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A Phase I study in healthy adults to investigate the safety and tolerability of an oral formulation of A3907

Submission date
25/01/2022

Recruitment status
No longer recruiting

Registration date
23/02/2022

Overall study status
Completed

Last Edited
30/08/2022

Condition category
Other

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

Plain English summary of protocol

Background and study aims
This is a study to investigate the safety and tolerability of single and multiple doses of A3907. The study also assesses how much A3907 is in the blood (called pharmacokinetics or PK) and what A3907 does to the body (called pharmacodynamics or PD). Albireo is developing A3907 as a potential treatment for cholestatic liver disease.
This study will be the first time the test medication A3907 has been given to humans. A3907 is experimental and has not been approved by any regulatory agency responsible for approving study drugs for general medical use.

Who can participate?
Healthy volunteers age 18-60 with a body mass index between 18.0 and 32.0 kg/m²

What does the study involve?
The study will be conducted in two parts:

Part A: single ascending dose (SAD)
It is planned to dose at least six groups in Part A. Each group will include eight participants. One optional group may be added (Group A7) that will also include eightparticipants, if planned. Participants will receive a single dose of the study drug or a placebo (a 'dummy' capsule that does not contain the study drug but looks just like it) on one dosing occasion (once in the morning on Day 1).

Part B: multiple ascending doses (MAD)
It is planned to dose at least four groups in Part B. Each group will include eightparticipants. Twoadditional groups (B5 and B6) of eight participants each may be added to Part B. Participants will receive single doses of the study drug or placebo once a day (in the morning) or twice a day (in the morning and evening) for 7 days, depending on the results from Part A.

What are the possible benefits and risks of participating?
Participants are not expected to receive any direct medical benefits from their participation in

the study. The information collected in this study may help other people with cholestatic liver disease in the future. As participants will be healthy volunteers who do not require treatment, their alternative is to not participate in this study.
This will be the first time the study drug (A3907) has been tested in humans. A3907 has been assessed in animals both as single and repeated doses. Overall, the doses administered were well-tolerated without significant adverse effects. The starting dose for this study is 1mg. This is about 9000-fold below a dose that did not cause any adverse effects in animal studies. Later dose levels will be based on collected data and determined by the study doctor (investigator) in conjunction with the sponsor. Dosing will only continue if the blood levels of the study drug are predicted to remain well below those seen at a dose level that showed no adverse effects in animals.

Where is the study run from:
Covance Clinical Research Unit Ltd (UK)

When is the study starting and how long is it expected to run for?
February 2020 to September 2021

Who is funding the study?
Albireo (USA)

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number
202000442317

IRAS number
288699

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
A3907-001, IRAS 288699

Study information

Scientific Title
A Phase I, interwoven, first-in-human, double-blind, single and multiple ascending dose study in healthy adult subjects to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of an oral formulation of A3907, a first-in-class IBAT inhibitor

Study objectives
The purpose of the present study is to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of A3907 administered orally in healthy adults.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 16/11/2020, North East - York Research Ethics Committee (Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 104 8079; York.rec@hra.nhs.uk), REC ref: 20/NE/0216

Study design
Single-center randomized double-blind placebo-controlled single and multiple ascending dose study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Other

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

Health condition(s) or problem(s) studied
Safety, tolerability, pharmacokinetics and pharmacodynamics of an oral formulation of A3907

Interventions
This trial will be conducted at a single treatment center. Part A is a double-blind, randomized, placebo-controlled, single ascending dose (SAD), sequential group design. Part B is a double-blind, randomized, placebo-controlled, multiple ascending dose (MAD), interwoven design.

For part A, Groups A1 to A6, six subjects will receive A3907 and two subjects will receive a placebo. Part B may start after completion of Group A3, and Groups B1 to B4 will have six subjects who will receive A3907 and two subjects who will receive placebo.

A1 Cohort – 1 mg
A2 Cohort – 3 mg
A3 Cohort – 9 mg
A4 Cohort – 27 mg
A5 Cohort – 81 mg
A6 Cohort – 162 mg
A7 Cohort – 162 mg
B1 Cohort – 9 mg
B2 Cohort – 27 mg
B3 Cohort – 67.5 mg

Reference product: placebo capsules, A3907 white, size 0 hydroxypropyl methylcellulose (HPMC) capsule.
Administration route: oral.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
A3907

Primary outcome measure
Safety and tolerability assessed using:
1. Incidence and severity of adverse events. AEs are recorded during each visit:
Part A: Screening (Days -28 to -2), Day -1, Day 1, Day 2, Day 3/ET Follow up Visit (Day 10±1)
Part B: Screening (Days -28 to -2), Day -1, Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9/ET Follow up Visit (Day 16±1)
2. Laboratory abnormalities (clinical chemistry, hematology, coagulation, urinalysis):
Part A: Screening (Days -28 to -2), Day -1, Day 2, Day 3/ET Follow up Visit (Day 10±1)
Part B: Screening (Days -28 to -2), Day -1, Day 2, Day 4, Day 7, Day 9/ET Follow up Visit (Day 16±1)
3. 12-lead ECG parameters obtained at predose, 1, 2, 4, and 8 hours post-dose. ECG predose will be measured in triplicate. All other measurements will be performed singly.
Part A: Screening (Days -28 to -2), Day -1, Day 1, Day 2, Day 3/ET Follow up Visit (Day 10±1)
Part B: Screening (Days -28 to -2), Day -1, Day 1, Day 3, Day 5, Day 7, Day 9/ET Follow up Visit (Day 16±1)
4. Vital signs measurements taken at predose, 1, 2, 4, and 8 hours post-dose:
Part A: Screening (Days -28 to -2), Day -1, Day 1, Day 2, Day 3/ET Follow up Visit (Day 10±1)
Part B: Screening (Days -28 to -2), Day -1, Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9/ET Follow up Visit (Day 16±1)
5. Physical examinations:
5.1. Complete physical exam performed on screening day (days-28 to -2) and on day-1
5.2. Symptom-directed physical examination for part A (single dose) will be performed on day 1 and day 3/ET. Part B (multiple dose) will collect symptom-directed physicals on days: 1, 4, 7, 9/ET, and day 17 follow up
5.3. On dosing days the physical examination should be performed post-dose
6. Number of bowel movements and consistency measured using the Bristol Stool Form Scale measured until 24 hours following the last dose
Part A: Day 1, Day 2
Part B: Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8

Secondary outcome measures
Blood and urine samples will be collected for the analysis of plasma and urinary concentrations of A3907. Pharmacokinetic parameters will be derived by noncompartmental analysis. For Part A, the PK parameters will include:
1. AUC from time zero to infinity (AUC0-∞)
2. AUC from time zero to the time of the last quantifiable concentration (AUC0-tlast)
•percentage of AUC that is due to extrapolation from the last quantifiable concentration to infinity (%AUCextrap)
3. AUC from time zero to 24 hours postdose (AUC0- 24)
4. Maximum observed concentration (Cmax)
5. Time of Cmax (tmax)
6. Apparent terminal elimination rate constant (λz)
7. Apparent terminal elimination half-life (t1/2)

8. Apparent total clearance (CL/F)
9. Apparent volume of distribution (Vz/F)
10. Amount of drug excreted in urine (Ae)
11. Percentage of dose recovered in urine (fe)
12. Renal clearance (CLR)

In Part B, the PK parameters will include:
1. AUC over a dosing interval (AUC0-τ)
2. Cmax
3. tmax
4. λz
5. t1/2
6. CL/F
7. Vz/F
8. Observed accumulation ratio based on AUC0-τ (ARAUC)
9. Ae
10. fe
11. CLR

Measured using:
1. Urine intervals collected at 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, and 36 to 48 hours postdose
2. Blood samples collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours post-dose
3. Blood samples collected Day 1 predose and at 4 and 24 hours post-dose

Overall study start date
08/02/2020

Completion date
03/09/2021

Eligibility

Key inclusion criteria
Healthy male subjects and female subjects of nonchildbearing potential aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 32.0 kg/m² (inclusive)

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants

Part A: 48, Part B: 32

Total final enrolment

75

Key exclusion criteria

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the investigator (or designee)
2. History of any illness that, in the opinion of the investigator (or designee), might confound the results of the study or pose an additional risk to the subject by their participation in the study
3. Significant history of gastric retention, constipation, urinary retention, urinary obstruction or difficulty in voiding, as determined by the investigator (or designee)
4. History of narrow-angle glaucoma
5. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, including the active ingredient, excipients, or related compounds
6. History of stomach or intestinal surgery or resection or other medical condition that would potentially alter the absorption, metabolism, and/or excretion of orally administered drugs (uncomplicated appendectomy and hernia repair will be allowed)
7. Planned weight loss, being on any weight-reducing diet, or being on or planning to start any prescription or over-the-counter anti-obesity agent
8. Confirmed (e.g., two consecutive measurements separated by 10 minutes) systolic blood pressure >140 or <90 mmHg, diastolic blood pressure >90 or <50 mmHg, pulse rate >90 or <40 bpm, or oral body temperature >37.8°C or <35.5°C
9. Clinical evidence of liver disease or injury as indicated by the following and confirmed by repeat testing:
9.1. Alanine transaminase or AST >1.5× ULN (upper limit of normal)
9.2. Total bilirubin >1.5× ULN (total bilirubin >1.5× ULN is acceptable if direct bilirubin <35%)
9.3. Alkaline phosphatase >2× ULN
10. History or presence of clinically significant impaired renal function as indicated by abnormal creatinine, urea, or urinary constituents as determined by the investigator (or designee) or glomerular filtration rate of <80 ml/min/1.73 m^2 at screening based on the Chronic Kidney Disease Epidemiology Collaboration creatinine equation
11. White blood cells <3.5 × 109/L or platelets <100 × 10e9/l
12. History of alcoholism or drug/chemical abuse within 2 years prior to check-in
13. Alcohol consumption of >21 units per week for males and >14 units for females. One unit of alcohol equals ½ pint (285 ml) of beer or lager, 1 glass (125 ml) of wine, or 1/6 gill (25 ml) of spirits
14. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at screening or check-in
15. Positive hepatitis B surface antigen or hepatitis C antibody test result within 3 months prior to dosing, or positive hepatitis panel or positive human immunodeficiency virus test at screening. Subjects with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory hepatitis C RNA test is negative.
16. Participation in a clinical study involving administration of an investigational drug (new chemical entity) within 90 days prior to dosing or in >4 clinical studies within 12 months prior to dosing
17. Use or intent to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John’s wort, within 30 days prior to dosing
18. Use or intent to use any prescription medications/products within 14 days prior to dosing, unless deemed acceptable by the investigator (or designee)

19. Use or intent to use slow-release medications/products considered to still be active within 14 days prior to dosing
20. Use or intent to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to dosing
21. Use of tobacco- or nicotine-containing products (including vaping devices) within 3 months prior to check-in, and/or positive cotinine at screening or check-in
22. Ingestion of poppy seed-, Seville orange-, grape juice-, cranberry juice-, or grapefruit-containing foods or beverages within 7 days prior to check-in
23. Has been on a diet incompatible with the on-study diet, in the opinion of the investigator (or designee), within 30 days prior to dosing. This includes: excessive caffeine intake (e.g., >5 cups of coffee or equivalent per day), vegan or vegetarian diet, and high consumption of cruciferous vegetables
24. Inability to swallow multiple capsules
25. Receipt of blood products within 2 months prior to check-in
26. Donation of blood (450 ml) from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening
27. Poor peripheral venous access
28. Subjects who are not willing to minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) following administration of study drug until 2 weeks after the last dose
29. Mental or legal incapacity or significant emotional problems at the time of the screening visit or expected during the conduct of the study
30. Subjects who, in the opinion of the investigator (or designee), should not participate in this study

Date of first enrolment
08/02/2021

Date of final enrolment
19/08/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Covance Clinical Research Unit Ltd
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Funder(s)

Funder type
Industry

Funder Name
Albireo

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal. Additional files such as protocol, statistical analysis plan etc will not be posted online.

Intention to publish date
02/09/2022

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

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?
Basic results		30/08/2022	30/08/2022	No	No
HRA research summary			28/06/2023	No	No