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Information Data Sheet
Remdesivir for intravenous use for the treatment of patients with COVID-19 (SARS-CoV-2) syndrome
24 April 2020

Drug description

Remdesivir (RDV, GS-5734) is a diastereomeric monophosphoramidate prodrug of an adenine nucleotide analogue GS-441524. Inside cells, the GS-441524 monophosphate undergoes conversion to the pharmacologically active nucleoside triphosphate form GS-443902, which is able to inhibit the viral RNA-dependent RNA-polymerase.
RDV has shown a broad-spectrum antiviral activity with a proven *in-vitro* and *in vivo* (on animal models) efficacy against different RNA viruses, not genetically linked but similar to SARS-CoV-2, like SARS-CoV and Middle-East Respiratory Syndrome Coronavirus (MERS-CoV).
According to several *in-vitro* studies, RDV seems to be a promising candidate drug for the treatment of the acute respiratory syndrome COVID-19, in association with chloroquine [Ref. 1-6].

Therapeutic plan for RDV off-label use in COVID-19 positive patients.

Proposed therapeutic plan
The treatment with RDV has already been used, with good results, in clinical trials for Ebola virus disease and, recently, has become object of several studies for the evaluation of its safety and efficacy in the context of COVID-19. These studies are both promoted by Gilead and free-standing (see Appendix, table 4), including two Phase III studies on COVID-19 patients in Italy [7-8], with a centers selection shared with AIFA, in order to identify those with the higher number of hospitalized patients.

Moreover, it has being activated a compassionate use program, based on a defined clinical protocol. Ten medical centers in Italy, identified together with AIFA, are now implementing this program [9].
As recommended for compassionate use, the treatment with RDV can be approved after a worsening of the patient's status. In that case, Gilead Science Inc. provides both the RDV and the instructions for the preparation and intravenous administration.

According to manufacturer recommendations, the therapeutic regimen for adult patients establishes a leading dose of 200 mg on day 1, followed by 100

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mg/day for 5 or 10 days (if the patient is into the sponsored study that plans 10 days of treatment), to be administered through intravenous infusion.

In the context of compassionate use, the treatment with remdesivir could be associated with other treatments (chloroquine/ hydroxychloroquine) and/or other antiviral agents (lopinavir/ritonavir or darunavir/ritonavir) and/or steroids (dexamethasone) and/or drugs against IL-6 (tocilizumab).

Patients selection criteria for compassionate use	
Inclusion criteria	*Exclusion criteria*
• Currently hospitalized with fever (defined as temperature ≥ 36.6 °C armpit, ≥ 37.2 °C oral, ≥ 37.8 °C rectal) • SARS-CoV-2 infection confirmed by PCR ≤ 4 days before randomization • Radiographic evidence of pulmonary infiltrates • Requiring mechanical ventilation	• Evidence of multiple organ dysfunction • Requirement of an aid to keep the blood pressure to constant values • ALT > 5x ULN (Upper Limit of Normal) • Creatinine Clearance < 30mL/min, or dialysis, or continuous veno-venous hemofiltration (CVVH)

Patients selection criteria for Gilead clinical study for moderate disease ID: NCT04292730 [10]	
Inclusion criteria	*Exclusion criteria*
• Willing and able to provide written informed consent prior to performing study procedures (participants ≥ 18 years of age) or assent (participants ≥ 12 and < 18 years of age) 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 • Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test ≤ 4 days before randomization • Currently hospitalized and requiring medical care for COVID-19	• Participation in any other clinical trial of an experimental treatment for COVID-19 • Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing • Requiring mechanical ventilation at screening • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 X upper limit of normal (ULN) • Creatinine clearance < 50 mL/min using the Cockcroft-Gault formula for participants ≥ 18 years of age {Cockcroft 1976} and Schwartz Formula for participants < 18 years of

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• Peripheral capillary oxygen saturation **(SpO2) > 94%** on room air at screening • Radiographic evidence of pulmonary infiltrates	age

Patients selection criteria for Gilead clinical study for severe disease ID: NCT04292899 [11]	
Inclusion criteria • Willing and able to provide written informed consent, or with a legal representative who can provide informed consent, or enrolled under International Conference on Harmonization (ICH) E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (age ≥18), or willing and able to provide assent (age ≥12 to <18, where locally and nationally approved) prior to performing study procedures • 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]) • Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test ≤ 4 days before randomization • Currently hospitalized • Peripheral capillary oxygen saturation **(SpO2) ≤ 94%** or requiring supplemental oxygen at screening	*Exclusion criteria* • Participation in any other clinical trial of an experimental treatment for COVID-19 • 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 • Evidence of multiorgan failure • Mechanically ventilated (including V-V ECMO) ≥ 5 days, or any duration of V-A ECMO. • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 X upper limit of normal (ULN) • Creatinine clearance < 50 mL/min using the Cockcroft-Gault formula for participants ≥ 18 years of age {Cockcroft 1976} and Schwartz Formula for participants < 18 years of age

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Clinical safety data

Note: Data obtained from studies in the context of Ebola [12].

Single dose of remdesivir IV infusion from 3 to 225 mg was well tolerated with no dose limiting toxicity observed. No treatment emergent AEs were observed in more than 1 subject per arm. No evidence of renal or liver toxicity was observed. All AEs were Grade 1 or 2.
Multiple-dose IV administration of remdesivir 150 mg once-daily for 7 or 14 days was generally well tolerated. No subjects had a Grade 3 or 4 treatment-emergent laboratory abnormality during the study. Reversible Grade 1 or 2 ALT or AST elevations were observed in several subjects without abnormalities in total bilirubin, alkaline phosphatase (ALP), or albumin. There was no abnormality or clinically significant change in international normalized ratio (INR) in any subjects. Remdesivir did not show any effects on renal function in the multiple-dose study.

Remdesivir Supply

How to formulate a request

Up to now RDV is not registered for the treatment of COVID-19 positive patients, as a consequence, if not part of a clinical study, the compassionate use request to Gilead is the only way to get access to the drug.

The compassionate use request must be completed for each single patient and, upon acceptance by Gilead, the approval of the Local Ethical Committee must be obtained.
Here, as an example, it is reported the procedure (referred to ASL Città di Torino) for the compassionate use request of RDV to Gilead.

STEP - 1

The clinician submits the compassionate use request to Gilead, for a single patient, through the committed platform: https://rdvcu.gilead.com/, informing the other clinicians and the pharmacy of its center.
Upon approval, Gilead must send a document to attest the nominal approval for each patient.

STEP - 2

The applicant clinician must fill in and sign the following documents for each single patient in order to submit the request to the Local Ethical Committee:

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- ACTIVATION request, in the case of the FIRST request from the hospital, or EXTENSION request, for all the following patients from the same hospital ward;
- Taking on responsibility
- Clinical report (it may be also available on Gilead platform)
- Declaration of the degree of comparability
- Curriculum vitae of the applicant clinician

STEP - 3

The applicant clinician must send a scan of all signed documents listed above to the hospital pharmacy by e-mail.

STEP - 4

The hospital pharmacy must forward the request to the Local Ethical Committee, including in the e-mail: the applicant clinician, the referring clinician and the contact person of the hospital pharmacy.

In this case, the hospital pharmacy, adds to the request of the applicant clinician the following documents:

- Information sheet and informed consent
- Privacy information and consent
- Treatment protocol
- Remdesivir IB (investigator's brochure)
- Instructions

STEP – 5

Once obtained the Local Ethical Committee approval, the applicant clinician will forward the request to Gilead, according to the hospital internal procedures, indicating a contact person from the hospital pharmacy and the involved PO to send the drug. The pharmacist must notice to the clinician when the drug arrives.

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Appendix

Remdesivir potential pharmacological interactions, stratified by recommendation (source: http://www.covid19-druginteractions.org/).

Table 1. Drugs at high interaction risk with remdesivir: they must not be coadministered.

Drug class	Molecule
Antibacterials	Rifampicin
	Rifapentine
Inotropes and Vasopressors	Adrenaline (Epinephrine)
	Dobutamine
	Noradrenaline
	Vasopressin
Antidepressants	St John's wort

Table 2. Drugs with potential interaction with remdesivir: may require close monitoring, alteration of drug dosage or timing of administration.

Drug class	Molecule
Antibacterials	Rifabutin
Steroids	Betamethasone
	Dexamethasone
Hypertension/Heart Failure Agents	Bosentan

Table 3. Potential interaction likely to be of weak intensity: additional action/monitoring or dosage adjustement is unlikely to be required.

Drug class	Molecule
NA	NA

NA: data not available

Table 4. Currently ongoing and terminated studies involving remdesivir in the context of COVID-19 disease (source: https://clinicaltrials.gov).

Two phase 3 randomized, double-blind, placebo-controlled, multicenter studies to evaluate the efficacy and safety of remdesivir in hospitalized adult patients with severe (NCT04257656) and mild/moderate (NCT04252664) COVID-19. These studies have been sponsored by the Capital Medical University and are now terminated.

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DisCoVeRy – a multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults (NCT04315948); the investigated drugs are: remdesivir, lopinavir/ritonavir, interferon beta-1A and hydroxychloroquine. This study was based on a OMS protocol (WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial) and sponsored by the Institut National de la Santé Et de la Recherche Médicale, France.
A multicenter, adaptive, randomized blinded controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized adults (NCT04280705). This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and carried out in USA, South Korea and Singapore.
Solidarity – The World Health Organization Norwegian COVID-19 study is a multi-centre, adaptive, randomized, open clinical trial to evaluate the safety and efficacy of hydroxychloroquine, remdesivir and standard of care in hospitalized adult patients diagnosed with COVID-19 (NCT04321616). This study is sponsored by the Oslo University Hospital.
Two phase 3 randomized studies to evaluate the safety and antiviral activity of remdesivir in participants with moderate (NCT04292730) or severe (NCT04292899) COVID-19, compared to standard of care treatment. These studies are sponsored by Gilead Sciences and carried out in those Countries with the highest number of COVID-19 positive patients (among which Italy).
Two studies carried out in USA in order to expand the access to remdesivir. NCT04302766: an intermediate-size patient population expanded access treatment protocol for COVID-19 remdesivir, sponsored by the U.S. Army Medical Research and Development Command; NCT04323761: expanded access to remdesivir for the treatment of SARS-Cov-2 infection, sponsored by Gilead Sciences.

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