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A study to investigate the safety, tolerability, and concentration in the blood of different dose strengths of SFX-01 tablets in healthy volunteers.

Submission date
20/09/2022

Recruitment status
No longer recruiting

Registration date
26/10/2022

Overall study status
Completed

Last Edited
20/11/2024

Condition category
Other

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The purpose of this study is to investigate the study drug SFX-01 (active compound sulforaphane - SFN).

The main objectives of the study are as follows:
- To determine the safety and tolerability (degree to which side effects of a drug can be tolerated) of SFN (delivered in the form of SFX-01 tablets) when it is administered as single and multiple doses at different dose strengths over a period of 7 days.
- To investigate the concentration of SFN (from SFX-01) and its' metabolites in the blood and urine, how this changes over a period of time and to evaluate whether there are differences in the concentrations when different dose strengths are given. Metabolites are by-products which are produced when a drug is broken down in the body.
- To investigate the effect of SFN (from SFX-01) on the body (known as pharmacodynamics (PD) by analysing the effect of SFN (from SFX-01) on the levels of specific biomarkers in the body. Biomarkers are markers within the body such as a gene, molecule or characteristic which can be used to identify the presence of a particular biological process occurring in the body or a particular disease.

As well as evaluating the above, the study will also investigate, as exploratory objectives, the levels of other key biomarkers associated with SFN (from SFX-01) through the analysis of blood samples and skin biopsies. In addition, the study will include an element of genetic testing where certain parts of DNA (known as genes) which are involved in the processes that break down drugs (metabolism) in the body will be evaluated. This evaluation will assess whether differences in DNA between participants affects how SFN from SFX-01 is broken down which may affect the effectiveness of SFX-01.

Who can participate?
A total of up to 32 participants are needed to fully complete this study. Participants must be healthy adult males aged between 18 and 55.

What does the study involve?
The study will consist of 4 planned groups of up to 8 participants (with the option to include additional participants/groups up to a maximum of 56 participants overall). Each group will first receive a single dose of the study drug (planned as either 300 milligrams (mg) or 600 mg) once or twice per day (dependent on study group) before taking SFX-01 once or twice daily for a further 6 days (up to Day 7) .The study will consist of a screening visit (between 36 and 9 days prior to first dose), a pre-dose skin biopsy visit (Day -8), 1 treatment period (consisting of 9 days with 8 overnight stays) and a post-study follow-up visit on Day 14.

Blood and urine samples will be taken at set time points throughout the study in order to measure the concentration of SFN (from SFX-01) in the blood and urine. The results from each of the groups will then be compared to determine if there are any significant differences in the safety profile of SFX-01, the concentration of SFN (from SFX-01) in the blood and urine and to determine whether there are any differences between different dose strengths, single and multiple doses or taking the drug once versus twice per day.

What are the possible benefits and risks of participating?
Taking part in this study is not expected to provide participants with any direct medical benefit. However, the information we get from this study may help improve the treatment of diseases including ASD and IPF, with other indications in glioma and certain types of breast cancer.

Possible risks include the following:
Blood Sampling: The procedure for blood collection either by direct venepuncture or indwelling cannula may cause mild pain and bruising at the collection site. Placement of an indwelling catheter is proposed in order to minimise these effects for rapid PK sampling. Very rarely, a blockage of a vein or a small nerve injury can occur, resulting in numbness and pain. If this occurs, it will resolve with time.

Blood pressure and pulse rate: The participants blood pressure and pulse will be measured using an inflatable cuff which will be placed on the arm. They may experience mild discomfort in the arm whilst the cuff is inflated.

ECG: Small sticky pads will be placed on the participants' upper body before the ECG and an ECG machine will measure the electrical activity of the participants' heart. Before the pads are applied, the skin needs to be cleaned. Trained staff may need to shave/clip small patches of the participants hair in these areas. Like Elastoplast® these sticky pads may be uncomfortable to remove.

Skin Biopsy Procedure: As part of the study, participants will be required to undergo a skin biopsy procedure at two biopsy sites on three occasions. Common side effects of a skin biopsy procedure include bleeding and bruising, pain, infection, allergic reaction to the numbing medicine used in the procedure, or damage to the structures beneath the skin site (such as an artery or a nerve). In order to minimise these risks, the procedure will be carried out by a trained and experienced medical professional and every due care will be taken to minimise these risks (including the use of local anaesthesia to numb the area and full wound care management post-procedure).

Participants will also be advised that if they do experience any of these effects noted, they should report these to a member of the Simbec-Orion team who will then be able to provide appropriate treatment and care as deemed necessary. In addition, participants will be informed that they can request to halt the procedure at any time whilst this is being performed.

COVID-19 Risks: Participants should also be aware of the risks of exposure to COVID-19. When participants attend the clinical unit at each visit, they may be asked to complete a self-declaration form and temperature check to confirm that they are not showing any early signs of COVID-19 infection and that they have not had any contact with individuals who are currently self-isolating or have tested positive (dependent on risk mitigation measures employed at the clinical unit at the time of clinical conduct).

Participants may also be required to have a negative COVID-19 test prior to admission to the clinical unit for any overnight stays as defined within the study protocol. This procedure may cause some mild discomfort in the nose or throat when the swab is being taken but this should resolve after the procedure has been completed.

Additionally, at the clinical unit, participants may be asked to wear a facemask during procedures where clinical staff cannot maintain a 2 m distance. It is noted that if participants have a medical exemption from wearing a face mask, they will not be required to do so. In any circumstance, to prevent risk of transmission between staff and participants, all staff will be wearing appropriate personal protective equipment i.e., face masks, face shields etc during the course of the study.

Harm to the unborn child: For male participants (of childbearing potential), they will be required to use a highly effective or 2 effective methods of contraception (including a condom) with their partner (of childbearing potential) from the point of first dose until at least 90 days following the last dose of IMP.

Throughout the study, the health of the participants will be regularly monitored and appropriate treatment for any medical condition will be provided if required. All doctors employed by Simbec-Orion are trained and certified in Advanced Life Support Procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures. Simbec-Orion also has an agreement with Prince Charles Hospital for referral of participants if required following a medical emergency.

Where is the study run from?
The study will be conducted at Simbec-Orion Clinical Pharmacology Unit, an MHRA Phase 1 accredited CRO based in South Wales (UK)

When is the study starting and how long is it expected to run for?
April 2022 to March 2023

Who is funding the study?
This study is funded and sponsored by a pharmaceutical company called Evgen Pharma plc, based and headquartered in the United Kingdom (UK).

Who is the main contact?
Dr Glen Clack, Sponsor’s Chief Medical Officer, Evgen Pharma plc, regulatory@evgen.com

Contact information

Type(s)
Scientific

Contact name
Dr Glen Clack

Contact details
Evgen Pharma plc
Alderley Park
Congleton Road
Nether Alderley
Macclesfield
United Kingdom
SK10 4TG
+44 (0)1625 466 591
regulatory@evgen.com

Type(s)
Principal Investigator

Contact name
Dr Annelize Koch

Contact details
Simbec-Orion Clinical Pharmacology
Merthyr Tydfil Industrial Park
Cardiff Road
Merthyr Tydfil
United Kingdom
CF48 4DR
+44 (0)1443 694313
annelize.koch@simbecorion.com

Additional identifiers

EudraCT/CTIS number
2022-001601-43

IRAS number
1005951

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
EVG003N, IRAS 1005951

Study information

Scientific Title

A phase 1, randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and repeated daily doses of SFX-01 tablets in healthy male participants

Acronym
EVG003N

Study objectives
The primary objective of this study is:
- To investigate the safety and tolerability of SFX-01 tablets in healthy male participants.

The secondary objectives of this study are:
- To characterise the PK of SFN and principal metabolites from SFX 01 after single and repeated daily dosing.
- To investigate the PD effect of SFX-01 on engagement on Nrf2 pathway genes in peripheral blood mononuclear cells (PBMCs) and correlation with PK.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 27/09/2022, Wales Research Ethics Committee 1 (Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 2920 230457; Wales.REC1@wales.nhs.uk), ref: 22/WA/0218

Study design
Interventional double-blind randomized placebo controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet.

Health condition(s) or problem(s) studied
Autism Spectrum Disorder (ASD), Idiopathic Pulmonary Fibrosis (IPF), Glioma & Breast Cancer

Interventions
This is a randomised, double-blinded, placebo-controlled dose-escalation study to evaluate the safety, tolerability, PK, and PD of the tablet formulation of SFX-01 following single and repeat daily dosing in healthy male participants. Treatment in each cohort will start as a single dose of SFX-01 or matching placebo on Day 1, with a starting dose of 300 mg once daily (QD), followed

by a 24-hour washout period. Multiple (QD or BID) dosing will start on Day 2, with participants being dosed from Day 2 to Day 7. Each participant will receive a low-fat meal 1 hour before each dose administration, to be eaten within 30 minutes or less.

It is initially planned to study 4 cohorts of 8 participants (32 participants in total). Eight participants will be randomised in each cohort at a ratio of 3:1 for SFX-01 to matching placebo.

The following indicative dose cohorts are planned:
• Cohort 1: 300 mg QD
• Cohort 2: 300 mg BID
• Cohort 3: 600 mg QD
• Cohort 4: 600 mg BID

Additional optional cohorts may also be studied to explore other lower or intermediate dosing regimens, subject to emerging data, and an addition to a cohort may be made if a participant is withdrawn from the study. However, the total number of participants will not exceed 56.

A Screening Visit will take place between Day -36 and Day -9, with the first dose of IMP administered on Day 1. Informed consent will be obtained, inclusion/exclusion criteria will be reviewed, and screening evaluations will be performed. A further Pre-dosing Visit will take place on Day -8 when, following confirmation of eligibility, 2 skin punch biopsies will be taken. Participants will be admitted to the unit on Day -1 and will be discharged from the unit on Day 8 following the collection of the final PK/PD samples.

The relationship between the SFN PK and potential PD biomarkers of SFN activity will be explored at the various dose levels. Serial blood and urine samples will be collected over a 24-hour period following dosing on Day 1 (single dose) and Day 7 (repeat dosing) for assessment of PK. Blood samples will be collected for assessment of PD biomarkers at multiple time points on Day -1 (Baseline), Day 1, Day 2, Day 7, and Day 8. Participants will have 2 granulation tissue over-punch biopsies on both Day -1 (following confirmation of eligibility) and Day 7. Safety assessments will include AEs, clinical laboratory assessments, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.

An End-of-Study Visit will be performed 7 days (± 2 days) after the last dose of IMP.

The study end is defined as last subject last visit.

The study will take place in the Clinical Unit of Simbec-Orion Clinical Pharmacology (Clinical Unit) under full medical and nursing supervision.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
SFX-01 (Sulforaphane-alpha cyclodextrin tablets)

Primary outcome measure

The primary endpoints for this study are safety endpoints and are defined as follows:
1. Adverse Events (AEs) will be recorded from the point of informed consent up to final post-study follow up visit.
2. Laboratory safety (biochemistry, haematology, coagulation and urinalysis) at screening, Day -8, Day -1, Day 4, Day 7 & End of Study
3. Vital signs (systolic/diastolic blood pressure, pulse, oral body temperature and respiratory rate) at screening, Day -8, Day -1, Day 1 (pre-dose and 1, 2, 4, 8 and 12 h post dose), Day 4, Day 7 (pre-dose and 1, 2, 4, 8, and 12 h post-dose), and End-of Study Visit
4. 12-lead ECG (heart rate, PR interval, QRS width, QT interval and QTcF interval) at screening, Day -1, Day 1 (Pre-dose, 2, 4, 8, and 12 h post dose), Day 2, Day 4, Day 7, and End-of Study Visit

Secondary outcome measures

The secondary endpoints for this study are pharmacokinetic/pharmacodynamic parameters derived from analysis of plasma and urine samples for concentrations of SFX-01 and its' major metabolites.

PK Endpoints are defined as follows:
1.1. Single Dose (Day 1)
AUC0-12 - area under the concentration-time curve from 0 to 12 hours
AUC0-24 - area under the concentration-time curve from 0 to 24 hours
Cmax - maximum observed concentration
AUC0-12 (norm) - area under the concentration-time curve from 0 to 12 hours normalised for dose
AUC0-24 (norm) - area under the concentration-time curve from 0 to 24 hours normalised for dose
Cmax (norm) - maximum observed concentration normalised for dose
C24 - concentration at 24 hours (pre-dose Day 2)
Tmax - time to maximum observed concentration
t½ - apparent terminal elimination half-life
λz - terminal elimination rate constant
CL/F - Apparent total body clearance following extravascular administration (parent only)
Vz/F - apparent volume of distribution in the terminal state (parent only)
Ae - amount excreted in urine
fe - fraction excreted in urine (parent only)
CLR - renal clearance

1.2. Steady-State (Day 7)
AUCtau - area under the concentration-time curve in the dosing interval
AUC0-∞ - area under the concentration-time curve from time 0 extrapolated to infinity
%AUCext - percentage extrapolated AUC
Cmax,ss - maximum observed concentration at steady-state
Cmin,ss - minimum observed concentration at steady-state
AUCtau (norm) - area under the concentration-time curve in the dosing interval normalised for dose
AUC0-∞ (norm) - area under the concentration-time curve from time 0 extrapolated to infinity normalised for dose
Cmax,ss (norm) - maximum observed concentration at steady-state normalised for dose
Cmin,ss (norm) - minimum observed concentration at steady-state normalised for dose
Tmax,ss - time to maximum observed concentration at steady state
t½ - apparent terminal elimination half-life
λz - terminal elimination rate constant

CL/F, ss - Apparent total body clearance at steady-state following extravascular administration (parent only)
MRT, ss - mean residence time at steady-state
RA1 - accumulation ratio based on AUCtau
RA2 - accumulation ratio based on Cmax

PK Samples (Serum – 1 sample per timepoint per participant per cohort)
Day 1 & Day 7: Pre dose, then 15 mins, 30 mins, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 14 h, and 18 h post dose
Day 2 & Day 8: Pre-dose (24 h after Day 1/7 dose)

PK Samples (Urine – single sample pre-dose with pooled urine samples per timepoint per participant per cohort)
Day 1 & Day 7: pre-dose, then 0-4 h, 4-8 h 8-12 h and 12-24 h post dose

PD endpoints are defined as follows:
2.1. Isolation of PBMCs for analysis of Nrf2 pathway messenger ribonucleic acid (mRNA) expression and Nrf2-anti-oxidant response element (Nrf2 ARE) activity in PBMC lysates
2.2. Ex-vivo lipopolysaccharide (LPS) stimulation for plasma soluble factors
2.3. TBNK analysis (flow cytometry)
2.4. Transcriptomics

3. Pharmacodynamic changes in Nrf2 pathways genes including NQO1, TXNDR1, and AKR1C1, mRNA expression in PBMC

4. Exploratory downstream PD biomarkers:
4.1. Nrf2-ARE activity in PBMC lysates
4.2. Pharmacodynamic changes in plasma chemokines/cytokines after ex-vivo whole blood LPS stimulation e.g., including but not limited to interferon-gamma, interleukin (IL)-1β, IL-6, IL-8, IL-4, IL-10, monocyte chemotactic protein-1 (MCP 1), TGF-β, IL-17A/F, IL-22
4.3. Whole blood TBNK immunophenotyping (absolute numbers and percentages of T cells, B cells, and natural killer [NK]-cells in peripheral blood)
4.4. Pharmacodynamic changes in phosphorylated Nrf2 (pNrf2), phosphorylated SHP2 (pSHP2), and pSTAT3 protein expression in over-punch biopsies by IHC

5. Other exploratory biomarkers may include but not be limited to the following:
5.1. Terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) and Ki67 IHC staining in over-punch biopsies
5.2. Transcriptomics (e.g., RNA sequencing) or proteomics analyses of over-punch biopsies and whole blood. Additional soluble protein/proteomics analyses may also be performed on serum and/or tissue

PD Samples (6 samples per timepoint per participant per cohort)
- Day -1: am (similar time of day as when Day 2 pre-dose sample will be taken)
- Day 1: 6 h after Day 1 dose
- Day 2: Pre dose (24 h after Day 1 dose)
- Day 7: 6 h after Day 7 dose
- Day 8: 24 h after Day 7 dose

Overall study start date
04/04/2022

Completion date
31/03/2023

Eligibility

Key inclusion criteria
1. Participants who are able to provide informed consent indicating they understand the purpose of, and procedures required, for the study and are willing to participate.
2. Participant must be 18 to 55 years of age inclusive, at the time of signing and dating the informed consent form (ICF).
3. Participants must be male.
4. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, safety laboratory tests, vital signs, and 12-lead ECGs.
5. Participants must have a body mass index (BMI) of 18-32 kg/m2, with body weight in the range of 50-100 kg.
6. Male participant (and partner of childbearing potential) willing to use a highly effective method of contraception or 2 effective methods of contraception, if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the participant) from first dose until 90 days after last dose of IMP.

To be re-confirmed on Day -8 (prior to skin punch biopsy) and Day -1 (prior to first dose administration):
7. Participant continues to meet all screening inclusion criteria.
8. Participant has a negative urinary drugs of abuse (DOA)/alcohol screen.
9. Participant has a negative COVID-19 test (if required at the time of study conduct).

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
Male

Target number of participants
32

Total final enrolment
24

Key exclusion criteria
1. Participants who are unable to refrain from eating brassica vegetables or using brassica containing supplements from at least 7 days prior to the Day -8 skin punch biopsies until the End

of- Study Visit. Brassica vegetables include cabbage, cauliflower, horseradish, landcress, Ethiopian mustard, kale, collard greens, Chinese broccoli, cabbage, Brussels sprouts, Kohlrabi broccoli, broccoli flower, broccoli romanesco, wild broccoli, bok choy, Komatsuna, mizuna, rapini, flowering cabbage, Chinese cabbage, Napa cabbage, turnip root, rutabaga, canola/rape seed, Siberian kale, wrapped heart mustard cabbage, mustard seed (brown, black, white), tatsoi, rocket (arugula), garden cress, water cress, radish, daikon, and wasabi.
2. Participants with a known sensitivity or intolerance to brassica vegetables.
3. Participants with any clinically relevant history (e.g., respiratory, renal, hepatic, GI, haematological, lymphatic, neurological, cardiovascular, psychiatric disease or diseases).
4. Participants with any clinically significant abnormal vital signs, physical examination, or other safety findings within 36 days before the first dose administration of the IMP.
5. Participants with any clinically significant abnormal test results for haematology, clinical chemistry, coagulation and/or urinalysis within 36 days before the first dose administration of the IMP.
6. Participants with gamma-glutamyl transferase (GGT) >1.5 x upper limit of normal (ULN).
7. Participants with disorders of the central nervous system, psychiatric disorders, and/or behavioural disturbances (e.g., cerebrovascular events, depression, post-traumatic stress disorder, anxiety, bipolar disorder, severe migraine, and Parkinson's disease).
8. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements, within 36 days or 5 half-lives (whichever is longer) prior to the first dose of IMP.
9. Participants with a positive screen for Hepatitis B (Hepatitis B surface antigen [HBsAg]), Hepatitis C (Hepatitis C antibody, anti-Hepatitis C virus [HCV]), COVID-19 (lateral flow test [LFT]) or human immunodeficiency virus (HIV).
10. Participants with a history or clinical evidence of alcoholism or drug abuse. Alcohol abuse is defined as regular weekly intake of more than 21 units if male. Drug abuse is defined as compulsive, repetitive and/or chronic use of drugs or other substances with or without problems related to their use and/or where stopping or a reduction in dose will lead to withdrawal symptoms.
11. Participants who smoke more than 10 cigarettes or the equivalent amount of tobacco per day and/or regularly use vaping products and/or are unwilling to refrain from smoking/vaping during the study.
12. Participants with a confirmed positive result from urinary DOA screen at Screening, Day -8, or Day -1 indicating drug abuse including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, methadone, opiates, phencyclidine (PCP), and tricyclic antidepressants, or a confirmed positive urine alcohol test at Screening, Day -8, or Day -1.
13. Participants who have received a COVID-19 vaccination within 28 days prior to the first dose or plan to receive a COVID-19 vaccination before the End-of-Study Visit.
14. Participants who had donated more than 500 mL of blood within 90 days prior to Screening.
15. Participation in a New Chemical Entity (NCE) clinical study within the previous 3 months or five half-lives, whichever is longer, or a marketed drug clinical study within the 30 days or five half-lives, whichever is longer, before the first dose of IMP. (Washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study).
16. Concomitant disease or condition that could interfere with dosing of IMP, conduct of the study, affect drug absorption, distribution, or excretion, or that would, in the opinion of the investigator, pose an unacceptable risk to the participant.
17. Participants with a known hypersensitivity to SFN or any excipients (including alpha cyclodextrin) contained within the IMP.
18. Vegans, vegetarians, or participants with other dietary restrictions (e.g., restrictions for medical, religious, or cultural reasons, etc) who would be unable to consume standardised meals.
19. Any other finding that, in the opinion of the investigator, deems the participant unsuitable for the study.

To be re-confirmed on Day -8 (prior to skin punch biopsy) and Day -1 (prior to first dose administration):
1. Development of any exclusion criteria since Screening.
2. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements, since Screening.
3. Participation in a clinical study since the Screening Visit.
4. Donation of 500 mL or more blood since the Screening Visit.

Date of first enrolment
13/10/2022

Date of final enrolment
06/02/2023

Locations

Countries of recruitment
United Kingdom

Study participating centre
Simbec-Orion Clinical Pharmacology (AKA Simbec Research Ltd)
Simbec-Orion Clinical Pharmacology
Merthyr Tydfil Industrial Park
Cardiff Road
Merthyr Tydfil
United Kingdom
CF48 4DR

Sponsor information

Organisation
Evgen Pharma (United Kingdom)

Sponsor details
Alderley Park
Congleton Road
Nether Alderley
Macclesfield
England
United Kingdom
SK10 4TG
+44 01625 466 591
regulatory@evgen.com

Sponsor type

Industry

Website
http://evgen.com/

ROR
https://ror.org/05b6k3g41

Funder(s)

Funder type
Industry

Funder Name
Evgen Pharma plc (United Kingdom)

Results and Publications

Publication and dissemination plan
Internal report
Submission to regulatory authorities

Intention to publish date
01/03/2024

Individual participant data (IPD) sharing plan
The study data will be shared with relevant research groups and external stakeholders collaborating with the study sponsor to support the future development of the IMP within the boundaries of strict confidentiality agreements.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Results article		09/11/2024	20/11/2024	Yes	No