A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Pimodivir in Combination With the Standard-of-care Treatment in Adolescent, Adult, and Elderly Hospitalized Patients With Influenza A Infection

Published: 29-03-2018
Last updated: 25-03-2025

Primary ObjectiveThe primary objective is to evaluate superiority of pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment on Day 6, with respect to the clinical outcome on the hospital recovery scale.

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

Summary

ID

NL-OMON48779

Source
ToetsingOnline

Brief title
Janssen Influenza A_3001

Condition

- Viral infectious disorders

Synonym
Flu, influenza A

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Efficacy, Influenza, Pimodivir, Safety

Outcome measures

Primary outcome

Primary Endpoint

The primary endpoint is the hospital recovery scale as assessed on Day 6.

Secondary outcome

1. Safety and tolerability based on assessment of adverse events (AEs),

clinical laboratory assessments, 12-lead electrocardiograms (ECGs), vital

signs, and peripheral capillary oxygen saturation.

2. Time from start of study drug to hospital discharge and total length of

hospital stay.

3. Time from ICU admission to ICU discharge and total time in ICU.

4. Time from start to end of mechanical ventilation and total time on

mechanical ventilation.

5. The hospital recovery scale as assessed each separate day from Days 2 to 14

(excluding the primary time point).

6. Time to return to daily activities.

7. Incidence of complications associated with influenza after the start of

study treatment.

8. All-cause mortality.

9. Incidence and duration of antibiotic treatment.

10. The number (proportion) of subjects needing extended treatment.

11. The number (proportion) of subjects requiring re-hospitalization.

12. The number (proportion) of subjects not hospitalized at Day 6.

13. Time to clinical response.

14. Time to respiratory response.

15. PK parameters of pimodivir (ie, plasma concentration just prior to the

beginning or at the end of a dosing interval [Ctrough], Cmax, tmax,

and AUC12h), as determined by population PK analysis.

16. The acceptability of the pimodivir formulation in adolescents, as measured

by a taste and swallowability questionnaire.

17. Time to viral negativity by qRT-PCR and viral culture.

18. Viral load over time by qRT-PCR and viral culture.

19. The emergence of viral resistance against pimodivir detected by genotyping

and/or phenotyping.

Study description

Background summary

Both seasonal and pandemic influenza are a significant cause of morbidity and mortality worldwide. Because the efficacy of the current annual hemagglutinin-based or modified live influenza virus vaccines depends on accurately predicting the viral strains prior to each influenza season or

pandemic and because vaccines are not provided universally, there remains annually a significant burden of disease due to influenza. Several antiviral drugs have been developed for the treatment of influenza. The 2 main classes of antiviral drugs used against influenza are the neuraminidase inhibitors (NAIs) and the viral matrix 2 (M2) protein inhibitors. Unfortunately, these drugs have several limitations and there remains a need for better therapeutic options for the treatment of influenza.
A desired profile of a novel influenza antiviral includes: (1) rapid onset of protective effects leading to an expanded treatment window; (2) better activity in patients with high viral load; (3) inhibition of both production and release of virus; (4) maintenance of potency against neuraminidase and M2 inhibitor resistant viral strains; (5) safe and well tolerated. Pimodivir, an inhibitor of the viral replication complex, potentially meets all of these criteria.

Study objective

Primary Objective
The primary objective is to evaluate superiority of pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment on Day 6, with respect to the clinical outcome on the hospital recovery scale.

Study design

This is a Phase 3 randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of pimodivir in combination with SOC treatment vs placebo in combination with SOC treatment in adolescent (13 to 17 years), adult (18 to 65 years), and elderly (>65 to *85 years) hospitalized subjects with influenza A infection.
A target of 600 hospitalized influenza infected subjects will be randomly assigned in a 1:1 ratio to receive 1 of the following treatments in this study with 300 subjects planned per treatment arm. The aim is to enroll a minimum of approximately 60 adolescent subjects in this study in selected countries and study sites consistent with local regulations. The randomization will be stratified for baseline NEWS2 (4-5 or >5), type of baseline SOC (including or not including influenza antiviral treatment), and time since onset of influenza symptoms (first administration of study drug within 72 hours or between 72 and 96 hours since onset of influenza symptoms). The study population should contain at least 75% of subjects (75% of the total planned sample size of 600 subjects) with first administration of study drug *72 hours since onset of influenza symptoms and the remaining subjects should have first administration of study drug between 72 and 96 hours since onset of influenza symptoms.
* Treatment Arm 1: pimodivir 600 mg twice daily (bid) for 5 days + SOC treatment*
* Treatment Arm 2: pimodivir placebo bid for 5 days + SOC treatment*
*SOC treatment is determined by the investigator based on local practice, and may include influenza antivirals and/or supportive care only. An influenza

antiviral as part of the SOC cannot be changed (eg, switching one influenza antiviral for another) or started during either the treatment period or extension phase, with the exception that an influenza antiviral may be discontinued in the case of a suspected adverse event.
Study drug will be taken orally. During hospitalization, in case of medical need, study drug tablets may be dispersed in water before intake (in case of administration via a nasogastric tube or if the subject has difficulties swallowing the tablets).
The study will consist of a screening/baseline visit, a double-blind treatment period of 5 days (with the possibility to extend the treatment period), and a follow-up period of 23 days after the last dosing day. The entire study duration for each subject will be 28 days, except for subjects receiving extended treatment, for whom the study will last 33 days. The study is considered complete with the completion of the last study assessment for the last subject participating in the study.
An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to monitor efficacy and safety data on a regular basis.

Intervention

Patients should take their prescribed doses of IP.
There are two treatment groups in this study:

* Pimodivir 600 mg, 2 tablets, twice per day for 5 days plus standard of care treatment
* Placebo, 2 tablets, twice per day for 5 days plus standard of care treatment
*
This may be extended by PI for up to 5 additional days

Furthermore, their data of Medical history (including status of influenza vaccinations) and demographic data will be collected They must undergo physical and vital
signs examinations. Female participants will have a pregnancy test. An electrocardiogram will be made. Blood, nasal swap sample and urine will be collected

.

Study burden and risks

Although generally a self-limited disease, infection with influenza A can cause significant morbidity and mortality and may result in hospitalization, especially in certain patient populations such as those at the extremes of age. Pimodivir is being developed for the treatment of patients who are hospitalized due to or at high risk of complications from influenza A, and who have the highest unmet medical need. As a therapeutic option intended for global use,

studying pimodivir in combination with the SOC accounts for worldwide differences in the treatment of this population. In the instances where pimodivir is administered with a NAI SOC option, an additive effect of pimodivir over NAI administration alone will be explored in high-risk and hospitalized subjects. Further, the FLZ3001 study design is based on a recognition that local SOC approaches, particularly NAI, may have some benefit to patients even if used off label, as was noted above. Accordingly, the study design allows subjects to gain any potential benefits of the current SOC therapies, while also assessing the benefit of pimodivir.
Pimodivir has been studied in healthy subjects, in subjects infected with a challenge dose of influenza A and in in subjects naturally infected with influenza. Pimodivir was generally safe and well tolerated.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Male or female, 13 to 85 years of age, inclusive. Note: Adolescent subjects (13-17 years) will be enrolled in selected countries and study sites consistent with local regulations.
* Tested positive for influenza A infection after the onset of symptoms using a polymerase chain reaction (PCR)-based or other rapid molecular diagnostic assay.
* Requires hospitalization to treat influenza infection and/or to treat complications of influenza infection (eg, radiological signs of lower respiratory tract disease, septic shock, central nervous system [CNS] involvement, myositis, rhabdomyolysis, acute exacerbation of chronic kidney disease, severe dehydration, myocarditis, pericarditis, ischemic heart disease, exacerbation of underlying chronic pulmonary disease, including asthma, chronic obstructive pulmonary disease [COPD], decompensation of previously controlled diabetes mellitus), including subjects admitted to the intensive care unit (ICU). Note: For the purpose of the protocol, subjects admitted under *observation* status with an anticipated length of stay beyond 24 hours are eligible for enrollment.
* Enrollment and initiation of study drug treatment *96 hours after onset of influenza symptoms.
* Being on invasive mechanical ventilation or having an SpO2 <94% on room air during screening. Subjects with known pre influenza SpO2 <94% must have an SpO2 decline *3% from pre-influenza SpO2.
* Having a screening/baseline National Early Warning Score (NEWS2) of *4.
For a full list of inclusion criteria please refer to the protocol.

Exclusion criteria

* Received more than 3 doses of influenza antiviral medication (eg, oseltamivir [OST] or zanamivir), or any dose of ribavirin within 2 weeks, prior to first study drug intake. Received intravenous (IV) peramivir more than one day prior to screening.
* Unwilling to undergo regular nasal mid-turbinate (MT) swabs or has any physical abnormality which limits the ability to collect regular nasal MT specimens.
* Unstable angina pectoris or myocardial infarction within 30 days prior to screening (inclusive).
* Presence of clinically significant heart arrhythmias, uncontrolled, unstable atrial arrhythmia, or sustained ventricular arrhythmia, or risk factors for Torsade de Pointes syndrome.
* Known severe hepatic impairment (Child Pugh C cirrhosis) or chronic hepatitis C infection undergoing hepatitis C antiviral therapy.
* Severely immunocompromised in the opinion of the investigator (eg,

known cluster of differentiation 4+ [CD4+] count <200 cells/mm3, absolute neutrophil count <750/mm3, first course of chemotherapy completed within 2 weeks prior to screening, history of stem cell transplant within 1 year prior to screening, any history of a lung transplant).
For a full list of exclusion criteria please refer to the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	07-03-2019
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pimodivir
Generic name:	Pimodivir

Ethics review

Approved WMO

Date:	29-03-2018
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-09-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	01-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-10-2019
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	EUCTR2017-002156-84-NL
ClinicalTrials.gov	NCTO3376321
CCMO	NL62660.056.18

Study results

Date completed: 28-08-2020

Results posted: 28-07-2021

Summary results
Trial ended prematurely

First publication
02-02-2021

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File