TITLE PAGE

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

Title: A Phase I Non-Randomized Multi Cohort, Open Label, Bridging Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of GSK557296 on Healthy Women Volunteers After Single and Repeat Dosing

Compound Number: GSK557296
Effective Date: 20-DEC-2012
Protocol Amendment Number: 02

Subject: Oxytocin Antagonist, Embryo/Blastocyst Implantation

Author: [Redacted]

Revision Chronology:

2012N138928_00 2012-JUL-02 Original
2012N138928_01 2012-SEP-25 Amendment No.: 01: Addition of 50 mg dose level per FDA requested changes and the determination of the pharmacokinetics of a metabolite (GSK2395448)
2012N138928_02 2012-DEC-20 Amendment No.: 02 Addition of a 200 mg single dose per approval by the FDA. Clarification on Cohort 4 based on regulatory feedback.

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SPONSOR SIGNATORY:

[Redacted]

Vice President Academic DPU

Date 20 Dec 2012
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<thead>
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<th>Role</th>
<th>Name</th>
<th>Day Time Phone Number</th>
<th>After-hours Phone/Cell/Pager Number</th>
<th>Fax Number</th>
<th>GSK Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Medical Monitor</td>
<td>M.D.</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>709 Swedeland Rd UW2112 King of Prussia, PA 19406</td>
</tr>
<tr>
<td>Secondary Medical Monitor</td>
<td>M.D.</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>ACCI, Addenbrooke’s Hospital Cambridge, CB2 2GG</td>
</tr>
<tr>
<td>Tertiary Medical Monitor</td>
<td>M.D.</td>
<td>[ ]</td>
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<td>1S245a, GlaxoSmithKline, Gunnels Wood Road, Stevenage</td>
</tr>
</tbody>
</table>

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Regulatory Agency Identifying Number(s): IND Number: 115676
INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

<table>
<thead>
<tr>
<th>Investigator Name:</th>
<th></th>
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<tr>
<td>Investigator Address:</td>
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<tr>
<td>Investigator Phone Number:</td>
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</tr>
<tr>
<td>Investigator Signature</td>
<td>Date</td>
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</tbody>
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<th>Description</th>
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<tbody>
<tr>
<td>Ae</td>
<td>Urinary recovery of unchanged drug</td>
</tr>
<tr>
<td>Ae(0-x)</td>
<td>Urinary recovery of unchanged drug up to fixed nominal time-point x</td>
</tr>
<tr>
<td>Ae(0-∞)</td>
<td>Complete urinary recovery of unchanged drug up to time of last measurable urinary concentration</td>
</tr>
<tr>
<td>Ae(0-τ)</td>
<td>Urinary recovery over a dosing interval</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase (SGPT)</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase (SGOT)</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under concentration-time curve</td>
</tr>
<tr>
<td>AUC(0-∞)</td>
<td>Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time</td>
</tr>
<tr>
<td>%AUCex</td>
<td>Percentage of AUC(0-∞) obtained by extrapolation</td>
</tr>
<tr>
<td>AUC(0-x)</td>
<td>Area under the concentration-time curve from zero (pre-dose) to some fixed nominal time x</td>
</tr>
<tr>
<td>AUC(0-t)</td>
<td>Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments</td>
</tr>
<tr>
<td>AUC(0-τ)</td>
<td>Area under the concentration-time curve over the dosing interval</td>
</tr>
<tr>
<td>β-HCG</td>
<td>Beta-Human Chorionic Gonadotropin</td>
</tr>
<tr>
<td>BA</td>
<td>Bioavailability</td>
</tr>
<tr>
<td>BE</td>
<td>Bioequivalence</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BPM</td>
<td>Beat Per Minute</td>
</tr>
<tr>
<td>BQL</td>
<td>Below the quantification limit</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CIB</td>
<td>Clinical Investigator’s Brochure</td>
</tr>
<tr>
<td>CLR</td>
<td>Renal clearance</td>
</tr>
<tr>
<td>CL</td>
<td>Systemic clearance of parent drug</td>
</tr>
<tr>
<td>CL/F</td>
<td>Apparent clearance following oral dosing</td>
</tr>
<tr>
<td>Cmax</td>
<td>Maximum observed concentration</td>
</tr>
<tr>
<td>Cmin</td>
<td>Minimum observed concentration</td>
</tr>
<tr>
<td>Cτ</td>
<td>Pre-dose (trough) concentration at the end of the dosing interval</td>
</tr>
<tr>
<td>Ct</td>
<td>Last observed quantifiable concentration</td>
</tr>
<tr>
<td>CDMP</td>
<td>Clinical Document Management and Publishing</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CPK</td>
<td>Creatine phosphokinase</td>
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<td>CPMS</td>
<td>Clinical Pharmacokinetics Modelling &amp; Simulation</td>
</tr>
<tr>
<td>CPSR</td>
<td>Clinical Pharmacology Study Report</td>
</tr>
<tr>
<td>CP-RAP</td>
<td>Clinical Pharmacology Reporting and Analysis Plan</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>CRU</td>
<td>Clinical Research Unit</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variance</td>
</tr>
<tr>
<td>DB</td>
<td>Discovery Biometrics</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>DDS</td>
<td>Drug Development Sciences</td>
</tr>
<tr>
<td>DILI</td>
<td>Drug Induced Liver Injury</td>
</tr>
<tr>
<td>DMPK</td>
<td>Drug Metabolism and Pharmacokinetics</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DRE</td>
<td>Disease Related Event</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic data capture</td>
</tr>
<tr>
<td>EISR</td>
<td>Expedited Investigator Safety Report</td>
</tr>
<tr>
<td>Fabs</td>
<td>Absolute bioavailability of drug determined following extravascular and intravascular dosing</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>Frel</td>
<td>Relative bioavailability of drug determined between two formulations of the same drug following similar or different extravascular route of administration</td>
</tr>
<tr>
<td>FTIH</td>
<td>First time in humans</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GCSP</td>
<td>Global Clinical Safety and Pharmacovigilence</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma glutamyltransferase</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
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<td>GLS</td>
<td>Geometric Least-Squares</td>
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<td>GSK</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>hCG</td>
<td>Human chorionic gonadotropin</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>h/hr</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>HWE</td>
<td>Hardy-Weinberg Equilibrium</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>IDSL</td>
<td>Integrated Data Standards Library</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
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<tr>
<td>IP</td>
<td>Investigational Product</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>IU</td>
<td>International Unit</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>IVF</td>
<td>In-vitro fertilization</td>
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<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>λz</td>
<td>Terminal phase rate constant</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>L</td>
<td>Liter</td>
</tr>
<tr>
<td>LFTs</td>
<td>Liver function tests</td>
</tr>
<tr>
<td>ln</td>
<td>Naperian (natural) logarithm</td>
</tr>
<tr>
<td>LOQ</td>
<td>Limit of quantification</td>
</tr>
<tr>
<td>LLQ</td>
<td>Lower limit of quantification</td>
</tr>
<tr>
<td>µg</td>
<td>Microgram</td>
</tr>
<tr>
<td>µL</td>
<td>Microliter</td>
</tr>
<tr>
<td>MAT</td>
<td>Mean absorption time</td>
</tr>
<tr>
<td>MCH</td>
<td>Mean corpuscular hemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>Mean corpuscular hemoglobin concentration</td>
</tr>
<tr>
<td>MCV</td>
<td>Mean corpuscular volume</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>Mg</td>
<td>Milligrams</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
</tr>
<tr>
<td>MRT</td>
<td>Mean residence time</td>
</tr>
<tr>
<td>MSDS</td>
<td>Material Safety Data Sheet</td>
</tr>
<tr>
<td>msec</td>
<td>Milliseconds</td>
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<tr>
<td>NQ</td>
<td>Non-quantifiable concentration measured as below LLQ</td>
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<tr>
<td>PD</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>PGx</td>
<td>Pharmacogenetics</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
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<tr>
<td>PSRI</td>
<td>Periodic Safety Reports for Investigators</td>
</tr>
<tr>
<td>QC</td>
<td>Quality control</td>
</tr>
<tr>
<td>QD</td>
<td>Once daily</td>
</tr>
<tr>
<td>QTcB</td>
<td>QT duration corrected for heart rate by Bazett’s formula</td>
</tr>
<tr>
<td>QTcF</td>
<td>QT duration corrected for heart rate by Fridericia’s formula</td>
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<tr>
<td>RAP</td>
<td>Reporting and Analysis Plan</td>
</tr>
<tr>
<td>RBA</td>
<td>Relative Bioavailability</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cells</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event(s)</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical Analysis Software</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum glutamic-oxaloacetic transaminase</td>
</tr>
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<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SPM</td>
<td>Study Procedures Manual</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected, Unexpected, Serious Adverse drug Reaction</td>
</tr>
<tr>
<td>T</td>
<td>Infusion duration</td>
</tr>
<tr>
<td>t</td>
<td>Time of last observed quantifiable concentration</td>
</tr>
<tr>
<td>t½</td>
<td>Terminal phase half-life</td>
</tr>
<tr>
<td>τ</td>
<td>Dosing interval</td>
</tr>
<tr>
<td>tlag</td>
<td>Lag time before observation of drug concentrations in sampled matrix</td>
</tr>
<tr>
<td>tlast</td>
<td>Time of last quantifiable concentration</td>
</tr>
<tr>
<td>tmax</td>
<td>Time of occurrence of Cmax</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>Vd/F</td>
<td>Apparent volume of distribution after extravascular (e.g., oral) administration</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cells</td>
</tr>
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<td>WGS</td>
<td>Whole genome screen</td>
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**Trademark Information**

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1. **INTRODUCTION**

1.1. **Background**

This study is being conducted to evaluate the pharmacokinetics, safety and tolerability of GSK557296 and its metabolite (GSK2395448) in healthy female volunteers following single and repeat dosing. Previous studies have been conducted with GSK557296 in healthy male volunteers and men with premature ejaculation (See Clinical Investigator Brochure GSK557296 GlaxoSmithKline Document Number: 2012N39040_00).

1.2. **Rationale**

1.2.1. **Study Rationale**

GSK557296 is being studied in women for the indication of enhanced embryo and or blastocyst implantation in women undergoing IVF treatment. This study will be the first dosing experience with this compound in women. There have been two previous studies in men dosed orally with doses ranging from 10 mg to 200 mg. It is important to characterize the pharmacokinetics of GSK557296 in women to determine the most appropriate doses and dosing regimens for future clinical studies. Understanding the pharmacokinetics of GSK557296 in women will also enable more accurate characterization of any exposure-response relationship in future studies.

1.2.2. **Dose Rationale**

In the first time in human (FTiH) clinical study in males, the doses: 10mg, 50mg, 100mg, 150mg and 200 mg were studied as single doses and 30mg, 100mg and 150 mg were studied as once daily, repeat doses for 14 days. GSK557296, as a minitablet formulation, was readily absorbed and eliminated with mean t1/2 values ranging from 3.74 to 5.39 hours. As the doses increased in the single dose portion, greater than dose proportional increases in GSK557296 Cmax, but not AUC were observed. The resultant exposures from the 150mg and 200 mg doses were very similar suggesting a plateau of exposure beyond the 150 mg dose. In the Premature Ejaculation Phase II Study, 50mg and 150 mg tablet formulation doses were studied in otherwise, healthy men. When comparing the exposures from this study to the FTiH study, there was a decrease in exposures with the new formulation.

From preclinical studies, a gender difference in GSK557296 exposure following oral administration in rats was noted. In female rats, the systemic exposure (both Cmax and AUC), was generally greater than double than what was observed in male rats. However, there was no gender difference in systemic exposure when GSK557296 was orally administered to dogs.

In this initial study in women, 10 mg (the lowest dose studied in males) will be administered as a single dose on Day 1 and four times a day (QID) on Days 2-6 to the first cohort of subjects. In a separate subsequent cohort of women, 50 mg will be administered as a single dose on Day 1 and then on a QID schedule on Days 2-6. It is anticipated that we will need to maintain a steady-state dosing regimen in the IVF patients and therefore, greater than once daily dosing regimen will be carried out in the repeat dose portion of this study to better characterize the exposures achieved. There will
be a minimum of six subjects on active drug for each dose cohort. Data obtained from the first two cohorts will be used to simulate exposures for additional cohort(s). A final decision on the dose and schedule selected for the third cohort will be made in consultation with the FDA based on the exposures seen in the 10mg and 50mg groups and modelled exposures for doses ranging up to 150mg. Additional doses may be studied in further cohorts if the pharmacokinetics are extremely different between the genders. A 30% difference in systemic exposure (Cmax and/or AUC) will be considered extremely different and additional dose groups may be investigated to better understand the pharmacokinetics in women. The repeat dosing regimen will be either twice, three or four times a day and will be decided once PK data are available from the first cohorts. Our current expectation based on the T1/2 seen in men is that QID is most likely. In addition we would like to evaluate a single 200 mg dose to investigate the upper limit of oral exposure with the current tablet formulation. As an upper limit of exposure was observed at the 150mg dose in men when compared to a 200mg dose, the same evaluation in women will take place to determine if this threshold still applies.

Dose escalation will proceed once preliminary safety/tolerability and PK data have been reviewed for at least 4 subjects at the previous dose level and will be made by the GSK Study Team and the Investigator. Given that a decision on the dose selected for the third cohort will be made in consultation with the FDA, a pause in the study will be required.

All chosen dose(s) will be appropriate to prevent the projected Cmax and AUC(0-∞) from exceeding 1500 ng/mL and 7500 ng.h/mL, respectively (based on communication with FDA) and will not exceed a maximum daily dose of 900 mg/day per genotoxin limits. The predicted exposures of 10, 50 and 150 mg doses are in Table 1.

### Table 1   Predicted Mean Exposures Following Once Daily (QD) and Four Times a Day (QID) Dosing

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>QD AUC (ng.h/mL)</th>
<th>QD Cmax (ng/mL)</th>
<th>QID AUC (ng.h/mL)</th>
<th>QID Cmax (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>189</td>
<td>88.5</td>
<td>762</td>
<td>106</td>
</tr>
<tr>
<td>50</td>
<td>991</td>
<td>482</td>
<td>4016</td>
<td>567</td>
</tr>
<tr>
<td>150</td>
<td>2738</td>
<td>1367</td>
<td>11023</td>
<td>1584</td>
</tr>
</tbody>
</table>

The dosing regimen for the repeat dose segment (Days 2-6) of doses greater than 50 mg will be chosen based on the PK of the 10 and 50mg doses and the predicted administration schedule that would provide steady-state average concentrations of ~100-200 ng/mL. This range is the current anticipated efficacious concentration for the IVF indication.

### 1.3. Summary of Risk Management

In clinical trials conducted to date in male subjects no laboratory, ECG, or vital sign abnormalities were detected following single and repeat (daily) dosing that would indicate that administration of GSK557296 would constitute a significant safety risk to female subjects. Standard laboratory, EKG, and vital sign monitoring will be conducted at regular intervals to assess for any clinically meaningful changes from baseline.
2. **OBJECTIVE(S)**

2.1. **Primary**

- To characterize the pharmacokinetics of GSK557296 and its metabolite (GSK2395448) following single and repeat oral dosing in healthy female volunteers.
- To assess the safety and tolerability of GSK557296 following single and repeat dosing

3. **ENDPOINT(S)**

3.1. **Primary**

- Pharmacokinetic endpoints will include as data permit:
  - AUC(0-t), AUC(0-τ)
  - AUC(0-inf), as permitted by the data
  - Cmax
  - Tmax
  - Half-life, as permitted by the data

- Safety and tolerability parameters, including adverse event, clinical laboratory, ECG, vital signs, and concurrent medication assessments.

4. **INVESTIGATIONAL PLAN**

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.

4.1. **Study Design/Schematic**

**Cohort 1 and Cohort 2**
Cohort 3

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong> Single Dose</td>
<td>Day 2 Repeat Dose (BID-QID)</td>
<td>Day 3 Repeat Dose (BID-QID)</td>
<td>Day 4 Repeat Dose (BID-QID)</td>
</tr>
<tr>
<td><strong>Day 2</strong> Wash-out</td>
<td>Day 5 Repeat Dose (BID-QID)</td>
<td>Day 6 Repeat Dose (BID-QID)</td>
<td></td>
</tr>
</tbody>
</table>

Cohort 4

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong> Single Dose</td>
<td>Day 2 Repeat Dose (TID-QID)</td>
<td>Day 3 Repeat Dose (TID-QID)</td>
<td>Day 4 Repeat Dose (TID-QID)</td>
</tr>
<tr>
<td><strong>Day 2</strong> Wash-out</td>
<td>Day 5 Repeat Dose (TID-QID)</td>
<td>Day 6 Repeat Dose (TID-QID)</td>
<td>Day 7 Repeat Dose (TID-QID)</td>
</tr>
</tbody>
</table>

Final dosing schedules of to be determined based on prior data.

4.2. Discussion of Design

This is a non-randomized, adaptive design, open label study in healthy female volunteers. Screening will occur within approximately 28 days of the first scheduled dose of study medication. Each subject will participate in one cohort. Prior to dosing, the investigator will review the scheduled assessments to confirm the subject’s suitability for the study including review of study entry criteria and lifestyle restrictions. Independent of the total number of cohorts studied, we will not exceed 48 subjects in this protocol.

The first two cohorts of women will receive 10 mg and 50 mg of GSK557296 QID, respectively, and if the single dose PK approximates what was achieved in men (<30% difference) then next dose level tested for Cohort 3 may be 150mg. A decision on the dose and frequency of dosing (BID, TID or QID) will be made in consultation with the FDA for the third and any subsequent cohorts based on the t1/2, AUC and Cmax observed from prior doses and modeling of proposed exposures for additional cohorts. The decision to add additional dosing sessions beyond the first three will be based on the PK data analyzed from the previous cohorts taking into account the single and repeat dose PK data.

For the first part of the dosing session, eligible subjects will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. On Days 2-6 subjects will receive repeat doses (four times a day for the 10 mg for the first cohort and 50mg for the second cohort and
either two times a day, three times a day or four times a day for the remaining cohort(s): based on the PK of the single 10 mg and 50mg doses) of GSK557296. Sparse PK sampling will occur on study Day 4 and a full PK profile will be obtained on Days 2 and 6. All PK samples (from both the single dose and repeat dose days) will be analyzed after the last PK sample is obtained on Day 7. Subjects will remain in the unit until the morning of Day 7 (after collection of the 24 plasma sample). Subjects will participate in only one dosing regimen.

A break will occur to allow for analysis of the PK data, prior to starting the third dosing session. Decisions on the dose and regimen for cohort 3 will be made in consultation with the FDA and the GSK study team based on the 10mg and 50mg single and repeat dose PK and modeled data for higher doses. The single dose to be administered on Day 1 in Cohort 3 may range from 75 mg to 150 mg.

For the third dosing session, eligible subjects for session three will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. On days 2-6 subjects will receive repeat doses (two, three or four times a day depending on the PK of the single 10 mg and 50mg doses) of GSK557296. Sparse PK sampling will occur on study Day 4 and a full PK profile will be obtained on Days 2 and 6. PK samples from the repeat portion of cohort 3 will be analyzed after the last PK sample is obtained on Day 6. An integration of all available PK data will then be undertaken. Subjects will remain in the unit until the morning of Day 7 (after collection of the 24 hour plasma sample). Subjects will participate in only one dosing regimen.

A break will occur to allow for analysis of the PK data, prior to starting the fourth dosing session. Decisions on the dose and regimen for cohort 4 will be made in consultation with the FDA and the GSK study team based on the 10mg, 50mg, and 150mg single and repeat dose PK and modeled data for higher doses. The single dose to be administered on Day 1 in Cohort 4 will be 200 mg.

For the fourth dosing session, eligible subjects for session four will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. Subjects will remain in the clinic on Day 2 to serve as a washout day. On days 3-7 subjects will receive repeat doses (three or four times a day 150mg doses) of GSK557296. Sparse PK sampling will occur on study Day 5 and a full PK profile will be obtained on Days 3 and 7. PK samples from the repeat portion of cohort 4 will be analyzed after the last PK sample is obtained on Day 8. An integration of all available PK data will then be undertaken. Subjects will remain in the unit until the morning of Day 8 (after collection of the 24 hour plasma sample). Subjects will participate in only one dosing regimen.

A follow-up visit will be conducted 7-14 days after administration of the last dose of study medication.

Additional cohorts may be added if there is a significant discrepancy between predicted and actual exposures.

The total duration of study could be approximately 15 weeks.
4.3. Treatment Assignment

Subjects will be assigned to a fixed treatment regimen sequence in accordance with the planned treatment schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software.

A description of each regimen is provided in the table below:

- **Treatment A:** GSK557296 10mg single dose on Day 1 followed by repeat dosing (4 times a day) on Days 2-6.
- **Treatment B:** GSK557296 50mg as a single dose on Day 1 followed by repeat nominal dosing of the same dose (4 times a day) on Days 2-6.
- **Treatment C:** GSK557296 dose and schedule to be determined in consultation with FDA. Single dose on Day 1 followed by repeat nominal dosing of the same dose (either 2, 3 or 4 times a day based on half life of 10mg and 50mg doses and modeling of exposures) on days 2-6.

Adaptive Design (additional arms and cohorts may be added depending on the PK profiles of treatment groups A, B and C):

- **Treatment D:** GSK557296 200 mg as a single dose on Day 1 followed by repeat nominal dosing of 150mg (3 or 4 times a day based on half-life demonstrated in treatment A, B and C) on Days 3-7.

4.4. Investigational Product and Other Study Treatment Dosage/Administration

<table>
<thead>
<tr>
<th>Study Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product name:</strong></td>
</tr>
<tr>
<td><strong>Dosage form:</strong></td>
</tr>
<tr>
<td><strong>Unit dose strength(s)/Dosage level(s):</strong></td>
</tr>
<tr>
<td><strong>Route/Administration/Duration:</strong></td>
</tr>
<tr>
<td><strong>Physical description:</strong></td>
</tr>
<tr>
<td><strong>Manufacturer/source of procurement:</strong></td>
</tr>
</tbody>
</table>

4.5. Dose Adjustment/Stopping Criteria

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum daily dose and/or (predicted) maximum/cumulative exposure will not exceed 200 mg/day, 1500 ng/ml Cmax, or 7500 ng.h/ml in the first two cohorts. The FDA has agreed to allow an additional cohort to be dosed at 150mg BID, and to review data in advance of dosing at 150mg QID, which has the potential to exceed the previously agreed
exposure limits. The decision to proceed to subsequent dose levels of GSK557296, will be made based on safety, tolerability and preliminary pharmacokinetic data obtained in at least 4 subjects at the prior dose level. The actual doses to be administered may be adjusted based on safety, tolerability and preliminary pharmacokinetic data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate pharmacokinetic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.

4.5.1. Dose Adjustment/Stopping Safety Criteria

4.5.1.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Study treatment will be stopped for a subject if the following liver chemistry stopping criteria is met:

- ALT ≥ 3xULN

Refer to Section 13, Liver Chemistry Follow-up Procedures, for details of the required assessments if a subject meets the above criteria.

4.5.1.2. QTc Withdrawal Criteria

A subject that meets either criteria below will be withdrawn from the study. The QT correction formula used to determine discontinuation should be the same one used throughout the study.

- QTcF > 500 msec, OR
- Change from baseline: QTc >60 ms

Withdrawal decisions are to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period (approximately 30 minutes), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.
### 4.6. Time and Events Table

#### Cohorts 1-3

<table>
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<tr>
<th>Day:</th>
<th>Screening</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to Unit</td>
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<td>Serum ß-hCG (women)</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Notes:**
- X indicates the day the event occurs.
- X^1 indicates the event occurs on the day before the screening.
- X^2 indicates the event occurs on the day before the day of the 12-lead ECG/Vital Signs.
- X^3 indicates the event occurs on the day before the day of the PK blood sample.
<table>
<thead>
<tr>
<th>Day</th>
<th>Screening</th>
<th>-1</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</tbody>
</table>

1. 12 lead ECG and Vital signs assessments will be taken predose and 0.5 hours post dose on Day 1 then approximately 0.5 hours post dose on days 3 and 6 to approximate the time of Cmax.

2. Subjects will be fasted at least 8 hours prior to dosing. Subjects will receive lunch 4 hours after receiving the first dose of study medication.

3. A full PK profile will be obtained on Day 1, 2, and 6 and trough samples on Day 4. For Day 1 PK blood samples will be taken at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dose. PK blood samples on Days 2 and 6 will be obtained at the following timepoints: pre-dose, 0.5, 2, 4, (before the next daily dose) 6, 6.5, 8, (before the next daily dose) 12, 12.5, 16, (before the next daily dose) 18, 18.5, 20, and 24 hours. PK blood samples will be obtained at pre-dose (first dose) on Day 4.
### Cohort 4

<table>
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</table>
1. 12 lead ECG and Vital signs assessments will be taken predose and 0.5 hours post dose on Day 1 then approximately 0.5 hours post dose on days 3 and 6 to approximate the time of Cmax.

2. Subjects will be fasted at least 8 hours prior to dosing. Subjects will receive lunch 4 hours after receiving the first dose of study medication.

3. If TID occurs the following pk samples will be taken: A full PK profile will be obtained on Day 1, 3, and 7 and trough samples on Day 5. For Day 1 PK blood samples will be taken at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dose. PK blood samples on Days 3 and 7 will be obtained at the following timepoints: pre-dose, 0.5, 2, 4, 6, (before the next daily dose) 8, 8.5, 10, 12, (before the next daily dose) 16, 16.5, 18, 20, and 24 hours. PK blood samples will be obtained at pre-dose (first dose) on Day 5.

If QID occurs the following pk samples will be taken: A full PK profile will be obtained on Day 1, 3, and 7 and trough samples on Day 5. For Day 1 PK blood samples will be taken at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dose. PK blood samples on Days 3 and 7 will be obtained at the following timepoints: pre-dose, 0.5, 2, 4, (before the next daily dose) 6, 6.5, 8, (before the next daily dose) 12, 12.5, 16, (before the next daily dose) 18, 18.5, 20, and 24 hours. PK blood samples will be obtained at pre-dose (first dose) on Day 5. Pharmacokinetic sampling may be adjusted throughout the study based on newly available date to ensure appropriate monitoring.

<table>
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</table>
5. **STUDY POPULATION**

5.1. **Number of Subjects**

Approximately 12 subjects will be enrolled in each dosing session such that approximately 9 subjects complete dosing and critical assessments in each session.

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

If all 4 dosing sessions are utilized 48 subjects will be enrolled such that 36 subjects complete the study.

5.2. **Eligibility Criteria**

5.2.1. **Inclusion Criteria**

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Clinical Investigator’s Brochure for GSK557296 GlaxoSmithKline Document Number 2012N39040_00.

Deviations from inclusion 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.

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

1. ALT, alkaline phosphatase and bilirubin $\leq 1.5\times$ULN (isolated bilirubin $>1.5\times$ULN is acceptable if bilirubin is fractionated and direct bilirubin $<35\%$).
2. Single or QTcF $< 450$ msec; or QTc $< 480$ msec in subjects with Bundle Branch Block.
3. 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. Female between 18 and 45 years of age inclusive, at the time of signing the informed consent.
4. A female subject is eligible to participate if she is of:
   - Child-bearing potential and is abstinent\(^1\) or agrees to use one of the contraception methods listed in Section 8.1 for a minimum of 28 days prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until 48 hours post last dose.

5. Body weight $\geq 50$ kg and BMI within the range 19-29.9 kg/m\(^2\) (inclusive).

5.2.2. Exclusion Criteria

Deviations from 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.

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

1. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result at screening or within 3 months of screening
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. A positive pre-study drug/alcohol screen.
4. A positive test for HIV antibody.
5. History of regular alcohol consumption within 6 months of the study defined as:
   - an average weekly intake of or $>7$ drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 ml) of beer, 5 ounces (150 ml) of wine or 1.5 ounces (45 ml) of 80 proof distilled spirits.
6. 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).
7. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
8. Unable to refrain from the use of prescription or non-prescription drugs, with the exception of Oral contraceptives, including vitamins, herbal and dietary supplements (including St John’s Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

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\(^1\) Abstinence from penile-vaginal intercourse must be consistent with the preferred and usual lifestyle of the subject.
9. History of sensitivity to any of the study medications, 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.

10. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period.

11. Pregnant females as determined by positive serum hCG test at screening, Day -1 or Day 8 or prior to dosing.

12. Lactating females.

13. Unwillingness or inability to follow the procedures outlined in the protocol.

14. Subject is mentally or legally incapacitated.

15. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening.

16. Unable to refrain from consumption of red wine, seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days prior to the first dose of study medication.

5.3. Screen and Baseline Failures

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to GSK.
6. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

6.1. Sample Size Considerations

Approximately 12 subjects will be enrolled in each dosing session such that approximately 9 subjects complete dosing and critical assessments in each session.

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

If all 4 dosing sessions are utilized 48 subjects will be enrolled such that 36 subjects complete the study.

6.1.1. Sample Size Assumptions

Sample size is based on feasibility. No formal power calculations were performed as no formal hypothesis testing is to be carried out. In terms of precision, with nine subjects providing data on each dose, and assuming the estimated %CV values from the clinical study report for OTB109039 (the same molecule, in the healthy male volunteer dose-escalation setting) are good estimates of the variability to be observed in this study, then the halfwidth of the 95% Confidence Interval for AUC(0-t) will be within 31% of the estimated mean value.

6.1.2. Sample Size Re-estimation

No sample size re-estimation will be performed.

6.2. Data Analysis Considerations

Any subject who completes at least one session will be included in the evaluation of safety and tolerability. Subjects who receive at least one active dose of GSK557296 and for whom all pharmacokinetic specimens have been collected (for the study session in which that dose was administered) will be considered as being evaluable for assessing the preliminary pharmacokinetics of GSK557296.

6.2.1. Interim Analysis

There will be no formal interim analysis between the 10mg and 50 mg doses in this study. A dose-escalation team will meet to review the observed profiles in each cohort, prior to making a decision about whether to escalate or otherwise change the regimen.

However, there will be a formal interim PK analysis, of GSK557296 PK in healthy women volunteers following both the 10 and 50mg dose groups in addition to a safety review. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t), AUC(0-τ) and AUC(0-∞)], and apparent terminal phase half-life (t1/2). The plasma concentration-time data and the pharmacokinetic parameter data will be summarized descriptively.
AUC(0-∞) or AUC(0-τ) and Cmax following single and repeat doses may be used for assessment of dose proportionality. With this data, PK modeling will be done to predict the exposures of both single and repeat doses of 150mg. Several regimens of the 150mg repeat dose will be simulated. The observed PK data and the safety data from the 10 and 50mg dose groups and the 150mg simulations will be presented to the FDA for consultation prior to dosing Cohort 3.

There will be no statistical stopping rule – decisions to stop or continue the study will be based on safety/tolerability & PK profiles and consultation with the FDA.

A formal PK interim analysis and safety review may also be conducted following the third cohort (which may be a 150mg dose group).

Responsibilities for the interim analysis will be the same as for the final analyses, as described below. The PK modeling, described above, will be performed by the Clinical Pharmacology Modeling and Simulation department within GlaxoSmithKline. Final Analyses

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

6.2.1.1. Safety Analyses

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

6.2.1.2. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation department within GlaxoSmithKline. Plasma (compound number) concentration-time data will be analyzed by non-compartmental methods with the most current version of WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t), AUC(0-τ) and AUC(0-∞)], and apparent terminal phase half-life (t1/2). AUC(0-∞) or AUC(0-τ) and Cmax following single and repeat doses may be used for assessment of dose proportionality. Trough concentration (Cτ) samples collected on the specified days may be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, Quantitative Sciences, GlaxoSmithKline.
Tmax of GSK557296 will be summarized using appropriate descriptive statistics. If data permit, an appropriate nonparametric test for differences in Tmax by dose and/or day will be carried out.

The focus of the statistical analysis will be to estimate the effect of repeat dosing relative to single dosing on the pharmacokinetics of GSK557296. All pharmacokinetic endpoints including AUC and Cmax, where data permit, will be descriptively summarized by dose and day.

Following loge-transformation, AUC(0-t) and Cmax of GSK557296 will be separately analyzed using a mixed effects model with fixed effect terms for dose, day, and dose-by-day interaction. Subject will be treated as a random effect in the model. Point estimates and their associated 90% confidence intervals will be constructed for the differences, Day 6-Day 1. The point estimates and their associated 90% confidence intervals will then be back-transformed to provide point estimates and 90% confidence intervals for the ratios, Day6:Day1.

Dose proportionality may be explored, if appropriate. An assessment of dose proportionality will be made on AUC and Cmax using the power model, fitting terms for dose as a fixed effect and subject as a random effect. AUC, Cmax, and dose, will be loge-transformed prior to analysis. An estimate of slope (with corresponding 90% CI) will be provided as a measure of potential dose proportionality. Estimates of within-subject and model based pooled between-subject variability estimates will be computed for AUC and Cmax of GSK557296 for use in future studies.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model.

Plots of trough concentration data from Days 2-6 and Days 3-7 will be produced for informal assessment of achievement of steady state. For both parts of the study, descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum, and CVb%) will be calculated for all pharmacokinetic endpoints by dose. In addition, for AUC(0-tau), AUC(0-∞), Cmax, and as data permit, T1/2, geometric means (and corresponding 95% confidence intervals) will be constructed.
7. STUDY ASSESSMENTS AND PROCEDURES

This section lists the parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 4.6). Detailed procedures for obtaining each assessment are provided in the Study Procedures Manual (SPM). Whenever vitals 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 and pharmacokinetic 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 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 IRB/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 over the duration of the study, including any extra assessments that may be required.

7.1. Demographic/Medical History Assessments

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

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

7.2. Safety

Planned timepoints for all safety assessments are listed in the Time and Events Table (Section 4.6). 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.

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).

Vital Signs

- Vital sign measurements will include systolic and diastolic blood pressure and pulse rate.
Electrocardiogram (ECG)

- Single 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 4.5.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary. Repeat 12-lead ECGs may be obtained and the average of the 2 readings will be utilized.

Clinical Laboratory Assessments

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

### Hematology

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### Clinical Chemistry

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<td>Chloride</td>
<td>ALT (SGPT)</td>
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<td>GGT</td>
<td>Albumin</td>
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<tr>
<td>Sodium</td>
<td>Calcium</td>
<td>Alkaline phosphatase</td>
<td>Total Protein</td>
</tr>
</tbody>
</table>

### Routine Urinalysis

- Specific gravity
- pH, glucose, protein, blood and ketones by dipstick
- Microscopic examination (if blood or protein is abnormal)

### Other screening 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).
- Urine Cotinine

7.3. Pregnancy

7.3.1. Time period for collecting pregnancy information

All pregnancies in female subjects will be collected after the start of dosing and until 48 hours post-last dose.
7.3.2. **Action to be taken if pregnancy occurs**

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

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study medication.

7.4. **Pharmacokinetics**

7.4.1. **Blood Sample Collection**

Blood samples for pharmacokinetic analysis of GSK557296 and its metabolite, GSK2395448, will be collected at the time points indicated in Section 4.6, Time and Events Table. 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 Procedures Manual (SPM).

7.4.2. **Sample Analysis**

Plasma analysis will be performed under the management of Bioanalytical Sciences and Toxicokinetics, PTS DMPK, GlaxoSmithKline. Concentrations of GSK557296 and its metabolite, GSK2395448, will be determined in plasma samples using a validated analytical methodology. Raw data will be stored in the GLP Archives, GlaxoSmithKline. Once the plasma has been analyzed for GSK557296 and its metabolite, GSK2395448, any remaining plasma may be analyzed qualitatively for other circulating metabolites and the results reported under a separate DMPK protocol.

7.5. **Pharmacogenetic Research**

Information regarding pharmacogenetic (PGx) research is included in Appendix 2.
8. LIFESTYLE AND/OR DIETARY RESTRICTIONS

8.1. Contraception Requirements

8.1.1. Female Subjects

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%.

**Abstinence**

Abstinence from penile-vaginal intercourse must be 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.

**Contraceptive Methods with a Failure Rate of < 1%**

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of etonogestrel or levonorgestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records.
- Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, cream or suppository).
- Male condom combined with a vaginal spermicide (foam, gel, cream or suppository)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

8.2. Meals and Dietary Restrictions

Cohorts 1-3: Days 1 and 6
Subjects will be fasted at least 8 hours prior to dosing on the first single dose day (Day 1) and last dosing day (Day 6) and will continue to fast for at least 4 hours post-dose. Additional restrictions are detailed below.

- Soft drinks without caffeine and fruit juices (except grapefruit juice) may be consumed ad libitum beginning 4 hours after dosing
- Consumption of products containing grapefruit will not be permitted within 7 days prior to the administration of study medication until collection of the final pharmacokinetic blood sample
- Subjects must fast from all food and drink (except water) for at least 4 hours prior to any clinical laboratory evaluations
- On Day 1, Lunch, dinner and snack will be provided as follows:
  - Lunch will be provided at approximately 4 hours after the first AM dosing
  - A Snack may be provided at approximately 7 hours after the first AM dosing
  - Dinner will be provided at approximately 10 hours after the first AM dosing
  - An evening snack will be permitted up until 22:00

Water may be consumed ad libitum beginning 2 hours after dosing (with the exception of the 240 mL water used for study drug administration)

**Days 2-5**

- Breakfast, will be provided as follows (Lunch, Dinner and snacks will be provided as above):
  - Breakfast will be provided at approximately 30 minutes prior to AM dosing. The meal should be completely consumed within 20 minutes or less. Administration of the study medication should occur approximately 30 minutes after the start of breakfast.

**Cohort 4 Days 1 and 7**

Subjects will be fasted at least 8 hours prior to dosing on the first single dose day (Day 1) and last dosing day (Day 7) and will continue to fast for at least 4 hours post-dose. Additional restrictions are detailed below.

- Soft drinks without caffeine and fruit juices (except grapefruit juice) may be consumed ad libitum beginning 4 hours after dosing
- Consumption of products containing grapefruit will not be permitted within 7 days prior to the administration of study medication until collection of the final pharmacokinetic blood sample
- Subjects must fast from all food and drink (except water) for at least 4 hours prior to any clinical laboratory evaluations
- On Day 1, Lunch, dinner and snack will be provided as follows:
  - Lunch will be provided at approximately 4 hours after the first AM dosing
• A Snack may be provided at approximately 7 hours after the first AM dosing
• Dinner will be provided at approximately 10 hours after the first AM dosing
• An evening snack will be permitted up until 22:00

Water may be consumed *ad libitum* beginning 2 hours after dosing (with the exception of the 240 mL water used for study drug administration)

**Days 3-6**

• Breakfast, will be provided as follows (Lunch, Dinner and snacks will be provided as above):
  • Breakfast will be provided at approximately 30 minutes prior to AM dosing. The meal should be completely consumed within 20 minutes or less. Administration of the study medication should occur approximately 30 minutes after the start of breakfast.

Water may be consumed *ad libitum* beginning 2 hours after dosing (with the exception of the 240 mL water used for study drug administration).

### 8.3. Caffeine, Alcohol, and Tobacco

• During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, chocolate) for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during each session.

• During each dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during each session.

### 8.4. Activity

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).
9. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

9.1. Permitted Medications

Acetaminophen, at doses of ≤ 2 grams/day is permitted for use any time during the study. Oral Contraceptives as listed in Section 8.1.1 will be permitted during the study.

9.2. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

10. COMPLETION OR EARLY WITHDRAWAL OF SUBJECTS

10.1. Subject 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.

10.2. Subject Withdrawal Criteria

Refer to Section 4.5 for dose adjustment/stoping criteria based on safety/PK criteria.

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons.

10.3. Subject Withdrawal Procedures

10.3.1. Subject Withdrawal from Study

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue the subject from participation in the study for any reason. In the event that a subject withdraws or is withdrawn from the study, the investigator must make every effort to perform the following evaluations: 12 lead ECG, heart rate and blood pressure, haematology biochemistry, urinalysis, and physical examination. These data will be recorded, as they compromise an essential evaluation that needs to be done prior to discharging any subject from the study.

In the event that a subject is prematurely discontinued from the study at any time due to an AE or SAE, the procedures stated in Section 12 (“AE’s and SAE’s) must be followed. Subjects that withdraw from the study may be replaced at the investigators discretion after consultation with the sponsor.

10.4. 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.
11. STUDY TREATMENT

Study treatment dosage and administration details are listed in Section 4.4.

11.1. Blinding

This will be an open-label study.

11.2. Packaging and Labeling

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

11.3. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

Study treatment must be dispensed or administered according to procedures described herein. 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. Study treatment is to be stored at 2-8°C. Maintenance of a temperature log (manual or automated) is required.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance. The investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain study treatment accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from and returned to GSK and the amount supplied and/or administered to and/or returned by subjects. The required accountability unit for this study will be bottle/tablet/vial/etc. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study treatment are listed in the SPM.

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. 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.

11.4. Assessment of Compliance

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When subjects are dosed at the study site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose
administered in the clinic will be recorded in the source documents. The dose of study
treatment and study participant identification will be confirmed at the time of dosing by a
member of the study site staff other than the person administering the study treatment.
Study site personnel will examine each subject’s mouth to ensure that the study treatment
was ingested.

11.5. Treatment of Study Treatment Overdose

GSK does not recommend specific treatment for an overdose. The investigator will use
clinical judgment to treat any overdose.
12. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of Study Treatment and until the follow-up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g. study treatment, 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 Section 12.6.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 would promptly notify GSK.

12.1. Definition of Adverse Events

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 meeting the definition of an AE 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 that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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.

### 12.2. Definition of Serious Adverse Events

If an event is not an AE per Section 12.1, then it can not 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).

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- 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.

- 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.

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

f. Medical or scientific 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 and 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.

12.3. 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?”

12.4. Recording of AEs and SAEs

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 appropriate data collection tool.

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 data collection tool. However, 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.
12.5. Evaluating AEs and SAEs

12.5.1. 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.

12.5.2. 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.

12.6. 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 AEs and 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.

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 data collection tool. The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.7. Prompt Reporting of SAEs to GSK

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to GSK within 24 hours. Any follow-up information on a previously reported SAE will also be reported to GSK within 24 hours.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the appropriate data collection tool. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 12.5.2, Assessment of Causality.

The 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 GSK Medical Monitor or protocol contact. Then the 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 participant 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 their GSK protocol contact by telephone.

GSK contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.8. Regulatory Reporting Requirements For SAEs

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

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

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

Refer to the diagram in Appendix 1 for a visual presentation of the procedures listed below.

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 4.5.1.1:

- Immediately withdraw the subject from study treatment
- Notify the GSK medical monitor within 24 hours of learning of the abnormality to confirm the subject’s study treatment cessation and follow-up.
- Complete the “Safety Follow-Up Procedures” listed below.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 12.2), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up withdraw the subject from the study unless further safety follow up is required or GSK Medical Governance approval of drug restart is granted.
- Do not restart investigational product unless written approval is granted by GSK Medical Governance, whereupon the subject continues in the study after completion of the liver chemistry monitoring.

Safety Follow-Up Procedures for subjects with ALT $\geq$ 3xULN:

- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for subjects with ALT $\geq$3xULN and total bilirubin $\geq$2xULN (>35% direct bilirubin); or ALT $\geq$ 3xULN and INR$^2 > 1.5$:

- This event is considered an SAE (see Section 12.2). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

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$^2$ INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants.
In addition, for all subjects with ALT $\geq 3\times$ULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody.
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
  - Hepatitis C RNA.
  - Cytomegalovirus IgM antibody.
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  - Hepatitis E IgM antibody.

- Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject’s best approximation. If the date/time of the last dose can not be approximated OR a PK sample can not be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are included in the SPM.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin $\geq 2\times$ULN.

- Assess eosinophilia

- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE CRF.

- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.

- Record alcohol use on the Liver Events CRF.

The following are required for subjects with ALT $\geq 3\times$ULN and bilirubin $\geq 2\times$ULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.

- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).

- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.
14. STUDY CONDUCT CONSIDERATIONS

14.1. 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.

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

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

The study will be conducted in accordance with all applicable regulatory requirements.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent (and any amendments) to be obtained for each subject before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in Appendix 1 unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.
14.3. Quality Control (Study Monitoring)

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

GSK will monitor the study 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

14.4. 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.

14.5. Study and Site Closure

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

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

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform investigators or the head of the medical institution (where applicable) and the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.
14.6. **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 by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

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

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

14.7. **Provision of Study Results to Investigators, Posting of Information on Publicly 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. Investigators 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 investigators with the full summary of the study results. Investigators are encouraged to share the summary results with the study subjects, as appropriate.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject’s last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.
14.8. Data Management

For this study subject data will be entered into GSK defined electronic case report forms (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 MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.
15. REFERENCES

GlaxoSmithKline Clinical Investigator Brochure for GSK557296. GSK Document Number: 2012N39040_00.

James LP. 2009. Pharmacokinetics of Acetaminophen - Protein Adducts ... Liver Failure. Drug Metab Disp, 37:1779-1784.

### APPENDICES

#### Appendix 1: Liver Safety Algorithms

**Decision Flowchart:**

- **ALT ≥ 3xULN?**
  - **No:** Continue investigational product (IP)
  - **Yes:**
    - **Bilirubin ≥ 2xULN (>35% direct) or INR > 1.5 (if measured)*?**
      - **No:**
        - Instruct subject to **stop IP**
        - Notify GSK within 24 hrs
        - Obtain weekly liver chemistries until resolved, stabilized or returned to baseline values
        - Perform **liver event follow up assessments** (serology, PK sample, etc as in protocol)
        - Complete liver event CRF
      - **Yes:**
        - Instruct subject to **stop IP**
        - Notify GSK and arrange clinical followup within 24 hrs
        - Perform **liver event follow up assessments** (serology, PK sample etc as in protocol)
        - **Report as SAE** (excl. hepatic impairment or cirrhosis studies); complete SAE & liver event CRF + liver imaging and biopsy CRFs (if these tests are performed)
        - Obtain twice weekly liver chemistries until resolved, stabilized or returned to baseline values
        - Consultation with hepatologist/specialist recommended
        - **Withdraw subject from study after liver chemistry monitoring complete (unless protocol offers option to restart drug).**

*INR threshold does not apply to subjects receiving anticoagulants.*
Appendix 2: Pharmacogenetic Research

Pharmacogenetics - Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic composition (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Collection of whole blood samples, even when no a priori hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation response to GSK557296.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to GSK557296. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with GSK557296 that may be attributable to genetic variations of subjects, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Pharmacokinetics
- Safety and/or tolerability

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any [blood/saliva] being taken for PGx research. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Study Population

Any subject who is enrolled in the clinical study can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study.

Study Assessments and Procedures

Blood or saliva samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.
In addition to any blood samples taken for the clinical study, a whole blood sample (~10 ml) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

No additional whole blood samples will be necessary for the PGx analysis. Saliva (2 ml) is collected into the DNA self-collection kit. A single sample will be taken but can be duplicated if the first sample is unusable. It is recommended that the saliva sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

The PGx sample is labelled (or “coded”) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood/saliva sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

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

The need to conduct PGx analysis may be identified after a study (or a set of studies) of GSK557296 has been completed and the clinical study data reviewed.

In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to GSK557296.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

**Subject Withdrawal from Study**

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

- Retain the sample for PGx research
- Destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK, and maintain the documentation in the site study records.
**Screen and Baseline Failures**

If a blood sample for PGx research has been collected and it is then determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

**Pharmacogenetics Analyses**

The need to conduct PGx analysis may be identified after a study (or set of studies) has been completed. For this reason, samples may be kept for up to 15 years after the last subject completes the study. GSK may destroy the samples sooner.

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

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, or drug transporters which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to [insert the name of the study treatment]. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

**Provision of Study Results and Confidentiality of Subject’s PGx Data**

GSK may summarize the PGx research results in the clinical study report separately or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject’s medical care at the time of the study, unless required by law. This is because the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.
Appendix 3: Protocol Amendment Changes

AMENDMENT 1

Where the Amendment Applies:

All sites

Summary of Amendment Changes with Rationale

Based on feedback from the FDA changes were made to the study design. An interim analysis is now planned between cohorts 2 and 3. An additional dose of 50 mg was added as a second cohort.

List of Specific Changes

Section 1.2.2 Dose Rationale

WAS:

In the first time in human (FTiH) clinical study in males, the doses: 10mg, 50mg, 100mg, 150mg and 200 mg were studied as single doses and 30mg, 100mg and 150 mg were studied as once daily, repeat doses for 14 days. GSK557296, as a minitablet formulation, was readily absorbed and eliminated with mean t1/2 values ranging from 3.74 to 5.39 hours. As the doses increased in the single dose portion, greater than dose proportional increases in GSK557296 Cmax, but not AUC were observed. The resultant exposures from the 150mg and 200 mg doses were very similar suggesting a plateau of exposure beyond the 150 mg dose. In the Premature Ejaculation Phase II Study, 50mg and 150 mg tablet formulation doses were studied in otherwise, healthy men. When comparing the exposures from this study to the FTiH study, there was a decrease in exposures with the new formulation.

From preclinical studies, a gender difference in GSK557296 exposure following oral administration in rats was noted. In female rats, the systemic exposure (both Cmax and AUC), was generally greater than double than what was observed in male rats. However, there was no gender difference in systemic exposure when GSK557296 was orally administered to dogs.

In this initial study in women, 10 mg (the lowest dose studied in males) will be administered as a single dose on Day 1 and four times a day (QID) on Days 2-6 to the first cohort of subjects. It is anticipated that we will need to maintain a steady-state dosing regimen in the IVF patients and therefore, greater than once daily dosing regimen will be carried out in the repeat dose portion of this study to better characterize the exposures achieved. There will be a minimum of six subjects on active drug for each dose cohort. Data obtained from the first cohort will be used to simulate exposures for the second cohort. If exposures from the single and repeat dosing approximate (within 30% of prior Cmax and AUC) that which was previously seen in men then our next cohort studied will be 150mg. A lower dose may be explored if the exposures in women are extremely different (>30% of prior Cmax and AUC) from that previously seen in men.
or a safety signal is identified. The second cohort will be conducted with an initial single
doze of 150mg with a full PK assessment and one week washout prior to repeat dosing.
Exposures observed from a single dose of 150mg will be used to simulate multi-dosing
(BID-QID) exposures, for 5 days. Additional doses may be studied in further cohorts if
the pharmacokinetics are extremely different between the genders. A 30% difference in
systemic exposure (Cmax and/or AUC) will be considered extremely different and
additional dose groups may be investigated to better understand the pharmacokinetics in
women. The repeat dosing regimen will be either twice, three or four times a day and
will be decided once PK data are available. Our current expectation based on the T1/2
seen in men is that QID is most likely.

Dose escalation will proceed once preliminary safety/tolerability and PK data have been
reviewed for at least 4 subjects at the previous dose level and will be made by the GSK
Study Team and the Investigator.

All chosen dose(s) will be appropriate to prevent the projected Cmax and AUC(0-∞)
from exceeding 5440 ng/mL and 40,800 ng.h/mL, respectively (NOAEL exposures from
the 14 day safety assessment study in female rat at 100 mg/kg) and will not exceed a
maximum daily dose of 900 mg/day per genotoxin limits. If the PK in females is similar
to that in males, a single 10 mg dose would result in a mean Cmax value of
approximately 88.5 ng/ml and a mean AUC(0-∞) value of 189 ng.h/mL. These
exposures are 60-and 100-fold lower than the NOAEL Cmax and AUC exposures,
respectively. Additionally, if the females and males have similar PK, simulations of the
150 mg dose administered QID resulted in steady state Cmax and AUC(0-∞) exposures
of approximately 1584 ng/mL and 11,024 ng.h/mL, respectively. These values are 3.4
and 3.7-fold lower than the NOAEL exposures.

The predicted exposures of 10, 50 and 150 mg doses are in Table 1.

Table 1. Predicted Mean Exposures Following Once Daily (QD) and Four Times a Day
(QID) Dosing

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>QD</th>
<th>QID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC (ng.h/mL)</td>
<td>Cmax (ng/mL)</td>
</tr>
<tr>
<td>10</td>
<td>189</td>
<td>88.5</td>
</tr>
<tr>
<td>50</td>
<td>991</td>
<td>482</td>
</tr>
<tr>
<td>150</td>
<td>2738</td>
<td>1367</td>
</tr>
</tbody>
</table>

The dosing regimen for the repeat dose segment (Days 2-6) of doses greater than 10 mg
will be chosen based on the PK of the 10 mg dose and the predicted administration
schedule that would provide steady-state average concentrations of ~100-200 ng/mL.
This range is the current anticipated efficacious concentration for the IVF indication.
IS:

In the first time in human (FTiH) clinical study in males, the doses: 10mg, 50mg, 100mg, 150mg and 200 mg were studied as single doses and 30mg, 100mg and 150 mg were studied as once daily, repeat doses for 14 days. GSK557296, as a minitablet formulation, was readily absorbed and eliminated with mean t1/2 values ranging from 3.74 to 5.39 hours. As the doses increased in the single dose portion, greater than dose proportional increases in GSK557296 Cmax, but not AUC were observed. The resultant exposures from the 150mg and 200 mg doses were very similar suggesting a plateau of exposure beyond the 150 mg dose. In the Premature Ejaculation Phase II Study, 50mg and 150 mg tablet formulation doses were studied in otherwise, healthy men. When comparing the exposures from this study to the FTiH study, there was a decrease in exposures with the new formulation.

From preclinical studies, a gender difference in GSK557296 exposure following oral administration in rats was noted. In female rats, the systemic exposure (both Cmax and AUC), was generally greater than double than what was observed in male rats. However, there was no gender difference in systemic exposure when GSK557296 was orally administered to dogs.

In this initial study in women, 10 mg (the lowest dose studied in males) will be administered as a single dose on Day 1 and four times a day (QID) on Days 2-6 to the first cohort of subjects. In a separate subsequent cohort of women, 50 mg will be administered as a single dose on Day 1 and then on a QID schedule on Days 2-6. It is anticipated that we will need to maintain a steady-state dosing regimen in the IVF patients and therefore, greater than once daily dosing regimen will be carried out in the repeat dose portion of this study to better characterize the exposures achieved. There will be a minimum of six subjects on active drug for each dose cohort. Data obtained from the first two cohorts will be used to simulate exposures for additional cohort(s). A final decision on the dose and schedule selected for the third cohort will be made in consultation with the FDA based on the exposures seen in the 10mg and 50mg groups and modelled exposures for doses ranging up to 150mg. Additional doses may be studied in further cohorts if the pharmacokinetics are extremely different between the genders. A 30% difference in systemic exposure (Cmax and/or AUC) will be considered extremely different and additional dose groups may be investigated to better understand the pharmacokinetics in women. The repeat dosing regimen will be either twice, three or four times a day and will be decided once PK data are available from the first cohorts. Our current expectation based on the T1/2 seen in men is that QID is most likely.

Dose escalation will proceed once preliminary safety/tolerability and PK data have been reviewed for at least 4 subjects at the previous dose level and will be made by the GSK Study Team and the Investigator. Given that a decision on the dose selected for the third cohort will be made in consultation with the FDA, a pause in the study will be required.

All chosen dose(s) will be appropriate to prevent the projected Cmax and AUC(0-∞) from exceeding 1500 ng/mL and 7500 ng.h/mL, respectively (based on communication with FDA) and will not exceed a maximum daily dose of 900 mg/day per genotoxin limits.
The predicted exposures of 10, 50 and 150 mg doses are in Table 2.

Table 2 Predicted Mean Exposures Following Once Daily (QD) and Four Times a Day (QID) Dosing

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>QD</th>
<th>Cmax (ng/mL)</th>
<th>AUC (ng.h/mL)</th>
<th>QID</th>
<th>Cmax (ng/mL)</th>
<th>AUC (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>189</td>
<td>88.5</td>
<td>762</td>
<td>106</td>
<td>567</td>
<td>4016</td>
</tr>
<tr>
<td>50</td>
<td>991</td>
<td>482</td>
<td>4016</td>
<td>567</td>
<td>567</td>
<td>4016</td>
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<tr>
<td>150</td>
<td>2738</td>
<td>1367</td>
<td>11023</td>
<td>1584</td>
<td>1584</td>
<td>1584</td>
</tr>
</tbody>
</table>

The dosing regimen for the repeat dose segment (Days 2-6) of doses greater than 50 mg will be chosen based on the PK of the 10 and 50mg doses and the predicted administration schedule that would provide steady-state average concentrations of ~100-200 ng/mL. This range is the current anticipated efficacious concentration for the IVF indication.

**Rationale:**

The dose rationale was updated with feedback regarding the Cmax and AUC limited upon consulting with the FDA.

**Section 1.3 Summary of Risk Management**

**WAS:**

There were no safety pharmacology findings in nonclinical studies of concern for clinical use at oral doses up to 600 mg/day based on the systemic exposures observed at the no observed adverse effect level (NOAEL) in female in the 13 week toxicity study which is approximately 3.4 and 3.7-fold lower based on Cmax (1584 ng/ml) and AUC 11,024 ng.h/mL respectively. In clinical trials conducted to date in male subjects no laboratory, ECG, or vital sign abnormalities were detected following single and repeat (daily) dosing that would indicate that administration of GSK557296 would constitute a significant safety risk to female subjects. Standard laboratory, EKG, and vital sign monitoring will be conducted at regular intervals to assess for any clinically meaningful changes from baseline.

**IS:**

In clinical trials conducted to date in male subjects no laboratory, ECG, or vital sign abnormalities were detected following single and repeat (daily) dosing that would indicate that administration of GSK557296 would constitute a significant safety risk to female subjects. Standard laboratory, EKG, and vital sign monitoring will be conducted at regular intervals to assess for any clinically meaningful changes from baseline.
Rationale:

Removal of the first sentence to better express the risk management summary for this study.

Section 2.1 Primary

WAS:

- To characterize the pharmacokinetics of GSK557296 following single and repeat oral dosing in healthy female volunteers.
- To assess the safety and tolerability of GSK557296 following single and repeat dosing

IS:

- To characterize the pharmacokinetics of GSK557296 and its metabolite (GSK2395448) following single and repeat oral dosing in healthy female volunteers.
- To assess the safety and tolerability of GSK557296 following single and repeat dosing

Rationale:

The primary endpoint was updated to reflect the characterization of GSK557296 and its metabolite (GSK2395448).

Section 3.1 Primary Endpoint

WAS:

- Pharmacokinetic endpoints will include as data permit:
  - AUC(0-t)
  - AUC(0-inf), as permitted by the data
  - Cmax
  - Tmax
  - Half-life, as permitted by the data
- Safety and tolerability parameters, including adverse event, clinical laboratory, ECG, vital signs, and concurrent medication assessments.

IS:

- Pharmacokinetic endpoints will include as data permit:
  - AUC(0-t), \textbf{AUC(0-t)}
  - AUC(0-inf), as permitted by the data
  - Cmax
- Tmax
- Half-life, as permitted by the data
- Safety and tolerability parameters, including adverse event, clinical laboratory, ECG, vital signs, and concurrent medication assessments.

**Rationale:**
AUC(0-t) was added to the primary endpoints to better characterize the pharmacokinetics.

**Section 4.1 Study Design/ Schematic**

**WAS:**

**Group 1**

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 Single Dose</td>
<td>Day 2 Repeat Dose (QID)</td>
<td>Day 3 Repeat Dose (QID)</td>
<td>Day 4 Repeat Dose (QID)</td>
</tr>
</tbody>
</table>

**Group 2**

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 Single Dose</td>
<td>Day 9 Repeat Dose (BID-QID)</td>
<td>Day 10 Repeat Dose (BID-QID)</td>
<td>Day 11 Repeat Dose (BID-QID)</td>
</tr>
</tbody>
</table>

**Optional Groups 3 and 4**

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 Single Dose</td>
<td>Day 2 Repeat Dose (BID-QID)</td>
<td>Day 3 Repeat Dose (BID-QID)</td>
<td>Day 4 Repeat Dose (BID-QID)</td>
</tr>
</tbody>
</table>
IS:

Cohort 1 and Cohort 2

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 Single Dose</td>
<td>Day 2 Repeat Dose (QID)</td>
<td>Day 3 Repeat Dose (QID)</td>
<td>Day 4 Repeat Dose (QID)</td>
</tr>
</tbody>
</table>

Cohort 3

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 Single Dose</td>
<td>Day 2 Repeat Dose (BID-QID)</td>
<td>Day 3 Repeat Dose (BID-QID)</td>
<td>Day 4 Repeat Dose (BID-QID)</td>
</tr>
</tbody>
</table>

Optional Cohorts(s)

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 Single Dose</td>
<td>Day 2 Repeat Dose (BID QID)</td>
<td>Day 3 Repeat Dose (BID QID)</td>
<td>Day 4 Repeat Dose (BID QID)</td>
</tr>
</tbody>
</table>

Final dosing schedules of to be determined based on prior data.

Rationale:

The study design schematic was updated based on feedback from the FDA. Cohorts 1 and 2 will be conducted and an interim analysis will be performed before proceeding to the 150 mg dose.
Section 4.2: Discussion of Design

WAS:

This is a non-randomized, adaptive design, open label study in healthy female volunteers. Screening will occur within approximately 28 days of the first scheduled dose of study medication. Each subject will participate in one cohort. Prior to dosing, the investigator will review the scheduled assessments to confirm the subject’s suitability for the study including review of study entry criteria and lifestyle restrictions.

The first cohort of women will receive 10mg of GSK557296 QID, and if the PK approximates what was achieved in men then next dose level tested will be 150mg. Frequency of dosing (BID, TID or QID) of the second and any subsequent cohorts will depend on the t1/2 observed in the first cohort. If the PK profile does not approximate what was achieved in men, by a difference of 30% or greater, then additional dosing cohort(s) will be administered as needed. The decision to add additional dosing sessions will be based on the PK data analyzed from each of the first 2 dosing sessions.

For the first dosing session, eligible subjects will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. On Days 2-6 subjects with receive repeat doses (four times a day for the 10 mg cohort and either two times a day, three times a day or four times a day for the remaining cohort(s)): based on the PK of the single 10 mg dose) of GSK557296. Sparse PK sampling will occur on study Day 4 and a full PK profile will be obtained on Days 2 and 6. All PK samples (from both the single dose and repeat dose days) will be analyzed after the last PK sample is obtained on Day 7. Subjects will remain in the unit until the morning of Day 7 (after collection of the 24 plasma sample). Subjects will participate in only one dosing regimen.

A one week break will occur to allow for analysis of the repeat dosing PK data, prior to starting the second dosing session.

For the second dosing session, eligible subjects for session two will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. Subjects will be discharged from the unit on Day 2. Then a 7 day washout will occur to allow analysis of Day 1 PK samples. Subjects will return to the unit on Day 8. Repeat dosing will start on Day 9 and continue for 5 days ending on Day 13. Subjects with receive repeat doses (two, three or four times a day depending on the PK of the single 10 mg dose) of GSK557296. Sparse PK sampling will occur on study Day 11 and a full PK profile will be obtained on Days 9 and 13. All PK samples (from both the single dose and repeat dose days) will be analyzed after the last PK sample is obtained on Day 14. Subjects will remain in the unit until the morning of Day 14 (after collection of the 24 hour plasma sample). Subjects will participate in only one dosing regimen.

A follow-up visit will be conducted 7-14 days after administration of the last dose of study medication.

The total duration of study could be approximately 15 weeks.
IS:

This is a non-randomized, adaptive design, open label study in healthy female volunteers. Screening will occur within approximately 28 days of the first scheduled dose of study medication. Each subject will participate in one cohort. Prior to dosing, the investigator will review the scheduled assessments to confirm the subject’s suitability for the study including review of study entry criteria and lifestyle restrictions. Independent of the total number of cohorts studied, we will not exceed 48 subjects in this protocol.

The first two cohorts of women will receive 10 mg and 50 mg of GSK557296 QID, respectively, and if the single dose PK approximates what was achieved in men (<30% difference) then next dose level tested for Cohort 3 may be 150mg. A decision on the dose and frequency of dosing (BID, TID or QID) will be made in consultation with the FDA for the third and any subsequent cohorts based on the t1/2, AUC and Cmax observed from prior doses and modeling of proposed exposures for additional cohorts. The decision to add additional dosing sessions beyond the first three will be based on the PK data analyzed from the previous cohorts taking into account the single and repeat dose PK data.

For the first part of the dosing session, eligible subjects will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. On Days 2-6 subjects will receive repeat doses (four times a day for the 10 mg for the first cohort and 50mg for the second cohort and either two times a day, three times a day or four times a day for the remaining cohort(s): based on the PK of the single 10 mg and 50mg doses) of GSK557296. Sparse PK sampling will occur on study Day 4 and a full PK profile will be obtained on Days 2 and 6. All PK samples (from both the single dose and repeat dose days) will be analyzed after the last PK sample is obtained on Day 7. Subjects will remain in the unit until the morning of Day 7 (after collection of the 24 plasma sample). Subjects will participate in only one dosing regimen.

A break will occur to allow for analysis of the PK data, prior to starting the third dosing session. Decisions on the dose and regimen for cohort 3 will be made in consultation with the FDA and the GSK study team based on the 10mg and 50mg single and repeat dose PK and modeled data for higher doses. The single dose to be administered on Day 1 in Cohort 3 may range from 75 mg to 150 mg.

For the third dosing session, eligible subjects for session three will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. On days 2-6 subjects will receive repeat doses (two, three or four times a day depending on the PK of the single 10 mg and 50mg doses) of GSK557296. Sparse PK sampling will occur on study Day 4 and a full PK profile will be obtained on Days 2 and 6. PK samples from the repeat portion of cohort 3 will be analyzed after the last PK sample is obtained on Day 6. An integration of all available PK data will then be undertaken. Subjects will remain in the unit until the morning of Day 7 (after collection of the 24 hour plasma sample). Subjects will participate in only one dosing regimen.
A follow-up visit will be conducted 7-14 days after administration of the last dose of study medication.

Additional cohorts may be added if there is a significant discrepancy between predicted and actual exposures.

The total duration of study could be approximately 15 weeks.

**Rationale:**

Changes to this section were made due to feedback from the FDA. New wording was placed in this section to add the 50 mg dose arm and to reflect the interim analysis after the first 2 cohorts.

**Section 4.3 Treatment Assignment**

**WAS:**

Subjects will be assigned a fixed treatment regimen sequence in accordance with the randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software.

A description of each regimen is provided in the table below:

- Treatment A: GSK557296 10mg single dose on Day 1 followed by repeat dosing (4 times a day) on Days 2-6.
- Treatment B: GSK557296 150mg as a single dose on Day 1 followed by repeat nominal dosing of the same dose (either 2, 3 or 4 times a day based on half-life demonstrated in treatment A) on Days 9-13.

Adaptive Design (additional arms and cohorts may be added depending on the PK profiles of treatment groups A, and B):

- If required Treatment C: GSK557296 (Dose to be determined) as a single dose on Day 1 followed by repeat nominal dosing of the same dose (either 2, 3 or 4 times a day based on half-life demonstrated in treatment A and B) on Days 2-6.
- If required Treatment D: GSK557296 dose to be determined by PK of prior doses, 10-150 mg single dose on Day 1 followed by repeat dosing (either 2, 3 or 4 times a day dependent on half-life demonstrated in prior groups) on Days 2-6.

**IS:**

Subjects will be assigned to a fixed treatment regimen sequence in accordance with the planned treatment schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software.

A description of each regimen is provided in the table below:

- Treatment A: GSK557296 10mg single dose on Day 1 followed by repeat dosing (4 times a day) on Days 2-6.
- Treatment B: GSK557296 50mg as a single dose on Day 1 followed by repeat nominal dosing of the same dose (4 times a day) on Days 2-6
- Treatment C: GSK557296 dose and schedule to be determined in consultation with FDA. Single dose on Day 1 followed by repeat nominal dosing of the same dose (either 2, 3 or 4 times a day based on half life of 10mg and 50mg doses and modeling of exposures) on days 2-6.

Adaptive Design (additional arms and cohorts may be added depending on the PK profiles of treatment groups A, B and C):

- If required Treatment D: GSK557296 (Dose to be determined) as a single dose on Day 1 followed by repeat nominal dosing of the same dose (either 2, 3 or 4 times a day based on half-life demonstrated in treatment A, B and C) on Days 2-6.
- If required Treatment E: GSK557296 dose to be determined by PK of prior doses, 10-150 mg single dose on Day 1 followed by repeat dosing (either 2, 3 or 4 times a day dependent on half-life demonstrated in prior groups) on Days 2-6.

Rationale:

Treatment assignments were edited in this section to reflect the change in cohort assignments in the study.

Section 4.5 Dose Adjustment/Stopping Criteria

WAS:

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum daily dose and/or (predicted) maximum/cumulative exposure will not exceed 900 mg/day.

The decision to proceed to the next dose level of GSK557296, will be made by the GSK Study Team and the investigator based on safety, tolerability and preliminary pharmacokinetic data obtained in at least 4 subjects at the prior dose level. The actual doses to be administered may be adjusted based on safety, tolerability and preliminary pharmacokinetic data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate pharmacokinetic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.

IS:

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum daily dose and/or (predicted) maximum/cumulative exposure will not exceed 200 mg/day, 1500 ng/ml Cmax, or 7500 ng.h/ml in the first two cohorts, a decision to exceed these doses and to proceed above these thresholds of exposure will be made in conjunction with the FDA
The decision to proceed to subsequent dose levels of GSK557296, will be made based on safety, tolerability and preliminary pharmacokinetic data obtained in at least 4 subjects at the prior dose level. The actual doses to be administered may be adjusted based on safety, tolerability and preliminary pharmacokinetic data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate pharmacokinetic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.

Rationale:

This section was updated to reflect feedback obtained by the FDA. The new wording in this section reflects the 10 and 50 mg dose selection and mentions the interim analysis and data review by the FDA.
Section 4.6: Time and Events Table

WAS:

Groups 1, 3(optional), and 4(optional)

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1. 12 lead ECG and Vital signs assessments will be taken predose and 0.5 hours post dose on Day 1 then approximately 0.5 hours post dose on days 3 and 6 to approximate the time of Cmax.
2. Subjects will be fasted at least 8 hours prior to dosing. Subjects will receive lunch 4 hours after receiving the first dose of study medication
3. A full PK profile will be obtained on Day 1, 2, and 6 and trough samples on Day 4. For Day 1 PK blood samples will be taken at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dose. PK blood samples on Days 2 and 6 will be obtained at the following timepoints: pre-dose, 0.5, 2, 4, (before the next daily dose) 6, 6.5, 8, (before the next daily dose) 12, 12.5, 16, (before the next daily dose) 18, 18.5, 20, and 24 hours. PK blood samples will be obtained at pre-dose (first dose) on Day 4.

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1. 12 lead ECG and Vital signs assessments will be taken predose and 0.5 hours post dose on Day 1 then approximately 0.5 hours post dose on days 10 and 13 to approximate the time of Cmax.
2. Hematology and chemistry/urine analysis labs will be taken on Day 2 before discharge from the unit and will be taken on Day 8 after checkin to the unit.
3. Subjects will be fasted at least 8 hours prior to dosing. Subjects will receive lunch 4 hours after receiving the first dose of study medication.
4. A full PK profile will be obtained on Day 1, 9, and 13 and trough samples on Day 11. For Day 1 PK blood samples will be taken at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dose. PK blood samples on Days 9 and 13 will be obtained at the following timepoints: pre-dose, 0.5, 2, 4, (before the next daily dose) 6, 6.5, 8, (before the next daily dose) 12, 12.5, 16, (before the next daily dose) 18, 18.5, 20, and 24 hours. PK blood samples will be obtained at pre-dose (first dose) on Day 11.
5. Discharge from the clinic will occur after the 24 hour PK blood draw is obtained.
IS:

### All Cohorts

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<td>X3</td>
<td>X</td>
</tr>
<tr>
<td>PGX-can be taken at anytime during the study</td>
<td>X</td>
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<tr>
<td>Discharge</td>
<td>X</td>
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</tr>
</tbody>
</table>
1. 12 lead ECG and Vital signs assessments will be taken predose and 0.5 hours post dose on Day 1 then approximately 0.5 hours post dose on days 3 and 6 to approximate the time of Cmax.

2. Subjects will be fasted at least 8 hours prior to dosing. Subjects will receive lunch 4 hours after receiving the first dose of study medication.

3. A full PK profile will be obtained on Day 1, 2, and 6 and trough samples on Day 4. For Day 1 PK blood samples will be taken at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dose. PK blood samples on Days 2 and 6 will be obtained at the following time points: pre-dose, 0.5, 2, 4, (before the next daily dose) 6, 6.5, 8, (before the next daily dose) 12, 12.5, 16, (before the next daily dose) 18, 18.5, 20, and 24 hours. PK blood samples will be obtained at pre-dose (first dose) on Day 4.

**Rationale:**

Changes were made to this section to reflect the design change of adding the 2nd 50 mg cohort and to reflect the new study design.
Section 6.2.1 Interim Analysis

WAS:

There will be no formal interim efficacy analysis, this being a study designed to characterize the PK, safety and tolerability profiles of GSK557296 in healthy women volunteers. A dose-escalation team will meet to review the observed profiles in each cohort, prior to making a decision about whether to escalate or otherwise change the regimen.

IS:

There will be no formal interim analysis between the 10mg and 50 mg doses in this study. A dose-escalation team will meet to review the observed profiles in each cohort, prior to making a decision about whether to escalate or otherwise change the regimen.

However, there will be a formal interim PK analysis, of GSK557296 PK in healthy women volunteers following both the 10 and 50mg dose groups in addition to a safety review. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t), AUC(0-τ) and AUC(0-∞)], and apparent terminal phase half-life (t1/2). The plasma concentration-time data and the pharmacokinetic parameter data will be summarized descriptively.

AUC(0-∞) or AUC(0-τ) and Cmax following single and repeat doses may be used for assessment of dose proportionality. With this data, PK modeling will be done to predict the exposures of both single and repeat doses of 150mg. Several regimens of the 150mg repeat dose will be simulated. The observed PK data and the safety data from the 10 and 50mg dose groups and the 150mg simulations will be presented to the FDA for consultation prior to dosing Cohort 3.

There will be no statistical stopping rule – decisions to stop or continue the study will be based on safety/tolerability & PK profiles and consultation with the FDA.

Responsibilities for the interim analysis will be the same as for the final analyses, as described below. The PK modeling, described above, will be performed by the Clinical Pharmacology Modeling and Simulation department within GlaxoSmithKline. Final Analyses

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

Rationale:

This section was updated to reflect the addition of the interim analysis after the first 2 cohorts of the study.
Section 6.2.1.2 Pharmacokinetic Analysis

WAS:

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation department within GlaxoSmithKline. Plasma (compound number) concentration-time data will be analyzed by non-compartmental methods with the most current version of WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t) and AUC(0-∞)], and apparent terminal phase half-life (t1/2). AUC(0-∞) or AUC(0-t) and Cmax following single and repeat doses may be used for assessment of dose proportionality. Trough concentration (Cτ) samples collected on the specified days may be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, Quantitative Sciences, GlaxoSmithKline.

Tmax of GSK557296 will be summarized using appropriate descriptive statistics. If data permit, an appropriate nonparametric test for differences in Tmax by dose and/or day will be carried out.

The focus of the statistical analysis will be to estimate the effect of repeat dosing relative to single dosing on the pharmacokinetics of GSK557296. All pharmacokinetic endpoints including AUC and Cmax, where data permit, will be descriptively summarized by dose and day.

Following loge-transformation, AUC(0-t) and Cmax of GSK557296 will be separately analyzed using a mixed effects model with fixed effect terms for dose, day, and dose-by-day interaction. Subject will be treated as a random effect in the model. Point estimates and their associated 90% confidence intervals will be constructed for the differences, Day 6-Day 1. The point estimates and their associated 90% confidence intervals will then be back-transformed to provide point estimates and 90% confidence intervals for the ratios, Day6:Day1.

Dose proportionality may be explored, if appropriate. An assessment of dose proportionality will be made on AUC and Cmax using the power model, fitting terms for dose as a fixed effect and subject as a random effect. AUC, Cmax, and dose, will be loge-transformed prior to analysis. An estimate of slope (with corresponding 90% CI) will be provided as a measure of potential dose proportionality. Estimates of within-subject and model based pooled between-subject variability estimates will be computed for AUC and Cmax of GSK557296 for use in future studies.
Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model.

Plots of trough concentration data from Days 2-6 will be produced for informal assessment of achievement of steady state. For both parts of the study, descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum, and CVb%) will be calculated for all pharmacokinetic endpoints by dose. In addition, for AUC(0-tau), AUC(0-\(\infty\)), Cmax, and as data permit, T1/2, geometric means (and corresponding 95% confidence intervals) will be constructed.

**IS:**

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation department within GlaxoSmithKline. Plasma (compound number) concentration-time data will be analyzed by non-compartmental methods with the most current version of WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [\(AUC(0-t)\), \(AUC(0-\tau)\) and \(AUC(0-\infty)\)], and apparent terminal phase half-life (t1/2). \(AUC(0-\infty)\) or \(AUC(0-\tau)\) and Cmax following single and repeat doses may be used for assessment of dose proportionality. Trough concentration (C\(\tau\)) samples collected on the specified days may be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, Quantitative Sciences, GlaxoSmithKline.

\(T_{max}\) of GSK557296 will be summarized using appropriate descriptive statistics. If data permit, an appropriate nonparametric test for differences in \(T_{max}\) by dose and/or day will be carried out.

The focus of the statistical analysis will be to estimate the effect of repeat dosing relative to single dosing on the pharmacokinetics of GSK557296. All pharmacokinetic endpoints including AUC and Cmax, where data permit, will be descriptively summarized by dose and day.

Following loge-transformation, \(AUC(0-t)\) and Cmax of GSK557296 will be separately analyzed using a mixed effects model with fixed effect terms for dose, day, and dose-by-day interaction. Subject will be treated as a random effect in the model. Point estimates and their associated 90% confidence intervals will be constructed for the differences, Day 6-Day 1. The point estimates and their associated 90% confidence intervals will then be back-transformed to provide point estimates and 90% confidence intervals for the ratios, Day6:Day1.
Dose proportionality may be explored, if appropriate. An assessment of dose proportionality will be made on AUC and Cmax using the power model, fitting terms for dose as a fixed effect and subject as a random effect. AUC, Cmax, and dose, will be loge-transformed prior to analysis. An estimate of slope (with corresponding 90% CI) will be provided as a measure of potential dose proportionality. Estimates of within-subject and model based pooled between-subject variability estimates will be computed for AUC and Cmax of GSK557296 for use in future studies.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model.

Plots of trough concentration data from Days 2-6 will be produced for informal assessment of achievement of steady state. For both parts of the study, descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum, and CVb%) will be calculated for all pharmacokinetic endpoints by dose. In addition, for AUC(0-τ), AUC(0-∞), Cmax, and as data permit, T1/2, geometric means (and corresponding 95% confidence intervals) will be constructed.

**Rationale:**

AUC(0-τ) was added to this section to reflect the primary endpoint pharmacokinetic analysis.

**Section 8.2 Meals and Dietary Restrictions**

**Was:**

**Days 1 and 6**

Subjects will be fasted at least 8 hours prior to dosing on the first single dose day (Day 1) and last dosing day (Day 6) and will continue to fast for at least 4 hours post-dose. Additional restrictions are detailed below.

- Soft drinks without caffeine and fruit juices (except grapefruit juice) may be consumed ad libitum beginning 4 hours after dosing
- Consumption of products containing grapefruit will not be permitted within 7 days prior to the administration of study medication until collection of the final pharmacokinetic blood sample
- Subjects must fast from all food and drink (except water) for at least 4 hours prior to any clinical laboratory evaluations
- On Day 1, Lunch, dinner and snack will be provided as follows:
  - Lunch will be provided at approximately 4 hours after the first AM dosing
  - A Snack may be provided at approximately 7 hours after the first AM dosing
  - Dinner will be provided at approximately 10 hours after the first AM dosing
• An evening snack will be permitted up until 22:00 after the first AM dosing

Water may be consumed *ad libitum* beginning 2 hours after dosing (with the exception of the 240 mL water used for study drug administration)

**Days 2-5**

• Breakfast, will be provided as follows (Lunch, Dinner and snacks will be provided as above):
  • Breakfast will be provided at approximately 30 minutes prior to AM dosing. The meal should be completely consumed within 20 minutes or less. Administration of the study medication should occur 30 minutes after the start of breakfast.

**Days 2-5**

• Breakfast, will be provided as follows (Lunch, Dinner and snacks will be provided as above):
  • Breakfast will be provided at approximately 30 minutes prior to AM dosing. The meal should be completely consumed within 20 minutes or less. Administration of the study medication should occur 30 minutes after the start of breakfast.

**Cohort 2 Days 1 and 13**

Subj ects will be fasted at least 8 hours prior to dosing on the first single dose day (Day 1) and last dosing day (Day 13) and will continue to fast for at least 4 hours post-dose. Additional restrictions are detailed below.

• Soft drinks without caffeine and fruit juices (except grapefruit juice) may be consumed *ad libitum* beginning 4 hours after dosing

• Consumption of products containing grapefruit will not be permitted within 7 days prior to the administration of study medication until collection of the final pharmacokinetic blood sample

• Subjects must fast from all food and drink (except water) for at least 4 hours prior to any clinical laboratory evaluations

• On Day 1, Lunch, dinner and snack will be provided as follows:
  • Lunch will be provided at approximately 4 hours after the first AM dosing
  • A Snack may be provided at approximately 7 hours after the first AM dosing
  • Dinner will be provided at approximately 10 hours after the first AM dosing
  • An evening snack will be permitted up until 22:00 after the first AM dosing

Water may be consumed *ad libitum* beginning 2 hours after dosing (with the exception of the 240 mL water used for study drug administration)
Days 8-14

- Breakfast, will be provided as follows (Lunch, Dinner and snacks will be provided as above):
- Breakfast will be provided at approximately 30 minutes prior to AM dosing. The meal should be completely consumed within 20 minutes or less. Administration of the study medication should occur 30 minutes after the start of breakfast.

**IS:**

**All Cohorts Days 1 and 6**

Subjects will be fasted at least 8 hours prior to dosing on the first single dose day (Day 1) and last dosing day (Day 6) and will continue to fast for at least 4 hours post-dose. Additional restrictions are detailed below.

- Soft drinks without caffeine and fruit juices (except grapefruit juice) may be consumed ad libitum beginning 4 hours after dosing
- Consumption of products containing grapefruit will not be permitted within 7 days prior to the administration of study medication until collection of the final pharmacokinetic blood sample
- Subjects must fast from all food and drink (except water) for at least 4 hours prior to any clinical laboratory evaluations
- On Day 1, Lunch, dinner and snack will be provided as follows:
  - Lunch will be provided at approximately 4 hours after the first AM dosing
  - A Snack may be provided at approximately 7 hours after the first AM dosing
  - Dinner will be provided at approximately 10 hours after the first AM dosing
  - An evening snack will be permitted up until 22:00

Water may be consumed *ad libitum* beginning 2 hours after dosing (with the exception of the 240 mL water used for study drug administration)

**Days 2-5**

- Breakfast, will be provided as follows (Lunch, Dinner and snacks will be provided as above):
- Breakfast will be provided at approximately 30 minutes prior to AM dosing. The meal should be completely consumed within 20 minutes or less. Administration of the study medication should occur approximately 30 minutes after the start of breakfast.

**Rationale:**

Study meals were updated in this section to reflect the design change in the protocol. Flexible wording was also added to aid in timings at the site for procedures.
AMENDMENT 2

Where the Amendment Applies

To all sites participating in IVF116741.

Summary of Amendment Changes with Rationale

Per a review of data from Cohorts 1 and 2, the FDA has granted permission for the Sponsor to dose subjects in Cohort 3 as a 150mg BID dose. Following dosing, PK samples will be analyzed and the data will be summarized and sent to the FDA for review. Per consultation with the FDA Cohort 4 will begin (150 mg of GSK557296 QID). An additional 200 mg single dose cohort has been added to the study for exploratory reasons. This amendment reflects those changes outlined above.

List of Specific Changes

Section 1.2.2 Dose Rationale

WAS:

In the first time in human (FTiH) clinical study in males, the doses: 10mg, 50mg, 100mg, 150mg and 200 mg were studied as single doses and 30mg, 100mg and 150 mg were studied as once daily, repeat doses for 14 days. GSK557296, as a minitablet formulation, was readily absorbed and eliminated with mean t1/2 values ranging from 3.74 to 5.39 hours. As the doses increased in the single dose portion, greater than dose proportional increases in GSK557296 Cmax, but not AUC were observed. The resultant exposures from the 150mg and 200 mg doses were very similar suggesting a plateau of exposure beyond the 150 mg dose. In the Premature Ejaculation Phase II Study, 50mg and 150 mg tablet formulation doses were studied in otherwise, healthy men. When comparing the exposures from this study to the FTiH study, there was a decrease in exposures with the new formulation.

From preclinical studies, a gender difference in GSK557296 exposure following oral administration in rats was noted. In female rats, the systemic exposure (both Cmax and AUC), was generally greater than double than what was observed in male rats. However, there was no gender difference in systemic exposure when GSK557296 was orally administered to dogs.

In this initial study in women, 10 mg (the lowest dose studied in males) will be administered as a single dose on Day 1 and four times a day (QID) on Days 2-6 to the first cohort of subjects. In a separate subsequent cohort of women, 50 mg will be administered as a single dose on Day 1 and then on a QID schedule on Days 2-6. It is anticipated that we will need to maintain a steady-state dosing regimen in the IVF patients and therefore, greater than once daily dosing regimen will be carried out in the repeat dose portion of this study to better characterize the exposures achieved. There will be a minimum of six subjects on active drug for each dose cohort. Data obtained from the first two cohorts will be used to simulate exposures for additional cohort(s). A final decision on the dose and schedule selected for the third cohort will be made in
consultation with the FDA based on the exposures seen in the 10mg and 50mg groups and modelled exposures for doses ranging up to 150mg. Additional doses may be studied in further cohorts if the pharmacokinetics are extremely different between the genders. A 30% difference in systemic exposure (Cmax and/or AUC) will be considered extremely different and additional dose groups may be investigated to better understand the pharmacokinetics in women. The repeat dosing regimen will be either twice, three or four times a day and will be decided once PK data are available from the first cohorts. Our current expectation based on the T1/2 seen in men is that QID is most likely.

Dose escalation will proceed once preliminary safety/tolerability and PK data have been reviewed for at least 4 subjects at the previous dose level and will be made by the GSK Study Team and the Investigator. Given that a decision on the dose selected for the third cohort will be made in consultation with the FDA, a pause in the study will be required.

All chosen dose(s) will be appropriate to prevent the projected Cmax and AUC(0-∞) from exceeding 1500 ng/mL and 7500 ng.h/mL, respectively (based on communication with FDA) and will not exceed a maximum daily dose of 900 mg/day per genotoxin limits. The predicted exposures of 10, 50 and 150 mg doses are in Table 1.

Table 2 Predicted Mean Exposures Following Once Daily (QD) and Four Times a Day (QID) Dosing

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>QD</th>
<th>QID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC (ng.h/mL)</td>
<td>Cmax (ng/mL)</td>
</tr>
<tr>
<td>10</td>
<td>189</td>
<td>88.5</td>
</tr>
<tr>
<td>50</td>
<td>991</td>
<td>482</td>
</tr>
<tr>
<td>150</td>
<td>2738</td>
<td>1367</td>
</tr>
</tbody>
</table>

The dosing regimen for the repeat dose segment (Days 2-6) of doses greater than 50 mg will be chosen based on the PK of the 10 and 50mg doses and the predicted administration schedule that would provide steady-state average concentrations of ~100-200 ng/mL. This range is the current anticipated efficacious concentration for the IVF indication.

IS:

In the first time in human (FTiH) clinical study in males, the doses: 10mg, 50mg, 100mg, 150mg and 200 mg were studied as single doses and 30mg, 100mg and 150 mg were studied as once daily, repeat doses for 14 days. GSK557296, as a minitable formulation, was readily absorbed and eliminated with mean t1/2 values ranging from 3.74 to 5.39 hours. As the doses increased in the single dose portion, greater than dose proportional increases in GSK557296 Cmax, but not AUC were observed. The resultant exposures from the 150mg and 200 mg doses were very similar suggesting a plateau of exposure beyond the 150 mg dose. In the Premature Ejaculation Phase II Study, 50mg and 150 mg tablet formulation doses were studied in otherwise, healthy men. When comparing the
exposures from this study to the FTiH study, there was a decrease in exposures with the new formulation.

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Dose escalation will proceed once preliminary safety/tolerability and PK data have been reviewed for at least 4 subjects at the previous dose level and will be made by the GSK Study Team and the Investigator. Given that a decision on the dose selected for the third cohort will be made in consultation with the FDA, a pause in the study will be required. All chosen dose(s) will be appropriate to prevent the projected Cmax and AUC(0-∞) from exceeding 1500 ng/mL and 7500 ng.h/mL, respectively (based on communication with FDA) and will not exceed a maximum daily dose of 900 mg/day per genotoxin limits. The predicted exposures of 10, 50 and 150 mg doses are in Table 1.
Table 3  Predicted Mean Exposures Following Once Daily (QD) and Four Times a Day (QID) Dosing

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>QD</th>
<th>QID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC (ng.h/mL)</td>
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</tr>
<tr>
<td>10</td>
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<td>482</td>
</tr>
<tr>
<td>150</td>
<td>2738</td>
<td>1367</td>
</tr>
</tbody>
</table>

The dosing regimen for the repeat dose segment (Days 2-6) of doses greater than 50 mg will be chosen based on the PK of the 10 and 50mg doses and the predicted administration schedule that would provide steady-state average concentrations of ~100-200 ng/mL. This range is the current anticipated efficacious concentration for the IVF indication.

Rationale:

This section was updated with the rationale for the 200 mg dose.

Section 4.1 Study Design/Schematic

WAS:

Cohort 1 and Cohort 2

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 Single Dose (QID)</td>
<td>Day 2 Repeat Dose (QID)</td>
<td>Day 3 Repeat Dose (QID)</td>
<td>Day 4 Repeat Dose (QID)</td>
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Cohort 3

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 Single Dose (BID-QID)</td>
<td>Day 2 Repeat Dose (BID-QID)</td>
<td>Day 3 Repeat Dose (BID-QID)</td>
<td>Day 4 Repeat Dose (BID-QID)</td>
</tr>
</tbody>
</table>
Optional Cohorts(s)

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong> Single Dose</td>
<td><strong>Day 2</strong> Repeat Dose (BID-QID)</td>
<td><strong>Day 3</strong> Repeat Dose (BID-QID)</td>
<td><strong>Day 5</strong> Repeat Dose (BID-QID)</td>
</tr>
<tr>
<td><strong>Day 2</strong> Repeat Dose (BID-QID)</td>
<td><strong>Day 3</strong> Repeat Dose (BID-QID)</td>
<td><strong>Day 4</strong> Repeat Dose (BID-QID)</td>
<td><strong>Day 6</strong> Repeat Dose (BID-QID)</td>
</tr>
</tbody>
</table>

Final dosing schedules of to be determined based on prior data.

**IS:**

**Cohort 1 and Cohort 2**

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong> Single Dose</td>
<td><strong>Day 2</strong> Repeat Dose (QID)</td>
<td><strong>Day 3</strong> Repeat Dose (QID)</td>
<td><strong>Day 5</strong> Repeat Dose (QID)</td>
</tr>
<tr>
<td><strong>Day 2</strong> Repeat Dose (QID)</td>
<td><strong>Day 3</strong> Repeat Dose (QID)</td>
<td><strong>Day 4</strong> Repeat Dose (QID)</td>
<td><strong>Day 6</strong> Repeat Dose (QID)</td>
</tr>
</tbody>
</table>

**Cohort 3**

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong> Single Dose</td>
<td><strong>Day 2</strong> Repeat Dose (BID-QID)</td>
<td><strong>Day 3</strong> Repeat Dose (BID-QID)</td>
<td><strong>Day 5</strong> Repeat Dose (BID-QID)</td>
</tr>
<tr>
<td><strong>Day 2</strong> Repeat Dose (BID-QID)</td>
<td><strong>Day 3</strong> Repeat Dose (BID-QID)</td>
<td><strong>Day 4</strong> Repeat Dose (BID-QID)</td>
<td><strong>Day 6</strong> Repeat Dose (BID-QID)</td>
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</table>

**Cohort 4**

<table>
<thead>
<tr>
<th>Full PK Profile</th>
<th>Full PK Sampling</th>
<th>Trough PK Sampling</th>
<th>Full PK Profile</th>
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<tbody>
<tr>
<td><strong>Day 1</strong> Single Dose</td>
<td><strong>Day 2</strong> Wash-out</td>
<td><strong>Day 3</strong> Repeat Dose (TID-QID)</td>
<td><strong>Day 5</strong> Repeat Dose (TID-QID)</td>
</tr>
<tr>
<td><strong>Day 2</strong> Repeat Dose (TID-QID)</td>
<td><strong>Day 3</strong> Repeat Dose (TID-QID)</td>
<td><strong>Day 4</strong> Repeat Dose (TID-QID)</td>
<td><strong>Day 6</strong> Repeat Dose (TID-QID)</td>
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<tr>
<td><strong>Day 5</strong> Repeat Dose (TID-QID)</td>
<td><strong>Day 6</strong> Repeat Dose (TID-QID)</td>
<td><strong>Day 7</strong> Repeat Dose (TID-QID)</td>
<td></td>
</tr>
</tbody>
</table>
Final dosing schedules of to be determined based on prior data.

**Rationale:**

Cohort 5 was added to the study based on regulatory feedback and for single dose exploration.

**Section 4.2 Discussion of Design**

**WAS:**

This is a non-randomized, adaptive design, open label study in healthy female volunteers. Screening will occur within approximately 28 days of the first scheduled dose of study medication. Each subject will participate in one cohort. Prior to dosing, the investigator will review the scheduled assessments to confirm the subject’s suitability for the study including review of study entry criteria and lifestyle restrictions. Independent of the total number of cohorts studied, we will not exceed 48 subjects in this protocol.

The first two cohorts of women will receive 10 mg and 50 mg of GSK557296 QID, respectively, and if the single dose PK approximates what was achieved in men (<30% difference) then next dose level tested for Cohort 3 may be 150mg. A decision on the dose and frequency of dosing (BID, TID or QID) will be made in consultation with the FDA for the third and any subsequent cohorts based on the t1/2, AUC and Cmax observed from prior doses and modeling of proposed exposures for additional cohorts. The decision to add additional dosing sessions beyond the first three will be based on the PK data analyzed from the previous cohorts taking into account the single and repeat dose PK data.

For the first part of the dosing session, eligible subjects will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. On Days 2-6 subjects will receive repeat doses (four times a day for the 10 mg for the first cohort and 50mg for the second cohort and either two times a day, three times a day or four times a day for the remaining cohort(s): based on the PK of the single 10 mg and 50mg doses) of GSK557296. Sparse PK sampling will occur on study Day 4 and a full PK profile will be obtained on Days 2 and 6. All PK samples (from both the single dose and repeat dose days) will be analyzed after the last PK sample is obtained on Day 7. Subjects will remain in the unit until the morning of Day 7 (after collection of the 24 plasma sample). Subjects will participate in only one dosing regimen.

A break will occur to allow for analysis of the PK data, prior to starting the third dosing session. Decisions on the dose and regimen for cohort 3 will be made in consultation with the FDA and the GSK study team based on the 10mg and 50mg single and repeat dose PK and modeled data for higher doses. The single dose to be administered on Day 1 in Cohort 3 may range from 75 mg to 150 mg.

For the third dosing session, eligible subjects for session three will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects
will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. On days 2-6 subjects will receive repeat doses (two, three or four times a day depending on the PK of the single 10 mg and 50mg doses) of GSK557296. Sparse PK sampling will occur on study Day 4 and a full PK profile will be obtained on Days 2 and 6. PK samples from the repeat portion of cohort 3 will be analyzed after the last PK sample is obtained on Day 6. An integration of all available PK data will then be undertaken. Subjects will remain in the unit until the morning of Day 7 (after collection of the 24 hour plasma sample). Subjects will participate in only one dosing regimen.

A follow-up visit will be conducted 7-14 days after administration of the last dose of study medication.

Additional cohorts may be added if there is a significant discrepancy between predicted and actual exposures.

The total duration of study could be approximately 15 weeks.

**IS:**

This is a non-randomized, adaptive design, open label study in healthy female volunteers. Screening will occur within approximately 28 days of the first scheduled dose of study medication. Each subject will participate in one cohort. Prior to dosing, the investigator will review the scheduled assessments to confirm the subject’s suitability for the study including review of study entry criteria and lifestyle restrictions. Independent of the total number of cohorts studied, we will not exceed 48 subjects in this protocol.

The first two cohorts of women will receive 10 mg and 50 mg of GSK557296 QID, respectively, and if the single dose PK approximates what was achieved in men (<30% difference) then next dose level tested for Cohort 3 may be 150mg. A decision on the dose and frequency of dosing (BID, TID or QID) will be made in consultation with the FDA for the third and any subsequent cohorts based on the t1/2, AUC and Cmax observed from prior doses and modeling of proposed exposures for additional cohorts. The decision to add additional dosing sessions beyond the first three will be based on the PK data analyzed from the previous cohorts taking into account the single and repeat dose PK data.

For the first part of the dosing session, eligible subjects will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. On Days 2-6 subjects will receive repeat doses (four times a day for the 10 mg for the first cohort and 50mg for the second cohort and either two times a day, three times a day or four times a day for the remaining cohort(s): based on the PK of the single 10 mg and 50mg doses) of GSK557296. Sparse PK sampling will occur on study Day 4 and a full PK profile will be obtained on Days 2 and 6. All PK samples (from both the single dose and repeat dose days) will be analyzed after the last PK sample is obtained on Day 7. Subjects will remain in the unit until the
morning of Day 7 (after collection of the 24 hour plasma sample). Subjects will participate in only one dosing regimen.

A break will occur to allow for analysis of the PK data, prior to starting the third dosing session. Decisions on the dose and regimen for cohort 3 will be made in consultation with the FDA and the GSK study team based on the 10mg and 50mg single and repeat dose PK and modeled data for higher doses. The single dose to be administered on Day 1 in Cohort 3 may range from 75 mg to 150 mg.

For the third dosing session, eligible subjects for session three will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. On days 2-6 subjects will receive repeat doses (two, three or four times a day depending on the PK of the single 10 mg and 50mg doses) of GSK557296. Sparse PK sampling will occur on study Day 4 and a full PK profile will be obtained on Days 2 and 6. PK samples from the repeat portion of cohort 3 will be analyzed after the last PK sample is obtained on Day 6. An integration of all available PK data will then be undertaken. Subjects will remain in the unit until the morning of Day 7 (after collection of the 24 hour plasma sample). Subjects will participate in only one dosing regimen.

A break will occur to allow for analysis of the PK data, prior to starting the fourth dosing session. Decisions on the dose and regimen for cohort 4 will be made in consultation with the FDA and the GSK study team based on the 10mg, 50mg, and 150mg single and repeat dose PK and modeled data for higher doses. The single dose to be administered on Day 1 in Cohort 4 will be 200 mg.

For the fourth dosing session, eligible subjects for session four will enter the unit on Day -1. Subjects will be fasted overnight (at least 8 hours). On Day 1 of this session subjects will receive a single dose of GSK557296. A full PK profile will be obtained on Day 1 following the single dose of GSK557296. Subjects will remain in the clinic on Day 2 to serve as a washout day. On days 3-7 subjects will receive repeat doses (three or four times a day 150mg doses) of GSK557296. Sparse PK sampling will occur on study Day 5 and a full PK profile will be obtained on Days 3 and 7. PK samples from the repeat portion of cohort 4 will be analyzed after the last PK sample is obtained on Day 8. An integration of all available PK data will then be undertaken. Subjects will remain in the unit until the morning of Day 8 (after collection of the 24 hour plasma sample). Subjects will participate in only one dosing regimen.

A follow-up visit will be conducted 7-14 days after administration of the last dose of study medication.

Additional cohorts may be added if there is a significant discrepancy between predicted and actual exposures.

The total duration of study could be approximately 15 weeks.

Rationale:
Additional wording was added to this section to better define the 4th cohort.

Section 4.3 Treatment Assignments

WAS:

Subjects will be assigned to a fixed treatment regimen sequence in accordance with the planned treatment schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software.

A description of each regimen is provided in the table below:

- Treatment A: GSK557296 10mg single dose on Day 1 followed by repeat dosing (4 times a day) on Days 2-6.
- Treatment B: GSK557296 50mg as a single dose on Day 1 followed by repeat nominal dosing of the same dose (4 times a day) on Days 2-6.
- Treatment C: GSK557296 dose and schedule to be determined in consultation with FDA. Single dose on Day 1 followed by repeat nominal dosing of the same dose (either 2, 3 or 4 times a day based on half life of 10mg and 50mg doses and modeling of exposures) on days 2-6.

Adaptive Design (additional arms and cohorts may be added depending on the PK profiles of treatment groups A, B and C):

- If required Treatment D: GSK557296 (Dose to be determined) as a single dose on Day 1 followed by repeat nominal dosing of the same dose (either 2, 3 or 4 times a day based on half-life demonstrated in treatment A, B and C) on Days 2-6.
- If required Treatment E: GSK557296 dose to be determined by PK of prior doses, 10-150 mg single dose on Day 1 followed by repeat dosing (either 2, 3 or 4 times a day dependent on half-life demonstrated in prior groups) on Days 2-6.

IS:

Subjects will be assigned to a fixed treatment regimen sequence in accordance with the planned treatment schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software.

A description of each regimen is provided in the table below:

- Treatment A: GSK557296 10mg single dose on Day 1 followed by repeat dosing (4 times a day) on Days 2-6.
- Treatment B: GSK557296 50mg as a single dose on Day 1 followed by repeat nominal dosing of the same dose (4 times a day) on Days 2-6.
- Treatment C: GSK557296 dose and schedule to be determined in consultation with FDA. Single dose on Day 1 followed by repeat nominal dosing of the same dose (either 2, 3 or 4 times a day based on half life of 10mg and 50mg doses and modeling of exposures) on days 2-6.
Adaptive Design (additional arms and cohorts may be added depending on the PK profiles of treatment groups A, B and C):

- Treatment D: GSK557296 200 mg as a single dose on Day 1 followed by repeat nominal dosing of 150mg (3 or 4 times a day based on half-life demonstrated in treatment A, B and C) on Days 3-7.

Rationale:

This section was changed to reflect the four times a day dosing of 150 mg for Treatment D and the addition of the 200 mg dose (treatment E) for Cohort 5.

Section 4.5 Dose Adjustment/Stopping Criteria

WAS:

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum daily dose and/or (predicted) maximum/cumulative exposure will not exceed 200 mg/day, 1500 ng/ml Cmax, or 7500 ng.h/ml in the first two cohorts. The decision to proceed to subsequent dose levels of GSK557296, will be made based on safety, tolerability and preliminary pharmacokinetic data obtained in at least 4 subjects at the prior dose level. The actual doses to be administered may be adjusted based on safety, tolerability and preliminary pharmacokinetic data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate pharmacokinetic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.

IS:

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum daily dose and/or (predicted) maximum/cumulative exposure will not exceed 200 mg/day, 1500 ng/ml Cmax, or 7500 ng.h/ml in the first two cohorts. The FDA has agreed to allow an additional cohort to be dosed at 150mg BID, and to review data in advance of dosing at 150mg QID, which has the potential to exceed the previously agreed exposure limits. The decision to proceed to subsequent dose levels of GSK557296, will be made based on safety, tolerability and preliminary pharmacokinetic data obtained in at least 4 subjects at the prior dose level. The actual doses to be administered may be adjusted based on safety, tolerability and preliminary pharmacokinetic data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate pharmacokinetic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.
Rationale:

This section was modified to reflect the changes in Cohorts 3 and 4.

Section 4.6: Time and Events Table

**Was:**

**All Cohorts**

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**PGX-can be taken anytime during the study**

- X

1. 12 lead ECG and Vital signs assessments will be taken predose and 0.5 hours post dose on Day 1 then approximately 0.5 hours post dose on days 3 and 6 to approximate the time of Cmax.
2. Subjects will be fasted at least 8 hours prior to dosing. Subjects will receive lunch 4 hours after receiving the first dose of study medication.
3. A full PK profile will be obtained on Day 1, 2, and 6 and trough samples on Day 4. For Day 1 PK blood samples will be taken at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dose. PK blood samples on Days 2 and 6 will be obtained at the following timepoints: pre-dose, 0.5, 2, 4, (before the next daily dose) 6, 6.5, 8, (before the next daily dose) 12, 12.5, 16, (before the next daily dose) 18, 18.5, 20, and 24 hours. PK blood samples will be obtained at pre-dose (first dose) on Day 4.
IS:

**Cohorts 1-3**

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1. 12 lead ECG and Vital signs assessments will be taken predose and 0.5 hours post dose on Day 1 then approximately 0.5 hours post dose on days 3 and 6 to approximate the time of Cmax.
2. Subjects will be fasted at least 8 hours prior to dosing. Subjects will receive lunch 4 hours after receiving the first dose of study medication.
3. A full PK profile will be obtained on Day 1, 2, and 6 and trough samples on Day 4. For Day 1 PK blood samples will be taken at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dose. PK blood samples on Days 2 and 6 will be obtained at the following timepoints: pre-dose, 0.5, 2, 4, (before the next daily dose) 6, 6.5, 8, (before the next daily dose) 12, 12.5, 16, (before the next daily dose) 18, 18.5, 20, and 24 hours. PK blood samples will be obtained at pre-dose (first dose) on Day 4.
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1. 12 lead ECG and Vital signs assessments will be taken predose and 0.5 hours post dose on Day 1 then approximately 0.5 hours post dose on days 3 and 6 to approximate the time of Cmax.
2. Subjects will be fasted at least 8 hours prior to dosing. Subjects will receive lunch 4 hours after receiving the first dose of study medication.
3. If TID occurs the following pk samples will be taken: A full PK profile will be obtained on Day 1, 3, and 7 and trough samples on Day 5. For Day 1 PK blood samples will be taken at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dose. PK blood samples on Days 3 and 7 will be obtained at the following timepoints: pre-dose, 0.5, 2, 4, 6, (before the next daily dose) 8, 8.5, 10, 12, (before the next daily dose) 16, 16.5, 18, 20, and 24 hours. PK blood samples will be obtained at pre-dose (first dose) on Day 5.

If QID occurs the following pk samples will be taken: A full PK profile will be obtained on Day 1, 3, and 7 and trough samples on Day 5. For Day 1 PK blood samples will be taken at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dose. PK blood samples on Days 3 and 7 will be obtained at the following timepoints: pre-dose, 0.5, 2, 4, (before the next daily dose) 6, 6.5, 8, (before the next daily dose) 12, 12.5, 16, (before the next daily dose) 18, 18.5, 20, and 24 hours. PK blood samples will be obtained at pre-dose (first dose) on Day 5. Pharmacokinetic sampling may be adjusted throughout the study based on newly available date to ensure appropriate monitoring.
Rationale:

A new time and events table was added to changes to cohort 4.

Section 5.1: Number of Subjects

WAS:

Approximately 12 subjects will be enrolled in each dosing session such that approximately 9 subjects complete dosing and critical assessments in each session.

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

If all 4 dosing sessions are utilized 48 subjects will be enrolled such that 36 subjects complete the study.

IS:

Approximately 12 subjects will be enrolled in each dosing session such that approximately 9 subjects complete dosing and critical assessments in each session.

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

If all 4 dosing sessions are utilized 48 subjects will be enrolled such that 36 subjects complete the study.

Rationale:

Additional subjects were added because of the changes to Cohort 4.

Section 5.2.1 Inclusion Criteria

WAS:

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Clinical Investigator’s Brochure for GSK557296 GlaxoSmithKline Document Number 2012N39040_00.

Deviations from inclusion 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.

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

1. ALT, alkaline phosphatase and bilirubin ≤ 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
2. Single or QTcF < 450 msec; or QTc < 480 msec in subjects with Bundle Branch Block.

3. 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. Female between 18 and 45 years of age inclusive, at the time of signing the informed consent.

4. A female subject is eligible to participate if she is of:
   - Child-bearing potential and is abstinent or agrees to use one of the contraception methods listed in Section 8.1 for an appropriate period of time (as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until 48 hours post last dose.

5. Body weight ≥ 50 kg and BMI within the range 19-29.9 kg/m² (inclusive).

IS:

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Clinical Investigator’s Brochure for GSK557296 GlaxoSmithKline Document Number 2012N39040_00.

Deviations from inclusion 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.

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

1. ALT, alkaline phosphatase and bilirubin ≤ 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

2. Single or QTcF < 450 msec; or QTc < 480 msec in subjects with Bundle Branch Block.

3. 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. Female between 18 and 45 years of age inclusive, at the time of signing the informed consent.

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3 Abstinence from penile-vaginal intercourse must be consistent with the preferred and usual lifestyle of the subject.
4. A female subject is eligible to participate if she is of:
   • Child-bearing potential and is abstinent\(^4\) or agrees to use one of the
     contraception methods listed in Section 8.1 for a **minimum of 28 days** prior to
     the start of dosing to sufficiently minimize the risk of pregnancy at that point.
     Female subjects must agree to use contraception until 48 hours post last dose.

5. Body weight \(\geq 50\) kg and BMI within the range 19-29.9 kg/m\(^2\) (inclusive).

**Rationale:**
Additional wording was added to this section to better define that a contraceptive method
must be used at a minimum of 28 days before dosing to cover a normal menstrual cycle.

**Section 6.1 Sample Size Considerations**

**WAS:**
Approximately 12 subjects will be enrolled in each dosing session such that
approximately 9 subjects complete dosing and critical assessments in each session.

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

If all 4 dosing sessions are utilized 48 subjects will be enrolled such that 36 subjects
complete the study.

**IS:**
Approximately 12 subjects will be enrolled in each dosing session such that
approximately 9 subjects complete dosing and critical assessments in each session.

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

If all 5 dosing sessions are utilized **48** subjects will be enrolled such that **36** subjects
complete the study.

**Rationale:**
This section was updated to reflect the addition of more subjects for the fifth cohort.

**Section 6.2.1 Interim Analysis**

\(^4\) Abstinence from penile-vaginal intercourse must be consistent with the preferred and usual lifestyle of the
subject.
WAS:

There will be no formal interim analysis between the 10mg and 50 mg doses in this study. A dose-escalation team will meet to review the observed profiles in each cohort, prior to making a decision about whether to escalate or otherwise change the regimen.

However, there will be a formal interim PK analysis, of GSK557296 PK in healthy women volunteers following both the 10 and 50mg dose groups in addition to a safety review. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t), AUC(0-τ) and AUC(0-∞)], and apparent terminal phase half-life (t1/2). The plasma concentration-time data and the pharmacokinetic parameter data will be summarized descriptively.

AUC(0-∞) or AUC(0-τ) and Cmax following single and repeat doses may be used for assessment of dose proportionality. With this data, PK modeling will be done to predict the exposures of both single and repeat doses of 150mg. Several regimens of the 150mg repeat dose will be simulated. The observed PK data and the safety data from the 10 and 50mg dose groups and the 150mg simulations will be presented to the FDA for consultation prior to dosing Cohort 3.

There will be no statistical stopping rule – decisions to stop or continue the study will be based on safety/tolerability & PK profiles and consultation with the FDA.

Responsibilities for the interim analysis will be the same as for the final analyses, as described below. The PK modeling, described above, will be performed by the Clinical Pharmacology Modeling and Simulation department within GlaxoSmithKline. Final Analyses

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

IS:

There will be no formal interim analysis between the 10mg and 50 mg doses in this study. A dose-escalation team will meet to review the observed profiles in each cohort, prior to making a decision about whether to escalate or otherwise change the regimen.

However, there will be a formal interim PK analysis, of GSK557296 PK in healthy women volunteers following both the 10 and 50mg dose groups in addition to a safety review. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t), AUC(0-τ) and AUC(0-∞)], and apparent terminal phase half-life (t1/2). The plasma concentration-time data and the pharmacokinetic parameter data will be summarized descriptively.
AUC(0-∞) or AUC(0-τ) and Cmax following single and repeat doses may be used for assessment of dose proportionality. With this data, PK modeling will be done to predict the exposures of both single and repeat doses of 150mg. Several regimens of the 150mg repeat dose will be simulated. The observed PK data and the safety data from the 10 and 50mg dose groups and the 150mg simulations will be presented to the FDA for consultation prior to dosing Cohort 3.

There will be no statistical stopping rule – decisions to stop or continue the study will be based on safety/tolerability & PK profiles and consultation with the FDA.

A formal PK interim analysis and safety review may also be conducted following the third cohort (which may be a 150mg dose group).

Responsibilities for the interim analysis will be the same as for the final analyses, as described below. The PK modeling, described above, will be performed by the Clinical Pharmacology Modeling and Simulation department within GlaxoSmithKline. Final Analyses

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

Rationale:

This section was updated to reflect the changes made to the fourth cohort of the study.

Section 6.2.1.2 Pharmacokinetic Analysis

WAS:

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation department within GlaxoSmithKline. Plasma (compound number) concentration-time data will be analyzed by non-compartmental methods with the most current version of WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t), AUC(0-τ) and AUC(0-∞)], and apparent terminal phase half-life (t1/2). AUC(0-∞) or AUC(0-τ) and Cmax following single and repeat doses may be used for assessment of dose proportionality. Trough concentration (Cτ) samples collected on the specified days may be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, Quantitative Sciences, GlaxoSmithKline.
Tmax of GSK557296 will be summarized using appropriate descriptive statistics. If data permit, an appropriate nonparametric test for differences in Tmax by dose and/or day will be carried out.

The focus of the statistical analysis will be to estimate the effect of repeat dosing relative to single dosing on the pharmacokinetics of GSK557296. All pharmacokinetic endpoints including AUC and Cmax, where data permit, will be descriptively summarized by dose and day.

Following loge-transformation, AUC(0-t) and Cmax of GSK557296 will be separately analyzed using a mixed effects model with fixed effect terms for dose, day, and dose-by-day interaction. Subject will be treated as a random effect in the model. Point estimates and their associated 90% confidence intervals will be constructed for the differences, Day 6-Day 1. The point estimates and their associated 90% confidence intervals will then be back-transformed to provide point estimates and 90% confidence intervals for the ratios, Day6:Day1.

Dose proportionality may be explored, if appropriate. An assessment of dose proportionality will be made on AUC and Cmax using the power model, fitting terms for dose as a fixed effect and subject as a random effect. AUC, Cmax, and dose, will be loge-transformed prior to analysis. An estimate of slope (with corresponding 90% CI) will be provided as a measure of potential dose proportionality. Estimates of within-subject and model based pooled between-subject variability estimates will be computed for AUC and Cmax of GSK557296 for use in future studies.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model.

Plots of trough concentration data from Days 2-6 will be produced for informal assessment of achievement of steady state. For both parts of the study, descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum, and CVb%) will be calculated for all pharmacokinetic endpoints by dose. In addition, for AUC(0-tau), AUC(0-∞), Cmax, and as data permit, T1/2, geometric means (and corresponding 95% confidence intervals) will be constructed.

**IS:**

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation department within GlaxoSmithKline. Plasma (compound number) concentration-time data will be analyzed by non-compartmental methods with the most current version of WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve \([AUC(0-t), AUC(0-τ) \text{ and } AUC(0-∞)]\), and apparent terminal phase half-life \((t1/2)\). AUC\((0-∞)\) or AUC\((0-τ)\) and Cmax following single and repeat doses may be used for assessment of dose proportionality. Trough concentration \((Cτ)\)
samples collected on the specified days may be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, Quantitative Sciences, GlaxoSmithKline.

Tmax of GSK557296 will be summarized using appropriate descriptive statistics. If data permit, an appropriate nonparametric test for differences in Tmax by dose and/or day will be carried out.

The focus of the statistical analysis will be to estimate the effect of repeat dosing relative to single dosing on the pharmacokinetics of GSK557296. All pharmacokinetic endpoints including AUC and Cmax, where data permit, will be descriptively summarized by dose and day.

Following loge-transformation, AUC(0-t) and Cmax of GSK557296 will be separately analyzed using a mixed effects model with fixed effect terms for dose, day, and dose-by-day interaction. Subject will be treated as a random effect in the model. Point estimates and their associated 90% confidence intervals will be constructed for the differences, Day 6-Day 1. The point estimates and their associated 90% confidence intervals will then be back-transformed to provide point estimates and 90% confidence intervals for the ratios, Day6:Day1.

Dose proportionality may be explored, if appropriate. An assessment of dose proportionality will be made on AUC and Cmax using the power model, fitting terms for dose as a fixed effect and subject as a random effect. AUC, Cmax, and dose, will be loge-transformed prior to analysis. An estimate of slope (with corresponding 90% CI) will be provided as a measure of potential dose proportionality. Estimates of within-subject and model based pooled between-subject variability estimates will be computed for AUC and Cmax of GSK557296 for use in future studies.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model.

Plots of trough concentration data from Days 2-6 and Days 3-7 will be produced for informal assessment of achievement of steady state. For both parts of the study, descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, maximum, and CVb%) will be calculated for all pharmacokinetic endpoints by dose. In addition, for AUC(0-tau), AUC(0-∞), Cmax, and as data permit, T1/2, geometric means (and corresponding 95% confidence intervals) will be constructed.

Rationale:
This section was updated due to the changes in the dosing schedule for the fourth cohort.

Section 8.2 Meals and Dietary Restrictions

WAS:

All Cohorts Days 1 and 6

Subjects will be fasted at least 8 hours prior to dosing on the first single dose day (Day 1) and last dosing day (Day 6) and will continue to fast for at least 4 hours post-dose. Additional restrictions are detailed below.

- Soft drinks without caffeine and fruit juices (except grapefruit juice) may be consumed ad libitum beginning 4 hours after dosing
- Consumption of products containing grapefruit will not be permitted within 7 days prior to the administration of study medication until collection of the final pharmacokinetic blood sample
- Subjects must fast from all food and drink (except water) for at least 4 hours prior to any clinical laboratory evaluations
- On Day 1, Lunch, dinner and snack will be provided as follows:
  - Lunch will be provided at approximately 4 hours after the first AM dosing
  - A Snack may be provided at approximately 7 hours after the first AM dosing
  - Dinner will be provided at approximately 10 hours after the first AM dosing
  - An evening snack will be permitted up until 22:00

Water may be consumed *ad libitum* beginning 2 hours after dosing (with the exception of the 240 mL water used for study drug administration)

Days 2-5

- Breakfast, will be provided as follows (Lunch, Dinner and snacks will be provided as above):
  - Breakfast will be provided at approximately 30 minutes prior to AM dosing. The meal should be completely consumed within 20 minutes or less. Administration of the study medication should occur approximately 30 minutes after the start of breakfast.

IS:

Cohorts 1-3: Days 1 and 6

Subjects will be fasted at least 8 hours prior to dosing on the first single dose day (Day 1) and last dosing day (Day 6) and will continue to fast for at least 4 hours post-dose. Additional restrictions are detailed below.
• Soft drinks without caffeine and fruit juices (except grapefruit juice) may be consumed ad libitum beginning 4 hours after dosing

• Consumption of products containing grapefruit will not be permitted within 7 days prior to the administration of study medication until collection of the final pharmacokinetic blood sample

• Subjects must fast from all food and drink (except water) for at least 4 hours prior to any clinical laboratory evaluations

• On Day 1, Lunch, dinner and snack will be provided as follows:
  • Lunch will be provided at approximately 4 hours after the first AM dosing
  • A Snack may be provided at approximately 7 hours after the first AM dosing
  • Dinner will be provided at approximately 10 hours after the first AM dosing
  • An evening snack will be permitted up until 22:00

Water may be consumed *ad libitum* beginning 2 hours after dosing (with the exception of the 240 mL water used for study drug administration)

**Days 2-5**

• Breakfast, will be provided as follows (Lunch, Dinner and snacks will be provided as above):
  • Breakfast will be provided at approximately 30 minutes prior to AM dosing. The meal should be completely consumed within 20 minutes or less. Administration of the study medication should occur approximately 30 minutes after the start of breakfast.

**Cohort 4 Days 1 and 7**

Subjects will be fasted at least 8 hours prior to dosing on the first single dose day (Day 1) and last dosing day (Day 7) and will continue to fast for at least 4 hours post-dose. Additional restrictions are detailed below.

• Soft drinks without caffeine and fruit juices (except grapefruit juice) may be consumed ad libitum beginning 4 hours after dosing

• Consumption of products containing grapefruit will not be permitted within 7 days prior to the administration of study medication until collection of the final pharmacokinetic blood sample

• Subjects must fast from all food and drink (except water) for at least 4 hours prior to any clinical laboratory evaluations

• On Day 1, Lunch, dinner and snack will be provided as follows:
  • Lunch will be provided at approximately 4 hours after the first AM dosing
  • A Snack may be provided at approximately 7 hours after the first AM dosing
  • Dinner will be provided at approximately 10 hours after the first AM dosing
An evening snack will be permitted up until 22:00. Water may be consumed *ad libitum* beginning 2 hours after dosing (with the exception of the 240 mL water used for study drug administration).

**Days 3-6**

- Breakfast, will be provided as follows (Lunch, Dinner and snacks will be provided as above):
  - Breakfast will be provided at approximately 30 minutes prior to AM dosing. The meal should be completely consumed within 20 minutes or less. Administration of the study medication should occur approximately 30 minutes after the start of breakfast.

  Water may be consumed *ad libitum* beginning 2 hours after dosing (with the exception of the 240 mL water used for study drug administration).

**Rationale:**

Additional wording was added to reflect the changes to Cohort 4 in the study.