A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734*) in Participants with Severe COVID-19

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The primary objective of this study is as follows: -To evaluate the efficacy of 2 remdesivir (RDV) regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14The secondary objective of this study is as follows: - To...

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

Summary

ID

NL-OMON49233

Source
ToetsingOnline

Brief title
Remdesivir in Participants with Severe COVID-19

Condition

- Viral infectious disorders

Synonym
COVID-19; Corona

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences

Source(s) of monetary or material Support: Gilead Sciences

Intervention

Keyword: Antiviral, COVID-19, Remdesivir, Safety

Outcome measures

Primary outcome

Clinical status assessed by a 7-point ordinal scale on Day 14

Secondary outcome

The proportion of participants with treatment emergent adverse events.

Study description

Background summary

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China. Sequencing analysis from the patients* respiratory tract samples indicated a novel coronavirus (CoV), which was named COVID-19. As of 23 February 2020, more than 78,000 confirmed cases have been identified in Wuhan, other provinces in China, and in multiple countries outside China {World Health Organisation (WHO) 2020}.

More than 2400 deaths associated with COVID-19 have been reported, making COVID-19 a major health emergency. Antiviral drugs that are being evaluated as potential treatments for COVID-19 include lopinavir/ritonavir (LPV/RTV; used in the treatment of HIV infection) and remdesivir (RDV, GS-5734*). In a study of Severe Acute Respiratory Syndrome (SARS), a significant reduction in acute respiratory distress syndrome/mortality was observed in 41 patients treated with the combination of LPV/RTV, compared with 111 patients receiving monotherapy ribavirin (2.4% vs 28.8%, p = 0.001). However, the use of historical control data does not allow for a reliable estimation of efficacy. Additionally, LPV/RTV has multiple known adverse reactions such as prolonged QT interval,severe gastrointestinal reactions, abnormal blood glucose, pancreatitis, hepatic impairment, and elevated blood lipids. It has multiple drug-to-drug interactions with many commonly used drugs in clinical practice; thus, its clinical safety is not determined. Remdesivir shows potent in vitro activity against the human pathogenic CoVs Middle East Respiratory Syndrome (MERS)-CoV and SARS-CoV in multiple relevant human cell types. In a mouse model of MERS-CoV infection, both prophylactic and therapeutic RDV significantly

improved pulmonary function and reduce lung viral loads and severe lung pathology compared with vehicle control animals. In contrast, prophylactic LPV/RTV + interferon-beta (LPV/RTV-IFNb) slightly reduced viral loads without impacting other disease parameters. Therapeutic LPV/RTV-IFNbimproves pulmonary function but did not reduce virus replication or severe lung pathology {Sheahan 2020}.

The evaluation of the safety and potential efficacy of RDV in people with COVID-19 is urgently needed.

Study objective

The primary objective of this study is as follows:
-To evaluate the efficacy of 2 remdesivir (RDV) regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14

The secondary objective of this study is as follows:
- To evaluate the safety and tolerability of RDV

Study design

This is a Phase 3 randomized, open-labeled, multi-center study of RDV therapy in participants with severe COVID-19.
The study will be conducted in two parts.
In Part A, approximately 400 participants who meet all eligibility criteria and who are not mechanically ventilated may be randomized in a 1:1 ratio into one of the following treatment groups:
Treatment Group 1: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5
Treatment Group 2: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10.

Part B will enroll participants on mechanical ventilation and, after enrollment to Part A is complete, any additional participants. In Part B, up to an additional approximately 2000 participants who meet all of the eligibility criteria will be enrolled, based on whether they are mechanically ventilated at enrollment, to receive:
Mechanically Ventilated Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10
Extension Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10
Enrollment in the mechanically ventilated treatment group will be capped at approximately 500 participants.
If the 5-day dosing regimen used in Treatment Group 1 of Part A is selected for

Part B, all participants in the Extension Treatment Group and all new participants will be reassigned to receive treatment for a total of 5 days.
National and local regulatory authorities will be informed.
Participants in Part A of the study will be the primary efficacy population.
Participants enrolled in Part B will have data reported descriptively at study completion.

Intervention

Remdesivir
Treatment Group 1:continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100mg on Days 2, 3, 4, and 5 Treatment Group 2:continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

Study burden and risks

A pertinent specific risk for participantsin this study is the potential for transient,Grade * 2, treatment-emergent elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which were observed after multiple daily RDV administrations in Studies GS-US-399-1954 and GS-US-399-5505.

To date in human studies, no serious adverse events (SAEs)have occurred in healthy individuals who have received at least 1 dose of RDV. Remdesivir has been tested in healthy volunteers as a single ascending dose over a dose range of 3 to 225 mg and in a multi-dose study of 150 mg for up to 14 days and at 200 mg loading dose followed by 100 mg for a total of 10 days. In nonclinical animal studies, toxicity findings were consistent with dose-dependent and reversible kidney injury and dysfunction. The clinical significance of the nephrotoxicity noted in animal species is unknown.The etiology of reversible kidney injury observed in rats is consistent with the ability of rat renal organic anion transporters (OATs), but not human OATs, to efficiently interact with blood metabolites of RDV, particularly GS-704277. This effect may lead to proportionally higher intracellular accumulation of drug metabolites in renal rat tubules, leading to kidney injury.

The 200 mg loading dose with 8 g of sulfobutylether *-cyclodextrin sodium (SBECD) on Day 1 will be followed by 100 mg of RDV each day for 4 or 9 days with 4 g of SBECD, which is within the range of daily SBECD administration considered safe in humans. A total of 250mg/kg/day of SBECD is considered safe by the European Medicines Agency and is therefore safe for all adults with weight over 32 kg. The 100 mg dose prepared in 0.9% saline will be hypertonic relative to human serum osmolality but approaches the normal physiological osmolar range for humans. The RDV regimen consisting of a loading dose of 200 mg followed by RDV 100 mg daily for up to 9 days is not anticipated to pose a safety risk to participants enrolled in this study.

There are currently no data available on the interaction of RDV and other investigational agents. Administering RDV concurrent with other investigational anti-CoV agents may lead to antagonism or synergy or have no effect.

The risk mitigation strategy for this study includes restriction of the study population to those without a history of significant renal or hepatic disease:
- Exclusion of participants with ALT > 5 ULN *
- Exclusion of participants with an estimated glomerular filtration rate (eGFR) <50mL/min *
- Exclusion of coadministration of other investigational agents against COVID-19 * Serum chemistry assessments, including liver function testing, will be closely monitored during the study period.

There are currently no investigational agents with demonstratedclinical efficacy or approved treatments for COVID-19. The timely evaluation of a safe and effective antiviral agent that works by directly and selectively blocking the virus replication and is broadly efficacious against COVID-19addresses a serious unmet medical need. In consideration of the information included in this protocol, the overall risks to participants are outweighed by the potential benefits of RDV experimental therapy for the treatment of COVID-19. The benefit-risk balance for this study is considered positive.

Contacts

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Gilead Sciences

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Willing and able to provide written informed consent, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (participants * 18 years of age), or willing and able to provide assent (participants * 12 and < 18 years of age, where locally and nationally approved) prior to performing study procedures. For participants * 12 and < 18 years of age, a parent or legal guardian willing and able to provide written informed consent prior to performing study procedures
2) Aged * 18 years (at all sites), or aged * 12 and < 18 years of age weighing * 40 kg (where permitted according to local law and approved nationally and by the relevant institutional review board [IRB] or independent ethics committee [IEC])
3) SARS-CoV-2 infection confirmed by PCR * 4 days before randomization
4) Currently hospitalized
5) SpO2 > 94% on room air or requiring supplemental oxygen at screening
6) Radiographc evidence of pulmonary infiltrates
7) Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Protocol Appendix 3.

Exclusion criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study:
1) Participation in any other clinical trial of an experimental treatment for COVID-19
2) Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 is prohibited < 24 hours prior to study drug dosing
3) Evidence of multiorgan failure
4) Mechanically ventilated (including V-V ECMO) * 5 days, or any duration of V-A ECMO.
5) ALT or AST >5xULN

6) Creatinine clearance < 50mL/min using the Cockroft-Gault formula for participants * 18 years of age {Cockroft 1976} and Schwartz Formula for participants < 18 years of age.
7) Positive pregnancy test
8) Breastfeeding woman
9) Known hypersensitivity to the study drug, the metabolites, or formulation excipient

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-03-2020
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Remdesivir
Generic name:	N.a.

Ethics review

Approved WMO

Date:	20-03-2020
Application type:	First submission

Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	27-03-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	31-03-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	03-04-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	10-04-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	17-04-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	29-04-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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	EUCTR2020-00841-15-NL
CCMO	NL73428.058.20