A PHASE 2 RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF MHAA4549A, A MONOCLONAL ANTIBODY, IN COMBINATION WITH OSELTAMIVIR VERSUS OSELTAMIVIR FOR TREATMENT OF SEVERE INFLUENZA A INFECTION

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2. OBJECTIVES2.1 SAFETY OBJECTIVESThe safety objectives for this study are as follows:* To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the...

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

Summary

ID

NL-OMON44177

Source
ToetsingOnline

Brief title
GNE Flu

Condition

- Viral infectious disorders

Synonym
Influenza A infection / Flu

Research involving
Human

Sponsors and support

Primary sponsor: Genentech Inc.
Source(s) of monetary or material Support: Sponsor: Genentech

Intervention

Keyword: MHAA4549A, MONOCLONAL ANTIBODY INFLUENZA A

Outcome measures

Primary outcome

The primary outcome measure for this study is as follows:

* Time to normalization of respiratory function defined as:

* The time to cessation of O2 support resulting in a stable SpO2 >95% for at

least 24 hours

Secondary outcome

The secondary efficacy outcome measures for this study are as follows:

* Clinical failure 24 hours post-infusion of study drug; defined as:

* Progression to increased O2 requirement defined by an increase in oxygen

supplementation from low flow oxygen (2 * 6 L/min) to high flow oxygen (> 6

L/min) or from oxygen supplementation alone to any PPV

* Progression to ICU

* Prolonged ventilation or O2 support defined by > 2 weeks, or

* Death

* Time to clinical normalization of vital signs (3/5 criteria must be met):

* SpO2 > 95% without supplemental O2 for at least 24 hours

* Respiratory rate < 24 without supplemental O2 for at least 24 hours

* Core temperature < 37.2°C immediately prior to receipt of any antipyretic drug, and at least 6-8 hours from the last dose of antipyretic or core temperature > 36°C in patients who are initially hypothermic

* Heart rate (HR) < 100/minute

* Systolic blood pressure (SBP) > 90 mmHg

* All-cause mortality at Day 14 and Day 30

* Influenza A viral load in nasopharyngeal samples

* AUEC

* Peak viral load

* Time to resolution of infection

* Duration of hospitalization

* Duration of ICU stay

* Antibiotic usage for respiratory infections

* Complications of influenza:

* Pneumonia (HAP/VAP)

* Exacerbations of chronic lung disease

* Myocarditis

* ARDS

* Otitis media

* Other related complications

* All-cause readmission at Day 30

* Duration of ventilation

Study description

Background summary

1. BACKGROUND
1.1 BACKGROUND ON INFLUENZA
Influenza A is a membrane-enveloped RNA virus that causes significant morbidity and mortality. Currently, there is a great need in hospitalized influenza patients for a parenteral therapeutic option that is well tolerated, can rapidly resolve influenza-related signs and symptoms, decrease mortality, reduce hospital and intensive care unit (ICU) stays, as well as have a prolonged window for initiation of treatment beyond the current standard of care (SOC) (i.e., within 48 hours of the onset of flu symptoms).
Approximately 200,000 to 278,000 patients are hospitalized with severe influenza infections annually in the United States (U.S.) (Thompson et al. 2004; Zhou et al. 2012), and assuming the same rate reported in the U.S., an estimated 319,000 to 445,000 patients are hospitalized in the European Union (E.U.). Hospitalization due to severe influenza is associated with high mortality (4%*8%), ICU admission (5%*17%; Lee and Ison 2012), mechanical ventilation support in an ICU setting (7%*11%; Doshi et al. 2011), and prolonged hospital stays (5*9 days; Lee and Ison 2012). During a pandemic season, the outcomes may be more serious, with up to 34% of patients requiring ICU care and a mortality rate as high as 15% (Lee and Ison 2012).
Influenza infection is an upper and lower respiratory disease with a broad spectrum of presentations that can result in fever, shortness-of-breath, pneumonia, respiratory failure, secondary respiratory infections, and even death. The SOC therapy for patients hospitalized with influenza consists of supportive measures and administration of available antiviral agents, primarily neuraminidase inhibitors (NAI) that include but are not limited to oseltamivir, zanamivir, and peramivir. However, a significant unmet medical need still exists in the severely ill patient population, as evidenced by the considerable degree of morbidity and mortality in this setting. To address this need, Genentech Inc. /F.Hoffmann-La Roche Ltd. (Genentech) is developing a highly-specific, anti-influenza A (MHAA4549A) antibody therapy for treatment of hospitalized patients with severe influenza.
1.2 BACKGROUND ON MHAA4549A
MHAA4549A is a human monoclonal IgG1 antibody (mAb) that binds to the influenza A virus and is cloned from a single-human plasmablast cell isolated from an influenza vaccinated donor (Nakamura et al. 2013). This antibody binds to a highly conserved epitope on the influenza A hemagglutinin stalk region, which allows broad neutralization of the influenza A virus by blocking the hemagglutinin-mediated, membrane-fusion event in the late endosome.

In vitro, MHAA4549A is capable of neutralizing all current clinically relevant influenza A strains. In vivo, efficacy of MHAA4549A has been demonstrated in mouse models of influenza A infection, both as a single agent and in combination with oseltamivir. MHAA4549A specifically targets an epitope on the human influenza A hemagglutinin
glycoprotein, which does not appear to be endogenously expressed on human or rat tissues and, therefore, is unlikely to be present in the absence of viral infection. Weekly administration of MHAA4549A (total of 5 doses) in Sprague-Dawley rats was well tolerated up to the maximum feasible dose of 150 mg/kg. The results of the ex vivo tissue cross-reactivity study indicates no specific binding of MHAA4549A to any of the human or rat tissues examined.
Clinical experience with MHAA4549A has consisted of two studies in 122 healthy volunteers, and has been shown to be safe and well tolerated to date. The first study was a Phase 1 study (GV28916) in 21 healthy volunteers where single doses of 1.5 mg/kg, 5 mg/kg, 15 mg/kg, and 45 mg/kg were tested with an extended follow-up period of 120 days. MHAA4549A was safe and well tolerated with no serious adverse events (SAEs). All adverse events (AEs) were mild or mild-to-moderate and resolved fully. In addition, the observed pharmacokinetics were generally dose proportional, appeared to have a pharmacokinetic (PK) profile consistent with that of a IgG1 human antibody that lack known endogenous host targets, and no anti-therapeutic antibodies (ATAs) were detected with available samples.
The second study was a Phase 2a (GV28985) challenge study in 101 healthy volunteers infected with a H3N2 strain of influenza virus. Fixed dosing was selected for this study. Three doses were tested: 400 mg, 1200 mg, and 3600 mg. All subjects have completed dosing, and interim PK and efficacy data are available for the 1200-mg and 3600-mg dose groups. During the Phase 2a (GV28985) study, the related AEs that were observed included elevated liver function tests (LFTs) and amylase levels. No dose relationship was observed for LFTs (i.e., placebo 30.8%, 1200 mg 40%, 3600 mg 35%), and no SAEs were observed that were related to MHAA4549A. Based on this data, MHAA4549A is considered generally safe and well tolerated to date at all doses tested including the 3600 mg dose. Analysis of efficacy from the 3600-mg dose level demonstrated a statistically significant decrease in viral shedding from upper respiratory tract as measured by area under the curve (97% reduction by quantitative polymerase chain reaction [qPCR]) and peak viral load (77% reduction by qPCR) .
In this study, oseltamivir was started on Day 7 for a 5-day course, and there were no observed AEs or imbalances in safety events that were considered attributable to interactions between oseltamivir and MHAA4549A. The PK profile of MHAA4549A and oseltamivir are being analyzed in GV28985 to exclude potential drug-drug interactions and will be available before the start of this study.
Testing for ATAs in the Phase 2a has not been concluded.

Study objective

2. OBJECTIVES
2.1 SAFETY OBJECTIVES

The safety objectives for this study are as follows:
* To evaluate the safety of MHAA4549A in combination with oseltamivir compared with placebo and oseltamivir in patients with severe influenza A, focusing on the nature, frequency, and severity of serious and non-serious adverse events as well as effects on laboratory values, vital signs, electrocardiogram (ECG) parameters, ATAs, or other safety biomarkers

2.2 PRIMARY EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:
* To determine the time to normalization of respiratory function of patients dosed with MHAA4549A in combination with oseltamivir compared to patients dosed with placebo and oseltamivir.

2.3 SECONDARY EFFICACY OBJECTIVES

The secondary efficacy objectives for this study are as follows:
* To measure clinical failure, after 24 hours post-infusion of study drug
* To determine the time to clinical resolution of vital signs
* To measure mortality in patients
* To determine changes in the extent and duration of viral shedding in upper respiratory samples
* To measure the duration of hospital and/or ICU stay
* To identify any potential viral resistance to MHAA4549A in influenza A isolates from upper respiratory samples
* To measure antibiotic usage for respiratory infections
* To measure the frequency and severity of the following secondary complications of influenza:
o Pneumonia (hospital acquired pneumonia [HAP]/ ventilator acquired pneumonia [VAP])
o Exacerbations of chronic lung disease
o Myocarditis
o Acute respiratory distress syndrome (ARDS)
o Otitis media
o Other related complications
o Readmission rates at 30 days after study treatment
* To measure duration of PPV
* To measure readmission rates

2.4 PHARMACOKINETIC OBJECTIVES

The major PK objective for this study is as follows:
* To characterize the PK profile of MHAA4549A in serum

The exploratory PK objectives for this study are as follows:
* To characterize the PK profile of MHAA4549A in upper and/or lower respiratory samples
* To assess the PK profile of oseltamivir and its metabolite, oseltamivir carboxylate, in plasma

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are as follows:
* To identify any potential resistance to MHAA4549A in influenza A isolates from tracheal aspirate samples
* To investigate the pre-existing and acquired host-immune response to

influenza A and other biomarkers related to influenza infection in patients treated with MHAA4549A
* To determine changes in the extent and duration of viral infection from lower respiratory samples
* To measure the effect of prior NAI therapy on clinical and virological parameters
* To assess patients* return to pre-influenza baseline activity, type of residence, and type of care assistance
* To determine the time to *ready for discharge* status in patients with influenza A treated with MHAA4549A
* To measure the frequency of secondary bacterial and/or viral infections in patients with influenza A treated with MHAA4549A

Study design

This is a Phase 2b (GV29216) randomized, double-blind, placebo-controlled study designed to assess the safety and clinical activity of a single IV dose of 3600mg MHAA4549A or a single IV dose of 8400mg MHAA4549A in hospitalized patients with severe influenza A in combination with oseltamivir versus a comparator arm of placebo with oseltamivir. This study is planned to take place in approximately 170 study centers globally.
In this version of the protocol patients will be randomized 1:1:1 into three treatment groups: a single IV dose of 3600 mg of MHAA4549A with oseltamivir, a single IV dose of 8400 mg of MHAA4549A with oseltamivir, or a single IV dose of placebo with oseltamivir. All patients will receive oseltamivir, a NAI, as standard therapy for a minimum of 5 days after study drug administration. Oseltamivir at doses of 75 BID or 150 mg BID is permitted in order to be consistent with local SOC practice. Treatment for longer than 5 days is permitted based on local investigator discretion. The patient must start oseltamivir no later than 8 hours of study drug administration. The study has a planned enrollment of approximately 334 patients globally.
Hospitalized patients with an O2 or PPV requirement will be evaluated for influenza A infection. Enrollment in this study requires ongoing treatment within 24 hours of hospital admission with one of the following:
* any PPV or
* any supplemental O2 to maintain oxygen saturation (SpO2) >92%
Patients on PPV should not exceed 45% of the total patients enrolled.
A Sponsor-supplied rapid influenza test and/or a local polymerase chain reaction (PCR) test must be used as an aid in the diagnosis of influenza A infection.
Patients who are intubated and mechanically ventilated should also have lower respiratory tract sampling performed, if it is determined to be safe by the patient*s medical care team. While patients are on supplementary low flow O2 (2 * 6 L/min), they should have a daily trial off O2 support, to check if they are able to maintain their SpO2 at 95% or above on room air.
At the time of randomization, patients who are eligible for enrollment as described above, will be randomized to receive MHAA4549A at a dose of 3600 mg

or placebo. Patients will be stratified by country, PPV versus supplemental O2 on the day of admission, and suspected or confirmed bacterial pneumonia versus no bacterial pneumonia based on the status on the day of admission.
Eligible patients who are enrolled into the study will receive either a single IV infusion of MHAA4549A or a single IV infusion of placebo on Day 1. All patients must have the study drug infused within 48 hours of hospital admission or sooner if possible. All patients will receive oseltamivir for a minimum of 5 days (10 doses), starting on Day 1, beginning no later than 8 hours after study drug administration.
All patients will be followed and evaluated at minimum on a daily basis for the duration of their hospital stay consistent with the planned schedule of assessments. Any suspicion of bacterial superinfection should be thoroughly evaluated including microbiological confirmation, if possible. A follow-up study visit should occur on Day 14 ± 1 (if discharged before Day 14) and Day 30 ± 4 days, if discharged before Day 30.

Intervention

The randomization of patients will be managed by a central Interactive Voice and Web Response System (IxRS). All patients will be randomly assigned to receive either MHAA4549A 3600 mg, 8400 mg or placebo at a 1:1:1 ratio stratified by country, whether patient is on PPV vs supplemental O2 on the day of admission, and whether the patient has suspected or confirmed bacterial pneumonia vs no bacterial pneumonia on the day of admission. All patients will receive oseltamivir (75 mg or 150 mg BID) for a minimum of 5 days. Treatment for longer than 5 days is permitted based on local investigator discretion.
The treatment assignments will be unblinded to an external IDCC to facilitate the iDMC assessment of safety.

Study burden and risks

The Study Drug MHAA4549A:

Common
* Elevated liver tests
Less common
Less common, non serious side effects associated with putting this type of drug into your vein (also known as an *infusion*) might include flushing, back pain, fainting, chills, feeling sick, headache, excessive sweating, light-headedness, and muscular aches and pains.
* Headache
Rare but serious (There have been no serious side effects seen in 121 study subjects who received this study drug.)
* Rare but serious risks associated with an infusion of this type of drug include severe allergic or hypersensitivity reactions.
* There is a rare chance that you could have a serious and potentially

life-threatening allergic reaction to the study drug called *anaphylaxis* that can lead to difficulty breathing and shock. Symptoms include rash; flushing; itching, sneezing, or runny nose; abdominal pain; diarrhea; swelling of the face, tongue, or throat; dizziness, light-headedness, or fainting; trouble breathing; irregular or racing heart rate; and seizures (fits).
* As with other drugs of this type, giving a person the study drug may cause them to develop antibodies to the drug, which could affect whether the drug works or the safety of this study drug or other drugs of the same type. If this occurs, it is not expected to result in any significant effects to your health, but it is difficult to know what symptoms might develop or the effect they might have on this drug or other similar drugs in the future.

Neuraminidase Inhibitor: Oseltamivir (Tamiflu):

Oseltamivir is a prescription medicine normally given to people who have had influenza symptoms for no more than 2 days. Oseltamivir was also shown to reduce the symptoms of influenza by 1 day in a study of adults with influenza who were not hospitalized. It is considered one of the accepted treatments to give patients hospitalized with influenza, although it has not been officially approved for this indication.
Everyone in this study is required to be given oseltamivir for a minimum of 5 days. Treatment of longer than 5 days is permitted based on local investigator discretion.
Common (occurred in 7% * 10% of patients treated during the clinical studies of oseltamivir):
* Nausea
* Vomiting
* Diarrhea

Less common (occurred in 2% of patients treated during the clinical studies of oseltamivir):
* Bronchitis,
* Abdominal pain
* Dizziness
* Headache

Rare but serious
* Cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis (blistering of the skin), Stevens-Johnson Syndrome (blistering of skin, mouth, eyes, genitals), and erythema multiforme (skin reaction) have been reported in postmarketing experience with oseltamivir.
* Influenza can be associated with hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. The contribution of oseltamivir to these events has not been established.

Contacts

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US
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Genentech Inc.

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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

Patients must meet the following criteria for study entry:
* Men or women * 18 years of age on day of signing informed consent or obtaining surrogate consent from an authorized representative
* Diagnosis of influenza A as determined by one or both of the following:
* A Sponsor-supplied rapid influenza test
* A local molecular test (PCR)
* One of the following markers of severity within 24 hours of hospital admission:
* Requirement for PPV, OR
* Requirement for O2 supplementation to maintain SpO2 >92%
* A negative urine or serum pregnancy test for women of childbearing potential
* Patients of reproductive potential must agree to use reliable means of contraception as described below as a minimum (adherence to more stringent local requirements may be

required):
* For female patients: Use of two acceptable methods of contraception throughout the trial, including the active treatment phase AND for 120 days after the last dose of MHAA4549A. Acceptable methods of contraception include: intrauterine device, systemic hormonal contraception (oral or depot), vaginal ring, tubal ligation of the female partner, vasectomy of the male partner, use of latex condoms plus spermicide by the male partner, or cervical cap plus spermicide (where the spermicide could be foam, vaginal suppository, gel, cream, etc.). Male partners who have had a vasectomy should have the appropriate post-vasectomy documentation available of the absence of sperm in the ejaculate. The vasectomized male partner should be the sole partner for that subject.
* For male patients: Use condoms and refrain from sperm donation until 30 days after dosing.
* Non-reproductive potential is defined below (but could be superseded by local definitions, if they are more stringent):
Women who are postmenopausal (i.e., spontaneous amenorrhea for the past year confirmed by an follicle stimulating hormone [FSH] level greater than 40 mIU/mL unless the patient is receiving a hormonal therapy for their menopause)
Women who are surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)
Men who are surgically sterile (castration)

Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:
* Pregnant or lactating, or intending to become pregnant during the study
* Women who are not postmenopausal (* 12 months of non-therapy-induced amenorrhea) or who are not surgically sterile must have a negative urine or serum pregnancy test result within 2 days prior to study treatment
* Hypersensitivity to monoclonal antibodies or to any constituents (sodium succinate, sucrose, polysorbate 20) excipients of MHAA4549Astudy drug
* Hypersensitivity to the active substance or to any excipients of oseltamivir
* Investigational therapy within the 30 days prior to study treatment
* Received prior therapy with any anti-influenza monoclonal antibody therapy including MHAA4549A within 8 months prior to study treatment
* Current treatment (within 7 days of dosing) with amantadine or rimantidine
* Patients who have taken more than a total of 3 days (6 doses) of approved anti-influenza therapy (i.e., oral oseltamivir, inhaled zanamivir, lanimivir, peramivir) in the period from onset of symptoms and prior to enrollment
* Admission > 48 hours prior to study treatment
* Onset of influenza symptoms > 5 days prior to study treatment
* Positive influenza B or influenza A +B infection within 2 weeks prior to study treatment
* High probability of mortality in the next 48 hours as determined by the investigator
* Patient requiring home or baseline oxygenation therapy
* Patient with history of chronic lung disease resulting in baseline SpO2 <95%
* Patient on chronic dose of corticosteroids exceeding 10 mg/day of prednisone or equivalent steroid dose for a duration of greater than 14 days within 30 days of entry into study
* Patients with the following significant immune suppression:

* Bone marrow or solid organ transplant in the previous 12 months
* Cancer chemotherapy in the previous 12 month
* HIV infection with most recent CD4 < 200 cells/mL
* Other significant immune suppression as determined by the investigator in discussion with the Sponsor Medical Monitor or representative
* Patient on extracorporeal membrane oxygenation (ECMO) at time of randomization
* Any disease or condition that would, in the opinion of the site investigator or Sponsor, place the patient at an unacceptable risk of injury or render the patient unable to meet the requirements of the protocol

Study design

Design

Study phase:	2
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):	14-01-2015
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MHAA4549A
Generic name:	MHAA4549A
Product type:	Medicine
Brand name:	OSELTAMIVIR
Generic name:	Tamiflu

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-11-2014
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	23-01-2015
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	15-09-2015
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	02-05-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	01-09-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	13-09-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Approved WMO Date:	18-11-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	13-03-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	17-03-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2014-000461-43-NL
CCMO	NL49824.075.14