A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Multi-Center Study Evaluating Antiviral Effects, Pharmacokinetics, Safety, and Tolerability of GS-5806 in Hematopoietic Cell Transplant (HCT) Recipients with Respiratory Syncytial Virus (RSV) Infection of the Upper Respiratory Tract

Published: 04-12-2014
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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Upper respiratory tract disorders (excl infections)
Study type	Interventional

Summary

ID

NL-OMON44310

Source
ToetsingOnline

Brief title
GS-US-218-0108

Condition

- Upper respiratory tract disorders (excl infections)

Synonym
HCT recipients with RSV URTI

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences, Inc.
Source(s) of monetary or material Support: Gilead Sciences;Inc.

Intervention

Keyword: Double-Blind, Placebo-Controlled, Respiratory Syncytial Virus, Upper Respiratory Tract

Outcome measures

Primary outcome

The co-primary endpoints are:

* The time-weighted average change in RSV nasal viral load (log10 copies/ml)

from Baseline (Day 1) to Day 9 as measured by RT qPCR.

* Proportion of subjects who develop a LRTC through Day 28, defined as one of

the below, as determined by the adjudication committee:

*- Primary RSV lower respiratory tract infection (LRTI)

*- Secondary bacterial LRTI

*- Lower respiratory tract infection due to unusual pathogens

*- Lower respiratory tract complication of unknown etiology

Secondary outcome

The secondary endpoint is the proportion of subjects who develop respiratory

failure (of any cause) requiring mechanical ventilation (invasive or

noninvasive) or all-cause mortality through Day 28.

The exploratory endpoints are:

* Respiratory syncytial virus log10 viral load and change from baseline in RSV log10 viral load in the nasal samples

* Time-weighted average RSV log10 viral load and time weighted average change from baseline in RSV log10 viral load in the nasal samples

* Proportion of subjects with detectable RSV in the nasal samples

* Respiratory syncytial virus log10 viral load and change from baseline in RSV log10 viral load in the blood

* Time-weighted average RSV log10 viral load and time-weighted average change from baseline in RSV log10 viral load in the blood

* Proportion of subjects who have detectable RSV in the blood

* Proportion of subjects requiring supplemental O2 (* 2L/min for > 24 hours) by Day 28

* Proportion of subjects whose O2 saturation drops to * 88% by Day 28

* O2 saturation and change from baseline in O2 saturation

* Time-weighted average O2 saturation and time-weighted average change from baseline in O2 saturation

* FLU-PRO score and change from Baseline in FLU-PRO score

* Time-weighted average and time-weighted average change from baseline in FLU-PRO score

* Number of days admitted to the hospital through Day 28

* Proportion of subjects requiring ICU care or equivalent of ICU care through Day 28

* Number of supplemental O2 free days through Day 28

Study description

Background summary

See Page 23 of the Protocol, section 1.1. Background.

Study objective

The co-primary objectives of this study are as follows:
* To evaluate the effect of presatovir (GS-5806) on RSV viral load and development of lower respiratory tract complication (LRTC) in RSV positive autologous or allogeneic HCT recipients with acute upper respiratory tract infection (URTI) symptoms

The secondary objectives of this study are as follows:
* To evaluate the effect of presatovir on progression to respiratory failure or all-cause mortality
* To evaluate the pharmacokinetics (PK), safety, and tolerability of presatovir

Study design

Randomized, double-blind, placebo-controlled study evaluating the effect of presatovir on efficacy, PK, safety, and tolerability in HCT recipients with RSV URTI.
All subjects will be permitted to receive the standard of care therapy for RSV infection per their local medical practices, in addition to the investigational medicinal product (IMP).
Subjects will be randomized in a 1:1 ratio to receive IMP (presatovir or placebo) and will be stratified by 2 factors:
1) Presence or absence of lymphopenia, defined as a lymphocyte count < 200 cells/*L versus * 200 cells/*L of blood
2) Treatment of RSV infection (yes or no) with ribavirin (oral, intravenous, or aerosolized)

Intervention

Patients will randomly be assigned to either receive presatovir (200mg) tablets or a matching placebo. (orally or via nasogastric (NG) tube)

Study burden and risks

There are risks to taking part in any research study. One risk is that you may get a drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be adverse events (side effects) that are caused by being in the study. A side effect is an unwanted or

unintended effect that may be caused by taking a drug or by having a study procedure performed. A side effect may be very mild or may be very severe or even fatal. A side effect may go away after you stop taking the study drug, it may last a long time, or it may never go away. There may be side effects that no one knows about yet. You might have new side effects that have not been seen before in people who have taken presatovir.

PRESATOVIR (GS-5806) COMMON ADVERSE EVENTS (SIDE EFFECTS)
Presatovir (GS-5806) is currently not approved and is being studied in people with infections due to the RSV virus.

There are risks involved with taking presatovir.

Presatovir has been given to almost 340 adults of whom 294 were healthy adult volunteers. Adults were treated with presatovir for as long as 7 days. No healthy adult treated with presatovir experienced a serious drug side effect or a side effect leading to stopping the study.

Adverse events reported by healthy volunteers who received presatovir are listed below.

Most Observed Less Observed Least Observed
* Bloody nose 8%
* Diarrhea 4% * Rash, itchy 3%
* Headache 3%
* Lower value on breathing test 3%
* Constipation 3% * Common cold 2%
* Nausea 2%
* Dizziness 2%
* Rash, red 2%
* Stuffy nose 1%
* Sore throat 1%
* Lightheaded 1%
* Back pain 1%
* High liver function test 1%
* Stomach pain 1%

These adverse events were generally mild. Most cases of bloody nose and itchy rash were due to study related procedures such as nasal swabs and adhesive tape, and not the study drug.

Presatovir has also been studied in animals. In studies conducted in baby rats, those that were treated with presatovir were noted to have an increase in heart weight compared to those who were treated with placebo. This increase was not seen in studies of adult rats, other animal species or in any human studies. The relevance of this finding to humans is unknown.

Presatovir is currently being studied in 4 trials of RSV infected adults who are either hospitalized due to their RSV infection or have had a bone marrow or lung transplant and are infected with RSV. As of November 2015, an estimated 43 RSV infected patients have been treated with presatovir. There have been no serious side effects or deaths that have been assessed as related to presatovir. The effect of the treatment on RSV infection in adults is still being studied.

There is a small chance that people with strong sulfa allergies (for instance, history of hypersensitivity, anaphylactic reaction, Stevens-Johnson Syndrome, or toxic epidermal necrolysis response to sulfas) may have an allergic reaction to presatovir. Allergic reactions can be mild, like a rash, or could be severe, like swelling of the throat, shortness of breath, rapid heartbeat, or even death. If you experience any of these symptoms, please tell your doctor immediately.
Please talk to the study doctor if you have more questions about adverse events.

PREGNANCY AND BREAST-FEEDING
Because the effects of presatovir on an unborn baby or a breastfeeding infant are not known, any female who is pregnant or breast feeding an infant will not be enrolled in this study.

If you become pregnant or suspect that you have become pregnant while in the study or within 30 days after the dose of study drug, you must notify your Study Doctor immediately, even if you are no longer in the study. The Study Doctor will request to track your pregnancy and will report the pregnancy to the Study Sponsor.

For more information on reproductive risks, please consult the Pregnancy and Partner Pregnancy sections in Appendix 2.

UNKNOWN/UNEXPECTED RISKS AND DISCOMFORTS
In addition to the risks listed above, there are risks that are not known or do not happen often when patients take these study drugs, including severe or life-threatening allergic reactions, interactions between study drugs or interactions with another medication. You will be informed in a timely manner, both verbally and in writing of any new information, findings or changes to the way the research will be done that might influence your willingness to continue to take part in this study.

For a complete overview of risks and discomforts related to the study procedures and more information on reproductive risks, please consult Appendix 2.

Contacts

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Gilead Sciences, Inc.

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Gilead Sciences, Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects must meet all of the following inclusion criteria at the time of randomization to be eligible for participation in this study:
1) Adult males and females 18 to 75 years of age. In Japan subjects must be 20 to 75 years of age. In Singapore subjects must be 21 to 75 years of age.
2) Received an autologous or allogeneic HCT using any conditioning regimen
3) Documented to be RSV-positive as determined by local testing (eg, polymerase chain reaction [PCR], direct fluorescence antibody [DFA], respiratory viral panel (RVP) assay, or culture) using an upper respiratory tract sample collected * 6 days prior to Day 1, or as determined at Screening as per Section 6.1.1.
4) New onset of at least 1 of the following respiratory symptoms for * 7 days prior to Day 1: nasal congestion, runny nose, cough, or sore throat, or worsening of one of these chronic (associated with a previously existing diagnosis, eg, chronic rhinorrhea, seasonal allergies,

chronic lung disease) respiratory symptoms * 7 days prior to Day 1
5) No evidence of new abnormalities consistent with LRTI on a chest X ray relative to the most recent chest X-ray, as determined by the local radiologist. If a chest X-ray is not available or was not obtained during standard care < 48 hours prior to Screening, a chest X-ray must be obtained for Screening
6) Oxygen saturation * 92% on room air
7) An informed consent document signed and dated by the subject or a legal guardian of the subject and the investigator or his/her designee. In Sweden ICFs signed by a legal guardian must also be signed by a close relative of the subject.
8) A negative urine or serum pregnancy test is required for female subjects (unless surgically sterile or greater than two years post menopausal)
9) Male and female subjects of childbearing potential must agree to contraceptive requirements as described in Appendix 5
10) Willingness to complete necessary study procedures and have available a working telephone or email

Exclusion criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study.
Related to concomitant or previous medication use:
1) Use of non-marketed (according to region) investigational agents within 30 days, OR use of any investigational monoclonal anti-RSV antibodies within 4 months or 5 half-lives of Screening, whichever is longer, OR use of any investigational RSV vaccines after HCT
2) Use of a moderate or strong cytochrome P450 enzyme (CYP) inducer including but not limited to rifampin, St. John*s Wort, carbamazepine, phenytoin, efavirenz, bosentan, etravirine, modafinil, and nafcillin, within 2 weeks prior to the first dose of IMP
Related to medical history:
3) Admitted to the hospital primarily for a lower respiratory tract disease of any cause as determined by the investigator
4) Pregnant, breastfeeding, or lactating females
5) Unable to tolerate nasal sampling required for this study, as determined by the investigator
6) Known history of HIV/AIDS with a CD4 count <200 cells/*L within the last month
7) History of drug and/or alcohol abuse that, in the opinion of the investigator, may prevent adherence to study activities
Related to medical condition at Screening:
8) Documented to be positive for other respiratory viruses (limited to influenza, parainfluenza, human rhinovirus, adenovirus, human metapneumovirus, or coronavirus) within 7 days prior to the Screening visit, as determined by local testing (additional testing is not required)
9) Clinically significant bacteremia or fungemia within 7 days prior to Screening that has not been adequately treated, as determined by the investigator
10) Clinically significant bacterial, fungal, or viral pneumonia within 2 weeks prior to Screening that has not been adequately treated, as determined by the investigator
11) Excessive nausea/vomiting at Screening, as determined by the investigator, or an

inability to swallow pills that precludes oral administration of the IMP (for subjects without an NG tube in place)
12) Any condition which, in the opinion of the investigator, would prevent full participation in this trial or would interfere with the evaluation of the trial endpoints
Related to allergies:
13) Known hypersensitivity or allergy to the IMP, its metabolites, or formulation excipients (microcrystalline cellulose, mannitol, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc)
14) History of hypersensitivity, anaphylactic reaction, Stevens-Johnson Syndrome, or toxic epidermal necrolysis response to sulfa drugs
Related to laboratory results:
15) Creatinine clearance < 30 mL/min (calculated using the Cockcroft Gault method)
16) Clinically significant ALT/AST, as determined by the investigator
17) Clinically significant total bilirubin (TB), as determined by the investigator

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):	23-01-2015
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n/a

Generic name:	presatovir (GS-5806)

Ethics review

Approved WMO Date:	04-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	05-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2014-002474-36-NL
ClinicalTrials.gov	NCT02254408
CCMO	NL50193.029.14