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High dose versus standard dose oseltamivir for the treatment of severe influenza and avian influenza

Submission date	Recruitment status	[_] Prospectively registered
12/07/2007	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
12/07/2007	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
14/09/2017	Infections and Infestations	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT00298233

Secondary identifying numbers
061330; USA FDA IND# 74,213

Study information

Scientific Title
High dose versus standard dose osaltamavir for the treatment of severe influenza and avian influenza: a phase II double-blind, randomised clinical trial

Acronym
SEA001

Study objectives
Human influenza is a serious disease causing an estimated 500,000 - 1,000,000 deaths worldwide each year. In addition, there have been increasing numbers of cases of avian influenza in the last several years, which may pose a threat of a future pandemic with a novel influenza virus.

Oseltamivir is one therapeutic agent available for human influenza, and would be considered standard therapy for treatment of avian influenza. Both severe human influenza and avian influenza have a higher mortality than uncomplicated human influenza, have higher viral replication, shed larger amounts of virus, and shed virus longer. Oseltamivir has been shown to decrease viral replication and shedding in uncomplicated influenza, but similar studies have not been performed in severe human and avian influenza.

The primary purpose of this protocol is to evaluate high-dose oseltamivir (twice the standard dose) as compared to standard-dose oseltamivir in the treatment of severe human or avian influenza with the hypothesis that high-dose will decrease viral replication and shedding, and therefore may confer a clinical or survival advantage. This protocol will also attempt to define differences in the clinical manifestation, the relationship between antiviral plasma concentrations and viral dynamics, and pathogenesis of human and avian influenza, which may help to improve the treatment of these diseases.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Oxford Tropical Research Ethics Committee (OXTREC), ref: 001-06

Study design
Phase II double-blind randomised clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Influenza in birds, severe influenza

Interventions
Current Interventions as of 19/01/2011:
Study duration: four years or until 270 subjects in the severe influenza group are enrolled, whichever comes first.

This study will compare the standard dose of the anti-influenza drug Tamiflu with a higher dose of the drug to see if the higher dose is more effective in treating severe influenza or avian influenza (bird flu) infections. The National Institutes of Health (NIH) is one of several international sites for this study.

People 18 years of age and older with severe influenza infection requiring hospitalisation or with avian influenza infections may be eligible for this study. Candidates are screened with a nasal swab, throat swab and nasal wash to look for virus. For the nasal wash, a small amount of salt water is squirted in the nose and removed by suction.

Participants are randomly assigned to receive either the standard dose or higher dose of Tamiflu. They take the medication twice a day for 5 days. Patients who are still very ill at 5 days and meet certain conditions are given the medicine for another 5 days. Patients are admitted to the hospital, in isolation, for the duration of treatment. In addition to treatment, patients have the following tests and procedures:
1. Nose and throat swabs, nasal wash, rectal swab, blood and urine tests and chest x-ray before starting treatment
2. Blood draws on study days 1, 3, 5 and 7
3. Nose and throat swabs every day for the first 5 days and on days 10, 14 and 28
4. Rectal swabs days every day for the first 5 days and on days 10, 14 and 28

Patients with bird flu are seen in the clinic at 2 and 6 months. A repeat blood test is done at 6 months.

Previous Study Duration:
Study duration: four years or until 300 subjects in the severe influenza group are enrolled, whichever comes first.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Oseltamivir (Tamiflu)

Primary outcome measure

The primary objective is to compare the antiviral efficacy of standard and high-dose oseltamivir in the treatment of severe influenza infections as assessed by negative reverse transcriptase (RT) -PCR for viral RNA in nose and throat swabs at day 5.

Secondary outcome measures
1. Compare the antiviral efficacy of standard and high-dose oseltamivir in the treatment of severe influenza infections as assessed by negative RT-PCR for viral Ribonucleic Acid (RNA) in nose and throat swabs at day 5 and day 7
2. Compare the antiviral efficacy of standard-dose versus high-dose oseltamivir in the treatment of severe human influenza infections as assessed by negative RT-PCR for viral RNA in nose and throat swabs at day 5
3. Compare the antiviral efficacy of standard-dose versus high-dose oseltamivir in the treatment of avian influenza infections as assessed by negative RT-PCR for viral RNA in nose and throat swab at day 5
4. Compare the antiviral efficacy of standard-dose versus high-dose oseltamivir in the treatment of avian influenza infections as assessed by time to sustained negativity of RT-PCR and viral culture in any sample
5. Compare the tolerability of high-dose versus standard-dose oseltamivir as assessed by the incidence and duration of clinical symptoms and the number of serious and grade IV adverse events that are possibly or probably related to oseltamivir
6. Compare the frequency of clinical failure of high-dose versus standard-dose oseltamivir in the treatment of severe influenza and avian influenza at days 5 and 10
7. Develop a population pharmacokinetic model of oseltamivir phosphate and oseltamivir carboxylate absorption and disposition, and characterize the sources of variance in pharmacokinetic parameters
8. Assess the relationship between pharmacokinetic variables and measures of viral clearance
9. Assess viral replication dynamics (frequency, duration, and level of viral replication) in the upper and lower respiratory tract, gastrointestinal tract (feces), and blood (viremia) in the high-dose versus standard-dose oseltamivir cohorts, and stratified by avian and human influenza
10. Assess the frequency, genetic basis, and duration of antiviral resistance during and after therapy
11. Characterize the innate and adaptive immune responses with respect to avian and human influenza, severe and mild disease, and standard-dose versus high-dose oseltamivir cohorts
12. Assess the absorption and achievable blood levels of oseltamivir carboxylate in seriously ill hospitalised patients with lower respiratory tract disease
13. Determine possible host genetic factors predisposing to severe influenza

Overall study start date
23/10/2006

Completion date
19/01/2010

Eligibility

Key inclusion criteria
1. Age greater than or equal to one year (National Institutes of Health [NIH] site specific: age greater than or equal to 18 years old)
2. Fever greater than or equal to 38.0 degrees Celsius
3. At least one respiratory symptom:

3.1. Cough
3.2. Dyspnea (shortness of breath)
3.3. Sore throat
4. Illness (onset of fever, respiratory symptoms, or constitutional symptoms) began in the last seven days
5. Have evidence of severe respiratory disease from influenza or avian influenza as defined below (A or B):

A. Evidence of severe influenza infection:
a. Need for hospitalisation (as determined by investigator or clinician)
b. One of the following (all criteria as judged by the investigator):
i. New infiltrate on chest x-ray (or any infiltrate if no prior chest x-ray or not known)
ii. Severe tachypnea (defined as: respiratory rate greater than or equal to 30 for age greater than or equal to 12 years, rate greater than or equal to 40 for age 6 - 12 years, rate greater than or equal to 45 for age 3 - 6 years, rate greater than or equal to 50 for age 1 - 3 years)
iii. Severe dyspnea (unable to speak full sentences, or use of accessory respiratory muscles)
iv. Arterial oxygen saturation less than 92% on room air measured by trans-cutaneous method
AND
c. Positive diagnostic testing for influenza defined as:
d. Rapid influenza Ag positive (A or B)
e. Qualitative Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) positive for influenza (any)

B. Evidence of avian influenza infection
a. Nasal wash, nasal swab, or throat swab that is RT-PCR positive for H5 influenza
AND
b. NIH site-specific

6. Willingness to have bloods stored

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
840

Key exclusion criteria
1. Pregnancy or urine beta-human Chorionic Gonadotropin (beta-hCG) positive
2. Active breast feeding
3. Receipt of more than 72 hours of oseltamivir within the last week
4. Receipt of oseltamivir at higher than standard doses (75 mg twice daily [bid], or equivalent dose adjusted for age, weight and creatinine clearance) within the last 14 days or during this

acute illness, whichever is longer
5. History of allergy or severe intolerance (as judged by the investigator) of oseltamivir
6. Alternate explanation for the clinical findings as determined by the investigator with the information immediately available
7. Creatinine (Cr) Clearance (estimated by serum Cr) of less than 10 ml/min

Date of first enrolment
23/10/2006

Date of final enrolment
19/01/2010

Locations

Countries of recruitment
United States of America

Viet Nam

Study participating centre
OUCRU-VN
Ho Chi Minh City
Viet Nam
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Sponsor information

Organisation
National Institute of Allergy and Infectious Diseases (NIAID) (USA)

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Sponsor type
Government

Website
http://www.nih.gov

ROR
https://ror.org/043z4tv69

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust (grant ref: 061330)

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results				No	No
Other publications	case report	17/02/2005		Yes	No
Results article	results	30/05/2013		Yes	No