A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Favipiravir in Adult Subjects with Uncomplicated Influenza.

Published: 30-08-2013
Last updated: 22-04-2024

Primary ObjectiveTo evaluate the clinical efficacy of favipiravir compared with placebo in treating adult subjects who have confirmed influenza.Secondary Objectives- To further evaluate the clinical and anti-viral effects of favipiravir.- To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON40560

Source
ToetsingOnline

Brief title
Favor - T705aUS316

Condition

- Viral infectious disorders

Synonym
simple Influenza infection

Research involving
Human

Sponsors and support

Primary sponsor: MDVI, LLC
Source(s) of monetary or material Support: Pharmaceutische Industrie

Intervention

Keyword: Adults, Favipiravir, Influenza

Outcome measures

Primary outcome

Time from the start of study treatment until alleviation of all primary influenza symptoms (i.e. cough, sore throat, headache, nasal congestion, body aches and pains, fatigue) and to resolution of fever by temperature (oral) measurements to be < 38.0°C (< 100.4°F) for subjects < 65 years old and < 37.8°C (< 100.0°F) for subjects >= 65 years old.

Secondary outcome

Time from the start of study treatment until alleviation of each of the following influenza symptoms (cough, sore throat, headache, nasal congestion, body aches and pains, and fatigue)

- Time from the start of study treatment until resolution of fever by temperature (oral) to be < 38.0°C (<100.4°F) for subjects < 65 years old and < 37.8°C (<100.0°F) for subjects >= 65 years old
- Changes in log-transformed viral load as measured by quantitative polymerase chain reaction (qPCR) and in the determination of median tissue culture infective dose (TCID50), from nasopharyngeal swabs at Visits 2, 3, 4, and 5; and logtransformed viral load (by qPCR and TCID50) area under the curves (AUCs)

- The total dose of acetaminophen (paracetamol) used during the study

- Incidence of physician-diagnosed secondary respiratory tract infections

leading to a prescription for antibiotic therapy

- Time to return to normal activity

- Safety: Adverse events (AEs) and clinical laboratory tests for systemic

safety including hematology, clinical chemistry, and urinalysis

- Population PK analysis of favipiravir with assessment of maximum plasma

concentration (Cmax), minimum plasma concentration (Cmin), and total daily

exposure AUC(0-24h) on Visits 1, 2, 3, 4 and 5

Study description

Background summary

Favipiravir is being studies for the treatment of uncomplicated influenza. Favipiravir, a small molecule, based on its potent and selective inhibitory activities against a broad spectrum of influenza A, B and C virusses, including strains poorly susceptible to amantadine hydrochloride or oseltamivir phosphate.

Host cellular enzymes convert favipiravir to T-705 ribosyl triphosphate which selectively inhibits viral RNA polymerase. Literature suggest early drug intervention, ideally 24 hours of symptom onset, can significantly reduce time to symptom alleviation and accelerate reduction in viral load and shedding.

Favipiravir is being developed as a novel anti-influenza agent for routine seasonal and pandemic strains. Besides, studies have shown that favipiravir as active agent against virulent avian influenza A (H5N1) viruses, for which no effective human therapy has been yet established.

This new medication represent a solution to a unmet medical need for active agents influenza resistant to amantadine hydrochloride or oseltamivir phosphate.

Study objective

Primary Objective
To evaluate the clinical efficacy of favipiravir compared with placebo in treating adult subjects who have confirmed influenza.

Secondary Objectives
- To further evaluate the clinical and anti-viral effects of favipiravir.
- To evaluate the safety of favipiravir in adult subjects with symptoms consistent with uncomplicated influenza.
- To characterize the pharmacokinetics (PK) of favipiravir when used under clinical conditions.

Study design

This study is a Phase 3, randomized, double-blind, placebocontrolled, study evaluating the efficacy and safety of favipiravir in adult subjects with uncomplicated influenza with a ratio of active to placebo of 1:1.

Group 1, 330 subjects:
Day 1: 1800mg (1st loading dose), 1800mg (2nd loading dose) favipiravir
Days 2-5: 800mg favipiravir twice daily (BID) (3rd to 10th doses)

Group 2, 330 subjects
Treatment: Placebo (matching pill numbers and presentation to Group 1)

Subjects will participate in the study for 22 days with a window of up to 7 additional days.

Intervention

- Favipiravir BID: 1800 mg (1st loading dose) + 1800 mg (2nd loading dose) on Day 1 followed by 800 mg BID for Days 2-5
- Placebo BID to mimic 9 tablets + 9 tablets on Day 1 followed by 4 tablets BID for Days 2-5

Subjects should not take more than 2 doses within a 24-hour period and doses should be taken no less than 10 hours and no more than 14 hours apart. If the loading dose is administered late in the day on Day 1, doses of study medication will be taken over a total of 6 calendar days. Visits 2 to 5 should be scheduled to coincide with a dosing time of study medication. During these visits, subjects will hold the scheduled dosing until indicated by the study clinician in order to complete the pre-dose assessments and collection of the predose PK sample.

Acetaminophen (paracetamol) will be provided to subjects for the duration of the study.

Subjects will be enrolled within 48 hours of onset of influenza clinical symptoms (symptoms must start 48 hours or less prior to the first dose of study medication). The treatment period is 5 days.

Study burden and risks

Over a two-thousand individuals in more than 37 studies have received at least one dose of favipiravir and the regimen was well tolerated with no SAE`s nor serieus AE`s were reported.

The most common side effects were elevated uric acid, diarrhea, headache, nausea, ALT increased, AST increased, blood fibrinogen increased, blood triglyceride increased, vomiting, dizziness and proteinuria (increased protein in urine).
Side effects known to occur in <5% of patients using favipiravir are:
• Mild to severe increases in blood uric acid
• Diarrhea
• Headache
• Abdominal discomfort/pain

Side effects due to study procedures:
Risks associated with the ECG include discomfort if the patches are removed from areas with hair. The procedure itself will not be painful.
Risks associated with nasopharyngeal swabs include discomfort from the swab passing through your nose causing watering eyes and coughing as well as a feeling of pressure at the back of your nose.
Risks associated with the lab draws may include pain, swelling or bruising at the needle insertion site, and a possibility of infection. The patient may feel dizzy or you may faint. draws.
There is a possibility that the study drug may damage an unborn child or nursing infant. Because of this, women who are breastfeeding, pregnant or plan to become pregnant within 3 months after the study is over may not be in this study.

Exposure of the skin directly to sun may result in a rash.

For a complete overview please refer to the schedule of events in the protocol. The patient must take study drug two times a day for five days, and must take a total of 10 doses to complete study therapy. There is a patient diary which should be completed at least 3 times per day, from day 1 - day 21.

Contacts

Public

MDVI, LLC

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US
Scientific
MDVI, LLC

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Understands the requirements of the study and provides written
informed consent prior to undergoing any study-related procedures.
2. Is an adult male or female between the ages of 18 and 80 years old,
inclusive (or according to national standards in each country).
3. Has 2 or more of the following symptoms (moderate to severe in intensity) at the time of enrollment that began 48 hours or less prior to the first dose of study medication:
a. Cough
b. Sore throat
c. Headache
d. Nasal congestion
e. Body aches and pains
f. Fatigue
4. Has a fever at the first visit or in the 6 hours prior if antipyretics were taken, defined as
a. >= 38.0°C (>= 100.4°F) for subjects < 65 years old; or
b. >= 37.8°C (>= 100.0°F) for subjects >= 65 years old.
5. Tests positive for influenza A or B during the 48 hours between onset of symptoms and

anticipated dosing with study medication
a. Confirmed at the site by a Rapid Antigen Test (RAT) provided for the study or real time polymerase chain reaction (PCR) OR
b. Confirmed by diagnostic assay (e.g. non-study RAT or PCR) from another clinic.
OR
c. A subject testing negative by RAT may still be enrolled if the Medical Monitor and Investigator agree that there is a known influenza outbreak circulating in the community or the subject has been in close contact with a person who was recently confirmed to have influenza by RAT or another laboratory test.
6. If male, subject must:
a. Be sterile (e.g., have had a vasectomy at least 6 months prior to Day 1 dosing) OR
b. Agree he will not donate sperm during the study and for 3 months following the last dose of study medication, AND
c. Will strictly adhere to the following contraceptive measures during the study and for 3 months following the last dose of study medication:
i. Abstain from sexual intercourse OR
ii. Use a condom during sexual intercourse with a female of child-bearing potential. In addition, the female partner must use another form of contraception (e.g. intrauterine device [IUD], diaphragm with spermicide, oral contraceptives, injectable progesterone, or subdermal implants).
iii. The final decision of effective contraception will be made in accordance with local regulations.
7. If female, subject must:
a. Be unable to bear children (have not had a period for >=12 consecutive months, have had her uterus or ovaries removed, or have had a tubal ligation) OR
b. Have a male partner incapable of fathering a child (e.g., has had a vasectomy at least 6 months prior to study entry) OR
c. Have a negative pregnancy test at screening AND
d. Not have had unprotected sex within the last month or used a medically approved method of contraception within the last month AND
e. If she is of childbearing potential, will strictly adhere to the following contraceptive measures during the study and for 3 months following the last dose of study medication:
i. Abstain from sexual intercourse OR
ii. Her male partner agrees to use a condom during sexual intercourse AND
iii. Agree to use an approved method of contraception (e.g., IUD, diaphragm with spermicide, oral
contraceptives, injectable progesterone, or subdermal implants).
iv. The final decision of effective contraception will be made in accordance with local regulations.

Exclusion criteria

1. Female subjects who are pregnant, currently breast-feeding, or have a positive pregnancy test at Screening.
2. Has taken an anti-influenza drug (e.g., amantadine hydrochloride, rimantadine, oseltamivir

phosphate, zanamivir hydrate, peramivir or other) within 4 weeks prior to signing the informed consent.
3. Has received any live attenuated influenza vaccine within 4 weeks prior to signing the informed consent.
4. Has underlying chronic respiratory disease (e.g., chronic obstructive pulmonary disease [COPD], chronic bronchitis, diffuse panbronchiolitis, bronchiectasis, pulmonary emphysema, pulmonary fibrosis, or active tuberculosis). Subjects with bronchial asthma will be excluded from the study if they presently experience asthma symptoms, are currently requiring treatment, or have had an asthma attack in the past year.
5. At the beginning of the study, is suspected of having bacterial respiratory infection (i.e., expectoration of purulent or mucopurulent sputum and/or infiltrate in lung observed on chest x-ray, or is on antibiotics for pulmonary disease).
6. Has a history of gout or is under treatment for gout or hyperuricemia.
7. Has hereditary xanthinuria.
8. Has a history of hypouricemia (under 1 mg/dL) or xanthine calculi of the urinary tract.
9. Has a history of hypersensitivity to an anti-viral nucleosideanalog drug targeting a viral RNA polymerase.
10. Is using adrenocorticosteroids (except topical preparation) or immunosuppressive drugs (e.g., immunosuppressants, anticancer drugs).
11. Has an allergy to acetaminophen (paracetamol) or has a contraindication for acetaminophen (paracetamol).
12. Has a serious chronic disease (e.g., human immunodeficiency virus [HIV], cancer requiring chemotherapy within the preceding 6 months, moderate or severe hepatic insufficiency
and/or unstable renal, cardiac, pulmonary, neurologic, vascular, or endocrinologic disease states requiring medication dose adjustments within the last 30 days).
13. Has previously received favipiravir (T-705a).
14. Has renal insufficiency requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).
15. Has a history of alcohol or drug abuse in the preceding 2 years.
16. Has a psychiatric disease that is not well controlled (not on a stable regimen for greater than one year).
17. Has taken another investigational drug within 30 days prior to signing the informed consent.
18. Is deemed by the Investigator to be ineligible for any reason.
19. Is employed by or is related to an employee of the clinical study site.

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-03-2014
Enrollment:	43
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Favipiravir
Generic name:	Favipiravir

Ethics review

Approved WMO Date:	30-08-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	10-10-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	05-12-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	18-12-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-03-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-09-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	13-10-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-12-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTRNL2013-002149--NL
CCMO	NL45623.056.13