determined by clinical staff.

10.3. Demographic and Baseline Characteristics

All baseline and demographic data recorded at screening and prior to dosing will be listed for all subjects in the Safety Population.

Demography (age, gender, non-childbearing potential, race, ethnicity, height, weight and BMI) will be summarized, by study part, treatment group and overall for all subjects.

Medical and surgical history, comprising of System Organ Class (SOC) and Preferred Term (PT) (coded using the MedDRA dictionary), start and end dates will be listed only for all subjects in the Safety Population.

Urine drug, cotinine, breath alcohol test, viral serology [Human Immunodeficiency Virus (HIV), Hepatitis B (HBsAG) and Hepatitis C antibody], Estradiol and Follicle Stimulating Hormone (FSH) levels will be listed only.

10.4. Study Drug Administration

All study drug administration data will be listed only for all subjects in the Safety Population.

11. EFFICACY ANALYSES

There are no efficacy endpoints defined for this study.

12. SAFETY ANALYSES

All safety analyses will be conducted on the Safety population.

12.1. Extent of Exposure

Extent of exposure will include the following analyses:

- In Part A only, the frequency and percentage of subjects who completed the study, 3 GSK3352589 dosing periods, 2 GSK3352589 dosing periods and 1 GSK3352589 dosing period will be summarized by cohort;
- Dosing along with the cumulative dosing will be summarized by treatment for Part A and by visit and treatment group, and overall, for Part B.

12.2. Adverse Events

Adverse Events will be coded using the MedDRA dictionary.

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Adverse Events will be grouped by SOC and PT and summarized by study part, treatment group and for all subjects overall (Part B only). The summary tables will present the frequency and percentage of total subjects, by SOC and by PT.

TEAEs are defined as AEs which commence on or after the start of first study drug administration. AEs without an onset date or time will be defined as treatment emergent except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to the start of study drug administration or if the AE stop date indicates that the event started and stopped prior to the start of study drug administration. Partial AE start dates will be imputed (Section 9.2).

The summary tables will include the number of subjects and the number of events. For summaries by SOC and PT, a subject will be counted once at the SOC level and once at each PT within the SOC level.

Relationships of un-assessable, unlikely, possibly, probably and certainly will be judged as being treatment-related for the summary tables. If the relationship to study drug is missing then the relationship will be counted as treatment-related for the summary tables. Similarly, missing intensity will be counted as the most severe intensity.

The summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The following AE tables will be provided:

- TEAEs overall and by system organ class and preferred term;
- TEAEs overall and by system organ class and preferred term and by severity;
- TEAEs overall and by preferred term;
- Treatment-related TEAEs overall and by system organ class and preferred term;
- Treatment-related TEAEs overall and by preferred term.

All AEs will be listed and any TEAEs will be flagged. This will include listings of Serious Adverse Events (SAEs) and AEs leading to withdrawal of study treatment.

12.3. Laboratory Evaluations

Hematology and clinical chemistry will be summarized at each protocol scheduled time point by study part, treatment group and for all subjects overall (Part B only). Actual values and actual changes from baseline will be presented for the standardized laboratory data.

Shift tables for hematology and clinical chemistry will be provided relative to the normal ranges by treatment group. Subjects with a missing baseline value are to be assumed to have a normal baseline value. The summary of normal range category changes will illustrate the number and percentage of subjects who fall into specified categories (Decrease to Low,

Change to Normal or No Change, Increase to High) by comparing the baseline normal range category to the end of treatment (Follow-up) normal range category and the worst-case on-therapy normal range category.

The worst-case post-baseline evaluation will be used to summarize the subjects' overall worst-case change during a given treatment period (including Follow-up). The determination of the worst-case during the on-therapy period will take into account both planned and unscheduled assessments. Worst-case can be either High or Low.

- If a subject has a 'Decrease to Low' and an 'Increase to High' during the same time interval, then the subject is counted in both the 'Decrease to Low' and 'Increase to High' categories.
- If a subject was high at baseline and decreases to low during the time interval, then the subject is counted in the 'Decrease to Low' category.
- Likewise, if a subject was Low at baseline and increases to High during the time interval, then the subject is counted in the 'Increase to High' category.
- Subjects are only counted in the 'Change to Normal or No Change' category if they are:
    - Normal at baseline and have no normal range high and no normal range low values during the time interval;
    - High at baseline and do not change to low during the time interval;
    - Low at baseline and do not change to high during the time interval.

In all cases, subjects are only counted once in the overall for all subjects column (by treatment summaries).

Liver stopping criteria will be summarized by treatment, using frequency tabulations and listed separately as follows:

Table 5: Liver Chemistry Stopping Criteria

Laboratory Parameter	Stopping Rule
ALT	ALT ≥ 3 x ULN
Bilirubin	Bilirubin ≥ 2 x ULN (> 35% direct bilirubin)
INR	INR > 1.5, if INR measured

For Part B only, liver function testing (LFT) will be performed and summarized along with the clinical chemistry results.

In addition, urinalysis results will be summarized at each protocol scheduled time point, by treatment, using frequency tabulations. Urine microscopy results will be listed only if available.

All abnormal laboratory values will be identified in the listings.

12.4. Bristol Stool Form Scale (BSFS)

BSFS daily scores and daily frequency of bowel movement will be listed for Parts A and B.

For Part B only, average BSFS daily score and daily frequency of bowel movement will be summarized by day (beginning with Day -1 through to Day 14) and by time intervals (Day -1, Days 1-3, Days 4-7, Days 1-7 and Days 8-14) by treatment group and for all subjects overall.

Time profiles for the average BSFS daily score and daily frequency of bowel movement for each individual subject by day will be presented by treatment for Part B only. The average BSFS daily score and average daily bowel movement frequencies will also be presented as box plots by time intervals and for each treatment separately for Part B only.

12.5. Vital Signs

Vital signs (systolic/diastolic blood pressure, pulse rate and temperature) will be summarized at each protocol scheduled time point by study part, treatment group and for all subjects overall (Part B only). Actual values and actual changes from baseline will be presented.

The Potential Clinical Importance (PCI) ranges are noted in the table below for vital sign results. Values outside these ranges will be flagged as either low or high relative to the PCI ranges. The number of subjects with out of PCI range results will be summarized by treatment group.

Table 6: Vital Signs PCI Ranges

Vital Signs Parameter	PCI Range	Unit
Systolic Blood Pressure	< 85 (Low) and > 160 (High)	mmHg
Diastolic Blood Pressure	< 50 (Low) and > 100 (High)	
Pulse Rate	< 40 (Low) and > 110 (High)	bpm

Three readings of blood pressure and pulse rate will be taken. The first reading should be rejected and the second and third readings recorded in the CRF. The average of the second and third values will be used for all summary tabulations and PCI range comparisons.

12.6. Electrocardiogram (ECG)

ECG data (heart rate, PR interval, QRS interval, QT interval, QTc interval (QTcF interval) values will be summarized at each protocol scheduled time point by study part, treatment group and for all subjects overall (Part B only). Actual values and actual changes from baseline will be presented.

In addition, a frequency tabulation of ECG interpretation (Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant) at each protocol scheduled time point, by study part, treatment group and overall (Part B only), will be provided.

The mean value of the triplicate assessments will be used for all summary tabulations and the worst clinical interpretation of the triplicate assessments will be used for the descriptive summaries.

Prolongation of QTcF intervals [as per the definition of International Conference on Harmonization (ICH)] will be summarized by treatment according to the following categories:

- QTcF > 500 msec;
- QTcF > 480 msec and ≤ 500 msec;
- QTcF > 450 msec and ≤ 480 msec;
- QTcF Change from Baseline > 30 and ≤ 60 msec;
- QTcF Change from Baseline > 60 msec.

12.7. Prior and Concomitant Medications

Prior and concomitant medications will be grouped by preferred drug name by using the GSK Drug dictionary. The summary tables will show the number and percentage of subjects taking each medication by preferred term, by study part and treatment group and for all subjects overall (Part B only) and sorted by descending frequency of preferred term.

Only concomitant medications will be summarized. Prior and concomitant medications will be listed separately.

Prior medications are those medications that were stopped prior to first study drug administration. Concomitant medications are medications taken at least once after first study drug administration. Medications stopped on the same day as first study drug administration will be considered as concomitant medication. Medications without an onset date will be defined as concomitant, except if an incomplete date (e.g., month and year) clearly indicates that the medication was started prior to the start of study drug administration or if the medication stop date indicates that the medication was started and stopped prior to the start of study drug administration. Partial medication start dates will be imputed (Section 9.2).

For the summaries of concomitant medications, subjects who take the same medication (in terms of the preferred term more than once will only be counted once for that medication.

12.8. Other Safety Parameters

Physical examination data and pregnancy data will be listed only.

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13. PHARMACOKINETIC ANALYSES

All GSK3352589 plasma concentrations and plasma PK parameter data will be listed. The PK Concentration population will be used for the descriptive statistics of the PK concentrations and the PK Parameter population will be used for the descriptive statistics of the PK parameters.

The merge of PK concentration-actual time data, randomization and CRF data will be performed under the direct auspices of GSK Clinical Statistics by INC Research, Inc.

Derivation of pharmacokinetic parameters will be performed under the direct auspices of GSK Clinical Pharmacology Modeling and Simulation by INC Research, Inc.

Statistical analysis of pharmacokinetic parameters will be performed by, or under the direct auspices of GSK Clinical Statistics by INC Research, Inc.

13.1. PK Sampling Schedule

The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

13.1.1. Part A Single Dose

PK sampling for GSK3352589 single dose PK will be collected on Days 1, 2 and 3, with time relative to Day 1 dose. Sampling will be taken pre-dose within 10 minutes prior to first dose at time zero and then post-dose at the following time points: 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 8 and 12 hrs on Day 1, at 16, 24, and 36 hrs on Day 2 and at 48 hrs on Day 3.

13.1.2. Part B Repeat Dose

PK sampling for GSK3352589 repeated (multiple) dosing, in either the fed or fasted condition, is to be determined based on the pilot food effect cohort (Cohort 2) in Part A. BID Dosing will be at approximately 0800, with the PM dose to be administered 10 hours following the AM dose.

On Days 1 and 14 PK blood samples will be obtained pre-dose within 10 minutes prior to first dose at time zero and then post-dose at the following time points: 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 8, 10 (10 mins prior to 2nd dose), 11, 12, 14, 16, and 24 hrs (within 10 minutes or less prior to next dose).

On Day 7, sparse sampling schedule for PK blood samples will be obtained pre-dose within 10 minutes prior to first dose at time zero and then post-dose at the following time points: 1, 2, 4, 8, 10 hrs (10 minutes or less prior to 2nd dose) and 24 hrs (10 minutes prior to next dose on Day 8).

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13.2. Plasma PK Endpoints for GSK3352589

The pharmacokinetic parameters will be calculated by non-compartmental analysis (data permitting), according to current working practices and using Phoenix WinNonLin version 6.4 or higher (Certara, Princeton, NJ, USA). The PK parameters will be derived using actual sampling time with the following considerations:

- The sampling time of pre-dose samples relative to dosing will be treated as zero for all sampling periods separately;
- Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero;
- Post-dose BLQ concentrations after the last quantifiable point will be set to missing.

Secondary parameters will be derived to assess the reliability of the elimination parameters – R_{2adj}, interval for calculation of λz, AUC_{extrap}. There parameters will be listed and will not be summarized.

Dose normalized C_{max} and AUC parameters will be calculated to facilitate the assessment of dose proportionality. Additional PK parameters for both parts of the study may be included if needed.

The PK parameters for the GSK3352589 will be estimated using concentrations in ng/ml units as follows:

- The apparent C_{max} and the corresponding T_{max} will be read directly from the concentration-time plot (observed data).
- AUC_t will be calculated using the Linear up-Log down Trapezoidal Rule for extravascular model.
- AUC_{tau} and AUC_{24hBID} will be calculated using the Linear up-Log down Trapezoidal Rule for extravascular model with the possible extrapolation to the end of dosing interval if needed.
- The terminal elimination rate constant (λ_z) will be determined by log linear regression obtained on at least the 3 last quantifiable concentrations and will not include C_{max}; $t_{1/2}$ is calculated by the program as ln2/λz.
- The AUC_{inf} is calculated by the program as:
    - $AUC_{inf} = AUC_t + AUC_{extrap}$

  where T_{last} is the sampling time point of the last measurable concentration. AUC_{extrap} is calculated by the program as: $C_{last}/\lambda z$, where C_{last} is the observed concentration at time T_{last} and λz is the elimination rate constant during the apparent terminal elimination phase; AUC_{inf} will only be presented for subjects with a reliable λz;

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R_{Cmax}, R_{AUCtau} and R_{AUCt} will be calculated as ratios of the parameters on Day 14 to Day 1 for Part B using the GMR from the ANOVA statistical model only and will not be calculated on a subject level basis.

The following PK acceptance criteria will be applied to assess the reliability of elimination parameters:

1. Number of points to calculate λ_z is greater than or equal to 3, excluding C_{max} point;
2. Interval for calculation of λ_z is longer than half-life;
3. The adjusted square of the correlation coefficient (Rsquare adjusted; R_{2adj}) for the goodness of fit of the regression line through the data points must be ≥0.80;
4. AUC_{extrap} ≤30%;
5. Estimation of initial half-life will use a minimum of 3 time points.

13.3. Derived and Imputed Data

13.3.1. Handling of Data below the Limit of Quantification for PK Concentration Listings, Individual Plots, Summaries and PK Parameters Derivation

- The sampling time of pre-dose samples relative to dosing will be treated as zero for all sampling periods separately for Days 1, 7 and 14;
- Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero for all purposes;
- Post-dose one or more consecutive BLQ concentrations flanked by quantifiable concentrations will be set to missing for all purposes;
- Post-dose BLQ concentrations after the last quantifiable point will be set to zero for mean and individual presentations of PK concentrations;
- The mean/median value at a time-point where one or more samples have BLQ values will be reported (in tabular or graphical fashion) even if the mean/median value is below the lower limit of quantification (BLQ) of the assay;
- Zero mean or median values will be included in summary tables.

It should be noted that a high proportion of BLQ values may affect the standard deviation (SD); if more than 30% of values are imputed, then the SD will not be displayed.

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Tables of summary statistics for concentration-time data will report N (number of subjects in the analysis population), n (number of actual observations) and the percentage of BLQ values relative to the total number of observations.

For linear plots, zero concentration value(s) before the first quantifiable concentration will be included in the plot. For log-linear plots, zero concentration value(s) before the first measurable concentration will be assigned a missing value.

For PK parameter estimation post-dose, one or more consecutive BLQ concentrations flanked by quantifiable concentrations as well as post-dose BLQ concentrations after the last quantifiable point will be set to missing.

13.3.2. Data Summarization and Presentation

All the derived parameters described in Section 13.2 will be listed and summarized for Parts A and B separately. For each of these parameters, the following statistics will be calculated for each active treatment group: n, median, minimum, maximum, arithmetic mean, standard deviation, between-subject coefficient of variation (CV) for the untransformed data, geometric mean, 95% CI for the geometric mean, standard deviation of logarithmically transformed data, and the between-subject CV based on the geometric standard deviation for the transformed data. For T_{max} and similar parameters (T_{last}), the median, maximum, minimum for the untransformed data will be calculated.

For the purposes of calculating summary statistics and for statistical analysis, all PK parameters, with the exception of T_{max} and similar will be $\log_e$ transformed. Geometric mean for the transformed data will be calculated according to the following method:

- Geometric mean = exp(mean on $\log_e$ scale).

The between-subject CV (%CVb) and Geometric %CVb will be calculated according to the following methods:

- Untransformed Data: %CVb = 100 * (SD/Mean), where SD and Mean are the standard deviation and mean of the untransformed data.
- Transformed Data: Geometric %CVb = 100 * (sqrt(exp(SD^2)-1)), where SD is the standard deviation of the $\log_e$-transformed data.

If a plasma drug concentration is excluded from the PK parameter analysis, it will be documented in the results and/or discussion of the study report.

The following conventions will be used for the presentation of the descriptive statistics of PK parameters and of plasma concentrations:

Table 7: PK Reporting Precision

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Statistics	Degree of Precision
Minimum, Maximum	Actual number of significant digits for raw data
Mean, SD (arithmetic and geometric), Median and 95% CI for the geometric mean	Actual number of significant digits for raw data + 1
%CVb and Geometric %CVb	1 decimal place

Additionally, the following inferential analyses will be performed, as described below in Sections 13.4, 13.5 and 13.6 of the SAP:

- Dose proportionality assessed using parameters C_{max}, AUC_t and AUC_{inf} (Parts A and B separately) and steady state parameter AUC_{tau}, (Part B only).

Nominal time will be used for the descriptive summaries and plots of summary measures. Actual time will be used in the listings, individual PK concentration-time profiles and in calculation of pharmacokinetic parameters. The PK concentrations obtained with the protocol deviations will be flagged (for example sampling obtained outside the nominal window) and may be excluded from summaries.

Any deviation(s) from the original analyses planned in the SAP will be reported in the Clinical Pharmacology Study Report (CPSR).

Individual subject PK parameters will be listed separately for Parts A and B by treatment group, subject and summarized by treatment group. The PK parameters with protocol deviations will be flagged (for example emesis after dosing, incomplete sampling or not meeting PK acceptance criteria) (Section 13.2) and may be excluded from summaries.

Individual plasma concentration-time profiles (one plot per subjects) and mean profiles by treatment group will be plotted. Each of the figures will contain one plot for the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. log-linear plot).

The following presentations of individual PK concentrations will be produced:

- Listing of PK sampling times including nominal and actual time elapsed from dose with the deviation from the nominal time and measured concentrations of the drug. The PK samples taken outside the scheduled window will be flagged in listing and may be excluded from summary statistics of PK concentrations by nominal time (± 10% of the nominal time point e.g. ±6 minutes for 1 hr point).

- Individual PK profiles in linear and log-linear scale for all subjects within the same treatment (dose level and fed/fasted condition for Cohort 2) combined on one graph and plotted vs. actual time of the samples elapsed from the start of infusion. For Part B these profiles will present the intense PK sampling on Days 1, 7 and 14 separately.

The following presentations of mean PK concentrations will be produced:

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- Table of PK concentrations summarized by nominal time within scheduled window for each treatment (dose level and fed/fasted condition) for Part A separately. For Part B summaries will be presented by Day 1 or 14.

- Plot for mean PK profiles in linear and log-linear scale for Part A will be combined for all dose levels in fasted condition in Cohort 1. Mean PK profiles for fed and fasted condition will be presented for Cohort 2 within Part A. Error bars on the plot will represent SD values.

- For Part B these profiles will present the intense PK sampling on Days 1, 7 and 14 separate for each day with all dose levels combined. Error bars on the plot will represent SD values.

- Additional presentation for Part B will combine the intense PK sampling on Days 1, 7 and 14 separately for each dose level. Error bars on the plot will represent SD values.

Additional figures will be produced for statistical models involving PK results as described below in Sections 13.4-13.6.

13.4. Assessment of Dose Proportionality for the PK of GSK3352589 in Cohort 1, 2 and 3 of Part A (fasted) and for Part B (fed) of the Study

Exploratory dose proportionality will be analyzed with the method originally described by Gough et al. (1995)[2] and modified as described by Smith et al. (2000)[3] and further adapted by Hummel et al. (2009)[4]. Hereby an ANOVA method will be performed on the logarithm transformed PK parameter endpoints. The model will be applied to following parameters separately for Parts A and B of the study:

- Part A: Single dose parameters C_{max}, AUC_t, AUC_{inf};

- Part B: multiple dose parameters C_{max}, AUC_t (for when AUC_{tau} not available), AUC_{tau} for Days 1 and 14 separately.

The model will include the $\log_e$-transformed GSK3352589 dose level as an independent variable. This model will be used to investigate the null hypothesis (H0: ß=1). Dose-proportionality will be rejected (H1: ß≠1) if the 90% CI of the estimated slope falls outside the critical interval.

The linear form of the model will be as following:

$$Y_{ij}=\alpha + \beta * X_i + \varepsilon_{ij}$$

Where:

- Y_{ij}= logarithm of the pharmacokinetic endpoint for subject j at dose level i; where i = 1, 2, …m, j = 1, 2, …, n;
- α = intercept parameter;

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- ß = slope parameter;
- X_i= logarithm of dose i;
- ε_{ij}= random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

The critical interval will be calculated as follows:

- The ratio (r) of the highest dose level to the lowest dose level will be calculated. The lower limit of the critical interval will be calculated as: ln(0.5)/ln(r) + 1.The upper limit of the critical interval will be calculated as: ln(2.0)/ln(r) + 1.

r value is based on the ratio between the highest and lowest dose levels of GSK3352589. For single dose, the planned dose level range is 2 to 400 mg and r equals 400 / 2 mg = 200. Thus, the critical interval for planned dose ranges in Part A to declare dose linearity will be 0.87 to 1.13 for the 90% CI of the slope estimate. The critical interval will be estimated for actual dose ranges used in the study.

The planned dose ranges in Part B are 25-200 mg for BID administrations. Alternative methods such as ANOVA comparison of dose normalized parameters between the two dose levels will be considered (see secondary analysis below). For the planned dose range of 25-200 mg BID the r equals to 200 / 25 = 8 and the respective critical interval for the range will be 0.67 to 1.33. The critical intervals will be adjusted based on the actual dose levels tested. The critical interval will be estimated for actual dose ranges used in the study.

This study (Parts A and B) was not powered to assess dose proportionality; therefore these critical interval limits for the 90% CI of the slope estimate are to be used as a guide only for comparison.

Secondary analysis of dose proportionality will be performed by an ANOVA model using the SAS Proc Mixed procedure for Parts A and B separately. The analysis will be performed for the $\log_e$-transformed, dose-normalized, parameters for single and multiple doses depending on the study part. For Part A C_{max}/D, AUC_t/D, AUC_{inf}/D will be compared between dose levels. For Part B AUC_{24h}/D, AUC_{tau}/D and C_{max}/D for Days 1 and 14 will be similarly compared with a fixed effect term for treatment. The reference dose will be 15 mg. 90% CIs for the geometric mean ratios (GMRs) will be obtained from the mixed-effects model. In the base model for Part B parameters for Days 1 and 14 will be modelled separately. If the model will not converge the data may be analyzed in combined model with day as a categorical fixed term with day*treatment interaction term. Subject ID will be included as a random term for both parts.

The formula for the calculation of the estimated ratio between the test and reference and the (1-2*α)*100 % CI of the ratio is given below.

- Difference = Estimate of difference between test and reference least square means;
- Ratio = $100 \times e^{Difference}$;
- (1-2*α)*100% CIs for the Ratio:

- Lower = $100 \times e^{(\text{Lower Bound } (1-2*\alpha)\% \text{ CIs for the Difference})}$;
- Upper = $100 \times e^{(\text{Upper Bound } (1-2*\alpha)\% \text{ CIs for the Difference})}$.

Where the differences and the (1-2*α)*100% CIs are obtained from the ANOVA model results.

Dose proportionality will also be explored graphically:

- Regression/scatter plot in the log-log scale for the Hummel power analysis by day;
- Box plot for ANOVA comparison of dose proportionality for dose-normalized PK parameters by treatment and day.

13.5. Assessment of Drug Accumulation using ANOVA for the PK of GSK3352589 for Part B of the Study

Accumulation ratio (R) for the GSK3352589 exposure will be determined by an ANOVA model using the SAS Proc Mixed procedure for Part B of the study. The analysis will be performed for the $\log_e$-transformed parameters for C_{max}, $AUC_{tau,}$ and AUC_t will be compared between Day 14 and 1. 90% CIs for the geometric mean ratios (GMRs) will be obtained from the mixed-effects model. The PK parameters will be log-transformed for the comparison and exponentiated for the estimate of GMR. The model will be evaluated as a cross-over comparison for the same subjects; the subject ID will be included as random effect to account for missing values on Day 14. Inter- and intra-subject variability will be evaluated. Treatment as a dose level for GSK3352589 will be used as fixed effect in the model. Treatment effect will be also included in the output to demonstrate if the dose has an effect on accumulation of exposure with visit by treatment interaction.

The graphic presentation for the analysis will be:

- Box plot for ANOVA comparison of PK parameters by treatment and day.

13.6. Assessment of the Pilot Food Effect for the PK of GSK3352589 in Cohort 2 of Part A of the Study

Assessment of the pilot food effect will be performed through the comparison of key PK parameters for the fed and fasted conditions, such as C_{max}, AUC_t and AUC_{inf}. The comparison will be done using the ANOVA approach. Log_e-transformed PK parameters will be compared using subject as a random effect and fed/fasted condition as a fixed effect in a cross-over design. Inter- and intra-subject variability will be assessed. The PK parameters obtained for the fasted conditions will be used as a reference whilst the PK parameters for the fed condition will be treated as test. 90% CIs for the geometric mean ratios (GMRs) will be obtained from the mixed-effects model for the ratio of PK parameters. The comparison will be also presented graphically as box plots:

- Box plot for ANOVA comparison of food effect for PK parameters by fasted/fed conditions.

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14. PHARMACODYNAMIC ANALYSES

The PD analysis will be based on the PD Concentration and PD Parameter populations. PD data for the subjects who received placebo will be pooled across all dose levels.

14.1. PD Sampling Schedule

PD sampling for total glucagon like peptide-1 (GLP-1) and total peptide YY (PYY) will be taken for multiple doses of study drug or placebo in Part B only. GLP-1 will be analyzed before PYY and if data suggests no PD effect then PYY will not be analyzed. If this happens then only GLP-1 data will be included as a PD endpoint.

Blood samples for PD on Days -1, 1 and 14 will be taken at the following time points: 15, 10, and 5 minutes prior to breakfast, and at 0.5, 1, 2, and 4 hrs post breakfast. Lunch is to be eaten after 4 hr sample. The average of pre-meal concentrations for PD biomarkers will be defined separately for each day of intense PD sampling as an average of the 3 measurements obtained prior to breakfast.

14.2. Handling of Data below the Limit of Quantification for PD Concentration Listings, Individual Plots, Summaries and PD Parameters Derivation

For the summary of PD concentration data and the calculation of PD parameters AUCs, C_{PDmax} and T_{PDmax} for postprandial challenge (mixed-meal) profiles of total GLP-1 and total PYY, the following imputation rules will be used for values below the limit of quantification (BLQ):

- The concentration values below the limit of quantification for the PD concentration summaries and plotting of individual and mean PD results will be imputed as 0;
- The concentration values below the limit of quantification for the PD parameters derivation will be imputed as missing. The impact of actual missing or BLQ measurements will be evaluated on a case by case basis and the affected derived PD parameters will be flagged and may be excluded from PD summaries and PK/PD analysis.

The PD concentration data will be summarized by nominal time. Samples taken outside the scheduled windows for nominal time points will be listed and presented on individual plots. The samples taken outside the scheduled windows may be used for the PD parameters derivation based on a case by case assessment.

The pre-meal PD values will be evaluated for outliers. Outliers will be identified on individual basis for each subject and each day of testing. The outliers will be defined as values of PD biomarker concentrations 3 fold higher or lower than the average of the remaining two pre-meal measurements. Excluded outliers will be flagged in PD listings and average values will be indicated in summaries with explanation in the footnote.

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14.3. Presentation of PD Concentration Data

Total GLP-1 and total PYY concentrations will be listed individually and presented graphically on individual plots. The PD concentrations will be summarized by actual treatment i.e. dose level, at each planned relative time point and presented graphically on mean plots. Data for placebo subjects will be pooled from all cohorts in Part B for the summaries and presentations. The pre-meal concentrations will be listed for reference and summarized by treatment.

14.4. Mixed Meal PD Parameters

The following PD parameters will be derived, presented individually and summarized by treatment and day of assessment (Days -1, 1 and 14) using absolute measured values only:

- Average pre-meal concentrations for PD biomarkers will be estimated for each subject and each PD sampling day from 3 pre-meal measurements with the removal of outliers as described in the Section 14.2 of the SAP;
- C_{PDmax} (maximum observed plasma concentration value) and T_{PDmax} (Time to Maximum Observed Plasma PD Concentration value);
- AUC_{PDlast} and AUC_{PD4h} (partial areas), calculated using the Linear Trapezoidal rule. The starting point (pre-dose) for y axis will be the average of the three pre-meals and start from zero for the linear trapezoidal rule and the x axis will be put at zero (even though the timepoints were -15, -10 and -5 mins).

14.5. Comparative Analysis for PD Parameters

14.5.1. Evaluation of the Short Term Variability Trends

To evaluate changes in baseline in the absence of drug treatment within short term, the following comparisons will be made using ANOVA model:

- Average pre-meal concentrations on Day 1 (test) vs. average pre-meal concentrations on Day -1 (reference) for all subjects including pooled placebo to evaluate natural short term day to day variability of pre-meal concentrations of PYY and GLP-1 without drug treatment;
- AUC_{PDlast} and AUC_{PD4h} on Day 1 (test) vs. Day -1 (reference) for placebo subjects to evaluate natural short term day to day variability of AUC of PYY and GLP-1 without drug treatment.

14.5.2. Evaluation of the Long Term Variability Trends for Placebo

To evaluate changes in baseline in the absence of drug treatment within long term, the following comparisons will be made using ANOVA model:

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- Average pre-meal concentrations on Day 14 (test) vs. average pre-meal concentrations on Day -1 (reference) for all placebo subjects to evaluate long-term trend in the drift of pre-meal concentrations of PYY and GLP-1 without drug treatment;

- AUC_{PDlast} and AUC_{PD4h} on Day 14 (test) vs. Day -1 (reference) for all placebo subjects to evaluate long-term trend in the drift of AUC of PYY and GLP-1 without drug treatment.

The concentrations will be log-transformed to give the estimated geometric mean ratios (GMRs) and 95% confidence interval for the natural short and long-term variability of the biomarkers before meal.

Intra- and inter-subject variability will be also estimated in the model with subject as a random effect.

The determined variability will be used to put into context any results observed when comparing between treatment groups.

14.5.3. Evaluation of the Effect of BMI

To evaluate the effect of BMI on PD parameters, scatter plots will be presented for each treatment and visit for visual comparison:

- Scatter plots of PD parameters (average pre-meal concentrations, AUC_{PDlast} and AUC_{PD4h}) vs. BMI on Days -1 and 14 by treatment;

- Scatter plots of the change from baseline PD parameters (average pre-meal concentrations, AUC_{PDlast} and AUC_{PD4h}) vs. Day -1 (baseline) BMI by treatment.

14.5.4. Statistical Models for the Comparison of PD Endpoints between Treatment Days and Pre-Treatment Data

The log-transformed PD parameters (average pre-meal concentrations, AUC_{PDlast} and AUC_{PD4h}) will be compared for the subjects on active treatments between Days 1 and 14 of treatment with the data on Day -1 using an ANOVA model, with treatment group including pooled placebo as fixed effect covariates. GMRs, 95% CIs for the GMRs and corresponding p-values will be presented. Intra- and inter-subject variability will be also estimated. The model will include subject as random effect and day as fixed effect. Interaction factor between treatment and day will be included in the model.

The results of the differences, including the GMRS, will be compared with the natural short and long-term variability described in the Section 14.5.

Box plots will be presented for each treatment and visit for visual comparison:

- Box plots for the comparison of PD parameters (average pre-meal concentrations, AUC_{PDlast} and AUC_{PD4h}) on Days -1, 1 and 14 combining all treatments, including placebo.

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14.5.5. Statistical Models for the Comparison of PD Endpoints between Active Treatments and Placebo Controls

The log transformed change from baseline PD parameters (average pre-meal concentrations, AUC_{PDlast} and AUC_{PD4h}) will be compared between each treatment and placebo for each of Day 1 and 14 separately using an ANCOVA model, with treatment group and day as a fixed effect. The model will include subject as a random effect and interaction factor between treatment and day as a fixed effect. PD parameters will be used as change from baseline with PD parameters on Day -1 subtracted as the baseline value. Baseline (Day -1) PD parameter will be used as a covariate in the model.

The models will be supported through graphic presentations:

- Box plots, with the individual data points plotted, for change from baseline PD parameters for Days 1 and 14, with all dose levels combined on the same plot;
- In addition, box plots, with the individual data points plotted, for AUC PD parameters for Days -1, 1 and 14, with all dose levels combined on the same plot.

14.6. PD/Dose Correlation Analysis

The comparison between natural variabilities in biomarker pre-meal concentrations and PD parameters (Section 14.5) and observed differences for active treatments with the pre-treatment results (Section 14.5.3), together with the findings about dose proportionality of pharmacokinetics for GSK3352589 will guide the further analyses.

If the differences between PD data for active treatments will be significantly outside the natural variability for one or both biomarkers and dose of GSK3352589 will be demonstrated to be dose proportional the linear mixed effect model will be applied to evaluate PD/dose correlation. The statistical model is described in the Section 13.6 of the SAP. PD parameters or pre-meal values on Days 1 and 14 will be used as dependent parameters. To allow the use of placebo data in the model the placebo dose will be imputed as 0 for untransformed data analysis and as $1/100^{th}$ of a lowest dose used for log-transformed data analysis.

The graphical presentation of the analysis will include scatter plots with a regression line for the PD parameters vs. dose levels. Data for pooled placebo subjects from all cohorts will be also presented using a value of 0 for dose.

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15. CHANGES FROM PROTOCOL

PK Concentration and PK Parameter populations were defined similar to prior studies.

The PK and PD parameters were further defined compared to protocol. Additional parameters were added to facilitate the analyses.

Additional analyses for the evaluation in pre-meal biomarker concentration and PD parameters post-meal variability were added.

PD/drug exposure and PD/PK exploration were planned as staged optional analyses predicated on the results for preceding comparisons.

Cohort 3, to complete dose escalation, was added in the analyses.

Added analysis of PD results relationship to BMI.

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