A Phase II, global, randomized study to evaluate the efficacy and safety of Danirixin (GSK1325756) co-administered with a standard-of-care antiviral (oseltamivir), in the treatment of adults hospitalized with influenza (study 201023, DAHLIA)

Published: 22-11-2016
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Primary:To assess the efficacy of treatment with IV danirixin twice daily given with oral oseltamivir compared to oral oseltamivir twice daily on time to clinical response (TTCR)Secondary:Time to respiratory response (TTRR), clinical measures of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON43171

Source
ToetsingOnline

Brief title
studie 201023

Condition

- Viral infectious disorders

Synonym
influenza; flu

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: GlaxoSmithKline BV

Intervention

Keyword: danirixin, hospitalization, influenza, oseltamivir

Outcome measures

Primary outcome

TTCR (hospital discharge or normalization of temperature, oxygen saturation and

2/3 of 1. respiratory status, 2. heart rate, 3. SBP).

Secondary outcome

TTRR (return to pre-morbid oxygen requirement or return to no requirement of

supplemental oxygen or respiratory rate *24/min (without supplemental oxygen),

clinical measures of influenza illness (see protocol page 10 for details),

adverse events, PK parameters.

Study description

Background summary

Seasonal influenza affects 5-10% of the world*s population annually, causing 3-5 million severe infections and 250,000 to 500,000 deaths. While early therapy with antivirals decreases severity and duration of symptoms of influenza, there are no drugs that have demonstrated clinical efficacy in randomized clinical trials in this population. Current treatment guidelines for hospitalized influenza recommend neuraminidase inhibitors as standard of care therapy. Following infection by a respiratory virus, neutrophils are the most abundant cells that migrate to the lungs. Influenza studies in animals have demonstrated that therapeutic treatment with the combination of a C-X-C chemokine receptor 2 (CXCR2) antagonist and a neuraminidase inhibitor reduced

lung neutrophils and showed trends for improvements in clinical scores, lung function and pathology with no evidence of worsening outcomes, including viral load.
This study is designed to investigate an anti-inflammatory agent, danirixin co-administered with an antiviral treatment oseltamivir for treatment of patients hospitalized for influenza infection and will be the first study to evaluate the efficacy and safety of intravenous danirixin in this population.

Study objective

Primary:
To assess the efficacy of treatment with IV danirixin twice daily given with oral oseltamivir compared to oral oseltamivir twice daily on time to clinical response (TTCR)
Secondary:
Time to respiratory response (TTRR), clinical measures of influenza illness (see protocol page 10 for details), safety and tolerability, pharmacokinetics (PK).

Study design

Phase 2, randomized, double-blind, placebo-controlled 3-arm study in adults.
Randomization to
* IV DNX 15 mg b.i.d. (infusion 250 ml 1 hour) co-administered with open-label oral 75 mg oseltamivir b.i.d.
* IV DNX 50 mg b.i.d. (infusion 250 ml 1 hour) co-administered with open-label oral 75 mg oseltamivir b.i.d.
* IV placebo to DNX b.i.d. (infusion 250 ml 1 hour) co-administered with open-label oral 75 mg oseltamivir b.i.d.
Treatment duration 5 days. Oseltamivir may be continued beyond day 5.
Follow-up 45 days.
Independent Data Monitoring Committee.
300 participants.

Intervention

Treatment with oseltamivir plus danirixin or placebo to danirixin.

Study burden and risks

Risk: Adverse events of the study medication.
Burden:
Hospitalized subjects. After discharge up to 2 visits, up to 4 phone calls with study team. Screening, treatment period (5 days), follow-up 45 days.
10 IV infusions (250 ml, 1 hour).
Physical examination: every day in hospital and every visit thereafter.

Blood draws 30-60 ml/day:
- safety 7 times,
- PK 3 days with 1 sample or in some patients 2 days with 1 and 1 day with 9 samples in 12 hours,
- biomarkers 5-8 times.
Pregnancy test: 3 times.
ECG: 3 times.
Chest X-ray: once.
Swab throat: at least 3 times.
Nasal fluid test: at least 5 times.
Pulmonary fluid test: at least 3 times.
Questionnaires: activities, signs and symptoms, ADL.
Optional: blood sample for pharmacogenetics.

Contacts

Public
GlaxoSmithKline

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NL
Scientific
GlaxoSmithKline

Huis ter Heideweg 62
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* 18 years or older.
* Fever (*38.0oC (by any route) at enrollment or history of fever/feverishness during the 48 hours prior to enrollment.
* O2 saturation <95% or need for any supplemental oxygenation increase in oxygen supplementation requirement of *2 liters for subjects with chronic oxygen dependency.
* At least 2/3: 1. respiratory rate >24 breaths per minute, 2. HR >100 bpm, 3. SBP <90 mmHg.
* Less severe and critically ill subjects. See protocol page 30-31 for details.
* Influenza that in the Investigator*s judgment requires hospitalization.
* Onset of influenza symptoms within 6 days prior to study enrolment. Description of symptoms: see protocol page 31.
* Positive rapid influenza test.
* Baseline creatinine clearance and liver function tests: see protocol page 31.
* Contraception requirements for female participants of child bearing potential and male participants with partner of child bearing potential: see protocol page 31-33.

Exclusion criteria

* Life expectancy at least 48 hours.
* Immunosuppression. See protocol page 33 for details.
* Documented current liver disease. See protocol page 33 for details.
* QTc prolongation. See protocol page 33 for details.
* For subjects enrolled in the sentinel cohorts: diabetes mellitus and chronic kidney disease.
* Pregnancy, lactation.
* Other treatments for influenza for more than 72 hours. See protocol page 34 for details.
* Immunoglobulins within 6 months or planned administration during the treatment period.
* Cytotoxic or immunosuppressive drugs within six months. See protocol page 34 for details.
* Neutrophil count <1.0 Gi/L.
* Having participated in a study with an investigational product in het past 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

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:	Will not start
Enrollment:	9
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Danirixin
Generic name:	Danirixin
Product type:	Medicine
Brand name:	Tamiflu
Generic name:	oseltamivir
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	22-11-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	15-02-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2016-002512-40-NL
CCMO	NL59647.100.16
Other	www.gsk-clinicalstudyregister.com (201023)