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Drug interaction assessment of GSK3882347 in healthy participants aged 18 to 65 years

Submission date	Recruitment status	[X] Prospectively registered
19/11/2022	No longer recruiting	[ ] Protocol
Registration date	Overall study status	[ ] Statistical analysis plan
24/03/2023	Completed	[ ] Results
Last Edited	Condition category	[ ] Individual participant data
04/03/2026	Other	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This research study will test a new GlaxoSmithKline (GSK) drug (GSK3882347). A second drug will also be used in this study, called Midazolam, which is a medicine approved by the national health agency in your country and is used to help with anxiety and relaxation before surgical procedures. This is an open-label study which means volunteers will know which treatment they are to receive.
The GSK drug (GSK3882347) tested in this study was made to potentially treat or prevent bladder infections, also known as acute cystitis or uncomplicated urinary tract infections. So far, the drug has been given to 51 individuals aged 18 to 65 years of age in clinical trials.
This research study is being completed to test how the body processes both study drugs individually and when given together. The study will also provide more information on the safety and tolerability of GSK3882347.

Who can participate?
Healthy females (who are not pregnant or breastfeeding) and male adults who are 18 to 65 years of age

What does the study involve?
Approximately 24 to 36 people will take part in this study. The study will last for approximately 7 weeks or approximately 9 weeks for females who are choosing hormonal contraception as a method of birth control.
The study will consist of screening (up to 28 days prior to study entry), a treatment phase and follow-up. In the treatment phase, volunteers will stay in the clinical unit overnight from Day -1 (day before the start of dosing) and for 16 nights in a row during the dosing period. The dosing period of the study will start on Day 1 (the day after screening visit on Day -1) and is split into a dosing period 1 and dosing period 2.

What are the possible benefits and risks of participating?
GSK3882347, the study drug, has been taken by healthy volunteers previously and has been well tolerated so far.
Preclinical studies in animals have shown that the study drug may have a risk of causing issues with the gastrointestinal (GI) system and the kidneys. Final studies to understand the effect on

reproduction have not been done and therefore participants are required to use birth control and barrier methods such as condoms as well if participants are taking hormonal birth control. Additionally, women who are breastfeeding or pregnant may not take part in this study.
GSK3882347 has been given to participants in a First Time In Human (FTIH) clinical trial, where the participants were given either a single dose or multiple doses. Due to the risk that was noted during the animal studies, particular attention was given to GI symptoms and the effect on the kidneys.
12 (24%) of the participants in the FTIH trial had GI symptoms. Only 2 cases of symptoms (diarrhoea and dry mouth) were considered by the study doctor to be related to taking the study drug GSK3882347. All of the cases were mild and resolved during the study, with no cases with serious effects, and no effects that increased as the dose of the study drug was increased. The GI findings above that were seen in animal studies were not seen during the FTIH clinical trial. However, we will continue to monitor for any GI symptoms for safety purposes during this study.
To date, there have been no reported kidney issues in humans after the use of GSK3882347. However, because of the risk noted during the animal studies, participants with kidney issues and participants on medications that may affect kidney function cannot take part in this study. Additionally, blood samples will be taken to monitor the health of the kidneys during this study for safety.
Other risks may be related to the use of midazolam, which will be given during this study to learn more about the effect of the study medicine on other medicines patients might be taking. Midazolam is a drug that, when given at high doses, has the potential to have effects on the heart, breathing, and brain. In particular, midazolam may cause trouble breathing at much higher doses than those planned in this study. We will be giving a low dose of midazolam.
To ensure the safety of participants, the study will be run at a clinical unit with experience running Phase I safety clinical trials and medical staff present 24 hours a day. Participants will be monitored closely and receive heart and oxygen monitoring for 10 hours after dosing with midazolam to monitor their safety. Additionally, flumazenil, a medication that helps reverse the effects of midazolam, will be available on-site in case of an emergency.

Where is the study run from?
GlaxoSmithKline Research & Development Limited (UK)

When is the study starting and how long is it expected to run for?
November 2022 to August 2024

Who is funding the study?
GlaxoSmithKline Research & Development Limited (UK)

Who is the main contact?
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Clinical Trials Information System (CTIS)
2022-002537-33

Integrated Research Application System (IRAS)
1006579

ClinicalTrials.gov (NCT)
NCT05760261

Protocol serial number
213252

Study information

Scientific Title
A Phase I, open-label study in healthy participants aged 18 to 65 years to investigate the CYP3A4 induction potential of GSK3882347

Study objectives
Primary objective:
To characterize the impact of 14 days of oral daily doses of GSK3882347 on the pharmacokinetics (PK) of MDZ and its primary metabolite 1-hydroxymidazolam in healthy adult participants.

Secondary objective:
To evaluate the safety and tolerability of GSK3882347 in healthy participants throughout the study. To evaluate GSK3882347 plasma PK following oral administration, once daily, single and repeat doses (Period 2).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/03/2023, Cambridgeshire and Hertfordshire Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)2071048096, +44 (0)207 104 8102, +44 (0)207 104 8265; cambsandherts.rec@hra.nhs.uk), ref: 22/EE/0296

Study design
Interventional non-randomized study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Healthy volunteer drug interaction study

Interventions
This is a Phase I, open-label, non-randomized, pharmacokinetic (PK), drug-drug interaction study in healthy participants to assess the effect of GSK3882347 as an inducer of CYP3A4 using Miprosed Oral Solution (Midazolam, MDZ), a sensitive substrate of hepatic and intestinal CYP3A4 in healthy participants. The study will investigate MDZ PK in two dosing periods:
1. Period 1: A single oral dose of MDZ 5 mg
2. Period 2: A single oral dose of 5 mg MDZ following 14 days of once-daily repeat dosing of GSK3882347 (14 days has been selected as this duration is required in order to maximize any potential CYP3A4 enzyme induction)

The study has an outpatient screening Period and the screening visit will occur within 28 days.

The treatment period consists of a second screening/enrolment review on Day -1 and a clinic admission day followed by two dosing periods (Period 1 and Period 2) and a one-day MDZ washout period where PK samples will be collected, and participants will be followed up for safety prior to discharge from the clinic and study. A follow-up telephone call will be conducted 3 days post the last dose of GSK3882347 (2 days post-discharge) for Adverse Event/Serious Adverse Event (AE/SAE) review. For only women of childbearing potential (WOCBP) choosing hormonal contraceptives, a second follow-up telephone call 14 days post-discharge will be conducted.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
GSK3882347, midazolam

Primary outcome(s)
Plasma pharmacokinetics of midazolam (MDZ) and 1-hydroxy-MDZ: AUC(0-24), AUC(0-t), AUC(0-inf), Cmax, tmax, tlag and t½ measured using noncompartmental PK analysis methods in Period 2 compared to Period 1 following 14 days dosing of GSK3882347

Key secondary outcome(s))
Measured throughout the study up to the telephone follow-up visit:
1. Occurrence of adverse events (AEs) and serious adverse events (SAEs) measured using AE and SAE reports submitted by the investigator in the study eCRF, or via paper reporting forms
2. Occurrence of clinically significant changes in laboratory values (hematology, chemistry, and urinalysis), vital signs and 12-lead electrocardiogram (ECG) readings
3. GSK3882347 AUC(0-24), Ctau, CL/F, Vd/F and MRT AUC(0-inf) and Cmax for single dose (Day 2) and AUC(0-tau) and Cmax for repeat dose (Day 15) measured using noncompartmental PK analysis methods
4. Ro (accumulation ratio) using AUC(0-tau) for repeat dose measured using the ratio of AUC(0-24)Day15/AUC(0-24)Day1
5. Time invariance using AUC(0-tau) (repeat dose) and AUC(0-inf) (single dose) measured using the ratio of AUC(0-24)Day15/AUC(0-inf)Day1
6. Achievement of steady-state (Ctau collected on multiple days) measured using the ratio of Ctau,Day15/Ctau,Day1

Completion date
20/08/2024

Eligibility

Key inclusion criteria
1. Participants must be ≥18 years of age and ≤65 years of age at the time of signing the informed consent.
2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring. A participant with a

clinical abnormality or laboratory parameter(s) not specifically listed in the exclusion or exclusion criteria that is outside the reference range for the population being studied may be included only if the investigator, in consultation with the Medical Monitor (if required), agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
3. Body weight at least 50.0 kg (110 lbs) for males and 45.0 kg (99 lbs) for females; and body mass index (BMI) within the range 18.5 – 32.0 kg/m² (inclusive).
4. Male and female participants
4.1. Male Participants: Male participants are eligible to participate if they agree to the following during the study intervention Period and for at least 3 days, after the last dose of study intervention:
4.1.1. Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent OR
4.1.2. Must agree to use contraception/barrier as detailed below:
- Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
- Agree to use a male condom when engaging in any activity that allows for the passage of ejaculate to another person.
4.2. Female Participants: A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
4.2.1. Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4 Contraceptive and Barrier Guidance. OR
4.2.2. Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 during the study intervention Period and for at least 3 days after the last dose of study (or for intervention). For WOCBP choosing hormonal contraceptives, the required duration for hormonal contraceptive use is during the study intervention period and for at least 14 days [with a double barrier as described in Section 10.4]) after the last dose of the study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of the study intervention
4.2.3. A WOCBP must have a negative highly sensitive pregnancy test [urine or serum] as required by local regulations) within 24 hrs before the first dose of the study intervention. See Section 8.3.6 Pregnancy Testing.
- If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.6 Pregnancy Testing.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk of inclusion of a woman with an early undetected pregnancy.
5. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group

Mixed

Lower age limit
18 years

Upper age limit
65 years

Sex
All

Total final enrolment
27

Key exclusion criteria
1. History or presence of significant cardiovascular, respiratory, hepatic, renal, urological, gastrointestinal, metabolic, endocrinological, hematological, immunologic, dermatologic, neurological or psychiatric disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data or in the opinion of the investigator places the subject at unacceptable risk or would make adhering to study procedures for the duration of the study difficult. Participants who have had a gastric bypass or a cholecystectomy are excluded from the study.
2. Abnormal blood pressure, as determined by the investigator.
3. Alanine transferase (ALT) value >1.5 × ULN.
4. Bilirubin value >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
5. The participant has a current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
6. The participant has congenital long QT syndrome or known prolongation of the corrected QT (QTc) interval.
7. The participant has any history of heart failure.
8. The participant has a family history of QT prolongation or sudden death.
9. The participant has any current or previous history of episodes of symptomatic bradycardia or bradyarrhythmia.
10. The participant has a QTc >450 msec. Note: The QTc is the QT interval corrected for heart rate according to the Fridericia formula, machine, or manual overread.
11. The participant has anuria, oliguria, or impairment of renal function (eGFR by CKD-EPI 2021 <90 mL/min/1.73m2 or serum creatinine >ULN or urine ACR (albumin-to-creatinine ratio) of ≥30 mg/g at screening).
12. The participant must agree to and adhere to the concomitant therapy (including nondrug therapies) restrictions as described in Section 6.9 from the Screening Visit through to the end of the study (including telephone visit).
13. Participation in the study would result in loss of blood or blood products in excess of 500 ml within 56 days.
14. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
15. Current enrolment or past participation within the last 30 days or 5 half-lives, whichever is longer, before signing of consent in any other clinical study involving an investigational study intervention or any other type of medical research.
16. Current enrolment or past participation in this clinical study.
17. Positive human immunodeficiency virus (HIV) antibody test.

18. Presence of Hepatitis B surface antigen (HbsAg) at screening or within 3 months prior to the first dose of the study intervention.
19. Hepatitis C antibody test result at screening or within 3 months prior to the first dose of the study intervention.NOTE: Participants with a positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if there is a history of a confirmatory negative Hepatitis C RNA. Positive Hepatitis C RNA test result within 3 months prior to the first dose of the study intervention.
20. A positive confirmation of COVID-19 infection, or high clinical index of suspicion for COVID-19.
21. The participant, in the judgment of the investigator, would not be able or willing to comply with the protocol or complete the study.
22. Regular alcohol consumption within 6 months prior to the study, defined as an average weekly intake of >14 units for males or females. One unit is equivalent to approximately 8 g of alcohol: a half-pint (~240 ml) of beer, one glass (125 ml) of wine or one (25 ml) measure of spirits.
23. Positive smoke breathalyzer indicative of smoking history at screening and each in-house admission to the clinical research unit or regular use of tobacco or nicotine-containing products (i.e. nicotine patches or vaporizing devices) within 3 months prior to screening.
24. Regular use of combustible tobacco products, and non-combustible nicotine delivery systems, inclusive of cigarettes, cigars, pipes, and materials used to “vape”.
25. Any history of substance abuse or a positive urine test for drugs of abuse/alcohol breath screen at screening or admission.
26. Known hypersensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.

Date of first enrolment
11/04/2023

Date of final enrolment
20/08/2024

Locations

Countries of recruitment
United Kingdom

Study participating centre
Not provided at time of registration
-
-
England
-

Sponsor information

Organisation

GlaxoSmithKline (United Kingdom)

ROR
https://ror.org/01xsqw823

Funder(s)

Funder type
Industry

Funder Name
GlaxoSmithKline

Alternative Name(s)
GlaxoSmithKline plc., GSK plc., GlaxoSmithKline plc, GSK

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No