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Safety and effects of oral ARV-1801 given in combination with intravenous ceftazidime or meropenem for treatment of melioidosis (a bacterial infection) in hospitalized patients

Submission date
21/10/2021

Recruitment status
No longer recruiting

Registration date
22/10/2021

Overall study status
Completed

Last Edited
22/10/2021

Condition category
Infections and Infestations

[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
This study will evaluate the safety (side effects) and the treatment effect of ARV-1801 in patients with melioidosis.
Melioidosis, also called Whitmore's disease, is an infectious disease that can infect humans or animals.
ARV-1801 is an oral dosage form and loading dose regimen of sodium fusidate. Sodium fusidate is a member of the fusidane class of antibiotics. Recent evidence demonstrates meaningful activity against the intracellular pathogen B. pseudomallei, which causes melioidosis. Once melioidosis is suspected clinically, treatment typically involves injected antibiotics such as ceftazidime or meropenem during an initial "intensive" phase (typically 2 weeks) and antibiotics taken by mouth such as co-trimoxazole during a more chronic "eradication" phase (typically 12 weeks). Nevertheless, death from the infection can still exceed 40% in some regions, with most deaths occurring early during the eradication phase of therapy.

The purpose of this study is to evaluate the effects of ARV-1801 administered for 14 days in conjunction with the current standard of care (meropenem or ceftazidime) against placebo in conjunction with the current standard of care. Day 1 dosing will include two doses of 1500mg of ARV-1801 or placebo administered 12 hours apart. Days 2-14 will include 600 mg doses of ARV-1801 or placebo administered every 12 hours.

Who can Participate?
Male or female patients 18 years of age or older hospitalized with suspected melioidosis may participate in this study.

What does the study involve?
Screening Procedures
• Patients will be asked some questions about their health (including family medical history), and about any medicines or treatments they have used in the past or are using now.

• A check-up of patients' health will be done. This will include checking ears, eyes, nose, throat, neck, skin, heart, lungs, stomach, muscles, bones, joints, lymph nodes, nervous system, and weight.
• Temperature, heart rate, breathing rate, and blood pressure will be measured.
• For women who can have children, a sample of blood (About 5 mL) will be collected and tested to make sure that they are not pregnant.

Baseline Procedures
The procedures and tests that will be performed during the baseline visit are described below.
• Patients will also be asked about any medicines or treatments they have used in the past 7 days or are using now.
• A check-up of patients health will be done.
• Temperature, heart rate, breathing rate, and blood pressure will be measured.
• Blood (20-25 mL) will be collected from each patient to check blood cells and chemicals in the blood that tell us how the organs (like liver and kidneys) are working.
• Blood (about 20 mL) , pus, mucous, urine, and/or saliva will be collected and tested to look for the presence of the bacteria that causes melioidosis.

Study Days 1-14
After randomization in the study, while in the hospital, patients will receive the following study assessments:
• Every day the study doctor or study staff member will record patients' health status and medications.
• Daily checks of temperature, heart rate, breathing rate and blood pressure.
• Recording of patients' medications and adverse events, including physical examination directed at areas of disease or reported adverse events.
• Daily administration of IV antibiotics as determined by the primary doctor.

Study Medication
Patients will be randomly assigned (like the flip of a coin) to receive either ARV-1801 or placebo. ARV-1801 or placebo will be given to patients in a tablet form. Patients will receive up to five (5) 300 mg tablets every 12 hours the first day. For the next 13 days patients will receive up to two (2) 300 mg tablets every 12 hours. If patients are unable to eat and have a feeding tube, the study drug will be ground up and given through a feeding tube. Whether patients receive ARV-1801 or placebo, all other standard treatments for melioidosis will still be given. If after patients begin taking study drug, they are found to not have melioidosis, the study drug will be discontinued, and the study doctor may switch the patients to a different treatment. However, those patients will be invited to continue on the study. Study drug or placebo will be given to patients for no more than 14 days, even if the patients stay in the hospital and continue with other treatments.

Patients will receive all normal treatments to reduce symptoms while participating in this study. These treatments may include oxygen, medicines to keep fever down, and/or to treat cough.

Laboratory Tests Done During the Study
The following laboratory tests will be done during the study:
• Blood (about 5-10 mL) will be drawn from patients' veins in an arm at four (4) scheduled visit days. These draws are for various tests to check blood cells and chemicals in the blood that tell us how organs (like liver and kidneys) are working.
• About three (3) mL of blood will be drawn at some study visits to measure the study drug in patients' bodies and how their bodies process the study drug. This is known as the pharmacokinetics (or PK) of the study drug. Blood will be drawn once on Day 2, Day 7, and Day

14.
• Blood (about 20 mL), saliva, and urine, will be collected and tested at Baseline and Days 1, 3, 7, and 14 to look for the presence of the bacteria that causes melioidosis. If present, pus and sputum will also be collected for the same testing at those visits.

Follow-up
After Day 14, if the patients are sent home from the hospital, the study doctor or a staff member will call the patients on Day 28 to ask about their condition and any medications being taken. If patients are discharged to another medical facility, the study doctor will regularly contact the new facility to get updates on the patients' condition and medications through Day 28.

What are the possible benefits and risks of participating?
There is no guarantee or promise that the study drug will help patient's condition. But patients will be helping others by contributing to medical research. Patients may feel that they are benefiting in the following ways:
• Taking part in the study will be at no cost to the patients. Their condition will be checked while their participation in the study lasts. However, the health and medical care they receive as part of the study is not a substitute for regular, ongoing medical care, or follow- up care by the patients' primary doctor.
• The study drug may help to treat patients' melioidosis or relieve their melioidosis symptoms.

Any study has risks, which may include things that could make patients sick, make them feel uncomfortable, or harm the patient. Patients might have side effects related to the study drug while taking part in the study. All people in the study will be watched carefully for any side effects. But the study team does not know all the side effects that the study drug may have. The study team may give patients other medicines to help reduce side effects. These side effects may be mild or serious. In some cases, these side effects might be long lasting or permanent and may even be life-threatening.
Taking part in this study involves some risks and possible discomfort to patients. If patients are assigned to take placebo, or if ARV-1801 does not work for patients, they may see no improvement in melioidosis symptoms compared to standard therapy.

Where is the study run from?
Arrevus, Inc., a pharmaceutical company located in the United States

When is the study starting and how long is it expected to run for?
June 2021 to conclude June 2023.

Who is funding the study?
The United States Department of Defense

Who is the main contact?
Arrevus, Inc.
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Contact information

Type(s)

Scientific

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Type(s)
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Additional identifiers

Protocol serial number
ARV-1801-001

Study information

Scientific Title
A randomized, double-blind, placebo-controlled, exploratory study to assess the efficacy, safety, and tolerability of oral ARV-1801 given in combination with intravenous ceftazidime or meropenem for intensive phase therapy of melioidosis in hospitalized patients

Study objectives
Study drug ARV-1801 with ceftazidime or meropenem will clear B. pseudomallei better than ceftazidime or meropenem alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, Office of Central Research Ethics Committee (CREC, 3rd Fl Building 3, The National Research Council of Thailand (NRCT), 196 Moo 5, Phaholyothin Rd., Ladyao, Chatuchak, Bangkok 10900, Thailand; +662 579 0117; no email provided), ref: none provided

Primary study design
Interventional

Study design
Multicenter interventional double-blinded randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Treatment of melioidosis in hospitalized patients

Interventions
The study investigates the effect of 14 days of twice daily doses of oral tablet ARV-1801 or oral tablet placebo in combination with IV meropenem or IV ceftazidime in patients hospitalized with melioidosis. Day 1 dosing will include two doses of 1500mg of ARV-1801 or placebo administered 12 hours apart. Days 2-14 will include 600 mg doses of ARV-1801 or placebo administered every 12 hours. Patients must be on either IV ceftazidime or meropenem for the duration of study Days 1-14. Randomization to active ARV-1801 or placebo will be determined via IWRS in a 2:1 ratio.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
ARV-1801

Primary outcome(s)
All-cause in-hospital mortality in the modified intent-to-treat population (mITT) measured as reported by the sites using patient records at Day 14

Key secondary outcome(s)
1. All-cause in-hospital mortality in mITT population measured as reported by the sites using patient records on the last study day, expected to be on Day 28
2. All-cause in-hospital mortality in the ITT population measured as reported by the sites using patient records at Day 14
3. All-cause in-hospital mortality in the ITT population measured as reported by the sites using patient records on the last study day, expected to be on Day 28
4. Clearance of positive baseline B. pseudomallei measured using blood cultures at Day 1, 3 and 7
5. Number of days in the ICU in the mITT population measured as reported by the sites using patient records on the last study day, expected to be on Day 28
6. Number of days on ventilator in the mITT population as reported by the sites using patient records on the last study day, expected to be on Day 28
7. Length of hospital stay in the mITT population as reported by the sites using patient records on the last study day, expected to be on Day 28
8. Seriousness of disease in mITT population as measured by the Melioidosis seriousness score at study baseline

Completion date
06/06/2023

Eligibility

Key inclusion criteria
1. Patient must provide written informed consent obtained prior to any study-specific procedure being performed.
2. Patient must be at least 18 years of age or older at time of consent.
3. Patient must be hospitalized with suspected community-acquired melioidosis, meeting at least one of the criteria below:
3.1 History of frequent contact with soil or surface water in an endemic area
3.2 Presence of a known underlying risk factor such as diabetes, renal insufficiency or renal stones, thalassemia
3.3 Special organ involvement such as splenic or hepatic abscess
3.4 An illness compatible with melioidosis, including the presence of sepsis, acute pneumonia, acute pyelonephritis, septic arthritis, parotid disease or skin or soft tissue infection
4. Patient must require intravenous antibiotics i.e., either ceftazidime or meropenem for treatment of suspected melioidosis.
5. Patient must agree to stay in hospital for duration of ARV-1801 therapy, i.e., for at least 14 days.
6. Females of childbearing potential must use an acceptable method of birth control (surgically sterile, intrauterine device, vasectomized partner, oral contraceptive plus barrier contraceptive, hormone delivery system plus barrier contraceptive or condom in combination with contraceptive cream, jelly or foam) for the duration of the study drug administration phase and for 30 days thereafter.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Patient is unable to tolerate oral therapy, either directly or via a nasogastric tube.
2. Patient has a known infection with an identified organism other than B. pseudomallei.
3. Patient is pregnant or lactating.
4. Patient has a known hypersensitivity to sodium fusidate, ceftazidime or meropenem.
5. Patient has been treated with intravenous antibiotics active against B. pseudomallei (including ceftazidime and meropenem) for longer than 48 hours prior to randomization.
6. Patient requires concomitant treatment with the following:

6.1 OATP1B1 and OATP1B3 substrates, in particular statins (e.g., HMG-CoA reductase inhibitors)
6.2 Medications metabolized by CYP2C8, such as glitazones (e.g., repaglinide)
6.3 CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital, and nafcillin)
7. Patient has had prior treatment with a CYP3A4 inducer, such as dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital, or nafcillin, within 7 days prior to enrollment.
8. Patient requires treatment with digoxin or warfarin unless a monitoring plan is in place to assess digoxin levels and/or prothrombin time as is relevant.

Date of first enrolment
01/05/2022

Date of final enrolment
13/12/2022

Locations

Countries of recruitment
Thailand

Study participating centre
Srinagarind Hospital, Khon Kaen University
123, Moo 16, Mittraphap Highway
Khon Kaen
Thailand
40002

Study participating centre
Sanpasitthiprasong Hospital
122 Sappasit Road, Nai Muang Subdistrict
Ubonratchatani
Thailand
34000

Study participating centre
Udon Thani Hospital
33 Pho Niyom Rd., Makkeng Subdistrict
Udon Thani
Thailand
41000

Study participating centre

Khon Kaen Hospital
54 Sri Chant Road, Nai Muang Sub district
Muang
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40000

Study participating centre
Surin Hospital
68 Lak Muang Road, Nai Muang Subdistrict
Surin
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32000

Study participating centre
Maharat Nakhonratchasima Hospital
49 Changpuek Road, Nai Muang Subdistrict
Nakhon Ratchasima
Thailand
30000

Sponsor information

Organisation
Arrevus, Inc.

Funder(s)

Funder type
Government

Funder Name
U.S. Department of Defense

Alternative Name(s)
United States Department of Defense, Department of Defense, U.S. Dept of Defense, US Department of Defense, US Dept of Defense, U.S. Department of Defense, Department of War, United States Department of War, War Department, War Office, DOW, DOD, USDOD

Funding Body Type
Government organisation

Funding Body Subtype
National government

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 available from the corresponding author on reasonable request.
• Requests should be sent to Carl Krause, MD ckraus@arrevus.com
• Any raw datasets available will be provided
• Data will be available after study publication for a duration of six months
• Upon receipt of email request, a data request form will be provided to requestor. Requestor must provide proof of affiliation with an accredited academic institution.
• Allowed analyses will be reviewed on a case-by-case basis
• Consent will be provided for data sharing by study participants
• Data will be anonymous
• We are not aware of any ethical or legal restrictions

IPD sharing plan summary
Available on request