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A study in healthy male volunteers to investigate how the test medicine is taken up, broken down and removed from the body

Submission date
12/05/2022

Recruitment status
No longer recruiting

Registration date
12/07/2022

Overall study status
Completed

Last Edited
26/10/2023

Condition category
Nervous System Diseases

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The Sponsor is developing the test medicine, SPN-817, for the treatment of neurological disorders such as epilepsy. Epilepsy is usually a lifelong disorder that affects the brain and can cause loss of awareness and seizures. This healthy volunteer study will try to assess how the test medicine is taken up, broken down and removed by the body. To help investigate this, the final dose of the test medicine will be radiolabelled. 'Radiolabelled' means that the test medicine has a radioactive component (Carbon-14) which enables the test medicine to be tracked in the body. The safety and tolerability of the test medicine will also be studied.

Who can participate?
Healthy male volunteers aged 30 to 64 years

What does the study involve?
On Days 1 to 20, volunteers will receive doses of the non-radiolabelled test medicine in the form of oral capsule(s), in the morning and evening. To increase tolerance to the potential adverse events (AEs) of the test medicine, the doses will be up-titrated from 0.25 mg to 1.25 mg, with an increment of 0.25 mg every 4 days. On Days 21 and 22, volunteers will receive a single dose of the test medicine in the form of an oral liquid. On Day 22, the test medicine will be radiolabeled. Volunteers will be dosed on an empty stomach on each occasion. Blood, urine and faecal samples will be collected throughout the study. Volunteers will remain in the clinic up to Day 29, however, if the relevant radioactivity criteria have not been met, volunteers may be required to remain at the clinic until Day 31. If relevant criteria have not been met at this point, home collections of urine and/or faeces may be required. Volunteers are expected to be involved in this study for approximately 8 weeks.

What are the possible benefits and risks of participating?
There are no medical benefits of participating as this is a healthy volunteer study, however, the development of a treatment for epilepsy may benefit the population as a whole. As this is a Phase I study, the most relevant population is healthy volunteers. It is considered that the risk /benefit evaluation in this study supports the use of healthy volunteers. There is always a risk

that the stipend in healthy volunteer studies could represent coercion. The time spent in the clinic, travel, inconvenience and other expenses factor in calculating the stipend. Perception of risk is not considered in this calculation. Volunteers may experience side effects from the test medicine. Full information on possible side effects is provided to volunteers in the PIS/ICF. When investigating new medicines there is also a risk of unexpected side effects and occasionally allergic reactions. All volunteers will be closely monitored during the study and safety assessments will be performed at regular intervals. Risks are further mitigated by ensuring that only volunteers who meet all inclusion/exclusion criteria are included and that if the safety of any volunteer represents a concern they will be withdrawn. There will be an extended period of fasting for the volunteers taking part in this study. Volunteers will be allowed water freely up to 1 hour before dosing and from 1-hour post-dose and will be monitored for signs of dehydration and fatigue. Blood samples will be collected during the study. Collection of these samples can cause soreness and bruising of the arms but these problems usually clear up within a few days to a few weeks. ECG stickers on volunteers' chests and limbs may cause some local irritation and may be uncomfortable to remove but volunteers will be closely monitored to ensure any local irritation does not persist. Volunteers will be required to answer a Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire to assess an individuals thoughts/behaviour related to suicide. The test medicine could affect the way a volunteer’s body reacts to direct sunlight. Once dosed, volunteers will need to avoid being outside in the sun until 7 days after their final dose. If volunteers need to go outside they should wear a suitable sunscreen, sunglasses and clothing. Volunteers should also not use sunbeds during this time. By taking part in the study the volunteers will be exposed to a small amount of radiation.

Where is the study run from?
Supernus Pharmaceuticals (USA)

When is the study starting and how long is it expected to run for?
May 2022 to September 2022

Who is funding the study?
Supernus Pharmaceuticals (USA)

Who is the main contact?
Dr Neeti Mehta, namehta@supernus.com

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-004066-35

Integrated Research Application System (IRAS)
1004367

Protocol serial number
817P111

Study information

Scientific Title
An open-label, single period, multiple-dose study designed to assess the mass balance, metabolite profile and metabolite identification of [14C]-SPN-817 in healthy male subjects

Acronym
QSC205262

Study objectives
Primary objectives:
1. To determine the mass balance (how much radioactivity can be recovered from the urine and faeces) after an oral dose of [14C]-SPN-817
2. To perform metabolite (breakdown products) profiling and structural identification from plasma, urine and faecal samples

Secondary objectives:
3. To determine the routes and rates of elimination of [14C]-SPN-817
4. To identify each metabolite (breakdown product) accounting for more than 10% of circulating total radioactivity or 10% of the excreted dose
5. To evaluate the extent of distribution of total radioactivity into blood cells
6. To explore the oral pharmacokinetics (what the body does to the test medicine, PK) of SPN-817 in plasma and whole blood
7. To explore the oral PK of SPN-817 in urine

8. To explore the oral PK of TR in plasma and whole blood following administration of [14C]-SPN-817
9. To provide additional safety and tolerability information for SPN-817

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/07/2022, London Bridge REC (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, UK; +44 (0)207 1048202; londonbridge.rec@hra.nhs.uk), ref: 22/LO/0377

Primary study design
Interventional

Study design
Single-centre open-label multiple-dose trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Epilepsy

Interventions
On Days 1 to 20, volunteers will receive single oral doses of the non-radiolabelled test medicine, SPN 817 Extended Release Capsules, twice daily, in the morning and evening. To increase tolerance to the potential adverse events (AEs) of the test medicine, the doses will be uptitrated from 0.25 mg to 1.25 mg, with an increment of 0.25 mg every 4 days.

On Day 21, volunteers will receive a single oral dose of the test medicine, SPN-817 Oral Solution, 1.0 mg, in the morning.

On Day 22, volunteers will receive a single oral dose of the radiolabelled test medicine, [14C]-SPN-817 Oral Solution, 1.0 mg (NMT 3.7 MBq), in the morning

Volunteers will be dosed on an empty stomach on each occasion.

This is a non-randomized study.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
[14C]-SPN-817

Primary outcome(s)

1. Mass balance of total radioactivity recovery in all excreta (urine and faeces): CumAe and Cum% Dose measured using mass spectrometry from samples taken at timepoints between Day 22 and Day 29
2. Metabolite profiling, structural identification, and quantification analysis in whole blood, plasma, urine and faeces samples using liquid chromatography-radio-detection with subsequent mass spectrometry where appropriate, from samples taken at timepoints between Day 22 and Day 24

Key secondary outcome(s)
1. Determination of routes and rates of elimination of total radioactivity (TR) by Ae, %Dose, CumAe and Cum%Dose by interval from blood, urine and faecal samples taken at timepoints between Day 22 and Day 29
2. Identification of the chemical structure of each metabolite accounting for more than 10% by AUC of circulating TR or 10% of the excreted dose from blood, urine and faecal samples taken at timepoints between Day 22 and Day 29
3. Evaluation of whole blood:plasma concentration ratios for TR from samples taken at timepoints between Day 22 and Day 29
3. Measurement of appropriate pharmacokinetic (PK) parameters of huperzine A in plasma and whole blood, including but not limited to: tlag, tmax, tlast, Cmax, AUCtau, AUClast, t1/2, Lambda-z, CL/Ftau, Vz/Ftau, MRTlast, whole blood:plasma concentration ratios for huperzine A, where possible and applicable from samples taken at timepoints between Day 1 and Day 29
4. Measurement of appropriate PK parameters of huperzine A in urine including but not limited to: Ae, CumAe, Fe%, CumFe% and CLR, where possible from samples taken at timepoints between Day 1 and Day 29
5. Measurement of appropriate PK parameters of TR in plasma and whole blood, including but not limited to: tlag, tmax, tlast, Cmax, AUClast, AUCinf, t1/2, Lambda-z, B/P AUC, where possible and applicable from samples taken at timepoints between Day 22 and Day 29
6. Safety and tolerability information for SPN-817 by assessing the incidence of adverse events (AEs), concomitant medications, physical examinations, medical history, change from baseline for vital signs, electrocardiograms (ECGs), suicidal ideation and behaviour as measured by the Columbia Suicide Severity Rating Scale (C-SSRS) and laboratory safety tests at screening and from Day -1 until discharge from the ward on (up to) Day 29

Completion date
14/09/2022

Eligibility

Key inclusion criteria
1. Healthy males
2. Aged 30 to 64 years inclusive at the time of signing informed consent
3. Body mass index (BMI) of 18.0 to 32.0 kg/m² as measured at screening
4. Must be willing and able to communicate and participate in the whole study
5. Must have regular bowel movements (ie average stool production of ≥1 and ≤3 stools per day)
6. Must provide written informed consent
7. Must agree to adhere to the contraception requirements defined in the clinical protocol

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
Male

Key exclusion criteria
1. Subjects who have received any IMP in a clinical research study within the 90 days prior to Day 1, or less than 5 elimination half-lives prior to Day 1, whichever is longer
2. Subjects who are, or are immediate family members of, a study site or sponsor employee
3. Subjects who have previously been administered IMP in this study
4. Evidence of current SARS-CoV-2 infection
5. History of any drug or alcohol abuse in the past 2 years
6. Regular alcohol consumption >21 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 ml glass of wine, depending on type)
7. A confirmed positive alcohol breath test at screening or admission
8. Current smokers and those who have smoked within the last 12 months. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission
9. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
10. Male subjects with pregnant or lactating partners
11. Radiation exposure, including that from the present study, excluding background radiation but including diagnostic x-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017, shall participate in the study
12. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening
13. Clinically significant abnormal clinical chemistry, haematology or urinalysis as judged by the investigator. Subjects with Gilbert's Syndrome are not allowed.
14. Confirmed positive drugs of abuse test result
15. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) antibody results
16. Evidence of renal impairment at screening, as indicated by an estimated CLcr of <80 mL/min using the Cockcroft-Gault equation
17. History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory or gastrointestinal disease, neurological or psychiatric disorder, as judged by the investigator
18. Resting heart rate <50 bpm at screening
19. History of bladder outflow obstruction such as benign prostatic hyperplasia or any history of acute urinary retention
20. Creatine kinase ≥1.5 x upper limit of normal
21. Serious adverse reaction or serious hypersensitivity to any drug or the formulation excipients
22. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active
23. Donation of blood or plasma within the previous 3 months or loss of greater than 400 ml of

blood
24. Subjects who are taking, or have taken, any prescribed or over-the-counter drug, or herbal remedies or vaccines, including the COVID-19 vaccine, (other than up to 4 g of paracetamol per day) in the 14 days before IMP administration. Exceptions may apply, as determined by the investigator, if each of the following criteria are met: medication with a short half-life if the washout is such that no pharmacodynamic activity is expected by the time of dosing with IMP; and if the use of medication does not jeopardize the safety of the trial subject; and if the use of medication is not considered to interfere with the objectives of the study.
25. Subjects answers "yes" to "Suicidal Ideation" Items 1 or 2 on the C-SSRS at screening
26. Failure to satisfy the investigator of fitness to participate for any other reason

Date of first enrolment
25/07/2022

Date of final enrolment
14/08/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Quotient Sciences Limited
Mere Way
Ruddington Fields
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NG11 6JS

Sponsor information

Organisation
Supernus Pharmaceuticals (United States)

ROR
https://ror.org/03sd6kg46

Funder(s)

Funder type
Industry

Funder Name
Supernus Pharmaceuticals

Alternative Name(s)
Supernus Pharmaceuticals, Inc.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available. The findings of this Phase I study will be shared with the Sponsor, Supernus Pharmaceuticals, only. As these findings are confidential due to commercial sensitivity, it is not appropriate to share the results of this study with other researchers at this time.

IPD sharing plan summary
Not expected to be made available

Study outputs

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