ISRCTN42835524 https://doi.org/10.1186/ISRCTN42835524

Phase I Single- and Multiple-Ascending Dose Trial of EVX-101

Submission date	Recruitment status	[X] Prospectively registered
01/03/2022	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
02/03/2022	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
21/04/2023	Mental and Behavioural Disorders	[ ] Record updated in last year

Plain English summary of protocol

Current plain English summary as of 21/04/2023:
Background and study aims
The Sponsor is developing the test medicine, EVX-101, as a potential adjunctive treatment of depression. Adjunctive treatment is something that is given in addition to initial primary treatment e.g therapy, when the initial treatment is only partially effective. Depression is a common mental health problem that causes people to experience low mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy and poor concentration. This two-part healthy volunteer study will try to identify what the body does to the test medicine (pharmacokinetics) and to assess the safety and tolerability of the test medicine, given as single and multiple doses.

Who can participate?
Male and female volunteers aged between 18 to 55 years old.

What does the study involve?
This study will take place at one non-NHS site, enrolling up to 40 participants. In order to reflect the intended clinical use of EVX-101, volunteers will receive pre-treatment and co-treatment, at approved doses, to stable blood levels with escitalopram (a marketed product for treatment of depression), both at outpatient visits and at home dosing, before and after test medicine /placebo dosing, for up to 28 days in Part 1 and up to 54 days in Part 2.

Volunteers in Part 1 will receive two doses of the test medicine or placebo on Day 21, which will be given as two equal administrations approx. 12 hours apart. Volunteers return to the unit approximately 7 days after test medicine/placebo dosing and received a follow up phone call 7 to 14 days after their final dose of escitalopram.

Volunteers in Part 2 will receive multiple doses of the test medicine or placebo from Day 21 up to and including Day 47. Doses will be given twice daily as two equal administrations approx. 12 hours apart, with the dose level increased every 7 days. Volunteers returned to the unit approximately 5 days after discharge, received follow up phone calls every 2 days for 6 days and returned for a final follow up visit on Day 61 7.

Volunteer’s blood and urine will be taken throughout the study for analysis of the test medicine and for their safety.

Volunteers are expected to be involved in this study for approximately 12 weeks from screening to the follow up call.

What are the possible benefits and risks of participating?
Participants will get no medical benefit from taking part in this study. We hope that the development of a product to improve the treatment of depression will be of benefit to patients with this condition
As this is a Phase I study, the most relevant population is healthy volunteers, and it is considered that the risk/benefit evaluation supports this. Females of childbearing potential (non-pregnant or lactating) will be allowed to participate as long as they comply with the contraception requirements detailed in the clinical protocol. 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 and/or escitalopram in this study. Full information on possible side effects is provided to volunteers in the Participant Information Sheet and Informed Consent Forms. When investigating new medicines there is always a risk of unexpected side effects and occasionally allergic reactions. Volunteers will be closely monitored during the study. 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. To ensure an adequate fluid intake, the volunteers will be allowed ad libitum fluids 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. As the test medicine and escitalopram are CNS acting and may have an effect on the volunteers’ mental health, an appropriately trained physician will assess their mood using the C-SSRS questionnaire at regular intervals during the study.

Where is the study run from?
Evecxia Therapeutics Inc (USA)

When is the study starting and how long is it expected to run for?
January 2022 to December 2022

Who is funding the study?
Evecxia Therapeutics Inc (USA)

Who is the main contact?
Jacob Jacobsen, jacob.jacobsen@evecxia.com

Previous plain English summary:
The sponsor has confirmed that the trial meets the criteria for deferral of publication of the full details of the trial. The full details will be added to the study record when the results are published, which will be within 30 months after the trial has ended.

Contact information

Type(s)
Principal investigator

Contact name
Dr Jacob Jacobson

Contact details
Chief Scientific Officer
Evecxia Therapeutics Inc.
2 Davis Drive
RTP
Durham
United States of America
NC 27709
None provided
jacob.jacobsen@evecxia.com

Type(s)
Scientific

Contact name
Dr Jacob Jacobson

Contact details
Chief Scientific Officer
Evecxia Therapeutics Inc.
2 Davis Drive
RTP
Durham
United States of America
NC 27709
None provided
jacob.jacobsen@evecxia.com

Type(s)
Public

Contact name
Dr Jacob Jacobson

Contact details
Chief Scientific Officer
Evecxia Therapeutics Inc.
2 Davis Drive
RTP
Durham
United States of America
NC 27709
None provided
jacob.jacobsen@evecxia.com

Additional identifiers

Clinical Trials Information System (CTIS)
2021-006715-28

Integrated Research Application System (IRAS)
1004711

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
EVX101-102, IRAS 1004711

Study information

Scientific Title
A Phase 1 Single- and Multiple-Ascending Dose Study of the Safety and Pharmacokinetics of a Gastro Retentive Formulation of 5-Hydroxytryptophan (5-HTP) and Low-Dose Carbidopa (EVX-101) in Healthy Subjects Taking Escitalopram

Study objectives
Current study hypothesis as of 21/04/2023:
Primary objectives:
Part 1
1. To evaluate the pharmacokinetic (what the body does to the test medicine, PK) profile of 5 hydroxytryptophan (5-HTP) and carbidopa, when administered as single ascending doses (SAD), split 12 hours apart, of gastro-retentive (GR) tablet, 5-HTP/carbidopa GR tablet, in healthy male and female subjects taking escitalopram at steady state
2. To assess the safety and tolerability of 5-HTP/carbidopa GR tablet when administered as SAD to healthy male and female subjects taking escitalopram at steady state
Part 2
1. To evaluate the PK profile of multiple-ascending doses (MAD) of a 5-HTP and carbidopa GR tablet, 5-HTP/carbidopa GR tablet, when administered twice daily (split dose) using a dose titration design in a single cohort of healthy male and female subjects taking escitalopram at steady state
2. To assess the safety and tolerability of 5-HTP/carbidopa GR tablet administered as MAD using a dose titration design to healthy male and female subjects taking escitalopram at steady state

Secondary objectives:
Part 1
1. To assess the effect of rising carbidopa doses in 5-HTP/carbidopa GR tablet on 5-HTP PK in SAD of carbidopa to healthy male and female subjects taking escitalopram at steady state
2. To assess the pharmacodynamic (PD) effect of SAD of 5-HTP/carbidopa GR tablet on a biomarker (cortisol) of acute elevations in brain extracellular serotonin concentrations in healthy male and female subjects taking escitalopram at steady state
Part 2
1. To assess the effect of rising carbidopa doses in 5-HTP/carbidopa GR tablet on 5-HTP PK in MAD of carbidopa using a dose titration design to healthy male and female subjects taking escitalopram at steady state

2. To assess the PD effect during MAD using a dose titration design of 5-HTP/carbidopa GR tablet on a biomarker (cortisol) of acute elevations in brain extracellular serotonin concentrations in healthy male and female subjects taking escitalopram at steady state

Previous study hypothesis:
The sponsor has confirmed that the trial meets the criteria for deferral of publication of the full details of the trial. The full details will be added to the study record when the results are published, which will be within 30 months after the trial has ended.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 02/03/2022 , Fast Track REC (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, UK; fasttrack.rec@hra.nhs.uk), REC ref: 22/FT/0020
2. 2. Approved 02/03/2022 , MHRA (10 South Colonnade, Canary Wharf, London, E14 4PU, UK; +44 (0)20 3080 6000; info@mhra.gov.uk)

Study design
Pharmacokinetics, safety and tolerability study in 38 healthy volunteers

Primary study design
Other

Study type(s)
Other

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

Interventions
Current interventions as of 21/04/2023:
In Part 1 volunteers received escitalopram once daily until Day 28 and received two doses of 5 HTP/carbidopa GR tablet or placebo (12 hours apart) on a single day of dosing (Day 21). Doses given were 250 mg / 0.625 mg 5 HTP/carbidopa GR tablet or 250 mg / 0.3125 mg 5 HTP /carbidopa GR tablet

In Part 2 volunteers received escitalopram once daily until Day 61 and received twice daily doses of 5 HTP/carbidopa GR tablet or placebo (12 hours apart) on Day 21 to Day 47. Doses given ranged from 250 mg / 0.3125 mg 5 HTP/carbidopa GR tablet to 250 mg / 2.5 mg 5 HTP/carbidopa GR tablet

Previous interventions:
The sponsor has confirmed that the trial meets the criteria for deferral of publication of the full details of the trial. The full details will be added to the study record when the results are published, which will be within 30 months after the trial has ended.

Intervention Type
Drug

Phase

Phase I

Drug/device/biological/vaccine name(s)

5-HTP/carbidopa Gastro Retentive (GR) sustained-release tablet, placebo for 5-HTP/carbidopa GR tablet

Primary outcome(s)

Current primary outcome measures as of 21/04/2023:
Part 1:
Pharmacokinetic (PK) parameters following dosing of 5-HTP/carbidopa GR tablet as single ascending doses split 12 hours apart were measured using analysis of plasma samples taken from pre dose to Day 28. PK parameters include but are not limited to: Tmax, Cmax, AUC(0-12), AUC(0 last), AUC(0 inf) and T1/2

Safety and tolerability was assessed throughout the study, from dosing to final follow up calls (Day 1 to Day 42). Safety endpoints will be measured via incidence of AEs, physical examinations and change from baseline for vital signs, ECGs, C-SSRS, Hunter serotonin toxicity criteria, and laboratory safety tests

Part 2:
PK parameters following dosing of 5-HTP/carbidopa GR tablet as multiple ascending doses split twice daily were measured using analysis of plasma samples taken from pre dose to Day 61. PK parameters include but are not limited to: Tmax, Cmax, AUC(0-12) and T1/2.

Safety and tolerability was assessed throughout the study, from dosing to final follow up visits (Day 1 to Day 61). Safety endpoints will be measured via incidence of AEs, physical examinations and change from baseline for vital signs, ECGs, C-SSRS, Hunter serotonin toxicity criteria, and laboratory safety tests.

Previous primary outcome measure:
The sponsor has confirmed that the trial meets the criteria for deferral of publication of the full details of the trial. The full details will be added to the study record when the results are published, which will be within 30 months after the trial has ended.

Key secondary outcome(s))

Current secondary outcome measures as of 21/04/2023:
Part 1:
PK parameters for 5-HTP following single ascending doses of carbidopa were measured using analysis of plasma samples taken from pre-dose to Day 28. PK parameters include but are not limited to: Cmax, AUC(0 12), AUC(0-last) and AUC(0-inf).

Changes from baseline in serum cortisol levels were measured using analysis of plasma samples taken from pre-dose to Day 28.

Part 2:
PK parameters for 5-HTP following multiple ascending doses of carbidopa were measured using analysis of plasma samples taken from pre-dose to Day 61. PK parameters include but are not limited to: Cmax and AUC(0-12).

Changes from baseline in serum cortisol levels were measured using analysis of plasma samples taken from pre-dose to Day 61.

Previous secondary outcome measure:
The sponsor has confirmed that the trial meets the criteria for deferral of publication of the full details of the trial. The full details will be added to the study record when the results are published, which will be within 30 months after the trial has ended.

Completion date
16/12/2022

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 21/04/2023:
1. Healthy males or non-pregnant, non-lactating healthy females
2. Aged 18 to 55 years old for Part 1 and aged 25 to 55 years old for Part 2 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. Weight ≥50 kg at screening
5. Must be willing and able to communicate and participate in the whole study
6. Must provide written informed consent
7. Must agree to adhere to the contraception requirements defined in the clinical protocol

Previous participant inclusion criteria:
Healthy volunteer

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
38

Key exclusion criteria
Current participant exclusion criteria as of 21/04/2023:
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 received 5-HTP/Carbidopa in study EVX101-101/QSC201140
4. Subjects who have previously been administered IMP (5-HTP/carbidopa GR tablet or placebo) in this study. Subjects who have taken part in Part 1 are not permitted to take part in Part 2

5. Evidence of current SARS-CoV-2 infection within 4 weeks of Day 1
6. History of any drug or alcohol abuse in the past 2 years
7. Regular alcohol consumption in males >21 units per week and females >14 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)
8. A confirmed positive alcohol breath test at screening or Day 1
9. Results at screening indicative of chronic excess alcohol intake
10. 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 Day 1
11. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
12. Females who are pregnant or lactating (all female subjects must have a negative highly sensitive pregnancy test)
13. Male subjects with pregnant or lactating partners
14. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening
15. Clinically significant abnormal clinical chemistry, haematology or urinalysis as judged by the investigator. Subjects with Gilbert's Syndrome are allowed
16. Platelet count, serum sodium, potassium or magnesium below the lower limit of the reference range at screening. For Part 2 only, haemoglobin below the lower limit of the reference range at screening
17. Clinically significant findings on ECG or vital signs as assessed by the investigator at screening or Day 1
18. QTcF >450 msec at screening or Day 1 or known QT interval prolongation or congenital long QT syndrome
19. Confirmed positive drugs of abuse test result
20. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) antibody results
21. History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory or neurological disorder, as judged by the investigator
22. History of any psychiatric disease requiring treatment in the last 5 years
23. Known history of glaucoma or raised intraocular pressure
24. Presence or history of any GI disease including peptic ulceration, GI bleeding, ulcerative colitis, Crohn's Disease
25. Subjects with a history of cholecystectomy or gall stones
26. Subjects unwilling to eat at least 90% of the pre-dose meals
27. Subject answers "yes" to "Suicidal Ideation" Items 1 or 2 on the C-SSRS (lifetime) at screening or Day 1
28. Serious adverse reaction or serious hypersensitivity to any drug (including serotonergic drugs such as anti-depressants and migraine medication) or the formulation excipients
29. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active
30. Donation of blood or plasma within the previous 3 months or loss of greater than 400 mL of blood prior to Day 1
31. Subjects who are taking, or have taken, any prescribed or over-the-counter drug or herbal remedies (other than up to 4 g of paracetamol per day, contraceptive pill/hormonal contraception or HRT) in the 14 days before escitalopram administration on Day 1. COVID-19 vaccines are accepted concomitant medications. 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 PD activity is expected by the time of dosing with IMP; and if the use of medication does not jeopardise the safety of the trial subject; and if the use of medication is not considered to interfere with the objectives of the study

32. Failure to satisfy the investigator of fitness to participate for any other reason

Previous participant exclusion criteria:
Healthy volunteer

Date of first enrolment
15/03/2022

Date of final enrolment
20/10/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Quotient Sciences Limited
Trent House
Mere Way
Ruddington Fields Business Park
Nottingham
United Kingdom
NG11 6JS

Sponsor information

Organisation
Evecxia Therapeutics Inc.

Funder(s)

Funder type
Industry

Funder Name
Evecxia Therapeutics Inc.

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 due to their high commercial sensitivity and negligible benefit to the public of publication of results of non-therapeutic clinical trials.

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			28/06/2023	No	No