A Phase 3 Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy and Safety of Pimodivir in Combination With the Standard-of-care Treatment in Adolescent, Adult, and Elderly Non-hospitalized Subjects With Influenza A Infection who Are at Risk of Developing Complications

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

Summary

ID

NL-OMON46793

Source
ToetsingOnline

Brief title
Janssen Influenza A_3002

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

The primary endpoint is the time to resolution of influenza-related symptoms as assessed by the PRO measure Flu-iiQTM. The resolution of influenza-related symptoms is defined as the beginning of the 24 hour period that the 7 primary influenza symptom scores (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue) are at most mild or at least back to previous level of symptom severity in case the subject reported the symptom as pre-existing.

Secondary outcome

1. Safety and tolerability based on assessment of adverse events (AEs), clinical laboratory assessments, 12-lead electrocardiograms (ECGs) and vital signs.

2. The hospital admission rate 28 days after treatment initiation.

3. Incidence of complications associated with influenza after the start of study treatment.

A blinded Adjudication Committee (AC) will be established to adjudicate AEs on predefined criteria for complications (pulmonary versus extrapulmonary, major versus minor, as well as infectious versus noninfectious complications). The AC will receive data on AEs, including medical assessments (eg chest X-ray results, lab results) and concomitant therapy of cases selected from the AEs. Details will be provided in an AC charter.

4. Time to resolution of each of the 10 individual influenza-related symptoms as assessed by the PRO measure Flu-iiQTM. The resolution of each influenza-related symptom is defined as the beginning of the 24- hour period when the influenza symptom score is at most mild or at least back to the previous level of symptom severity in case the subject reported the symptom as pre-existing.

5. Time to return to daily activities as assessed by the subject.

6. Time to resolution of fever. Resolution of fever is defined as a body temperature <37.0°C during a period of 24 hours without the use of antipyretics.

7. All-cause mortality.

8. 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.

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

by a taste and swallowability questionnaire.

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

and/or phenotyping.

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

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

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

The primary objective is to evaluate superiority of pimodivir (Pi) in combination with standard-of-care (SOC) treatment (tmt) compared to placebo in combination with SOC treatment, with respect to the time to resolution of influenza-related symptoms.

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 versus placebo in combination with SOC treatment in adolescent (13 to 17 years), adult (18 to 65 years), and elderly (>65 to <=85 years) non hospitalized subjects with influenza A infection who are at risk of developing complications.

A target of 720 subjects will be randomly assigned in this study with 360 subjects planned per treatment arm. The aim is to enroll a minimum of approximately 72 adolescent subjects in this study in selected countries and study sites consistent with local regulations. The target population of the study are influenza infected, non hospitalized subjects who, due to their age (>65 to 85 years of age) or underlying comorbidities (regardless of age), are at increased risk of developing influenza-related complications. The randomization will be stratified by type of baseline SOC (including or not including influenza antiviral treatment), and time since onset of symptoms (first administration of study drug <=48 hours or >48 hours since onset of influenza symptoms). The study population should contain at least 60% of subjects with first administration of study drug <=48 hours since onset of influenza symptoms and the remaining subjects should have first administration of study drug between 48 and 72 hours since onset of influenza symptoms.

Intervention

• 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

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 FLZ3002 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.;• Present to the clinic with symptoms suggestive of a diagnosis of acute influenza and have at least 1 respiratory symptom and at least 1 systemic symptom, both scored as at least *moderate* if the symptom did not pre-exist before influenza onset, or scored worse than

usual if the symptom pre existed as determined by subject's ratings on Module 1 of the Flu-iiQTM and the Pre-existing Symptom Questionnaire in the ePRO device. Symptoms must include the following by category: respiratory symptoms: cough, sore throat, nasal congestion; systemic symptoms: headache, body aches or pain, feverishness, fatigue.;• Tested positive for influenza A infection after the onset of symptoms, using a rapid influenza diagnostic test (RIDT) or, if available, a PCR-based molecular diagnostic assay. ;• Not be in need of hospitalized medical care at screening. Emergency room or hospital observation status for <24 hours is not considered hospitalization as long as a determination of the need for hospitalization has not been made.;• Enrollment and initiation of study drug treatment <=72 hours after onset of influenza symptoms. ;• Subjects 13 to 65 years of age, inclusive must also have at least one of the following: ;- Cardiovascular or cerebrovascular disease (including congenital heart disease, chronic heart failure, coronary artery disease, or stroke; excluding isolated hypertension).;- Chronic lung disease (eg, asthma, chronic obstructive lung disease [COPD] or cystic fibrosis).;- Weakened immune system due to disease or medication (eg, subjects with human immunodeficiency virus [HIV], cancer, or chronic liver or kidney disease, or subjects taking chronic systemic steroids).

Exclusion criteria

• Received more than 1 dose of influenza antiviral medication (eg, oseltamivir [OST] or zanamivir), or any dose of ribavirin within 2 weeks, prior to first study drug intake, or received intravenous (IV) peramivir more than 1 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.;• 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, history of a lung transplant).

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):	20-09-2018
Enrollment:	6
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	20-04-2018
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:	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)

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	EUCTR2017-002217-59-NL
ClinicalTrials.gov	NCT03381196
CCMO	NL64446.056.18

Study results

Date completed:	10-09-2020
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