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Phase 1 study to evaluate the pharmacokinetics, safety, tolerability, and taste of tecovirimat pediatric formulations

Submission date 08/07/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 28/07/2021	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 12/06/2023	**Condition category** Other	[_] Individual participant data

Plain English summary of protocol

Background and study aims
This is a research study to develop a liquid formulation of the drug TPOXX (tecovirimat) which is an oral antiviral drug (capsules) approved in the US for the treatment of children weighing less than 13 kg. The effect on the body and the taste of the liquid formulation will also be assessed in the study.

Who can participate?
Healthy men and women ages 18-50 years of age may participate in this study.

What does the study involve?
The study involves taking two different liquid formulations of tecovirimat and the tecovirmat capsule once with a 7 day washout in between.

What are the possible benefits and risks of participating?
This study is for research purposes only. You will get no medical benefit from taking part in this study, but the development of a treatment for smallpox in babies and young children may benefit the population as a whole.
Risk of participating in the study:
• Blood sampling - During the study you will have frequent blood samples taken. This is a standard procedure which is unlikely to cause you any problems but can sometimes cause discomfort. Collecting a blood sample from a vein may cause pain, swelling, bruising, light headedness, fainting, and very rarely, clot formation, nerve damage and/or infection at the site of the needle stick. If a cannula or intravenous (in the vein) catheter, is used to collect blood samples, it could cause pain, swelling, and redness of the vein which may not resolve quickly.
• ECG - 12-lead electrocardiograms (ECGs) - ECG stickers on your chests and limbs may cause some local irritation, redness, and itching. If the hair under the patches needs to be shaved, your skin may be irritated from shaving. ECG stickers may be uncomfortable to remove but you will be closely watched by study staff to make sure any local irritation does not persist. A reaction to the electrode tape may cause redness or swelling of your skin.
• Test medicine - The liquid test medicine in the study has not been tested yet to see how it acts

in the body and if it is safe to use.
• Loss of sleep- When staying overnight at the clinical unit, we may have to perform some tests early in the morning or during the night, which we will have to wake you up for. You may be on a clinical unit with up to 20 other people and your sleep may be interrupted.

Where is the study run from?
Quotient Sciences (UK)

When is the study starting and how long is it expected to run for?
July 2021 to October 2022

Who is funding the study?
SIGA Technologies, Inc. (USA)
Biomedical Advanced Research and Development Authority (USA)

Who is the main contact?
Dr Emily Blum, eblum@siga.com

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2021-002866-42

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
SIGA-246-027

Study information

Scientific Title
A phase 1, single-center, open label, up to two-part, single dose study to evaluate the pharmacokinetics, safety, tolerability, effect of refrigerated storage on taste of tecovirimat pediatric formulation prototype(s) for oral suspension in healthy adult subjects

Study objectives
Our goal of the study is to select a tecovirimat formulation prototype for tecovirimat oral suspension in healthy adult volunteers for use in the pediatric population.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/09/2021, Wales REC 2 (Health and Care Research Wales Support and Delivery Centre, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)2920 230457; Wales.REC2@wales.nhs.uk), ref: 21/WA/0262

Study design
Single-center open-label up to 2-part interventional single-dose study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied
Evaluation of the pharmacokinetics, safety, tolerability, and taste of tecovirimat pediatric formulations

Interventions
Current interventions as of 06/10/2022:
In Part 1, subjects will receive each of the following treatments in a sequential manner:
Period 1, Regimen A-Tecovirimat Formulation Prototype 1 for Oral Suspension, 600 mg in the fed state on Day 1 and Day 8
Period 2, Regimen B-600 mg (3 x 200 mg) TPOXX capsule reference in the fed state
Period 3, Regimen C-Tecovirimat Formulation Prototype 1 for Oral Suspension, 100 mg in the fed state

There will be an interim decision meeting after the completion of Part 1 to review the data from all Part 1 regimens to decide whether to stop the study or to continue to study Part 2.

In Part 2 (optional), up to 4 additional prototypes will be manufactured (prototypes 2 to 5) for administration. Subjects will receive each of the following treatment regimens in a sequential manner (note that Regimens F, G, H and I are optional):
Period 1, Regimen D-Tecovirimat Formulation Prototype 2 for Oral Suspension 600 mg in the fed state
Period 2, Regimen E-600 mg (3 x 200 mg) TPOXX capsule reference in the fed state
Period 3, Regimen F-Tecovirimat Formulation Prototype 3 for Oral Suspension 600 mg in the fed state OR Tecovirimat Formulation Prototype 2 for Oral Suspension 600 mg in the fed state on Day 1 and Day 8
Period 4, Regimen G-Tecovirimat Formulation Prototype 4 for Oral Suspension 600 mg in the fed state OR Tecovirimat Formulation Prototype 3 for Oral Suspension 600 mg in the fed state on Day 1 and Day 8 OR Tecovirimat Formulation Prototype 2 for Oral Suspension 100 mg in the fed state
Period 5, Regimen H-Tecovirimat Formulation Prototype 5 for Oral Suspension 600 mg in the fed state OR Tecovirimat Formulation Prototype 4 for Oral Suspension 600 mg in the fed state dosed on Day 1 and Day 8 OR Tecovirimat Formulation Prototype 3 for Oral Suspension 100 mg in the fed state
Period 6, Regimen I-Tecovirimat Formulation Prototype 5 for Oral Suspension 600 mg in the fed state on Day 1 and Day 8 OR Tecovirimat Formulation Prototype 4 for Oral Suspension 100 mg in the fed state

The study will be open-label since the primary objectives are the evaluation of PK parameters, which are not subject to bias.

Previous interventions:
TPOXX capsule reference should be administered in the fed state and the IMP will be administered in the fed state in Part 1.
In Part 2, the effect of dosing in a fasted state may be investigated to provide further information regarding the PK of tecovirimat and the PfR formulation prototypes.

The study will be open-label since the primary objectives are the evaluation of PK parameters, which are not subject to bias.

Randomisation will be used in Part 1 to minimise bias in the assignment of subjects to treatment sequences and to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment sequences.

Randomisation will not be used in Parts 2a and 2b; 2 single doses separated by a 7-day washout will be administered in Regimen H or I and J, respectively, and therefore it is more appropriate from a logistical perspective for all subjects to be administered these regimens in the same period.

In addition, in Part 2a, the tecovirimat formulation prototypes to be administered in Periods 3, 4, 5 and optional Period 6 will be determined based on an interim analysis of data from the respective preceding periods. The Clinical Trial Authorisation (CTA) application for this study describes a flexible protocol design using the concept of formulation design space to allow decision-making in response to interim PK observations. The principles of a flexible protocol were discussed and agreed upon with the Medicines and Healthcare products Regulatory Agency (MHRA) at a Scientific Advice Meeting between the MHRA and Quotient (formerly Pharmaceutical Profiles).

Treatment summary:
Part 1
In Part 1, 12 subjects will receive each of the following treatments in a randomised manner:
Regimen A: Tecovirimat Formulation 1 Prototype 1 for Oral Suspension, 600 mg in the fed state
Regimen B: 600 mg (3 x 200 mg) TPOXX capsule reference in the fed state
Regimen C: Tecovirimat Formulation 2 Prototype 1 for Oral Suspension, 600 mg in the fed state

Part 2a (optional)
Regimen D: Tecovirimat Formulation 1 or 2a Prototype 2 for Oral Suspension in the fed state
Regimen E: 600 mg (3 x 200 mg) TPOXX capsule reference in the fed state
Regimen F: Tecovirimat Formulation 1 or 2a Prototype 3 for Oral Suspension in the fed state OR
Tecovirimat Formulation 1 or 2a Prototype 2 for Oral Suspension in the fasted state
Regimen G: Tecovirimat Formulation 1 or 2a Prototype 4 for Oral Suspension in the fed state OR
Tecovirimat Formulation 1 or 2a Prototype 3 for Oral Suspension in the fasted state OR
Tecovirimat Formulation 1 or 2a Prototype 2 for Oral Suspension in the fed state on Day 1 and Day 8
Regimen H: Tecovirimat Formulation 1 or 2a Prototype 5 for Oral Suspension in the fed state OR
Tecovirimat Formulation 1 or 2a Prototype 4 for Oral Suspension in the fasted state OR
Tecovirimat Formulation 1 or 2a Prototype 3 for Oral Suspension in the fed state dosed on Day 1 and Day 8 OR
600 mg (3 x 200 mg) TPOXX capsule reference in the fasted state
Regimen I: Tecovirimat Formulation 1 or 2a Prototype 5 for Oral Suspension in the fasted state OR
Tecovirimat Formulation 1 or 2a Prototype 4 for Oral Suspension in the fed state dosed on Day 1 and Day 8 OR
Tecovirimat Formulation 1 or 2a Prototype 5 for Oral Suspension in the fed state dosed on Day 1 and Day 8 OR
600 mg (3 x 200 mg) TPOXX capsule reference in the fasted state

Part 2b
Regimen J: Tecovirimat Formulation 1 or 2a Prototype 1 for Oral Suspension, 600 mg in the fed

state on Day 1 and Day 8
Regimen K: Tecovirimat Formulation 1 or 2a Prototype 1 for Oral Suspension, 600 mg in the fasted state
Regimen L: 600 mg (3 x 200 mg) TPOXX capsule reference in the fed state
Regimen M: 600 mg (3 x 200 mg) TPOXX capsule reference in the fasted state

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Tecovirimat Formulation 1 Prototype X for Oral Suspension 1200 mg, Tecovirimat Formulation 2 Prototype X for Oral Suspension 1200 mg, TPOXX capsule reference 200 mg

Primary outcome measure
Current primary outcome measures as of 06/10/2022:
Measurement of PK parameters of tecovirimat following administration of tecovirimat formulation prototype 1 for oral suspension, including but not limited to: Tmax, Cmax, C24, AUC (0-24), AUC(0-last), AUC(0-inf), Lambda-z, T1/2, CL/F and Vz/F measured using blood samples at timepoints 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after dosing

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Previous primary outcome measures:
PK parameters of tecovirimat measured using blood samples at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after dosing:
Tmax, Cmax, C24, AUC(0 24), AUC(0 last), AUC(0-inf), Lambda-z, T1/2, CL/F and Vz/F and Relative bioavailability (Frel) for Cmax, AUC(0-last) and AUC(0-inf)

Secondary outcome measures
Current secondary outcome measures as of 06/10/2022:
1. Taste attributes (smell, sweetness, bitterness, flavor, mouthfeel/texture, grittiness and aftertaste) and overall acceptability of the prototypes of the selected tecovirimat formulation for oral suspension measured using a 9-point scale at Part 1: Day 1 after investigational medicinal product (IMP) administration, Part 2: Day 1 and Day 8 after IMP administration
2. Adverse events (AEs), serious adverse events measured using case report forms at Parts 1 & 2: Day 1 after IMP administration through D7 post-dose
3. Comparison of the appropriate PK parameters of tecovirimat following administration of prototype 1 of the selected tecovirimat formulation for oral suspension including but not limited to: Tmax, Cmax, C24, AUC(0-24), AUC(0-last), AUC(0- inf), Lambda-z, T1/2, CL/F and Vz/F measured using blood samples on Day 1 and Day 8
4. Comparison of Cmax, AUC(0-last) and AUC(0-inf) following administration of the formulation prototype 1 of the tecovirimat formulation for oral suspension at 100 mg and 600 mg measured using blood samples at timepoints 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after dosing.

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Previous primary outcome measures:
1. Taste attributes (smell, sweetness, bitterness, flavor, mouthfeel/texture, grittiness and aftertaste) and overall acceptability of the prototypes of the selected tecovirimat formulation for oral suspension measured using the taste questionnaire at Part 1: Day 1 after IMP administration, Part 2: Day 1 and Day 8 after IMP administration
2. Adverse events (AEs), serious adverse events measured using case report forms at Parts 1 & 2: Day 1 after IMP administration through D7 post dose
3. Clinical laboratory evaluations, (haematology, serum chemistry, urinalysis) at Parts 1 & 2: Screening, Pre-dose and 48 hrs. post dose (Discharge)
4. 12-lead ECGs measured at Part 1: Screening, Pre-dose; and 4,6,24, and 48 hrs, post dose (Discharge), Part 2: Screening, Pre-Dose, Day 1, D2, and D3 (Discharge), Part 2a: Regimen G, H or I /Part 2b: Regimen J, Day 8, 9 and 10 (Discharge)
5. Blood pressure (mmHg) measured using a sphygmomanometer at at Part 1: Screening, Pre-dose; and 4,6,24, and 48 hrs, post dose (Discharge), Part 2: Screening, Pre-Dose, Day 1, D2, and D3 (Discharge), Part 2a: Regimen G, H or I/Part 2b: Regimen J, Day 8, 9 and 10 (Discharge)
6. Heart rate measured using ECG at at Part 1: Screening, Pre-dose; and 4,6,24, and 48 hrs, post dose (Discharge), Part 2: Screening, Pre-Dose, Day 1, D2, and D3 (Discharge), Part 2a: Regimen G, H or I/Part 2b: Regimen J, Day 8, 9 and 10 (Discharge)
7. Respiratory rate measured by observation at at Part 1: Screening, Pre-dose; and 4,6,24, and 48 hrs, post dose (Discharge), Part 2: Screening, Pre-Dose, Day 1, D2, and D3 (Discharge), Part 2a: Regimen G, H or I/Part 2b: Regimen J, Day 8, 9 and 10 (Discharge)
8. Body temperature (Celsius) measured using thermometer at at Part 1: Screening, Pre-dose; and 4,6,24, and 48 hrs, post dose (Discharge), Part 2: Screening, Pre-Dose, Day 1, D2, and D3 (Discharge), Part 2a: Regimen G, H or I/Part 2b: Regimen J, Day 8, 9 and 10 (Discharge)
9. Physical examinations measured using physician assessment at at Part 1: Screening, Pre-dose; and 4,6,24, and 48 hrs, post dose (Discharge), Part 2: Screening, Pre-Dose, Day 1, D2, and D3 (Discharge), Part 2a: Regimen G, H or I/Part 2b: Regimen J, Day 8, 9 and 10 (Discharge)

Overall study start date
08/07/2021

Completion date
09/10/2022

Eligibility

Key inclusion criteria
1. Healthy males and female subjects between 18 and 50 years of age, inclusive.
2. Female subjects of childbearing potential must not be pregnant, lactating, or planning to become pregnant before 3 months after the last dose of study drug, and have a negative urine pregnancy test at screening and admission. Female subjects of childbearing potential (including perimenopausal women who have had a menstrual bleeding within 1 year) must use appropriate birth control from 30 days before study drug administration until 35 days after last IMP administration. Women are considered to be not of childbearing potential if they have been surgically sterilized (documented hysterectomy or tubal ligation/occlusion) or are postmenopausal (had no menses for 12 months without an alternative medical cause and a serum follicle stimulating hormone [FSH] concentration ≥40 IU/L)
3. Male subjects must agree to not donate sperm from the first dose of study drug through 95 days after the last dose of study drug.
4. Subject has a body mass index between 18.0 and 32.0 kg/m2, inclusive, at screening

5. Subject is considered by the investigator to be in good general health as determined by medical history, clinical laboratory results, vital sign measurements, 12 lead electrocardiogram (ECG) results, and physical examination findings at screening
6. Subject agrees to comply with all protocol requirements
7. Subject is able to provide written informed consent

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
50 Years

Sex
Both

Target number of participants
12-40

Total final enrolment
12

Key exclusion criteria
1. Subject has received any vaccination within 28 days prior to Day 1 or plans to receive a vaccination at any time during the study until the follow-up phone call.
2. Subject has received treatment in another clinical study of an investigational drug (or medical device) within 90 days before the first dose of study drug.
3. Subjects who have previously been administered IMP in this study. Subjects who have taken part in Part 1 are not permitted to take part in Part 2.
4. Subject has any condition possibly affecting drug absorption (e.g., previous surgery on the gastrointestinal tract, including removal of parts of stomach, bowel, liver, gallbladder, or pancreas).
5. Subject has evidence or history of clinically significant allergies (except for untreated, asymptomatic, seasonal allergies at time of the first dose of study drug), haematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, renal, dermatological, or neurological disease. Exceptions to these criteria (e.g., stable, mild joint disease unassociated with collagen vascular disease) may be made following discussions with the medical monitor.
6. Subject reports lactose intolerance.
7. Subject has a history of cardiac disease, symptomatic or asymptomatic arrhythmias, syncopal episodes, or risk factors for torsades de pointes (e.g., heart failure, hypokalaemia).
8. Subject has a family history of sudden cardiac death not clearly due to acute myocardial infarction.
9. Subject has a seizure disorder or history of seizures (does not include childhood febrile seizures) or family history of idiopathic seizures.
10. Subject has a history of drug or alcohol abuse or dependency within the last 2 years before

screening.
11. Regular alcohol consumption >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).
12. Subject has a current or recent (<30 days before screening) history of clinically significant bacterial, fungal, or mycobacterial infection.
13. Subject has a current clinically significant viral infection.
14. Subject has used any prescription (excluding hormonal birth control or hormone replacement therapy [HRT]) or over the counter medication (including herbal or nutritional supplements, excluding up to 4 g per day paracetamol) within 14 days before the first dose of study drug.
15. Subject demonstrates long-term use (≥14 consecutive days) of glucocorticoids including oral or parenteral prednisone or equivalent (>20 mg total dose per day) or high dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the preceding 1 month. (Low dose [≤800 µg/day of beclomethasone dipropionate or equivalent] inhaled and topical steroids are allowed).
16. Subject has donated >450 mL blood or blood components within 30 days before the first dose of study drug. The investigator should instruct subjects who participate in this study to not donate blood or blood components for 90 days following the last dose of study drug.
17. Subject is a smoker or has used nicotine or nicotine-containing products (e.g., cigarettes, electronic vapor cigarettes, cigars, chewing tobacco, snuff, nicotine patches, or nicotine gum) within 6 months before the first dose of study drug.
18. Subject has consumed grapefruit or grapefruit juice, pomegranate or pomegranate juice, pomelo fruits or pomelo juice, or alcohol-, caffeine-, or xanthine-containing products (e.g., tea, coffee, chocolate, cola) within 72 hours before study drug administration.
19. Subject reports participation in strenuous activity or contact sports within 24 hours before the first dose of study drug.
20. Subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus types 1 or 2 antibodies at screening.
21. Subject has a confirmed positive test result for amphetamines, barbiturates, benzodiazepines, cocaine, marijuana/cannabis, methadone, methamphetamine/ ecstasy, morphine/opiates, phencyclidine, tricyclic antidepressants, or alcohol at screening or admission.
22. Subject has any of the following laboratory test results within 28 days before the first scheduled dose of study drug:
– Estimated serum creatinine clearance (Cockcroft Gault) <60 mL/min
– Creatinine in males >145 µmol/L and in females >120 µmol/L (1.3 times the upper central laboratory reference range)
– Haemoglobin not within ≤10% of the lower central laboratory reference range
– White blood cell count not within the central laboratory reference range
– Absolute neutrophil count <1 x 10^9/L
– Platelets not within ± 10% of central laboratory reference range
– Alanine aminotransferase >2 times above the upper central laboratory reference range
– Aspartate aminotransferase >2 times above the upper central laboratory reference range
– Alkaline phosphatase >20% above the upper central laboratory reference range
– Cholesterol ≥5.0 mmol/L and low density lipoprotein ≥3.0 mmol/L.
23. Subject has clinically significant abnormal serum chemistry, haematology or urinalysis as judged by the investigator.
24. Subject has a sustained supine systolic blood pressure >140 mmHg or <100 mmHg or a diastolic blood pressure >90 mmHg at screening. Blood pressure may be retested twice in the supine position at 5-minute intervals. The pressure elevation is considered sustained if either the systolic or the diastolic pressure exceeds the stated limits on all 3 assessments.
25. Subject has a resting heart rate of <40 beats per minute or >100 beats per minute at screening, confirmed by repeat.
26. Subject has an abnormal ECG at screening that is determined by the investigator to be

clinically significant, confirmed by repeat.
27. Male subject has a QT interval corrected using Fridericia's formula (QTcF) >450 ms or female subject has a QTcF >470 ms at screening, confirmed by repeat.
28. In the opinion of the investigator, the subject is not suitable for entry into the study.
29. Subjects who are, or are immediate family members of, a study site or sponsor employee.
30. Evidence of current severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection. A minimum period of 3 months from resolution of Coronavirus Disease 2019 (COVID-19) symptoms to dosing must have passed.
31. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening.

Date of first enrolment
01/08/2022

Date of final enrolment
14/10/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Quotient Sciences
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Sponsor information

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Sponsor type
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Funder(s)

Funder type
Government

Funder Name
Biomedical Advanced Research and Development Authority

Alternative Name(s)
BARDA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Results and Publications

Publication and dissemination plan
Basic results will be added to the ISRCTN record.

Intention to publish date

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 the type of study.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		09/06/2023	09/06/2023	No	No
HRA research summary			28/06/2023	No	No