HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
OPINION
16 SEPTEMBER 2020

remdesivir

VEKLURY 100 mg powder for concentrate for solution for infusion and concentrate for solution for infusion

First assessment

Application for reimbursement withdrawn by the pharmaceutical company

Key points

Favourable opinion for reimbursement only in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring low-flow supplemental oxygen and at the MA dosages.

Unfavourable opinion for reimbursement in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

Maintenance of the conclusions of this opinion is subject to submission of data at D28, in particular mortality data from the American ACTT trial whenever these become available and, at the latest, in October 2020.

On 31 August 2020, the pharmaceutical company Gilead withdrew its application for reimbursement of the proprietary medicinal product VEKLURY (remdesivir).

What therapeutic improvement?

No clinical added value on the basis of currently available data.

Role in the care pathway?

Currently, the supportive standard of care (SOC) remains the reference treatment for COVID-19 in France. Corticosteroids (off-label) have recently been recommended in severe forms of COVID-19 (WHO, HCSP).

Role of the medicinal product in the care pathway

Despite numerous clinical uncertainties with respect to the efficacy of VEKLURY (remdesivir) in a context of very rapidly evolving treatment strategies, the role of VEKLURY (remdesivir) has been defined considering its potential usefulness for some patients with severe SARS-CoV-2 infection.

Hence, and primarily based on preliminary data from the ACTT trial conducted by the NIAID:

- which suggest an at best weak effect size of remdesivir *versus* placebo, in combination with the standard of care: 4-day reduction in the time to clinical recovery (11 days *versus* 15 days; HR=1.32 [1.12-1.55]), primary endpoint of debatable clinical relevance;
- subgroup analyses having demonstrated a statistically significant difference in terms of the time to clinical recovery only in patients requiring low-flow supplemental oxygen at baseline (HR of 1.47; 95% CI [1.17; 1.84]) and the absence of a statistically significant difference in the most severe forms (patients requiring high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
- and the absence of any demonstrated impact in this study on the reduction in mortality at D14 (7.1% in the remdesivir group *versus* 11.9% in the placebo group (HR = 0.70; 95% CI [0.47 to 1.04], NS, secondary endpoint)), although the subgroup analyses suggest a positive effect on this endpoint only in the subgroup of patients receiving low-flow supplemental oxygen;

pending D28 mortality results, the Committee considers that VEKLURY (remdesivir) could constitute, in combination with the standard of care, a therapeutic option in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring low-flow supplemental oxygen, excluding high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

Additional data are required and expected to be able to determine, with a better level of evidence, the efficacy, adverse effects and risks of VEKLURY (remdesivir) in the MA indication.

The Committee reiterates the fact that there are no data concerning patients with renal or hepatic impairment or in pregnant women.

The use of VEKLURY (remdesivir) must be accompanied by close clinical monitoring given the potential adverse reactions following injection (in particular, hypotension) along with monitoring of renal and hepatic function (important potential or identified risks in the context of the RMP).

Special recommendations

In view of the current uncertainties concerning the efficacy, safety and methods of use (clinical stage, optimal use duration and patient follow-up) of VEKLURY (remdesivir), in a context of very rapidly evolving treatment strategies, and insofar as the Committee has restricted the reimbursement scope of VEKLURY (remdesivir) compared to the MA, it recommends that prescriptions be made following a collective opinion.

Reason for assessment	**Inclusion in list**
Indication concerned	**Remdesivir is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen.**
Clinical Benefit	**The Committee considers that the clinical benefit of VEKLURY (remdesivir) is:** **- LOW in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring low-flow supplemental oxygen;** **- INSUFFICIENT to justify its funding by the French national health insurance system in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).** **The Committee indicates that maintenance of this assessment is conditional on reevaluation of VEKLURY (remdesivir), in particular based on D28 mortality data from the American ACTT trial, whenever these become available and, at the latest, by October 2020.** **This assessment reflects the still high level of uncertainty with respect to the efficacy and safety of VEKLURY (remdesivir) in a context of very rapidly evolving treatment strategies and the public health need.**
Clinical Added Value	**Considering:** **- the available clinical data limited to the results of 3 comparative studies conducted in hospitalised patients (Chinese study NCT04257656 stopped early, preliminary results of the American ACTT study, SIMPLE study without a control group) presenting numerous methodological limitations and conflicting results,** **- preliminary results from the pivotal American ACTT study with the biggest population (n = 1,063 hospitalised patients with pneumonia, including 88.7% with a severe form requiring oxygen), which suggest an at best weak effect size of remdesivir *versus* placebo, in combination with the standard of care: 4-day reduction in the time to clinical recovery (11 days *versus* 15 days; HR=1.32 [1.12-1.55]), primary endpoint of debatable clinical relevance,** **- and the absence of any demonstrated impact in this study on the reduction in mortality at D14 (7.1% in the remdesivir group *versus* 11.9% in the placebo group (HR = 0.70; 95% CI [0.47 to 1.04], NS, secondary endpoint), although the subgroup analyses suggest a positive effect on this endpoint only in the subgroup of patients receiving low-flow supplemental oxygen,** **- the absence of mortality data at D28 in the ACTT study,** **- the absence of data enabling a robust conclusion to be reached with respect to efficacy depending on the stage of the disease and the optimal treatment duration;** **- the absence of a demonstrated impact of remdesivir in terms of the expected negative conversion of viral load;** **- and despite the medical need to have access to effective and well-tolerated curative treatments for COVID-19 due to its severity, its contagiousness and its impact on healthcare organisation, particularly in intensive care units, as well as the absence of an available curative treatment;** **On the basis of currently available data, the Committee considers that VEKLURY (remdesivir) provides no clinical added value (CAV V) for the treatment of COVID-19 in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia and receiving low-flow supplemental oxygen.**
Public health impact	**In view of the data currently available, VEKLURY (remdesivir) is unlikely to have an impact on public health**.

Role in the care pathway	**Despite numerous clinical uncertainties with respect to the efficacy of VEKLURY (remdesivir) in a context of very rapidly evolving treatment strategies, the role of VEKLURY (remdesivir) has been defined considering its potential usefulness for some patients with severe SARS-CoV-2 infection.** **Hence, and primarily based on preliminary data from the ACTT trial conducted by the NIAID:** **- which suggest an at best weak effect size of remdesivir *versus* placebo, in combination with the standard of care: 4-day reduction in the time to clinical recovery (11 days *versus* 15 days; HR=1.32 [1.12-1.55]), primary endpoint of debatable clinical relevance;** **- subgroup analyses having demonstrated a statistically significant difference in terms of the time to clinical recovery only in patients requiring low-flow supplemental oxygen at baseline (HR of 1.47; 95% CI [1.17; 1.84]) and the absence of a statistically significant difference in the most severe forms (patients requiring high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);** **- and the absence of any demonstrated impact in this study on the reduction in mortality at D14 (7.1% in the remdesivir group *versus* 11.9% in the placebo group (HR = 0.70; 95% CI [0.47 to 1.04], NS, secondary endpoint)), although the subgroup analyses suggest a positive effect on this endpoint only in the subgroup of patients receiving low-flow supplemental oxygen;** **pending D28 mortality results, the Committee considers that VEKLURY (remdesivir) could constitute, in combination with the standard of care, a therapeutic option in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring low-flow supplemental oxygen, excluding high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).** **Additional data are required and expected to be able to determine, with a better level of evidence, the efficacy, adverse effects and risks of VEKLURY (remdesivir) in the MA indication.** **The Committee reiterates the fact that there are no data concerning patients with renal or hepatic impairment or in pregnant women.** **The use of VEKLURY (remdesivir) must be accompanied by close clinical monitoring given the potential adverse reactions following injection (in particular, hypotension) along with monitoring of renal and hepatic function (important potential or identified risks in the context of the RMP).**
Target population	**The target population of VEKLURY (remdesivir) can be estimated to correspond to 30% of new cases of hospitalised patients with COVID-19.**
Recommendations	◗ **Specific requests inherent to funding** **In view of the current uncertainties concerning the efficacy, safety and methods of use (clinical stage, optimal use duration and patient follow-up) of VEKLURY (remdesivir), in a context of very rapidly evolving treatment strategies, and insofar as the Committee has restricted the reimbursement scope of VEKLURY (remdesivir) compared to the MA, it recommends that prescriptions be made following a collective opinion.** ◗ **Requests for data** **Considering that the available data in this indication are preliminary with, in particular, uncertainties concerning quantification of the therapeutic contribution of VEKLURY (remdesivir) compared to placebo, the Committee makes maintenance of its favourable opinion for reimbursement conditional on the submission of data at D28 and, in particular mortality data from the American ACTT study, with submission expected whenever these become available and, at the latest, by October 2020. At this point, the Committee will specify the clinical data to be collected in the context of real-life use of VEKLURY (remdesivir).**

	In addition, the Transparency Committee will reevaluate VEKLURY (remdesivir) in this indication once the consolidated results of clinical studies are available (including the DisCoVeRy and SOLIDARITY trials) and whenever the national COVID-19 management strategy evolves.

01 CONTEXT

This is an application for the inclusion of VEKLURY (remdesivir) in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indication obtained on 3 July 2020 *"treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen".* This indication therefore includes all patients requiring supplemental oxygen, whether they are ventilated or not.

VEKLURY (remdesivir) is a broad-spectrum antiviral that is a monophosphate derivative of a nucleoside analogue of adenine, previously developed in the viral disease Ebola due to its activity *in vitro* and in animal models of this virus, but which did not demonstrate clinical activity against this disease in humans. In January 2020, this antiviral drug was identified as an option to be evaluated in the clinical development of coronavirus disease 2019 (COVID-19), due to its activity in cell cultures and animal models against MERS-CoV and SARS-CoV coronaviruses[1,2]. A recent study documented the *in vitro* activity of VEKLURY (remdesivir) against SARS-CoV-2[3].

As a reminder, on 8 June 2020, the EMA[4] announced that it had started assessing a conditional MA application for VEKLURY (remdesivir). The CHMP returned a favourable opinion on 25 June. The final decision concerning the conditional MA granted by the European Commission (EC) was returned on 3 July 2020.

In France, following a request for a cohort compassionate use programme (ATU) submitted on 26 March 2020, the ANSM granted a cohort ATU on 2 July 2020 in a similar perimeter to the indication of the conditional MA, i.e.: "Remdesivir is indicated for the treatment of COVID-19 disease in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (see section 5.1 of the SPC). In view of the limitations of the clinical demonstration in terms of efficacy (see section 5.1 of the SPC) and safety, any treatment initiation must be the subject of a prior collective opinion."[5]

At present, it is the only medicinal product with a conditional MA in the treatment of COVID-19.

Reminder concerning the use of VEKLURY (remdesivir) during the pandemic and before the MA
Before the MA was granted, on 23 March 2020 the French High Council for Public Health (HCSP) recommended the use of VEKLURY (remdesivir) from that date onwards in the context of therapeutic trials on a compassionate prescription basis in severe hospitalised cases of COVID-19: *"in the event of pneumonia with acute respiratory failure (≥ 6 L O_2 per minute) or with organ failure. In the absence of multiorgan failure, treatment with remdesivir is the only formalised therapeutic option although it has no level of evidence, if viral excretion is documented in nasopharyngeal or lower respiratory samples (e.g. induced sputum, endotracheal aspiration, bronchoalveolar lavage), and in the absence of contraindications (vasopressive amines , inotropic agents, catecholamines, hepatic cytolysis > 5 N, clearance < 30 mL/min or haemodialysis)"*.

In addition, on 3 April 2020, the European Medicines Agency (EMA) provided recommendations on the compassionate use of VEKLURY (remdesivir) within Member States in the indication "*For the treatment of adult and paediatric patients from 12 years of age weighing at least 40 kg with severe COVID-19 requiring invasive mechanical ventilation, confirmed by Polymerase chain reaction (PCR)*

[1] Sheahan T et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Science Translational Medicine, 2017.
[2] Sheahan T et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nature Communications, 2020.
[3] Wang M et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research, 2020.
[4] EMA. EMA receives application for conditional authorisation of first COVID-19 treatment in the EU. 08/06/2020.
[5] ANSM. Cohort compassionate use programme (ATU) for VEKLURY (remdesivir). Link: https://ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/ATU-de-cohorte-en-cours/Liste-des-ATU-de-cohorte-en-cours/REMDESIVIR-100-mg-solution-a-diluer-pour-perfusion. [Consulted on 16/07/2020].

or who have had known contact with a confirmed case of COVID-19, with PCR pending" at a dosage of 200 mg on D1 then 100 mg for 9 days[6,7].
On 11 May 2020[8], the EMA expanded the indications for compassionate use to *"for the treatment of adult and paediatric patients from 12 years of age weighing at least 40 kg with severe COVID-19 (hospitalisation requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO), confirmed by Polymerase chain reaction (PCR) or who have had known contact with a confirmed case of COVID-19, with PCR pending.*".
On 1 May 2020, the FDA granted an Emergency Use Authorisation or EUA[9] to allow the emergency use of VEKLURY (remdesivir) for the treatment of confirmed or suspected SARS-CoV-2 infection in hospitalised adults and children (from 3.5 kg) with severe disease.
On 5 June 2020, NICE communicated about the issue of a positive scientific opinion by the British Agency MHRA with a view to a rapid early access to medicines scheme for remdesivir[10].

According to the pharmaceutical company, 1,800 patients have received VEKLURY (remdesivir) around the world, including 110 in France (83 of whom received it in the context of the compassionate use programme).

On 31 August 2020, the pharmaceutical company Gilead withdrew its application for reimbursement of the proprietary medicinal product VEKLURY (remdesivir).

02 THERAPEUTIC INDICATION

"VEKLURY is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (see section 5.1 of the SPC)".

03 DOSAGE

"Use of remdesivir is confined to healthcare facilities in which patients can be monitored closely (see section 4.4 of the SPC).

Dosage
The recommended dosage of remdesivir in patients 12 years of age and older and weighing at least 40 kg is:

- Day 1: single loading dose of remdesivir 200 mg given by intravenous infusion,
- Day 2 onwards: 100 mg given once daily by intravenous infusion.

The total duration of treatment should be at least 5 days and not more than 10 days.

Special populations
Elderly
No dose adjustment of remdesivir is required in patients over the age of 65 years (see sections 5.1 and 5.2 of the SPC).

Renal impairment

[6] EMA. 3 April 2020. EMA provides recommendations on compassionate use of remdesivir for COVID-19.
[7] EMA. 3 April 2020. Conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring addressed to member states for remdesivir available for compassionate use.
[8] EMA. 11 May 2020. EMA recommends expanding remdesivir compassionate use to patients not on mechanical ventilation.
[9] FDA press release. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment.May 01, 2020.
[10] https://www.nice.org.uk/advice/es27/chapter/Key-messages [Consulted on 22/06/2020].

The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Patients with eGFR ≥ 30 mL/min have received remdesivir for treatment of COVID-19 with no dose adjustment. Remdesivir should not be used in patients with eGFR < 30 mL/min (see sections 4.4 and 5.2 of the SPC).

Hepatic impairment
The pharmacokinetics of remdesivir have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment (see sections 4.4 and 5.2 of the SPC).

Paediatric population
The safety and efficacy of remdesivir in children under the age of 12 years and weighing < 40 kg have not yet been established. No data are available.

Method of administration
For intravenous use.
Remdesivir is for administration by intravenous infusion after further dilution.
It must not be given as an intramuscular (IM) injection.
For instructions on dilution of the medicinal product before administration, see section 6.6 of the SPC."

Table 1: Recommended rate of infusion – for diluted remdesivir concentrate for solution for infusion

Infusion Bag Volume	Infusion Time	Rate of Infusion
250 ml	30 min	8.33 ml/min
	60 min	4.17 ml/min
	120 min	2.08 ml/min

04 MEDICAL NEED[11,12,13,14]

04.1 The disease

In December 2019, the emergence of a new disease (COVID-19) due to a novel coronavirus (SARS-CoV-2) was reported, with its starting point located in Wuhan, China, and which became a pandemic within a few weeks (WHO – 11 March 2020)[15].
Globally, 7,759,691 confirmed cases had been reported on 14 June 2020 (of which 1,472,636 in Europe) with 430,127 deaths (of which 171,358 in Europe) since 31 December 2019[16].
France has been facing the pandemic wave since February 2020. At 7 July 2020, 168,810 confirmed cases (38 cases on 27 February 2020) and 29,933 deaths had been reported by Santé Publique France[16].

In France, as in numerous other countries, it is difficult to estimate the real COVID-19 infection rate because a very large number of patients have not been tested and cases suspected on a syndromic basis have not been reported. The same is true for the fatality ratio (number of deaths relative to the number of infected individuals), estimated to be between 0.3 and 0.6% for the population as a whole, therefore much lower than the Spanish flu (2 to 4%), but higher than that of seasonal influenza

[11] https://www.hcsp.fr/Explore.cgi/PointSur?clef=2 [Consulted on 22/06/2020].
[12] https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/articles/infection-au-nouveau-coronavirus-sars-cov-2-covid-19-france-et-monde [Consulted on 15/07/2020].
[13] http://www.academie-medecine.fr/communique-de-lacademie-nationale-de-medecine-covid-19-tracage-epidemiologique-et-ethique-medicale/ [Consulted on 22/06/2020].
[14] https://www.has-sante.fr/jcms/p_3165982/fr/coronavirus-covid-19 [Consulted on 22/06/2020].
[15] https://www.who.int/fr/news-room/detail/27-04-2020-who-timeline---covid-19 [Consulted on 22/06/2020].
[16] https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/articles/infection-au-nouveau-coronavirus-sars-cov-2-COVID-19-france-et-monde#block-242818 [Consulted on 21/06/2020].

(0.1%). On the basis of a cumulative number of deaths at the start of June 2020 of 28,940 deaths for 151,325 cases confirmed by RT-PCR, the fatality ratio would be 19% for a mortality rate of 432 per million people[17].

04.2 Virological aspects

Coronaviruses belong to the *Nidovirales* order and the *Coronaviridae* family. They are large, enveloped, single-stranded RNA viruses subdivided into 4 genera - *Alpha*-, *Beta*-, *Gamma*- and *Deltacoronavirus* - responsible for various infections in numerous animals. In humans, only some alpha- and beta-coronaviruses are pathogenic; these are responsible for upper and lower respiratory infections that may be mild or severe. Their single-stranded RNA encodes a bulky RNA-dependent RNA polymerase (RdRp) and several structural proteins including a surface glycoprotein (S for *Spike protein*) responsible for the crown-like appearance of the virus under an electron microscope and enabling it to bind to a host receptor.
Prior to the current episode, two human coronaviruses had been responsible for major epidemics at the start of the 21st century: SARS-CoV (Severe acute respiratory syndrome-related coronavirus) and MERS-CoV (Middle-East respiratory syndrome-related coronavirus).

SARS-CoV-2 (initially called 2019-nCoV) emerged in humans in the last quarter of 2019 in Wuhan, China. On a virological level, this virus is very similar to SARS-CoV, leading taxonomists to place it in the same species (followed by the digit 2 to differentiate it from the previous one)[18], despite a sequence homology of only 79% between the two viruses[19].

SARS-CoV-2 shares two major similarities with SARS-CoV:
- the RdRp polymerase,
- and the S glycoprotein, which explains why the two viruses use the same cell receptor, i.e., the type-2 angiotensin converting enzyme (ACE).

SARS-CoV-2 has a very high sequence homology (96%) with certain bat viruses but the source of human contamination is still unknown.

04.3 Transmission methods

Although the first cases of SARS-CoV-2 were identified as being linked to contact with live animals at the Wuhan seafood market, human-to-human transmission has since been documented, with the identification of clusters and a rapid increase in the number of cases[20].
The different estimations for the basic reproduction number (R_0) compatible with the initial dynamics in Wuhan published to date are, globally, between 2 and 3[21,22], indicating a higher transmissibility of SARS-CoV-2 than that of seasonal influenza or MERS-CoV, and comparable to that of SARS-CoV.
As with other human coronaviruses, SARS-CoV-2 is transmitted during close contact via the inhalation of infectious droplets emitted when the patient sneezes or coughs. The virus is found in the upper airways and, potentially, in the lower airways.
Transmission of coronavirus from contaminated surfaces to the hands has not been proved. However, the possibility cannot be excluded from surfaces freshly contaminated by secretions. In

[17] http://www.academie-medecine.fr/COVID-19-interpretation-des-donnees-de-morbidite-et-mortalite/ [Consulted on 21/06/2020].
[18] Gorbalenya AE et al., Severe acute respiratory syndrome-related coronavirus: The species and its viruses – a statement of the Coronavirus Study Group.Bio RiX 2020.
[19] Lu et al, Lancet, 2020: Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; S0140-6736(20)30251-8.
[20] https://jidc.org/index.php/journal/article/view/12425/2181, Diseases, P.I.S.f.I. 20200110.6881082 Undiagnosed Pneumonia China (Hubei)(08): Novel Coronavirus, WHO. 2020.
[21] Imai N, Cori A, Dorigatti I, Baguelin M, Donnelly C, Riley S, et al. Report 3: Transmissibility of 2019-nCoV. London: Imperial College London; 2020.
[22] Abbott S, Hellewell J, Munday J, null null, Funk S. The transmissibility of novel Coronavirus in the early stages of the 2019-20 outbreak in Wuhan: Exploring initial point-source exposure sizes and durations using scenario analysis [version 1; peer review: awaiting peer review]. Wellcome Open Research 2020;5.

addition, coronaviruses survive for up to 3 hours on dry insert surfaces and for up to 6 days in moist environments. Hence hand-borne transmission from the environment is possible. SARS-CoV-2 can be found in biological fluids, including faeces. The presence of the virus in organs such as the liver, heart and kidneys has not been documented. Only one study reports the presence of the virus in the conjunctiva[23]. Moreover, the transmission of SARS-CoV-2 from asymptomatic individuals has been reported in the context of intrafamily clusters.

04.4 Clinical characteristics of SARS-CoV-2 infection

According to the data currently available, the incubation period is 4.9 days [4.4-5.5][24] to 6.4 days[25]; the median is 4 days (2-7) in the study conducted by Guan W et al.[26]
The time to hospital admission following the onset of signs is 6.5 days to 8 days.
More than 80% of cases are moderate forms, while 14% are severe forms.
The time to onset of acute respiratory distress syndrome (ARDS) after the onset of signs is 9 days.
The most common clinical signs are fever, cough, myalgia and asthenia. Ageusia (loss of sense of taste) and anosmia (loss of sense of smell) have been reported recently. Diarrhoea seems to be found in the elderly[27].
Although the majority of infections resolve spontaneously, approximately 15% of infected adults develop severe pneumonia, requiring supplemental oxygen, and around 5% progress to a serious form, with hypoxaemic respiratory failure, acute respiratory distress syndrome and multiorgan failure requiring ventilatory support, often for several weeks. At least half of COVID-19 patients requiring invasive mechanical ventilation have died in hospital and the associated burden on healthcare systems, especially intensive care units, has been overwhelming in most of the countries affected[28,29,30,31].
The median age of hospitalised patients is 72 years and a little over half are men[32].
In almost all cases, chest CT scan reveals the presence of bilateral ground-glass opacities; in addition, parenchymal infiltrates have been observed in intermediate forms, as well as lobar and subsegmental pulmonary consolidation syndromes in forms requiring ICU treatment, in the absence of any bacterial or fungal infections.
Clinically, there are different presentations:

- simple presentation during which the virus remains undetectable in the blood (current data): asymptomatic forms (which may be contagious), pauci-symptomatic forms and pneumonia.
- severe forms, from the outset or from around the 7th day of progression, resulting in parenchymal involvement, sepsis, bacterial or fungal secondary infections. In these severe forms, viraemia may be detected and thrombocytopenia, marked lymphopenia and high neutrophil counts are also observed.

[23] Zhang X, Chen X, Chen L., Deng C, Zou X, Liu W et al. The infection evidence of SARS-COV- 2 in ocular surface: a single-center cross-sectional study. https://doi.org/10.1101/2020.02.26.20027938.
[24] Jiang X, Rayner S, Luo MH. Does SARS-CoV-2 has a longer incubation period than SARS and MERS? J Med Virol. 2020 Feb 13.
[25] Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020 Feb 17:105924.
[26] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Feb 28;NEJMoa2002032.
[27] HCSP. Opinion relative to therapeutic guidelines in the treatment of COVID-19 (supplement to the opinion of 5 March 2020). 23 March 2020.
[28] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020.
[29] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-13.
[30] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-62.
[31] Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle region–case series. N Engl J Med 2020.
[32] Santé Publique France. COVID-19: epidemiological update of 9 July 2020. https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-9-juillet-2020

The risk factors for an unfavourable course are:

- **Demographic characteristics**

Age is a major factor, with an unfavourable course from the age of 70 years especially. Mortality increases with the age of patients. The published data reveal a mortality rate of zero before the age of 9 years, 8% in the 70-79 years age group and 14.8% in the ≥ 80 years age category.

- **Comorbidities**
    - **According to the data in the literature**

- Individuals aged 70 years and over (although individuals aged from 50 to 70 years must be monitored more closely);
- Individuals with a cardiovascular history: complicated hypertension*, history of stroke or coronary heart disease, heart surgery, NYHA stage III or IV heart failure;
- Individuals with poorly-controlled diabetes* or diabetes complications;
- Individuals with a chronic respiratory disease liable to decompensate in the event of viral infection;
- Chronic kidney disease patients on dialysis;
- Patients receiving treatment for active cancer.

    - **Despite the absence of data in the literature, due to a presumed risk of severe COVID-19 given the known data for other respiratory infections, the following are also considered to be at risk of severe COVID-19:**

- Individuals with congenital or acquired immunosuppression:
    - Drug-related: anticancer chemotherapy, immunosuppressive therapy, biologic therapy and/or corticosteroid therapy at immunosuppressive doses,
    - uncontrolled HIV infection or with a CD4 count < 200/mm^3,
    - consecutive to a solid organ or haematopoietic stem cell transplant,
    - related to a treated malignant blood disease;
- Patients with Child Pugh stage B cirrhosis at least;
- Individuals with morbid obesity (body mass index (BMI) >40 kg/m^2): by analogy with influenza A(H1N1) pdm09 but also, in the event of obesity with a BMI > 30 kg/m^2 [33],
- A history of splenectomy or homozygous sickle cell disease due to an increased risk of secondary bacterial infection;
- In the case of pregnant women, given the available data and considering that they are very limited, it is recommended to apply the measures detailed in the HCSP document in the third trimester of pregnancy only.

04.5 Treatments

There is a strong demand for a treatment for this disease.
French and international research has been mobilised with unprecedented speed, and several trials are still in progress at present (clinicaltrials.gov), including trials with several drugs already available in other indications and “repositioned” in COVID-19. These primarily consist of antiviral, antiretroviral and immunomodulatory drugs.

4.5.1 Hydroxychloroquine and lopinavir/ritonavir

On an exceptional and temporary basis, therapeutic recommendations for curative treatment were drafted by the HCSP (French National Council for Public Health) on 5 and 23 March 2020, followed by decrees issued within the context of the public health emergency. The use of hydroxychloroquine and lopinavir/ritonavir was thus authorised in severe forms of COVID-19, in a hospital setting only and following a collective decision up to 26 May 2020. On this date, the HCSP modified its recommendations following an analysis of the international recommendations relative to the use of hydroxychloroquine in COVID-19, the publications on the topic, including an article published in the

[33] Given the experience of ICU professionals consulted (unpublished).

Lancet[34], and reports from regional pharmacovigilance centres reporting potentially serious side effects, particularly cardiovascular, associated with the use of this medicinal product, and recommended:

- "not using hydroxychloroquine (alone or in combination with a macrolide) in the treatment of COVID-19,
- assessment of the benefit/risk ratio of the use of hydroxychloroquine in clinical trials,
- reinforcement of national and international regulation of the various trials evaluating hydroxychloroquine in COVID-19."

4.5.2 Other

On 27 April 2020, the HCSP also recommended[35] the use of convalescent plasma when inclusion of a patient in a clinical trial is not possible, in particular for reasons of geographic distance, maintaining the same indications as those defined by the inclusion criteria for the clinical trials being conducted in France, i.e., moderate or severe forms of COVID-19, following a collective medical decision taken in the intensive care unit where the patient is being treated.

Data from the RECOVERY (Randomised Evaluation of COVID-19 thERapY, NCT04381936) trial concerning the use of dexamethasone demonstrated a beneficial effect on mortality in patients requiring mechanical ventilation or supplemental oxygen[36].

In its updated opinion of 23 July 2020, the HCSP updated its recommendations concerning the treatment of COVID-19 patients. It concludes that the currently available data drawn from the literature do not provide evidence of a benefit on the course of COVID-19 of supposed antiviral therapies, immunomodulatory agents or convalescent plasma; the HCSP does not recommend their use outside clinical trials. The HCSP recommends the use of corticosteroid therapy (dexamethasone at a dose of 6 mg/d for a maximum duration of 10 days), following assessment of the individual benefit/risk ratio (provisional recommendation pending the complete results of the RECOVERY study or other studies) in patients under the age of 70 years requiring supplemental oxygen in medical wards or ICUs[37].

On 2 September 2020, the WHO published guidelines concerning the use of corticosteroids following the performance of a meta-analysis[38] suggesting a benefit in terms of mortality. It recommends the use of systemic corticosteroids (dexamethasone, hydrocortisone) for the treatment of patients with severe and critical COVID-19[39]. Therefore corticosteroid therapy is an integral part of the standard of care (see 05.2 non-medicinal comparators).

It should be noted that the Transparency Committee did not evaluate these medicinal products, which do not have an MA, in the context of its assessments with a view to funding by the French national health insurance system.

Considering the sometimes serious nature of COVID-19, its contagiousness and the impact on the organisation of care and, particularly on intensive care units, as well as the absence of any available curative treatments, there is a major medical need to have access to effective and well-tolerated drugs in the treatment of SARS-CoV-2 infection.

[34] Mehra MR et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. The Lancet. Published Online May 22, 2020.
[35] HCSP. Opinion relative to the use of convalescent plasma in Covid-19 patients. 27 April 2020.
[36] The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. published on July 17, 2020, at NEJM.org.
[37] HCSP. Report relative to updating of the treatment of Covid-19 patients. 23 July 2020.
[38] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA. 2020.
[39] Corticosteroids for COVID-19. Living guidance. WHO. 2 September 2020.

05 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators of VEKLURY (remdesivir) are medicinal products used for the treatment of COVID-19 in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen.

05.1 Medicinal products

At present, VEKLURY (remdesivir) is the only antiviral drug with a conditional MA in the treatment of COVID-19.

No other medicinal products currently have an MA or even an authorisation as part of a compassionate use programme (in France, ATU (temporary authorisation for use) or RTU (temporary recommendation for use)) in the curative or preventive (pre or post-exposure prophylaxis or vaccination) treatment of COVID-19.

Several drug candidates are currently being studied, targeting various mechanisms of action against SARS-CoV-2 (Annex 1):

- medicinal products that aim to slow down multiplication of the virus (antivirals);
- medicinal products aimed at modulating the immune system: vaccines (BCG), donor antibodies (convalescent plasma)[35], monoclonal antibodies (anakinra, canakinumab, sarilumab, tocilizumab), corticosteroids, in particular dexamethasone (preliminary data from the RECOVERY trial (*Randomised Evaluation of COVID-19 thERapY, NCT04381936*) demonstrated a beneficial effect on mortality of the use of dexamethasone in patients requiring mechanical ventilation or supplemental oxygen)[36], interferons. In fact, SARS-CoV-2 has the capacity to trigger a strong inflammatory reaction in the pulmonary tissue, related to an explosive and uncontrolled release of pro-inflammatory substances (cytokines), often the cause of serious complications (ARDS) leading to hospitalisation in an ICU with an increased mortality rate.

On 2 September 2020, the WHO published guidelines[39] concerning the use of systemic corticosteroids (dexamethasone, hydrocortisone) for the treatment of **severe and critical COVID-19**. In addition, the WHO highlights the fact that: *"As additional therapies emerge for COVID-19, notably novel immunomodulators, it will become increasingly important to ascertain how these interact with systemic corticosteroids. All investigational therapies for severe and critical COVID-19 (including remdesivir) should be compared with systemic corticosteroids or evaluated in combination with systemic corticosteroids vs. systemic corticosteroids alone."*[39]
Therefore corticosteroid therapy is an integral part of the standard of care outlined below.

05.2 Non-medicinal comparators

The standard of care consists of hospital management of symptomatic patients with severe forms of COVID-19, including supportive care, primarily to prevent deterioration of patients' respiratory function. This supportive treatment may include: supplemental oxygen, mechanical ventilation, extracorporeal membrane oxygenation (ECMO), ventilation strategies to protect the lung, the use of inotropic drugs, antibiotic therapy to prevent or treat secondary infections and haemodialysis. It now includes corticosteroids in severe and critical forms of COVID-19.
The HCSP specified that supportive care constituting the current standard of care (SOC), remains the reference treatment, irrespective of the severity of COVID-19[Erreur ! Signet non défini.].

◗ Conclusion

Currently, there are no clinically relevant comparators with an MA. VEKLURY (remdesivir) is the only antiviral therapy with a conditional MA in the treatment of COVID-19.

06 INFORMATION ON THE INDICATION ASSESSED INTERNATIONALLY

Country	MA		FUNDING	
	Yes / No / Ongoing If no, why	Indication Identical to the one assessed or restricted	Yes / No / Ongoing If no, why	Population(s) MA or restricted
Germany	Yes	-	Ongoing	-
Netherlands	Yes	-	Ongoing	-
Belgium	Yes	-	Ongoing	-
Spain	Yes	-	Ongoing	-
Italy	Yes	-	Ongoing	-
United Kingdom*	Ongoing	-	Ongoing	-
USA**	Ongoing	-	Ongoing	-

*On 5 June 2020, NICE and the British MHRA communicated that an MA had been granted for remdesivir via a fast-track procedure. NICE published an "evidence summary" on 5 June 2020 summarising the clinical data concerning remdesivir[40].

**On 1 May 2020, the FDA urgently authorised the use of remdesivir, based on the unpublished preliminary results of the Adaptive COVID-19 Treatment Trial (NCT04280705) conducted by the National Institute of Allergy and Infectious Diseases (NIAID)[9].

On 24 July 2020, the US NIH[41] issued guidelines with respect to the use of remdesivir in the treatment of severe COVID-19:
"Recommendation for Prioritizing Limited Supplies of Remdesivir: Because remdesivir supplies are limited, the Panel recommends prioritizing **remdesivir** for use in hospitalized patients with COVID-19 who require supplemental oxygen but who do not require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) **(BI)**.
Recommendation for Patients With Mild or Moderate COVID-19: There are insufficient data for the Panel to recommend either for or against the use of **remdesivir** in patients with mild or moderate COVID-19."

On 7 May 2020, Japan also approved the use of remdesivir.

On 11 June 2020, the Department for the evaluation of medicinal products and health technologies for the purpose of reimbursement and the Department of Health Services at the *Institut national d'excellence en santé et en services sociaux* (INESSS) in Quebec issued an opinion concerning the role of remdesivir in the treatment of COVID-19 (see summary in annex 2)[42].

07 ANALYSIS OF AVAILABLE DATA

The development plan for VEKLURY (remdesivir) is based on 5 clinical studies:

- Randomised, double-blind, placebo-controlled, multicentre **phase 3 trial**[43] **conducted in China, in the province of Hubei,in patients with severe COVID-19** . The patients included

[40] NICE. COVID 19 rapid evidence summary: Remdesivir for treating hospitalised patients with suspected or confirmed COVID-19. Published on 5 June 2020.
[41] NIH. Available at: https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/ [Consulted on 24/07/2020].
[42] COVID-19 and Remdesivir. Quebec, Qc: INESSS; 2020. 48 p. https://www.inesss.qc.ca/fileadmin/doc/INESSS/COVID-19/COVID-19_remdesivir.pdf [Consulted on 21/06/2020].
[43] Wang Y et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial [published correction appears in Lancet. 2020 May 30;395(10238):1694]. Lancet. 2020;395(10236):1569-1578.

were aged at least 18 years and were PCR positive for SARS-CoV-2, with SpO2 ≤ 94% in ambient air and a PaO_2/FiO_2 ratio ≤ 300 mmHg and pneumonia confirmed by imaging. They had presented symptoms for less than 12 days. This study is completed and published.

- Double-blind, randomised, placebo-controlled, adaptive multicentre **phase 3 ACTT trial (Adaptive COVID-19 Treatment Trial)**[44] **in patients with moderate to severe COVID-19**. The patients included were aged at least 18 years, were hospitalised and PCR positive for SARS-CoV-2 with either SpO_2 ≤ 94% in ambient air or pulmonary infiltrates confirmed by imaging or requiring supplemental oxygen. Two patient profiles were included in this study: patients with "severe" disease (88.7%) with SpO_2 ≤ 94% in ambient air, or requiring supplemental oxygen, or requiring mechanical ventilation; patients with "moderate" disease (11.3%) with SpO_2 > 94% and a respiratory rate < 24 breaths/min without need for supplemental oxygen. Since this study is still ongoing, **only preliminary results are available and published.**
- Randomized, open-label, multicentre, **phase 3 trial (SIMPLE)**[45] **in patients with severe COVID-19** (GS-US-540-5774), comparing two remdesivir treatment regimens: one group received remdesivir for 5 days and one group received remdesivir for 10 days. This study did not include a placebo control or standard of care alone group. The patients were aged at least 12 years, were PCR positive for SARS-CoV-2 and had pulmonary infiltrates confirmed by imaging. These patients were considered to be "severe" since they had SpO_2 ≤ 94% or required supplemental oxygen. This study is completed and published.
- Randomised, open-label, multicentre, **phase 3 trial (SIMPLE) in patients with moderate COVID-19** (GS-US-540-5773) comparing two remdesivir treatment regimens *versus* standard of care alone: one treatment group with remdesivir for 5 days or 10 days, in combination with standard of care *versus* standard of care alone. The patients were aged at least 12 years, were PCR positive for SARS-CoV-2 and had pulmonary infiltrates confirmed by imaging. The patients were considered to have "moderate" disease since they had SpO_2 > 94% in ambient air (**Population not retained by the MA**). The results of this study conducted in patients with moderate infection will not be taken into account.
- Randomised, open-label, adaptive, multicentre **phase 3 trial (DisCoVeRy) in patients with severe COVID-19**, comparing different treatment strategies, including treatment with remdesivir combined with standard of care. The patients included were aged at least 18 years, were PCR positive for SARS-CoV-2 with SpO_2 ≤ 94% in ambient air, or requiring mechanical ventilation or supplemental oxygen. At present, the study treatment is remdesivir; the other treatment arms (hydroxychloroquine, lopinavir/ritonavir with or without interferon ß-1a) have been stopped. The results of this study are awaited and no findings have been communicated.

For this assessment, the pharmaceutical company provided the publications for the studies for which the results are available, i.e., the Chinese study, the ACTT study, and the SIMPLE study in severe patients, but not the study reports.

07.1 Efficacy

7.1.1 Placebo-controlled study conducted in China in patients with severe COVID-19.

Reference	Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial[43]
Clinicaltrials.gov	Registration number: NCT04257656
Primary objective of the study	To evaluate the efficacy and safety of remdesivir compared to placebo in adult patients admitted to hospital for severe COVID-19.
Study type	Phase 3, randomised, double-blind, multi-centre superiority study in parallel groups.

[44] Beigel et al. Remdesivir for the Treatment of COVID-19 — Preliminary Report. NEJM. Published Online on 22 May 2020.
[45] Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. 27 May 2020.

Study date and duration	Start of enrolments (first patient included): 6 February 2020 Date of data extraction for the primary analysis: 29 March 2020 Study conducted at 10 centres in China (Wuhan, Hubei province).

Main inclusion criteria	- Age ≥ 18 years;
	- SARS-CoV-2 infection confirmed by RT-PCR, with the following complications:
	  ○ pneumonia confirmed by chest imaging,
	  ○ SpO_2 ≤ 94 % <u>or</u> PaO_2/FiO_2 ratio ≤ 300 mmHg;
	- ≤ 12 days since illness onset.

Main exclusion criteria	- Pregnant or breastfeeding; - Cirrhosis of the liver; - ALT or AST > 5 times the upper limit of normal (ULN); - Estimated glomerular filtration rate (eGFR) < 30 mL/min or renal replacement therapy, haemodialysis, peritoneal dialysis; - Possibility of transfer of the patient to a non-university hospital within 72 hours; - Inclusion in a clinical trial for COVID-19 treatment within 30 days prior to screening.
Study treatments	Patients were randomised (allocation ratio of 2:1) to receive: - <u>remdesivir</u> by IV administration (200 mg on D1, then 100 mg per day from D2 to D10); - <u>placebo</u> by IV administration (same dosage regimen). <u>Concomitant treatments</u>: lopinavir-ritonavir, interferon alfa-2b and corticosteroids. Randomisation was stratified on the basis of requirement for supplemental oxygen: - No ventilatory support or low-flow supplemental oxygen (nasal cannula or mask), - High-flow oxygen, non-invasive ventilation, invasive ventilation or ECMO.
Primary endpoint	**<u>Time to clinical improvement up to day 28</u>,** defined as a decline of two levels on a six-point ordinal scale of clinical status, or discharge from hospital. <u>6-point clinical scale:</u> 1. discharged or having reached discharge criteria (defined as clinical recovery, normalisation of temperature, respiratory rate < 24 breaths per minute, saturation of peripheral oxygen > 94% in ambient air, and relief of cough, all maintained for at least 72 h); 2. hospital admission, not requiring supplemental oxygen; 3. low-flow supplemental oxygen (but not requiring high-flow ventilation or non-invasive ventilation); 4. non-invasive ventilation or high-flow supplemental oxygen; 5. invasive mechanical ventilation or ECMO; 6. death.
Main secondary outcome measures	- All-cause mortality at day 28; - Proportions of patients with viral RNA detected and viral RNA load (measured by quantitative RT-PCR).
Sample size	To demonstrate a hazard ratio of 1.4 between the two treatment groups, assuming a time to clinical improvement of 21 days in the control group and of 15 days in the study group (i.e., a difference of 6 days), with a power of 80% and a one-sided alpha risk of 0.05, the number of subjects required was estimated to be 453 (151 in the placebo group and 302 in the remdesivir group). *No patients were enrolled after 12 March 2020, because of the control of the outbreak in Wuhan and on the basis of the termination criteria specified in the protocol, the independent data safety and monitoring board recommended that the study be terminated and data analysed on 29 March 2020. Consequently, the interim analysis scheduled in the protocol was abandoned. The statistical power of the study was reduced from 80% to 58% with the enrolment of 236 patients (other statistical assumptions unchanged).*
Results analysis method	<u>Interim analysis:</u> An interim analysis had been scheduled after enrolment of 240 patients if requested by the independent data safety and monitoring board. <u>Analysis of final endpoints</u> Time to clinical improvement was assessed after all patients had reached day 28; no clinical improvement at day 28 or death before day 28 were considered as right censored at day 28.

	Time to clinical improvement was portrayed by Kaplan-Meier plot and compared with a log-rank test. The HR and 95% confidence intervals (95% CI) for clinical improvement and for clinical deterioration were calculated using a Cox proportional hazards model.

Results:

Sample size

In total, 237 patients were randomised in the study:
- 158 patients in the remdesivir group;
- 79 patients in the placebo group.

In the placebo group, 1 patient withdrew from the study (withdrawal of consent). In the remdesivir group, 3 patients did not receive the treatment.
A total of 155 patients were treated with remdesivir (including 5 patients having received less than 5 days of treatment) and 78 patients received placebo (including 5 patients having received less than 5 days of treatment).

Main baseline characteristics of patients

The median age of study patients was 65 years (Table 1). The majority of patients were men (56% in the remdesivir group and 65% in the placebo group). The most common comorbidity was hypertension, followed by diabetes and coronary heart disease. The groups were not balanced with respect to comorbidities and disease severity.

At baseline, concomitant administration of lopinavir-ritonavir was administered in 18% (42/236) of patients. Most patients were in category 3 of the six-point ordinal scale of clinical status.

Table 1. Baseline patient and disease characteristics

	RDV group (N = 158)	Pbo group (N = 78)
Median age, years (min – Max)	66 (57 - 73)	64 (53 – 70)
Male, n (%)	89 (56)	51 (65)
Hypertension, n (%)	72 (46)	30 (38)
Diabetes, n (%)	40 (25)	16 (21)
Coronary heart disease, n (%)	15 (9)	2 (3)
Respiratory rate > 24 breaths per minute, n (%)	36 (23)	11 (14)
Six-category scale at day 1, n (%)		
2 - hospital admission, not requiring supplemental oxygen	0	3 (4)
3 - hospital admission, requiring supplemental oxygen	129 (82)	65 (83)
4 - hospital admission, requiring non-invasive mechanical ventilation or high-flow supplemental oxygen	28 (18)	9 (12)
5 - hospital admission, requiring invasive mechanical ventilation or ECMO	0	1 (1)
6 - death	1 (1)	0
Viral load of nasopharyngeal and oropharyngeal swabs, log_{10} copies per ml		
Mean (SD)	4.7 (0.3)	4.7 (0.4)
Treatment history, n (%)		
Interferon alfa-2b	29 (18)	15 (19)
Lopinavir-ritonavir	27 (17)	15 (19)
Antibiotics	121 (77)	63 (81)
Corticosteroids	60 (38)	31 (40)

ECMO = extracorporeal membrane oxygenation; SD = standard deviation; Max = maximum; min = minimum; Pbo = placebo; RDV = remdesivir

Median time from symptom onset to starting study treatment was 10 days (Table 2). During their hospital stay, 155 (66%) patients received corticosteroids, with a median time from symptom onset to corticosteroid therapy of 8 days; 91 (39%) patients received corticosteroids before enrolment.

Table 2. Treatments received before and after enrolment

	RDV group (N = 158)	Pbo group (N = 78)
Time from symptom onset to starting study treatment, in days, n/N (%)*		
Median (min – Max)	11 (9 – 12)	10 (9-12)
Early (≤ 10 days from symptom onset)	71/155 (46)	47 (60)
Late (> 10 days from symptom onset)	84/155 (54)	31 (40)
Interferon alfa-2b, n (%)	**46 (29)**	**30 (38)**
Lopinavir-ritonavir, n (%)	**44 (28)**	**23 (29)**
Vasopressors, n (%)	**25 (16)**	**13 (17)**
Renal replacement therapy, n (%)	3 (2)	3 (4)
High-flow supplemental oxygen, n (%)		
Non-invasive mechanical ventilation	14 (9)	3 (4)
Invasive mechanical ventilation	11 (7)	10 (13)
Mechanical ventilation or ECMO	2 (1)	0
Antibiotics, n (%)	**142 (90)**	**73 (94)**
Corticosteroids, n (%)	**102 (65)**	**53 (68)**
Time from symptom onset to corticosteroid therapy, in days		
Median (min – Max)	9 (7 – 11)	8 (6 – 10)
Duration of corticosteroid therapy, in days		
Median (min – Max)	9 (5 – 15)	10 (6 – 16)

ECMO = extracorporeal membrane oxygenation standard deviation; Max = maximum; min = minimum; Pbo = placebo; RDV = remdesivir

**Three patients did not start treatment so are not included in time from symptom onset to start of study treatment subgroup analyses.*

- **Primary endpoint: time to clinical improvement assessed by the investigators (ITT population)**

No superiority of remdesivir was demonstrated compared to placebo in terms of time to clinical improvement at day 28 (median of 21.0 days in the remdesivir group [IQR: 13.0-28.0] *versus* 23.0 days [15.0-28.0] in the placebo group; HR = 1.23 [$CI_{95\%}$: 0.87–1.75], NS); and on mortality at 28 days (14% in the remdesivir group *versus* 13% in the placebo group (difference = 1.1%; $CI_{95\%}$ [-8.1; 10.3])).

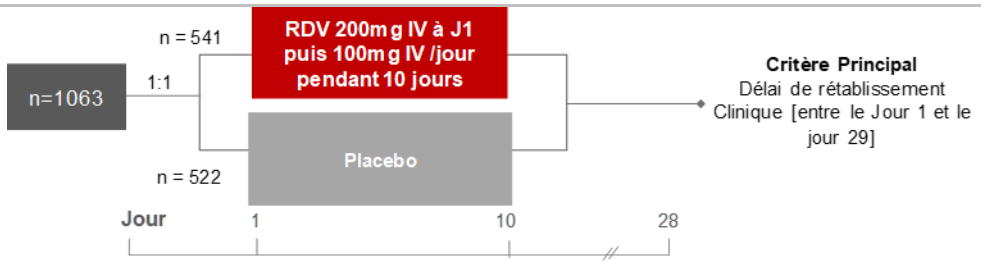
- **Unranked secondary endpoints**

No superiority of remdesivir was demonstrated compared to placebo in terms of mortality at 28 days (14% in the remdesivir group *versus* 13% in the placebo group (difference = 1.1%; $CI_{95\%}$ [-8.1; 10.3]), NS).
The SARS-CoV-2 viral load measured by RT-PCR in the nasopharyngeal or oropharyngeal secretions was 4.7 log at baseline in both groups and no difference was demonstrated between the two groups in terms of its reduction.

7.1.2 Placebo-controlled ACTT study in patients with moderate to severe COVID-19 (NIH/NIAID)[44]

The ACTT study is an adaptive study with the overall objective of evaluating the efficacy and safety of COVID-19 treatments in hospitalised patients.
According to the protocol registered on the Clinicaltrials.gov website, the ACTT trial compares investigational therapeutic agents with a control arm. There will be interim monitoring to introduce new arms and allow early stopping for futility, efficacy, or safety. If one therapy proves to be efficacious, then this treatment may become the control arm for comparison(s) with new experimental treatment(s). Any such change would be accompanied by an updated sample size. Because standards of care may evolve/improve over time as more is learned about successful management of COVID-19, comparisons of safety and efficacy will be based on data from concurrently randomised subjects. An independent Data and Safety Monitoring Board (DSMB) will actively monitor interim data to make recommendations about early study closure or changes to study arms.
The data published to date solely concern preliminary results relating to VEKLURY (remdesivir).

Reference	**Beigel JH et al. Remdesivir for the Treatment of COVID-19 — Preliminary Report**
Clinicaltrials.gov	Registration number: NCT04280705
Primary objective of the study	To evaluate the efficacy of remdesivir (RDV) compared to placebo with respect to the time to clinical recovery of patients with COVID-19
Study type	Phase 3, adaptive, randomised, double-blind, placebo-controlled, multicentre superiority trial in parallel groups in hospitalised adults diagnosed with SARS-CoV-2 infection.
Study date and duration	Start of enrolments (first patient included): 21 February 2020 Date of data extraction for the primary analysis: 19 April 2020 Study conducted at 60 centres in the USA (45 sites), Denmark (8), United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1) and Singapore (1).
Main inclusion criteria	- Adult patients (18 to 99 years), - Admitted to hospital with symptoms suggestive of SARS-CoV-2 infection and confirmed (PCR or other test), - Rales / crepitation observed on examination AND $SpO_2 \leq 94\%$ on ambient air OR need for supplemental oxygen OR requiring mechanical ventilation. Women of childbearing potential: authorised if abstinence or effective contraception.
Main exclusion criteria	- ALT or AST > 5 times the ULN, - eGFR < 30 mL/min, - Pregnant or breastfeeding, - Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours, - Allergy to any study medication.

Study design	 [*critère principal: primary endpoint.* *Délai de rétablissement clinique : time to clinical recovery*] Randomisation was stratified by study site and disease severity at enrolment.
Study treatments	Eligible patients were randomised (ratio 1: 1) to receive: - intravenous remdesivir (RDV) with a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death. - placebo by IV administration at the same dosage regimen. Concomitant treatments: All patients received the standard of care.
Primary endpoint	The primary outcome was initially defined as the percentage of patients reporting each severity score on an eight-category ordinal scale at D15 (ranging from 1: death to 8: not hospitalised, no limitations on activities). This outcome became the key secondary outcome*. After amendment, the primary endpoint was defined as follows: Time to clinical recovery, defined as the first day in the 28 days following enrolment on which the subject satisfies categories 1, 2 or 3 on the eight-category ordinal scale: 1. Not hospitalised, no limitations on activities; 2. Not hospitalised, limitation on activities and/or requiring home oxygen; 3. Hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4. Hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions); 5. Hospitalised, requiring supplemental oxygen; 6. Hospitalised, requiring noninvasive ventilation or use of high-flow oxygen devices; 7. Hospitalised, receiving invasive mechanical ventilation or ECMO; 8. Death. **According to the authors, the change was proposed on 22 March 2020 by trial statisticians who were unaware of treatment assignments and had no knowledge of outcome data. When this change was proposed, 72 patients had been enrolled and no interim data were available. The amendment was finalised on 2 April 2020, without any knowledge of outcome data from the trial and before any interim data were available. This change in primary outcome was made in response to evolving information, external to the trial, indicating that Covid-19 may have a more protracted course than previously appreciated.*
Secondary outcomes, in particular	- Percentage of patients reporting each severity score on an 8-category ordinal scale at D15 (ranging from 1: death to 8: not hospitalised, no limitations on activities). - Time to clinical improvement in days: improvements of at least 1 point on the 8-category ordinal scale or discharge, - All-cause mortality at day 14 and 28, - Grade 3 and 4 adverse events (AEs) and serious AEs.
Sample size	Initial sample size *The initial sample size was projected to be 572 subjects to achieve 400 subjects with a "recovered" status (per the primary objective). The primary analysis was to be based on those subjects enrolled in order to 400 recoveries. An additional analysis of the moderate severity subgroup (those with baseline status of "Hospitalised, requiring supplemental oxygen" or "Hospitalised, not requiring supplemental oxygen - requiring ongoing medical care") were also considered to be of public health importance. Hence, enrolment was permitted until the date of 20 April 2020 to ensure 400 recoveries and provide additional data about this important subgroup. With recent enrolment rates, the total sample size could be 600 to over 800.*

	New calculation following change of the primary endpoint The study was designed to achieve a power of 85% to detect a clinical recovery rate of 1.35 with a two-tailed p-value of 5%. Inclusion continued until 19 April 2020 to guarantee at least 400 patients with clinical data in order to be able to perform the subgroup analyses. Because the statistical analysis plan did not take into account the multiplicity of statistical tests, the results for the secondary measures are presented in the form of individual estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and therefore must be interpreted with caution.
Results analysis method	The primary analysis was a stratified log-rank test of the time to recovery as a function of disease severity between the RDV and placebo arms. The treatment efficacy result is the "rate ratio for recovery" (RDV compared to placebo), which is related to the risk ratio in a survival analysis. The mortality estimates are presented on the basis of the Kaplan-Meier estimates since numerous patients were still being followed up at the time of the analysis. The main secondary analysis tested a difference in the distribution of ordinal scores between RDV and placebo at D15 using the "odds ratio = OR" as determined by a stratified Cox proportional odds model on disease severity.

Results:

The results presented are from a preliminary analysis scheduled in the protocol. On 27 April 2020, the Data and Safety Monitoring Board (DSMB) reviewed the results. Although this review was originally planned as an interim analysis, because of the rapid pace of enrolment, the review occurred after completion of enrolment while follow-up was still ongoing. At the time of the DSMB report, which was based on data cutoff date of 22 April 2020, a total of 482 "recoveries" (exceeding the estimated number of recoveries needed for the trial) and 81 deaths had been entered in the database. Hence the DSMB recommended that the preliminary primary analysis report and mortality data from the safety report be provided to trial team members from the National Institute of Allergy and Infectious Diseases (NIAID). These results were subsequently made public; the treating physician could request to be made aware of the treatment assignment of patients who had not completed day 29 if clinically indicated (e.g., because of worsening clinical status), and patients originally in the placebo group could be given remdesivir. The results presented are the preliminary results from this ongoing trial. **These results will subsequently be completed by data including the whole study population and mortality data at D28.**

Sample size

Of the 1,107 patients selected, 1,063 underwent randomisation, including 541 in the remdesivir group and 522 in the placebo group. Of those randomised into the remdesivir group, 531 (98.2%) received at least one dose of treatment, 49 (9.2%) patients discontinued before day 10 due to an adverse event or death (36 [6,7%]) or withdrawal of consent (13 [2.4%]). Of those randomised into the placebo group, 518 (99.2%) received at least one dose, 53 (10.2%) patients discontinued before day 10 due to an adverse event or death (36 [6,9%]) or withdrawal of consent (15 [2.9%]) or due to the absence of inclusion criteria (2 patients).

As of 28 April 2020, a total of 391 (72.3%) patients in the remdesivir group and 340 (65.1%) in the placebo group had completed the trial through day 29 (including recoveries or deaths). There were 132 patients (24.4%) in the remdesivir group and 169 (32.4%) in the placebo group who had not recovered and had not completed the day 29 follow-up visit at the data cutoff date.

The analysis population included 1,059 patients for whom follow-up data were available (538 [99.5%] in the remdesivir group and 521 [99.8%] in the placebo group). Four of the 1,063 patients were not included in the primary analysis because no post-baseline data were available at the time of the database freeze.

Table 3. Breakdown of patients (ACTT trial)

Patients	RDV group	Pbo group
Screened, n	1107	
Randomised, n	541	522
Received at least one treatment dose, n (%)	531 (98.2)	518 (99.2)
Received at least 10 treatment doses, n (%)	180 (33.3)	185 (35.4)

Patients	RDV group	Pbo group
Reasons for not receiving 10 doses, n (%)	251 (46.4)	255 (48.9)
• Recovery	168 (31.1)	120 (23.0)
• Death	21 (3.9)	28 (5.4)
• Missed dose	13 (2.4)	24 (4.6)
• Discontinued due to AE or death	36 (6.7)	36 (6.9)
• Withdrawal of consent	13 (2.4)	15 (2.9)
Completed study through to D29 (including recoveries and deaths), n (%)	391 (72.3)	340 (65.1)
Terminated study before D29 (AE or withdrawal of consent), n (%)	8 (1.5)	9 (1.7)
Study ongoing, n (%)	132 (24.4)	169 (32.4)
Patients analysed, n (%)	538 (99.5)	521 (99.8)

Pbo = placebo; RDV = remdesivir

Main baseline characteristics of patients

The mean age of patients was 58.9 years (36.2% were aged over 65 years) and 64.3% were male. Most of the patients had one (27.0%) or at least two (52.1%) comorbidities; the most common were hypertension (49.6%), obesity (37.0%), and type 2 diabetes mellitus (29.7%).

The median time from symptom onset to randomisation was 9 days (IQR: 6 to 12); 943 (88.7%) patients had a form considered to be "severe" at baseline; 272 patients (25,6%) met category 7 criteria on the ordinal scale, 197 (18.5%) category 6, 421 (39.6%) category 5 and 127 (11.9%) category 4; 46 patients (4.3%) had missing data for the score.

The patient characteristics at baseline were comparable between the 2 groups, except in terms of initial disease severity: the proportion of hospitalised patients with invasive ventilation or ECMO (severity score 7) was higher in the placebo group (23.1% in the RDV group *versus* 28.2% in the placebo group) and missing severity score data were more frequent in the RDV group (5.4% *versus* 3.3%) (Table 4).

Table 4. Baseline characteristics of patients (ACTT trial)

Patients	RDV group (N=541)	Pbo group (N=522)	Total (N=1063)
Age, mean (SD)	58.6 (14.6)	59.2 (15.4)	58.9 (15.0)
Male, n (%)	352 (65.1)	332 (63.6)	684 (64.3)
Race or ethnic group, n (%)			
American Indian or Alaska Native	*4 (0.7)*	*3 (0.6)*	*7 (0.7)*
Asian	*77 (14.2)*	*57 (10.9)*	*134 (12.6)*
Black or African American	*108 (20.0)*	*111 (21.3)*	*219 (20.6)*
Hispanic or Latino	*132 (24.4)*	*117 (22.4)*	*249 (23.4)*
Median time (IQR) from symptom onset to randomisation, in days	9 (6 – 12)	9 (7 – 13)	9 (6 – 12)
Coexisting conditions, n/N (%)			
0	91/467 (19.5)	102/453 (22.5)	193/920 (21.0)
1	131/467 (28.1)	117/453 (25.8)	248/920 (27.0)
≥ 2	245/467 (52.5)	234/453 (51.7)	479/920 (52.1)
Hypertension	231/469 (49.3)	229/459 (51.7)	460/928 (49.6)
Obesity	177/469 (37.7)	165/456 (36.2)	342/925 (37.0)
Type 2 diabetes	144/470 (30.6)	131/457 (28.7)	275/927 (29.7)
Score on ordinal scale, n (%)			
4 (hospitalised, not requiring O2)	67 (12.4)	60 (11.5)	127 (11.9)
5 (hospitalised, requiring O2)	222 (41.0)	199 (38.1)	421 (39.6)
6 (hospitalised, with NIV or high-flow O2)	98 (18.1)	99 (19.0)	197 (8.5)
7 (hospitalised, with IV or ECMO)	**125 (23.1)**	**147 (28.2)**	**272 (25.6)**
Missing data	**29 (5.4)**	**17 (3.3)**	**46 (4.3)**

ECMO = extracorporeal membrane oxygenation; Pbo = placebo; RDV = remdesivir; NIV = non-invasive ventilation; IV = invasive ventilation.

Primary endpoint: time to recovery (ITT population) at D28 assessed by the investigators

The preliminary analysis shows a superiority of remdesivir over placebo in terms of time to clinical recovery, with 11 days in the remdesivir group *versus* 15 days in the placebo group ("HR equivalent"

rate ratio for recovery = 1.32; $IC_{95\%}$ [1.12; 1.55], p < 0.001). An analysis adjusted on the basis of ordinal score at baseline led to a similar estimation of the treatment effect (recovery RR = 1.31; $CI_{95\%}$ [1.12 to 1.54]).

In the subgroup analyses according to stratification factors, a statistically significant difference in terms of time to clinical recovery was only observed in patients with a category-5 clinical status (hospitalised with low-flow supplemental oxygen; 421 patients) at baseline (HR of 1.47; $CI_{95\%}$ [1.17; 1.84]). In category-4 clinical status patients (hospitalised, not requiring O_2; 127 patients) and in category-6 (non-invasive ventilation or high-flow supplemental oxygen; 197 patients) or category-7 clinical status patients (hospitalised, with invasive ventilation or ECMO; n = 272) at baseline, the differences were not statistically significant, with the rate ratio for recovery having been 1.38 ($CI_{95\%}$ [0.94; 2.03]), 1.20 ($CI_{95\%}$ [0.79; 1.81]) and 0.95 ($CI_{95\%}$ [0.64; 1.42]), respectively.

The effect of remdesivir on the rate ratio for recovery did not appear to differ on the basis of time to treatment initiation (< 10 days *versus* > 10 days after the onset of symptoms).

Table 5. Outcomes overall and according to clinical status at inclusion - ITT population (ACTT trial)

Population	Overall outcome[a]		Hospitalised, not requiring O_2 at baseline (score 4)		Hospitalised, requiring O_2 at baseline (score 5)		Non-invasive ventilation or HFO (score 6)		Invasive ventilation or ECMO (score 7)	
	RDV (N = 538)	Pbo (N = 521)	RDV (N = 67)	Pbo (N = 60)	RDV (N = 222)	Pbo (N = 199)	RDV (N = 98)	Pbo (N = 99)	RDV (N = 125)	Pbo (N = 147)
Recovery at D28										
Patient, n	334	273	61	47	177	128	47	43	45	51
Days, median ($CI_{95\%}$)	11 (9-12)	15 (13-19)	5 (4-6)	6 (4-8)	7 (6-8)	9 (7-11)	16 (NE-10)	22 (NE-12)	NE-NE	28 (NE-22)
RR of recovery ($CI_{95\%}$)[b]	1.32 (1.12-1.55) p<0.001		1.38 (0.94-2.03)		1.47 (1.17-1.84)		1.20 (0.79-1.81)		0.95 (0.64-1.42)	
Mortality at D14										
Death	32	54	1	1	4	19	13	13	13	19
KM estimate % ($CI_{95\%}$)	7.1 (5.0-9.9)	11.9 (9.2-15.4)	1.5 (0.2-10.1)	2.5 (0.4-16.5)	2.4 (0.9-6.4)	10.9 (7.1-16.7)	15.2 (9.0-25.0)	14.7 (8.7-24.3)	11.3 (6.7-18.8)	14.1 (9.2-21.2)
HR ($CI_{95\%}$)[b]	**0.70 (0.47-1.04)**		**0.46 (0.04-5.08)**		**0.22 (0.08-0.58)**		**1.12 (0.53-2.38)**		**1.06 (0.59-1.92)**	
Ordinal score at D15 (± 2 days)[c] , n (%)										
Patients, n	434	410	60	51	196	161	71	77	101	115
1	99 (22.8)	76 (18.5)	22 (36.7)	15 (29.4)	54 (27.6)	45 (28.0)	13 (18.3)	7 (9.1)	10 (9.9)	8 (7.0)
2	158 (36.4)	127 (31.0)	25 (41.7)	21 (41.2)	95 (48.5)	66 (41.0)	28 (39.4)	27 (35.1)	6 (5.9)	10 (8.7)
3	11 (2.5)	6 (1.5)	7 (11.7)	4 (7.8)	4 (2.0)	2 (1.2)	0	0	0	0
4	23 (5.3)	20 (4.9)	1 (1.7)	3 (5.9)	12 (6.1)	7 (4.3)	4 (5.6)	4 (5.2)	6 (5.9)	6 (5.2)
5	34 (7.8)	40 (9.8)	3 (5.0)	5 (9.8)	14 (7.1)	6 (3.7)	2 (2.8)	7 (9.1)	15 (14.9)	22 (19.1)
6	16 (3.7)	14 (3.4)	1 (1.7)	0	1 (0.5)	3 (1.9)	6 (8.5)	6 (7.8)	7 (6.9)	5 (4.3)
7	60 (13.8)	72 (17.6)	0	2 (3.9)	12 (6.1)	12 (7.5)	5 (7.0)	13 (16.9)	43 (42.6)	45 (39.1)
8	33 (7.6)	55 (13.4)	1 (1.7)	1 (2.0)	4 (2.0)	20 (12.4)	13 (18.3)	13 (16.9)	14 (13.9)	19 (16.5)
OR ($CI_{95\%}$)	1.50 (1.18 – 1.91), p=0.001		1.51 (0.76-3.00)		1.31 (0.89-1.92)		1.60 (0.89-2.86)		1.04 (0.64-1.68)	

HR = hazard ratio; $CI_{95\%}$ = 95% confidence interval; NE = not possible to estimate; OR = Odds ratio; Pbo = Placebo; RDV = remdesivir; RR = rate ratio

[a] P values and confidence intervals have not been adjusted for multiple comparisons. [b] Recovery rate ratios and hazard ratios were calculated from the stratified Cox model; P values for these ratios were calculated with the stratified log-rank test. Recovery rate ratios greater than 1 indicate a benefit for remdesivir; hazard ratios less than 1 indicate a benefit for remdesivir. [C] The ordinal score at day 15 is the patient's worst score on the ordinal scale during the previous day. In the remdesivir group, 103 patients did not have ordinal scale scores for the day 15 visit at the time of the data freeze (11 with mild-to-moderate illness and 92 with severe illness). In the placebo group, 109 patients did not have ordinal scale scores for the day 15 visit at the time of the data freeze (12 with mild-to-moderate illness and 97 with severe illness). Two patients died 15 days after randomization and are included in the ordinal scale scores but not in the estimate of mortality by day 14. Scores on the ordinal scale are as follows: 1, not hospitalised, no limitations of activities; 2, not hospitalised, limitation of activities, home oxygen requirement, or both; 3, hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control reasons); 4, hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions); 5, hospitalised, requiring any supplemental oxygen; 6, hospitalised, requiring non-invasive ventilation or use of high-flow oxygen devices; 7, hospitalised, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death. Odds ratios and P values were calculated with the use of a proportional odds model. Odds ratio values greater than 1 indicate a benefit for remdesivir.

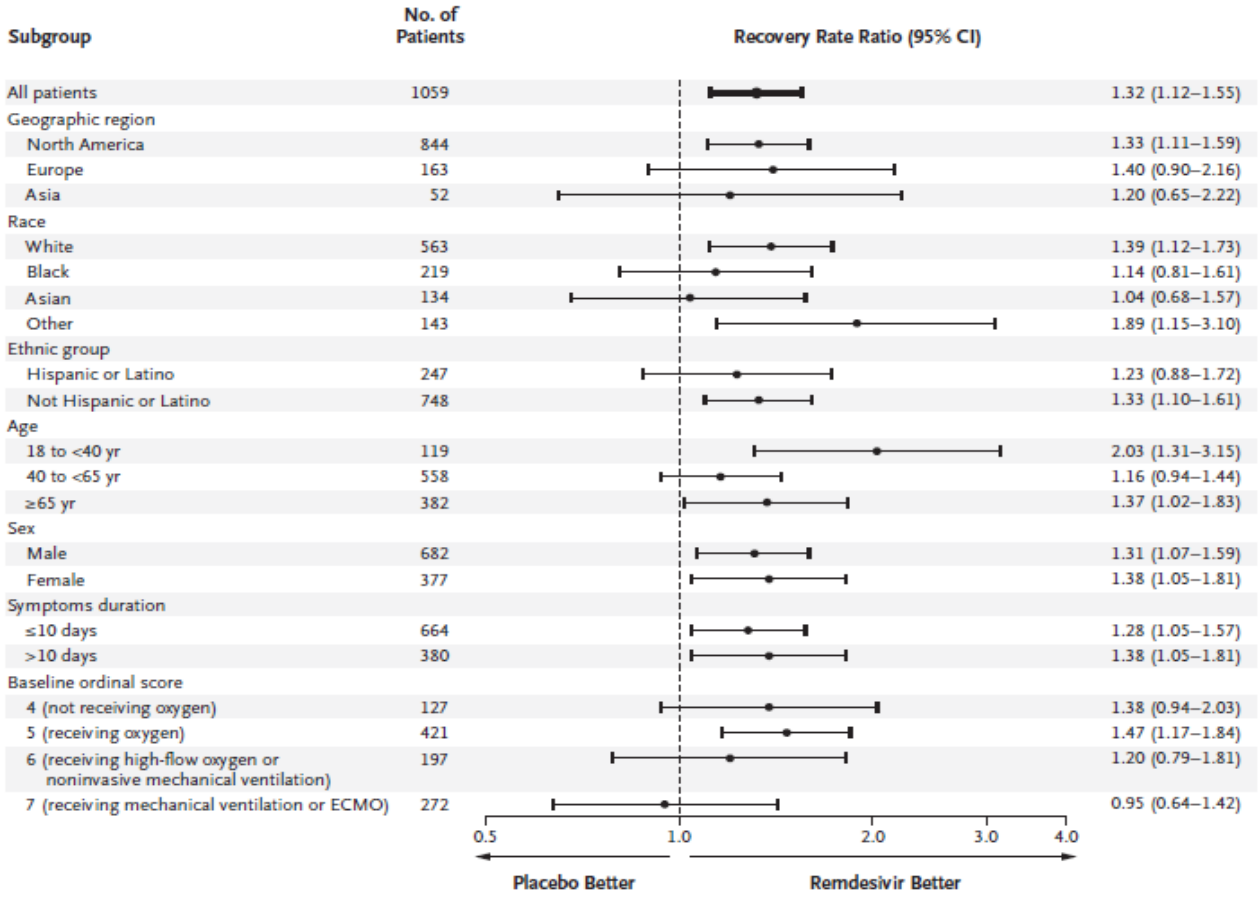


Figure 1. Analysis of rate ratio for recovery according to subgroup

Unranked secondary endpoints

- Comparison of clinical statuses at Day 15

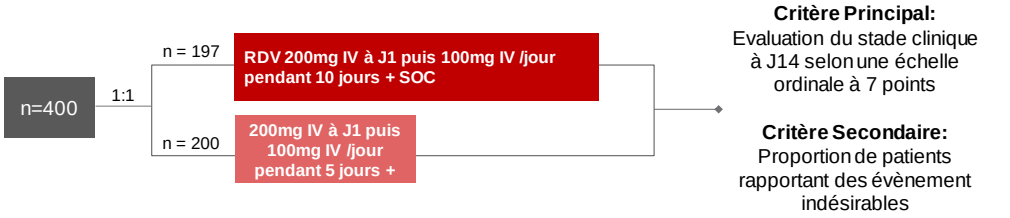
The odds of improvement in the patient's clinical status, measured by the ordinal scale score at D15 were significantly higher in the RDV group compared to the placebo group (OR = 1.50; $CI_{95\%}$ [1.18; 1.91]).

- Other secondary endpoint: mortality at D14

No statistically significant difference was revealed for the mortality rate at 14 days between the 2 groups, with 7.1% in the remdesivir group *versus* 11.9% in the placebo group (HR=0.70; $CI_{95\%}$ [0.47 to 1.04], NS).

The estimates of mortality by 28 days are not reported in this preliminary analysis, given the large number of patients that had yet to complete day 29 visits. An analysis with adjustment for baseline ordinal score as a stratification variable showed a hazard ratio for death of 0.74 ($CI_{95\%}$, [0.50 to 1.10]).

7.1.3 SIMPLE study: remdesivir for 5 days *versus* 10 days in patients with severe COVID-19 (GS-US-540-5773)

Reference	Goldman J et al. Remdesivir for 5 or 10 Days in Patients with Severe COVID-19. N Engl J Med. 2020 Apr 10; NEJMoa2007016[45]
Clinicaltrials.gov	Registration number: NCT04292899
Primary objective of the study	To evaluate the clinical improvement at Day 14 and the safety of 2 RDV treatment regimens: treatment for 5 days compared to treatment for 10 days.
Study type	Multicentre, randomised, open-label, phase 3 superiority trial in patients least 12 years of age with severe COVID-19.
Study date and duration	Start of enrolments (first patient included): 6 March 2020 Last visit: 22 March 2020 Study conducted in 55 centres in 8 countries (USA, Italy, Germany, Taiwan, Hong-Kong, Singapore, South Korea, Spain), including 5 centres in France having enrolled 27 patients.
Main inclusion criteria	- Men and women aged over 18 years for all countries (≥ 12 and < 18 years possible in some countries, if weight > 40 kg), - SARS-CoV-2 infection confirmed by PCR, - Hospitalised, - **SpO_2 ≤ 94% in ambient air or requiring supplemental oxygen,** - Pulmonary infiltrates confirmed by imaging.
Main exclusion criteria	- Other concurrent treatment with a potential activity on SARS-CoV-2, - **Mechanical ventilation or ECMO,** - **Multiorgan failure,** - AST/ALT > 5 times the ULN, - eGFR < 50 mL/min, - Pregnant or breastfeeding women.
Study design	Part A:  [*critère principal : évaluation du stade clinique à J14 selon une échelle ordinale à 7 points / primary endpoint : asessment of clinical status at D14 on 7-point ordinal scale. Critère secondaire : proportion de patients rapportant des événements indésirables / secondary endpoint : proportion of patients reporting adverse events*] Part B: evaluation of the efficacy and safety of RDV for 5 to 10 days in 4,505 additional patients.
Study treatments	Patients were randomised (allocation ratio of 1: 1) to receive: - RDV for 5 days: 200 mg IV on D1 then 100 mg IV/day for 5 days + SOC, - RDV for 10 days: 200 mg IV on D1 then 100 mg IV/day for 10 days + SOC. Concomitant treatments: antiviral treatments with a potential activity on SARS-CoV-2 were prohibited, including lopinavir/ritonavir.
Primary endpoint	**Assessment of clinical status at D14 on a 7-point ordinal scale:** 1. death, 2. hospitalised, receiving mechanical ventilation or ECMO, 3. hospitalised, receiving non-invasive ventilation (NIV) or high-flow supplemental oxygen, 4. hospitalised, with low-flow supplemental oxygen, 5. hospitalised, without oxygen support but with medical care, 6. hospitalised, not requiring medical care or oxygen support, 7. non-hospitalised. Clinical improvement at D14 was defined as an improvement of at least 2 points on the ordinal scale.

	Note: The protocol was significantly amended after the start of inclusion. The primary endpoint - the proportion of patients with normalisation of temperature at day 14 - was replaced by assessment of clinical status on a 7-point ordinal scale at day 14.
Secondary endpoints	- Time to recovery, defined by the NIAID as an improvement from a baseline score of 2 to 5 to a score of 6 or 7, - Modified time to recovery, defined as an improvement from a baseline score of 2 to 4 to a score of 5 to 7 or from a score of 5 to a score of 6 or 7, - All-cause mortality at 28 days, - Safety.
Sample size	A sample of 400 patients (200 in each group) provided an 85% power to detect an odds ratio (OR) for improvement of 1.75, using a two-sided significance level of 0.05.
Results analysis method	Analysis of the primary endpoint was conducted on a modified intention-to-treat basis. The primary analysis, performed after all patients completed 14 days in the trial, used the proportional odds model, including treatment as the independent variable and baseline clinical status as a continuous covariate. RDV for 10 days of treatment was superior to RDV for 5 days of treatment if the lower bound of the two-sided 95% confidence interval of the odds ratio (OR interval (10 days vs 5 days)) on day 14 was > 1. The stratified Wilcoxon rank-sum test was used to compare the treatment groups if the proportional odds assumption was not met. For time-to-event endpoints (such as the time to clinical improvement), the HR and its 95% confidence interval were estimated from a Cox model that included treatment and baseline clinical status as covariates and treated death as the competing risk.

Results:

Sample size

Of the 408 patients selected, 402 were randomised and 397 started treatment (200 patients in the RDV 5 days group and 197 patients in the RDV 10 days group) (Table 6). Of the 200 patients in the RDV 5-day group, 172 (86%) completed the 5 days of treatment and 28 did not complete the course of treatment, primarily due to hospital discharge (16 patients [8%]) or adverse events (9 [4%]).
Of the 197 patients in the RDV 10-day group, 86 (44%) completed the 10 days of treatment and 111 did not complete the course of treatment, primarily due to hospital discharge (68 patients [35%]), adverse events (12 [6%]) or death (12 [6%]).

Table 6. Breakdown of patients (SIMPLE trial severe patients)

	RDV 5 days group	RDV 10 days group
Screened	408	
Enrolled	402	
Randomised	202	200
Received at least one treatment dose	200	197
Completed treatment at D5 vs D10	**172 (86%)**	**86 (44%)**
Population analysed	200	197

RDV = remdesivir

Main baseline characteristics of patients

The mean age of patients was 61 years and 64% of them were males; 23% were diabetic and half had hypertension. A median dose of 8 days was observed between the start of symptoms and the first dose of RDV (table 7).
The patient characteristics were comparable between the two groups, except for gender (more men in the 10 days group) and initial disease severity, which was lower in the 5 days group (26% on ventilation in the RDV 5 days group *versus* 35% in the RDV 10 days group); including 4 (2%) patients on mechanical ventilation in the RDV 5 days group *versus* 9 (5%) in the RDV 10 days group (exclusion criterion).

At D14, 16 patients (8%) in the RDV 5 days group *versus* 21 patients (11%) in the RDV 10 days group had died, and 120 (60%) *versus* 103 (52%) had left the study.

Table 7. Baseline characteristics of patients (SIMPLE trial severe patients)

	RDV 5 days group (n=200)	RDV 10 days group (n=197)
Age, years (IQR)	61 (50-69)	62 (50-71)
Male gender, n (%)	120 (60)	133 (68)
Hypertension, n (%)	100 (50)	98 (50)
Diabetes, n (%)	47 (24)	43 (22)
Hyperlipidaemia	40 (20)	49 (25)
Asthma	27 (14)	22 (11)
Ordinal scale at D1		
2 – Mechanical ventilation or ECMO	4 (2)	9 (5)
3 – Non-invasive ventilation or high-flow O2	49 (24)	60 (30)
4 – Low-flow O2	113 (56)	107 (54)
5 – Ongoing medical care only	34 (17)	21 (11)
Median duration of symptoms before first dose (IQR)	8 days (5-11)	9 days (6-12)
Median duration of hospitalisation before first dose (IQR)	2 days (1-3)	2 days (1-3)
AST (U/L), median (IQR)	41 (29-58)	46 (34-67)
ALT (U/L), median (IQR)	32 (22-50)	36 (23-58)
Creatinine clearance (mL/min), median (IQR)	106 (80-142)	103 (80-140)

IQR = interquartile range; *RDV = remdesivir*

Primary endpoint: clinical status (clinical improvement) at D14 (ITTm population) assessed by the investigator

In total, 65% of patients in the remdesivir 5 days group had a clinical improvement at D14 of at least 2 points on the ordinal scale *versus* 54% of patients in the remdesivir 10 days group. After adjustment, no statistically significant difference between the two groups was demonstrated (p=0.14 by stratified Wilcoxon rank-sum test; adjusted difference -6.5% [$CI_{95\%}$ of -15.7% to 2.8%]). Hence the hypothesis of the superiority of a 10-day treatment course *versus* a 5-day treatment course is not demonstrated in this study.

Table 8. Primary endpoint: clinical improvement at D14 – ITTm population (SIMPLE study severe patients)

	RDV for 5 days (n=200)	RDV for 10 days (n=197)	Adjusted difference P and HR [95% CI]
Ordinal scale at D14, n (%)			P = 0.14
1 – Death	16 (8)	21 (11)	
2 – Mechanical ventilation or ECMO	16 (8)	33 (17)	
3 – Non-invasive ventilation or high-flow O_2	9 (4)	10 (5)	
4 – Low-flow O_2	19 (10)	14 (7)	
5 – Ongoing medical care only	11 (6)	13 (7)	
6 – Hospitalised without O_2 or medical care	9 (4)	3 (2)	
7 – Non-hospitalised	120 (60)	103 (52)	
Time to clinical improvement (days)*	**10**	**11**	**0.79 (0.61 to 1.01)**
Clinical improvement (improvement of at least 2 points), n (%)			
D5	33 (16)	29 (15)	0.2 [-7.0; 7.5]
D7	71 (36)	54 (27)	-5.0 [-14.0; 4.0]
D11	16 (58)	97 (49)	-4.8 [-14.1; 4.6]
D14	**129 (64)**	**107 (54)**	**-6.5 [-15.7; 2.8]**

**median day for 50% incidence*

07.2 Resistance to treatment

According to the current SPC:
"*Resistance*
Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified 2 substitutions (F476L and V553L) in the viral RNA-dependent RNA polymerase at residues conserved across CoVs that conferred 5.6-fold reduced susceptibility to remdesivir. Introduction of the corresponding substitutions (F480L and V557L) into SARS-CoV resulted in 6-fold reduced susceptibility to remdesivir cell culture and attenuated SARS-CoV pathogenesis in a mouse model. The cell culture development of SARS-CoV-2 resistance to remdesivir has not been assessed to date. No clinical data are available on the development of SARS-CoV-2 resistance to remdesivir."

07.3 Quality of life

No quality of life assessment was scheduled in the studies for which the efficacy and safety data are described in the present opinion.

07.4 Safety

7.4.1 Data from clinical studies

7.4.1.1 Placebo-controlled study conducted in China in patients with severe COVID-19[43]

In this study, remdesivir was given by the IV route at a dose of 200 mg on D1, then 100 mg per day from D2 to D10. Adverse events (AEs) were reported in 66% (102/155) of patients treated with remdesivir and 64% (55/78) of patients having received placebo.

The most common reported AEs (≥ 10%) in the remdesivir group were constipation (14%), hypoalbuminaemia (13%), hypokalaemia (12%), anaemia (12%), thrombocytopenia (10%) and increased total bilirubin (10%).
The most common reported AEs (≥ 10%) in the placebo group were hypoalbuminaemia (15%), constipation (15%), anaemia (15%), hypokalaemia (14%), increased AST (12%), increased blood lipids (10%) and hyperlipidemia (10%).

Serious adverse events (SAEs) were reported in 18% (28/155) of patients treated with remdesivir and 26% (20/78) in the placebo group. The most common reported SAEs were respiratory failure or acute respiratory distress syndrome (10%) in the remdesivir group and cardiopulmonary failure (9%) in the placebo group.
AEs leading to treatment discontinuation were more frequently reported in the remdesivir group than in the placebo group: 12% *versus* 5%. The majority of treatment discontinuations were subsequent to respiratory failure or acute respiratory distress syndrome (5%) in the remdesivir group and nosocomial infection (9%) in the placebo group.

All the deaths observed were judged by the investigators to be unrelated to the treatment.

7.4.1.2 Placebo-controlled ACTT study in patients with moderate to severe COVID-19 (NIH/NIAID)[44]

In this study remdesivir was administered by the IV route with a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death. The most common adverse events reported in the remdesivir group were anaemia or decreased haemoglobin (7.9% *versus* 9.0% in the placebo group); acute kidney injury, decreased eGFR or creatinine clearance or increased blood creatinine (7.4% *versus* 7.3%); fever (5.0% *versus* 3.3%); hyperglycaemia or increased blood glucose level (4.1% *versus* 3.3%); and increased aminotransferase levels (4.1% *versus* 5.9%).

Grade 3 or 4 adverse events were reported in 28.8% (156/541) of patients treated with remdesivir and 33.0% (172/522) of patients having received placebo.
Serious adverse events (SAEs) were reported in 21.1% (114/541) of patients treated with remdesivir *versus* 27.0% (141/522) in the placebo group. The most common reported SAEs (≥ 5%) were respiratory failure in both groups (5,2% *versus* 8%).

There were four AEs (2 AEs in each group) considered to be related to the treatments by the investigators. No deaths were judged to be related to the treatment by the investigators.

7.4.1.3 SIMPLE study: remdesivir for 5 days versus 10 days in patients with severe COVID-19 (GS-US-540-5773)[45]

AEs were reported with a comparable frequency between the two groups: 70% (141/200) in the remdesivir 5 days group *versus* 74% (145/197) in the remdesivir 10 days group.

The most common reported AEs (≥ 5%) in the remdesivir 5 days group were nausea (10%), acute respiratory failure (6%), increased ALT (6%) and AST (5%), constipation (6%), hypokalaemia (5%) and insomnia (5%).
The most common reported AEs (≥ 5%) in the remdesivir 10 days group were acute respiratory failure (11%), nausea (9%), increased ALT (8%) and AST (7%), acute kidney injury (8%), constipation (7%), respiratory failure (7%), hypokalaemia (6%), hypotension (6%) and insomnia (6%).

Grade 3 or 4 AEs were reported in 27% (53/195) of patients in the remdesivir 5 days group and 34% (64/191) of patients in the remdesivir 10 days group.

SAEs were reported in 21% (42/200) of patients treated with remdesivir for 5 days *versus* 35% (68/197) of patients treated with remdesivir for 10 days. The most common reported SAEs were acute respiratory failure in both groups (5% *versus* 9%).

AEs leading to treatment discontinuation were reported in 4% (9/200) of patients in the remdesivir 5 days group and 10% (20/197) of patients in the remdesivir 10 days group.

7.4.2 Data from the Risk Management Plan (RMP)

The pharmaceutical company supplied the risk management plan (RMP) version 1.0 dated 24 June 2020. The important identified and potential risks, along with missing data are summarised in the table below.

Important identified risks	- Hypersensitivity including infusion-related reaction
Important potential risks	- Hepatotoxicity - Nephrotoxicity
Missing information	- Safety in patients with hepatic impairment - Safety in patients with severe renal impairment - Safety in pregnant and lactating women

7.4.3 Data from PSURs

Not applicable.

7.4.4 Data from the SPC

"4.8. Undesirable effects
Summary of the safety profile
The most common adverse reaction in healthy volunteers is increased transaminases (14%). The most common adverse reaction in patients with COVID-19 is nausea (4%).

Tabulated summary of adverse reactions
The adverse reactions in Table 2 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

Tabulated list of adverse reactions

Frequency	Adverse reaction
Immune system disorders	
Rare	Hypersensitivity
Nervous system disorders	
Common	Headache
Gastrointestinal disorders	
Common	Nausea
Hepatobiliary disorders	
Very common	Transaminases increased
Skin and subcutaneous tissue disorders	
Common	Rash
Injury, poisoning and procedural complications	
Rare	Infusion-related reaction

Description of selected adverse reactions
Transaminases increased
In healthy volunteer studies, increases in ALT, aspartate aminotransferase (AST) or both in subjects who received remdesivir were grade 1 (10%) or grade 2 (4%). In a randomised, double-blind, placebo-controlled clinical study of patients with COVID-19 (NIAID ACTT-1), the incidence of grade ≥3 non-serious adverse events of increased aminotransferase levels including ALT, AST, or both was 4% in patients receiving remdesivir compared with 6% in receiving placebo. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5773) in hospitalised patients with severe COVID-19 receiving remdesivir for 5 (n=200) or 10 days (n=197), any grade (≥1.25 × upper limit of normal (ULN)) laboratory abnormalities of increased AST and increased ALT occurred in 40% and 42% of patients, respectively, receiving remdesivir. Grade ≥3 (≥5.0 × ULN) laboratory abnormalities of increased AST and increased ALT both occurred in 7% of patients receiving remdesivir. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5774) in hospitalised patients with moderate COVID-19 receiving remdesivir for 5 (n=191) or 10 days (n=193) compared to standard of care (n=200), any grade laboratory abnormalities of increased AST and increased ALT occurred in 32% and 33% of patients, respectively, receiving remdesivir, and 33% and 39% of patients, respectively, receiving standard of care. Grade ≥3 laboratory abnormalities of increased AST and increased ALT occurred in 2% and 3% of patients, respectively, receiving remdesivir and 6% and 7%, respectively, receiving standard of care."

07.5 Use data

On 3 April 2020[4,6], then on 11 May 2020[8] in the expanded indications, the EMA recommended the compassionate use of remdesivir within the European Union. A total of 1,800 patients have received remdesivir around the world, including 110 in France (83 patients in the compassionate use programme and 12 in the Expanded Access Programme (EAP) since 27 January 2020).

In France, an application for a cohort compassionate use programme (ATU - temporary authorisation for use) [5] was submitted to the ANSM on 26 March 2020 and granted on 2 July 2020 in the indication:

“treatment of COVID-19 disease in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (see section 5.1 of the SPC). In view of the limitations of the clinical demonstration in terms of efficacy (see section 5.1 of the SPC) and safety, any treatment initiation must be the subject of a prior collective opinion”.

Access via	CU	EAP	TE (=ATU)	SIMPLE study Severe patients	SIMPLE study Moderate patients	DisCoVeRy study
Number of patients treated with remdesivir	83	8	0	27	8	150

ATU = Autorisation temporaire d’utilisation (Temporary authorisation for use), a French early access programme; CU = Compassionate Use; EAP = Expanded Access Program

Compassionate use data[46] for hospitalised patients with a SpO_2 ≤ 94% or requiring supplemental oxygen or mechanical ventilation have demonstrated that after median follow-up of 18 days from the first dose of remdesivir, 36 of the 53 patients (68%) showed an improvement in oxygen support class, with 17/30 patients extubated following mechanical ventilation.

After 28 days of follow-up, the cumulative incidence of clinical improvement, defined as either a decrease of ≥ 2 points from baseline on a 6-point ordinal scale, or discharge from hospital, was 84% ($CI_{95\%}$: 70% - 99%).

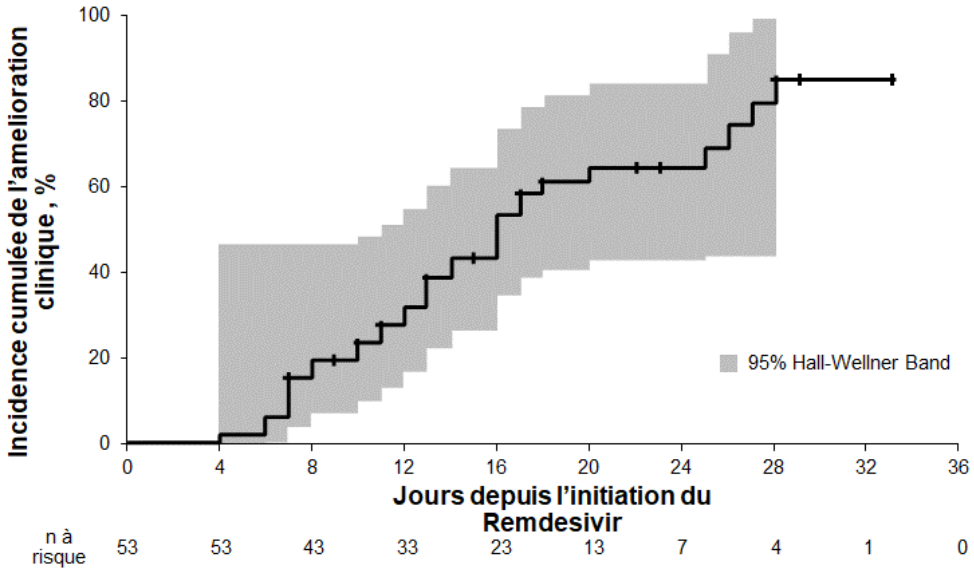


Figure 2. Clinical improvement between baseline and D28 (compassionate use programme)

Incidence cumulée de l’amélioration clinique, %	*Cumulative incidence of clinical improvement, %*
Jours depuis l’initiation du Remdesivir	*Days since initiation of Remdesivir*
n à risque	*n at risk*
95% Hall-Wellner Band	*95% Hall-Wellner Band*

07.6 Summary & discussion

VEKLURY (remdesivir) is a broad-spectrum antiviral that is a monophosphate derivative of a nucleoside analogue of adenine. In January 2020, this antiviral drug was identified as an option to be evaluated in the clinical development of COVID-19, due to its activity in cell cultures and animal models against MERS-CoV and SARS-CoV coronaviruses[1],[1]. A recent study documented the *in vitro* activity of VEKLURY (remdesivir) against SARS-CoV-2[3]. No data have demonstrated the *in vivo* antiviral activity of VEKLURY (remdesivir).

[46] Grein J, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. New Eng J Med. 2020. https://www.nejm.org/doi/full/10.1056/NEJMoa2007016.

This is the first medicinal product with a conditional MA, granted on 3 July 2020, in *"the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen"*. The VEKLURY (remdesivir) dosage recommended by the MA is single loading dose of VEKLURY (remdesivir) 200 mg on day 1, followed by once-daily maintenance doses of 100 mg from day 2. The total duration of treatment should be at least 5 days and not more than 10 days.
At present, no other medicinal products have an MA in this indication.

The dossier is based on:

- two clinical trials having evaluated the efficacy and safety of treatment with VEKLURY (remdesivir) administered for 10 days *versus* placebo, in combination with standard of care (Trial in China, ACTT trial) in patients considered to be "severe": hospitalised and PCR positive for SARS-CoV-2, with pulmonary imaging characteristic of pneumonia or pulmonary infiltrates. These patients have an oxygen saturation rate (SpO_2) ≤ 94% in ambient air or require supplemental oxygen or mechanical ventilation.
- and one study having compared two administration regimens of VEKLURY (remdesivir) for 5 *versus* 10 days (Simple Phase 3 trials in severe patients).

For this evaluation, only the study publications were provided, not the study reports.

◗ Efficacy

Placebo-controlled study conducted in China in patients with severe COVID-19[43]

This is a phase 3, randomised, double-blind, placebo-controlled, multicentre trial (Wuhan, Hubei province in China) in hospitalised adult patients (≥ 18 years) with confirmed SARS-CoV-2 infection, with 12 days or less since symptom onset, an O_2 saturation rate ≤ 94% in ambient air or a PaO_2/FiO_2 ratio < 300 mmHg and pneumonia confirmed by X-ray.

The patients were randomised (ratio 2: 1) into the remdesivir IV group (200 mg on D1, then 100 mg from D2 to D10) or into the placebo group. At baseline, the patients had received lopinavir–ritonavir (approximately 20%), interferon (approximately 20%) and corticosteroids (approximately 40%). The majority (65% remdesivir group *versus* 68% placebo group) of study patients received corticosteroid therapy before or after the start of treatment.
The majority of patients included were men (56% in the remdesivir group *versus* 65% in the placebo group). The most common comorbidity was hypertension, followed by diabetes and coronary heart disease. The majority of patients included required supplemental oxygen (82% *versus* 83%) without ventilation, non-invasive mechanical ventilation or high-flow O_2 (18% *versus* 12%) and no patients were on invasive ventilation or extracorporeal membrane oxygenation (ECMO) in the remdesivir group (*versus* 1 in the placebo group).

The primary endpoint was time to clinical improvement up to day 28, defined by the time (in days) from randomisation until a decline of two levels on a six-point ordinal scale (1 = discharge from hospital to 6 = death) or live discharge from hospital (first event to occur).

Between February 2020 and March 2020, 237 patients underwent randomization (n =158 in the remdesivir group *versus* 79 in the placebo group). One patient in the placebo group left the study after randomisation and was not included in the ITT population. It should be noted that the protocol scheduled the enrolment of 453 patients (151 on placebo and 302 on remdesivir), in order to demonstrate an HR of 1.4 (i.e., a difference of 6 days, assuming a time to clinical improvement of 21 days in the placebo group), with a statistical power of 80% and a one-sided alpha risk of 2.5%.

No benefit of remdesivir was demonstrated compared to placebo in terms of time to clinical improvement (primary endpoint): median of 21.0 days in the remdesivir group [IQR: 13.0-28.0] *versus* 23.0 days [15.0-28.0] in the placebo group; HR = 1.23 [$CI_{95\%}$: 0.87–1.75], NS); on mortality at 28 days (14% in the remdesivir group *versus* 13% in the placebo group (difference = 1.1%; $CI_{95\%}$ [-8.1; 10.3]) and on reduction of viral load (secondary endpoints).

Placebo-controlled study in patients with severe COVID-19 (ACTT)[44]

This is a phase 3, randomised, double-blind, placebo-controlled, multicentre trial conducted in hospitalised patients with SARS-CoV-2 lower respiratory tract infection. A total of 1,063 patients were enrolled: 120 [11.3%] patients with a mild to moderate form and 943 [88.7%] with a severe

form. A total of 272 patients (25.6%) (n = 125 received remdesivir) were on mechanical ventilation or ECMO.

The patients were randomised (ratio 1: 1), following stratification on the basis of disease severity at baseline, to receive remdesivir (n = 541) or a placebo (n = 522), plus standard of care.
The patient characteristics at baseline were comparable between the 2 groups, except in terms of initial disease severity, with patients on invasive ventilation or ECMO being more frequent in the placebo group (23.1% in the RDV group *versus* 28.2% in the placebo group) and missing severity score data being more frequent in the RDV group (5.4% *versus* 3.3%).
Around 33% (180/541) of patients received remdesivir for a period of 10 days.

The primary outcome was initially defined as the percentage of patients reporting each severity score on an eight-category ordinal scale on D15 (ranging from 1. Death to 8. Not hospitalised, no limitations on activities). This outcome became the key secondary outcome following the change of primary endpoint to time to clinical recovery, defined as the first day in the 28 days following enrolment on which the subject satisfies categories 1, 2 or 3 on the eight-category ordinal scale:

1. Not hospitalised, no limitations on activities;
2. Not hospitalised, limitation on activities and/or requiring home oxygen;
3. Hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons);
4. Hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions);
5. Hospitalised, requiring supplemental oxygen;
6. Hospitalised, requiring noninvasive ventilation or use of high-flow oxygen devices;
7. Hospitalised, receiving invasive mechanical ventilation or ECMO;
8. Death.

The results of a preliminary analysis demonstrated a superiority of remdesivir compared to placebo in terms of time to clinical recovery, with 11 days in the remdesivir group *versus* 15 days in the placebo group (RR = 1.32; $CI_{95\%}$ [1.12; 1.55], p < 0.001).
In the subgroup analyses according to stratification factors, a statistically significant difference in terms of time to clinical recovery was only observed in patients with a category-5 clinical status (n = 421 patients) at baseline (HR of 1.47; $CI_{95\%}$ [1.17; 1.84]). In category-4 clinical status patients 4 (n = 127 patients) and in category-6 (n = 197 patients) or category-7 clinical status patients (n = 272) at baseline, the differences were not statistically significant, HR of 1.38 ($CI_{95\%}$ [0.94; 2.03]), 1.20 ($CI_{95\%}$ [0.79; 1.81]) and 0.95 ($CI_{95\%}$ [0.64; 1.42]), respectively.
The effect of RDV on the rate ratio for recovery did not differ on the basis of time to treatment initiation (< 10 days *versus* > 10 days after the onset of symptoms).
No statistically significant difference was revealed for the mortality rate at 14 days between the 2 groups, with 7.1% in the remdesivir group *versus* 11.9% in the placebo group (HR=0.70; $CI_{95\%}$ [0.47 to 1.04], NS). An analysis with adjustment for baseline ordinal score showed an HR for death of 0.74 ($CI_{95\%}$ [0.50 to 1.10]). The estimates of mortality by 28 days are not reported in this preliminary analysis, given the large number of patients that had yet to complete day 29 visits. There were 132 patients (24.4%) in the remdesivir group and 169 (32.4%) in the placebo group who had not recovered and had not completed the day 29 follow-up visit at the data cutoff date.
This study did not evaluate the change in viral load under remdesivir treatment.

SIMPLE study: remdesivir for 5 days versus 10 days in patients with severe COVID-19 (GS-US-540-5773)[45]

An open-label phase 3 trial having included 397 patients with a severe form of COVID-19 compared the efficacy of 5 days of treatment with remdesivir *versus* 10 days of treatment. The patients enrolled were hospitalised, aged at least 12 years (median age 61 years [50 - 71 ans], 64% men) with SARS-CoV-2 infection, confirmed by PCR in the 4 days preceding randomisation, with radiological pulmonary infiltrates and either $SpO_2 \leq 94\%$ in ambient air or supplemental oxygen. The exclusion criteria were mechanical ventilation or ECMO, signs of multiorgan failure or treatment with other agents with putative activity against SARS-CoV-2.

Four hundred and two patients were enrolled and randomised (ratio 1: 1); 397 began treatment, 200 in the remdesivir 5 days group and 197 in the remdesivir 10 days group. The patient characteristics were comparable between the two groups, except for gender (more men in the 10 days group) and

initial disease severity, which was lower in the 5 days group (26% on ventilation in the RDV 5 days group *versus* 35% in the RDV 10 days group); including 4 (2%) patients on mechanical ventilation in the RDV 5 days group *versus* 9 (5%) in the RDV 10 days group (exclusion criterion).

The primary efficacy endpoint was clinical status assessed on day 14 on a 7-point ordinal scale (1 = death to 7 = discharge from hospital). Clinical improvement at D14 was defined as an improvement of at least 2 points on the ordinal scale.

In total, 65% of patients in the 5 days group had a clinical improvement at D14 *versus* 54% of patients in the 10 days group. After adjustment, there was no statistically significant difference between the two treatment groups (p=0.14 by stratified Wilcoxon rank-sum test; adjusted difference -6.5%, $CI_{95\%}$: [-15.7%; 2.8%]). Hence the hypothesis of the superiority of a 10-day treatment course *versus* a 5-day treatment course is not demonstrated in this study. In addition, the absence of a placebo control group and the fact that this study was conducted on an open-label basis constitute study limitations.

Safety

In all the trials available, the safety profile of remdesivir administered for 5 or 10 days was favourable, with the incidence of events (particularly renal and hepatic) having been comparable to that observed with placebo or standard of care alone. It should be noted that the exclusion criteria in the trials include eGFR< 30 ml/min or 50 ml/min and ALT or AST > 5 times the upper limit of normal. The follow-up of patients treated with remdesivir must include, in particular, close clinical monitoring given the potential reactions following injection (in particular, hypotension) along with monitoring of renal and hepatic function (important potential or identified risks in the context of the RMP).

Discussion

In total, the available data are based on 3 studies (of which 1 still ongoing) including numerous limitations (heterogeneous populations in terms of severity and limited sample sizes for the subgroup analyses, imbalances between the groups, change of primary endpoint, open-label studies for the treatment regimens, etc.) with conflicting results (1 positive study [ACTT trial] and 2 negative studies [Chinese trial and SIMPLE trial]).
These data suggest an at best weak effect size of VEKLURY (remdesivir) *versus* placebo, in combination with the standard of care, in terms of the reduction in the time to clinical recovery (4 days, ACTT trial), without any demonstrated impact on the reduction of mortality or worsening of the disease and hospital discharge.
The Committee highlights the fact that the primary endpoint can be criticised. Firstly, it is based on a non-consensual categorisation of the patient's global clinical status of debatable clinical relevance. In addition, by defining success as the first day on which the patient satisfies a status corresponding to categories 1, 2 or 3 and not as a return to a satisfactory status within a fixed period of time following diagnosis (for example on D28), the endpoint here is a "time to event" endpoint, making an implicit assumption that a patient that achieves status 3 early on, for example, will not then deteriorate (even if subsequent deterioration occurs, this patient example would be considered to be a success). This endpoint measured in this way is therefore an early outcome and not a clinical assessment outcome of a status after an appropriate fixed time.

These data do not enable a robust conclusion to be reached with respect to efficacy depending on the stage of the disease nor the optimal treatment duration. However, they suggest a potential benefit in terms of time to recovery and mortality only in the subgroup of hospitalised patients requiring low-flow supplemental oxygen.
The Committee regrets and is surprised by the fact that the antiviral activity of VEKLURY (remdesivir) was not evaluated in the studies provided, apart from the Chinese trial, in which no activity of VEKLURY (remdesivir) on viral load was demonstrated.

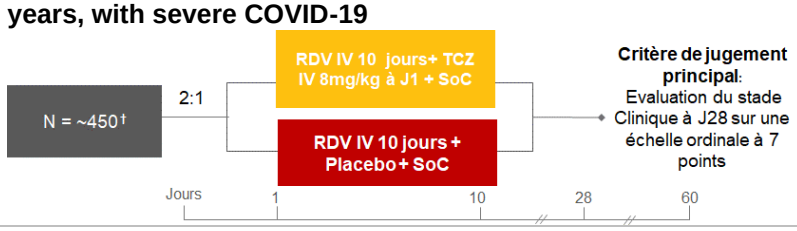
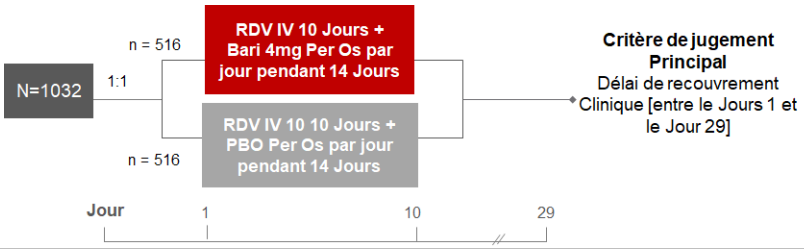
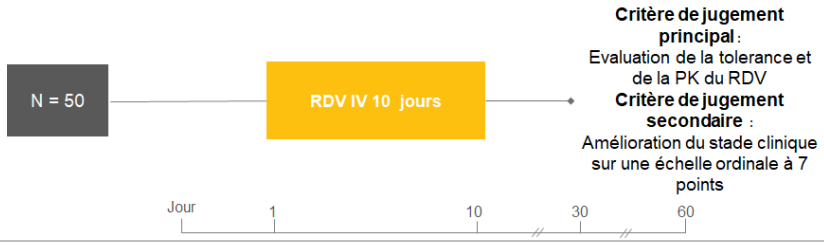
Given that the MA is conditional and that the results of the ACTT trial are preliminary, additional data are required in order to determine, with a better level of evidence, the efficacy and risks related to the use of VEKLURY (remdesivir). Consequently, the pharmaceutical company must submit to the Transparency Committee the final results concerning mortality in the ACTT trial whenever these are available, along with the final reports of the ongoing

studies by December 2020 at the latest (see Section 011 Administrative and regulatory information).

In view of the available efficacy and safety data and the difficulty of transposing the results, there are no robust data supporting an impact of VEKLURY (remdesivir) in terms of reducing morbidity and mortality and viral load or improving the quality of life of patients with COVID-19. No data are available concerning a potential impact of VEKLURY (remdesivir) on the organisation of care, particularly in terms of reducing hospital stay duration or the rate of transfer to intensive care or resuscitation units.
Consequently, VEKLURY (remdesivir) provides a partial response to the unmet medical need only in the subgroup of hospitalised patients requiring low-dose supplemental oxygen.

07.7 Study programme

The clinical study programme evaluating VEKLURY (remdesivir) in the treatment of COVID-19 is presented in the table below.

Study name	Study design	Availability of data
REMDACTA trial	Phase 3, randomised, double-blind, multicentre study of the Remdesivir plus Tocilizumab combination **in hospitalised patients, aged over 12 years, with severe COVID-19** 	NA
ACTT-2 trial	Phase 3, randomised, controlled, double-blind, multicentre study of the Remdesivir plus Baricitinib combination **in hospitalised adult patients with moderate to severe COVID-19** 	NA
CARAVAN trial	Phase 2/3, single-arm, open-label study evaluating the efficacy, safety and pharmacokinetics of RDV **in patients aged 0 to 18 years with moderate to severe COVID-19** 	NA

8.1.1 Recommendations of the *Haut Conseil de Santé Publique* (HCSP)

On an exceptional and temporary basis, therapeutic recommendations for curative treatment were drafted by the *Haut Conseil de la Santé Publique* (HCSP - French National Council for Public Health), on 5 and 23 March 2020, followed by decrees issued within the context of the public health emergency.

The HCSP's opinions have evolved as medical knowledge has improved. Several opinions have been issued; only the latest recommendations are presented here.

In its letter of 20 May 2020[47]Erreur ! Signet non défini., published online on 2 June 2020, the HCSP updated its opinions of 5 and 23 March 2020 on the basis of evolving data relative to the treatments that may be prescribed in COVID-19. The HCSP recommends:

- that supportive care constituting the current standard of care (SOC), remain the reference treatment, irrespective of the severity of COVID-19;
- that, except in the event of inclusion in a prospective, comparative, controlled, randomised clinical trial, the use of the medicinal products cited in its opinion must be based on a collective decision, and that the patient must be followed-up in the Izaric cohort (or French cohort study) or an official registry, or a compassionate use programme (ATU) if one exists. The HCSP therefore calls for the urgent implementation of academic clinical trials, in order to evaluate the value, efficacy and safety of use of the various antiviral therapies, as well as anti-IL6, interferon-beta, and corticosteroids, noting that there is no validated treatment to date.

For interventions going beyond the supportive symptomatic treatment constituting the current standard of care, the HCSP has proposed guidance. The HCSP specifies that this guidance is based more on collective expert opinions and clinical experience in the field than on evidence.

Furthermore, **in its opinion of 15 May 2020**[48] published online on 15 June 2020, the HCSP responded to a referral from the Directorate-General for Health (DGS) asking it to propose a strategy to be adopted for appropriate organisation of the distribution of VEKLURY (remdesivir) doses. The HCSP estimated that current data were insufficient to be able to estimate a benefit/risk ratio as a function of patient subgroups.

"In particular, the data supplied do not include the characteristics of the patients included in the NIAID-ACTT trial (in terms of demographic data and clinical data including comorbidities and classification of the severity of respiratory involvement) and do not provide the results of the efficacy and safety analysis stratified on the basis of these characteristics, in particular severity criteria and ICU transfer criteria."
Consequently, the HCSP stressed the difficulty of defining priority patient groups for treatment with VEKLURY (remdesivir) and thus noted the inconsistency between the number of patients in intensive care units, the number of new hospitalised cases on 14 May 2020, the persistence of virus circulation and the number of treatments available.

HCSP recommendations on the basis of patient status updated on 23 July 2020.

On 23 July 2020[37]**, the HCSP updated its therapeutic recommendations for COVID-19. It concludes that the currently available data drawn from the literature do not provide evidence of a benefit on the course of COVID-19 of supposed antiviral therapies, immunomodulatory agents or convalescent plasma; the HCSP does not recommend their use outside clinical trials.**

[47] HCSP. Letter relative to updating of therapeutic recommendations in the treatment of Covid-19. 20 May 2020.
[48] HCSP. Opinion relative to the distribution of remdesivir doses for Covid-19 patients. 15 May 2020.

COVID-19 patients treated on an outpatient care basis:

- The initiation of symptomatic treatment;
- No prescription of a specific treatment, except as part a therapeutic trial[49].

COVID-19 patients hospitalised in a medical ward (with pneumonia requiring supplemental oxygen) or in an intensive care unit:

- The initiation of supportive symptomatic treatment constituting the current standard of care (SOC) adapted to the patient's condition, which constitutes the reference treatment;
- Priority inclusion in a therapeutic trial for specific treatments[49];
- For patients not eligible for inclusion in a therapeutic trial, the SOC is the reference treatment;
- The prescription of any specific medicinal product[49] is left to the prescriber's discretion, following assessment of the benefit/risk ratio and based on a collective decision (compassionate use);
- Corticosteroid therapy: dexamethasone at a dose of 6 mg/d for a maximum duration of 10 days may be proposed, following assessment of the individual benefit/risk ratio (provisional recommendation pending the complete results of the RECOVERY study or other studies) in patients under the age of 70 years requiring supplemental oxygen in medical wards or ICUs.

8.1.2 Role of VEKLURY (remdesivir) in the care pathway

Despite numerous clinical uncertainties with respect to the efficacy of VEKLURY (remdesivir) in a context of very rapidly evolving treatment strategies, the role of VEKLURY (remdesivir) has been defined considering its potential usefulness for some patients with severe SARS-CoV-2 infection.

Hence, and primarily based on preliminary data from the ACTT trial conducted by the NIAID:

- which suggest an at best weak effect size of remdesivir versus placebo, in combination with the standard of care: 4-day reduction in the time to clinical recovery (11 days versus 15 days; HR=1.32 [1.12-1.55]), primary endpoint of debatable clinical relevance;
- subgroup analyses having demonstrated a statistically significant difference in terms of the time to clinical recovery only in patients requiring low-flow supplemental oxygen at baseline (HR of 1.47; 95% CI [1.17; 1.,84]) and the absence of a statistically significant difference in the most severe forms (patients requiring high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
- and the absence of any demonstrated impact in this study on the reduction in mortality at D14 (7.1% in the remdesivir group versus 11.9% in the placebo group (HR = 0.70; 95% CI [0.47 to 1.04], NS, secondary endpoint), although the subgroup analyses suggest a positive effect on this endpoint only in the subgroup of patients receiving low-flow supplemental oxygen;

pending D28 mortality results, the Committee considers that VEKLURY (remdesivir) could constitute, in combination with the standard of care, a therapeutic option in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring low-flow supplemental oxygen, excluding high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

Additional data are required and expected to be able to determine, with a better level of evidence, the efficacy, adverse effects and risks of VEKLURY (remdesivir) in the MA indication.

[49] The list of specific medicinal products defined by the HCSP is as follows:

- Antiviral drugs: remdesivir; lopinavir/ritonavir; oseltamivir; umifenovir; favipiravir;
- Immunotherapy: convalescent plasma; polyvalent immunoglobulins; immunomodulatory agents (anti-IL6: tocilizumab, sarilumab; anti-IL1: anakinra); interferon (and ribavirin); corticosteroids;
- Other "repositioned" medicinal products: chloroquine and hydroxychloroquine (combined or otherwise with azithromycin); ivermectin; diltiazem and baricitinib.

The Committee reiterates the fact that there are no data concerning patients with renal or hepatic impairment or in pregnant women.

The use of VEKLURY (remdesivir) must be accompanied by close clinical monitoring given the potential adverse reactions following injection (in particular, hypotension) along with monitoring of renal and hepatic function (important potential or identified risks in the context of the RMP).

The prescription of VEKLURY (remdesivir) must be the subject of a prior collective opinion.

09 COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

09.1 Clinical benefit

◗ SARS-CoV-2 is an acute viral disease that is potentially life-threatening, primarily in its severe form, following complications. It is a major public health problem of global concern due to its contagiousness, its severity and its impact on healthcare system organisation and, in particular, intensive care units.

◗ VEKLURY (remdesivir) is a curative antiviral treatment.

◗ The efficacy/adverse effects ratio of VEKLURY (remdesivir) has not currently been adequately established. However, preliminary data (ACTT trial) suggest a clinical benefit that is:

- low in hospitalised COVID-19 patients with pneumonia, on low-flow supplemental O_2 but not ventilated,
- uncertain in the other clinical situations covered by the MA wording (high-flow supplemental oxygen, non-invasive or invasive ventilation, ECMO).

Additional data are required and expected, particularly concerning mortality at 28 days, to be able to determine, with a better level of evidence, the efficacy, adverse effects and risks of VEKLURY (remdesivir) in the MA indication.

◗ There is no reference antiviral therapy in the treatment of COVID-19. The supportive standard of care (SOC) remains the reference treatment for COVID-19, irrespective of severity. Corticosteroids should now be considered to be part of the supportive standard of care in severe forms.

◗ VEKLURY (remdesivir) could constitute, in combination with the standard of care, a therapeutic option in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring low-flow supplemental oxygen, excluding high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

Public health impact

Considering:

- the severity, contagiousness and impact on healthcare organisation, particularly in intensive care units, and the Public Health Emergency of International Concern (PHEIC),
- the major medical need to have access to effective, well-tolerated medicines in the treatment of SARS-CoV-2 infection due to the absence of any available curative treatment,
- the modest clinical impact, of uncertain scope, observed mainly in hospitalised patients with respiratory involvement requiring low-dose supplemental oxygen and the absence of any robust data currently in terms of mortality,
- the absence of data at this stage supporting an impact of VEKLURY (remdesivir) on the reduction of viral load and improvement of quality of life of COVID-19 patients,
- the absence of data supporting a potential impact of VEKLURY (remdesivir) on the organisation of care, particularly in terms of reducing hospital stay duration or the rate of transfer to intensive care or resuscitation units,

In view of the data currently available, VEKLURY (remdesivir) is unlikely to have an impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of VEKLURY (remdesivir) is:

- **low in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring low-flow supplemental oxygen;**
- **insufficient to justify its funding by the French national health insurance system in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).**

The Committee issues a favourable opinion for inclusion of VEKLURY (remdesivir) in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring low-flow supplemental oxygen and at the MA dosages.

The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the treatment of COVID-19 in hospitalised patients aged 12 years and older with body weight at least 40 kg with pneumonia requiring high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

The Committee indicates that maintenance of this assessment is conditional on reevaluation of VEKLURY (remdesivir), in particular based on D28 mortality data from the American ACTT trial , whenever these become available and, at the latest, by October 2020.

This assessment reflects the still high level of uncertainty with respect to the efficacy and safety of VEKLURY (remdesivir) in a context of very rapidly evolving treatment strategies and the public health need.

09.2 Clinical added value

Considering:

- **the available clinical data limited to the results of 3 comparative studies conducted in hospitalised patients (Chinese study NCT04257656 stopped early, preliminary results of the American ACTT study, SIMPLE study without a control group) presenting numerous methodological limitations and conflicting results,**
- **preliminary results from the pivotal American ACTT study with the biggest population (n = 1,063 hospitalised patients with pneumonia, including 88.7% with a severe form requiring oxygen), which suggest an at best weak effect size of remdesivir *versus* placebo, in combination with the standard of care: 4-day reduction in the time to**

clinical recovery (11 days versus 15 days; HR=1.32 [1.12-1.55]), primary endpoint of debatable clinical relevance,

- **and the absence of any demonstrated impact in this study on the reduction in mortality at D14 (7.1% in the remdesivir group *versus* 11.9% in the placebo group (HR = 0.70; 95% CI [0.47 to 1.04], NS, secondary endpoint), although the subgroup analyses suggest a positive effect on this endpoint only in the subgroup of patients receiving low-flow supplemental oxygen,**
- **the absence of mortality data at D28 in the ACTT study,**
- **the absence of data enabling a robust conclusion to be reached with respect to efficacy depending on the stage of the disease and the optimal treatment duration;**
- **the absence of a demonstrated impact of remdesivir in terms of the expected negative conversion of viral load;**
- **and despite the medical need to have access to effective and well-tolerated curative treatments for COVID-19 due to its severity, its contagiousness and its impact on healthcare organisation, particularly in intensive care units, as well as the absence of an available curative treatment;**

On the basis of currently available data, the Committee considers that VEKLURY (remdesivir) provides no clinical added value (CAV V) for the treatment of COVID-19 in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia and receiving low-flow supplemental oxygen.

09.3 Target population

The target population for VEKLURY (remdesivir) is composed of, in the hospital care strategy, adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) with COVID-19, with pneumonia requiring low-flow supplemental oxygen, excluding high-flow supplemental oxygen or supplemental oxygen during non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

The population of COVID-19 patients is, by definition, very difficult to estimate in advance. Modelling studies are available but these include uncertainties given evolving knowledge, the dynamics of the epidemic and the epidemic control strategies put in place.

It is therefore particularly risky to attempt to predict the course of this pandemic in France and to define, even approximately, an absolute value for the size of the target population that could potentially benefit from treatment with VEKLURY (remdesivir).

In a publication[50] concerning 5,700 COVID-19 patients hospitalised in New York, the target population described above represented 27.8% ($CI_{95\%}$ from 26.6% to 29.0%) of patients.

The target population of VEKLURY (remdesivir) can be estimated to correspond to 30% of new cases of hospitalised patients with COVID-19.

010 OTHER COMMITTEE RECOMMENDATIONS

Specific requests inherent to funding

In view of the current uncertainties concerning the efficacy, safety and methods of use (clinical stage, optimal use duration and patient follow-up) of VEKLURY (remdesivir), in a context of very rapidly evolving treatment strategies, and insofar as the Committee has restricted the reimbursement scope of VEKLURY (remdesivir) compared to the MA, it recommends that prescriptions be made following a collective opinion.

Requests for data

[50] Richardson S et al, and the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with covid-19 in the New York City area. JAMA 2020.

Considering that the available data in this indication are preliminary with, in particular, uncertainties concerning quantification of the therapeutic contribution of VEKLURY (remdesivir) compared to placebo, the Committee makes maintenance of its favourable opinion for reimbursement conditional on the submission of data at D28 and, in particular mortality data from the American ACTT study, with submission expected whenever these become available and, at the latest, by October 2020. At this point, the Committee will specify the clinical data to be collected in the context of real-life use of VEKLURY (remdesivir).

011 ADMINISTRATIVE AND REGULATORY INFORMATION

Assessment schedule	Date of examination: 8 July 2020 Date of adoption: 22 July 2020 Date of examination of the pharmaceutical company's comments: 16 September 2020
Stakeholders / external expertise	Yes
Presentations concerned	VEKLURY (remdesivir) 100 mg powder for concentrate for solution for infusion B/1 Vial (glass) (CIP: 34009 550 742 6 7) VEKLURY (remdesivir) 100 mg concentrate for solution for infusion B/1 Vial (glass) – 20 ml (5 mg/ml) (CIP: 34009 550 742 7 4)
Applicant	GILEAD SCIENCES
List concerned	Hospital (CSP L.5123-2)
MA	Conditional MA (centralised procedure): 03 July 2020
Prescribing and dispensing conditions / special status	List I Additional list Cohort ATU: 2 July 2020 Medicinal product for hospital use only (RH)
ATC code	J05AB16 Antivirals for systemic use, direct acting antivirals, other antivirals

Obligation to put in place post-authorisation measures for the conditional MA[51]

Post-authorisation measures	Deadline
In patients on invasive mechanical ventilation or ECMO, submission of final published data on mortality at D28 by ordinal scale category in study CO-US-540-5776 (NIAID-ACTT1). **Discussion of a potential imbalance in the use of corticosteroids and modification of the effects in study NIAID-ACTT1.**	August 2020
Submission of the final clinical study report (CSR) for study CO-US-540-5776 (NIAID-ACTT1).	December 2020
Submission of the final CSR for part A (day 28) of study GS-US-540-5773 (SIMPLE severe).	December 2020
Submission of the final CSR for part A (day 28) of study GS-US-540-5774 (SIMPLE moderate).	December 2020
Presentation in module 2.7.4 of an analysis of all available safety data from clinical trials CO-US-540-5776, GS-US-540-5773, GS-US-540-5774 and CO-US-540-5758 when they are completed, including case series, detailed information of adverse effects and exposure data, as well as an analysis of the occurrence and worsening of AEs, SAEs and treatment-emergent AEs associated with growing exposure.	December 2020

[51] Since this is a conditional marketing authorisation and in accordance with article 14a, paragraph 4, of regulation (EC) No. 726/2004, the marketing authorisation holder must take the following measures within the period specified. Only measures concerning efficacy and safety are indicated in the table. See Annex 2 of the SPC.

012 ANNEXES

Annex 1. Non-exhaustive list of other therapies being investigated in the treatment of COVID-19 (subject to new studies or for which publication ongoing)

Study treatment	Development stage and recommendations
Antivirals	
Lopinavir / ritonavir (+/- Interferon ß-1a)	Study ongoing Withdrawal of recommendations outside clinical trials
Favipiravir	Study ongoing Withdrawal of recommendations outside clinical trials
Other	
Hydroxychloroquine (+/- azithromycin)	Study ongoing Withdrawal of recommendations outside clinical trials
Nivolumab (anti-PD1)	Study ongoing
Vitamin D supplementation	Study ongoing Included in the recommendations
Immunomodulatory drugs	
Convalescent patient plasma	Study ongoing
Specific anti-SARS-CoV-2 antibodies	Study ongoing
Interferon	Study ongoing
Anti-inflammatories	
Tocilizumab (anti-IL6)	Study ongoing
Sarilimab (anti-IL6)	Study ongoing
Anakinra (anti-IL1)	Study ongoing
Baricitinib (anti-JAK1&2)	Study ongoing
Prednisone (corticosteroids)	Study ongoing
Dexamethasone (corticosteroids)	Study ongoing Included in the recommendations
Hydrocortisone (corticosteroids)	Study ongoing Included in the recommendations

Annex 2. Rapid response from the Department for the evaluation of medicinal products and health technologies for the purpose of reimbursement and the Department of Health Services at the *Institut national d'excellence en santé et en services sociaux* (INESSS) in Quebec concerning the role of remdesivir in the treatment of COVID-19[52]

COVID-19 and Remdesivir

CONTEXT

The present document and its statements were drafted in response to a request by the Ministry of Health and Social Services in the context of the health emergency related to coronavirus disease (COVID-19) in Quebec. The aim is to carry out a summary review of published data and to mobilise key knowledge in order to inform public decision-makers and health and social services professionals. Although the findings are based on an exhaustive survey of published scientific data, the selection and evaluation of the methodological quality of the studies is not based on a systematic method according to the usual INESSS standards. Moreover, the positions do not result from an extensive consultation process. In a public health emergency situation of this type, the INESSS remains on the lookout for any new data likely to lead it to modify this response.

INESSS POSITION
Based on the scientific documentation available at the time of writing, and on the consultations carried out, despite the uncertainty existing in this documentation and in the approach used, the INESSS considers that:

PROPHYLAXIS

The absence of efficacy data concerning the use of remdesivir as pre- and post-exposure prophylaxis of SRAS-CoV-2 infection does not enable its use to be recommended in this context, outside a research protocol.

Current scientific knowledge does not enable assessment of the effect of prophylactic use of remdesivir pre- or post- exposure to SRAS-CoV-2. [Level of scientific evidence inadequate]

No clinical trials are ongoing concerning the use of remdesivir as pre- or post-exposure prophylaxis.

TREATMENT
Confirmed COVID-19, non-hospitalised patients

No data enable recommendation of the use of remdesivir outside a research protocol in patients with a confirmed diagnosis of COVID-19 whose condition does not require hospitalisation.

Current scientific knowledge does not enable assessment of the effect of remdesivir in COVID-19 patients whose condition does not require hospitalisation. [Level of scientific evidence inadequate]

[52] COVID-19 and Remdesivir. Quebec, Qc: INESSS; 2020. 48 p. https://www.inesss.qc.ca/fileadmin/doc/INESSS/COVID-19/COVID-19_remdesivir.pdf

No clinical trials are ongoing concerning the use of remdesivir in patients with a confirmed diagnosis of COVID-19 whose condition does not require hospitalisation.

Confirmed COVID-19, hospitalised patients in a serious or critical condition

Although encouraging, data documenting the efficacy, safety and availability context of this medicinal product in Canada do not enable recommendation of the use of remdesivir outside a research protocol in patients with a confirmed diagnosis of COVID-19 whose condition requires hospitalisation.

Current scientific knowledge based on three randomised comparative trials suggests that the use of remdesivir may lead to an improvement in patients (≥ 12 years) with COVID-19 whose condition requires hospitalisation. [Level of scientific evidence: Moderate].

Patients who have had symptoms for less than 10 days and patients associated with a severe stage of COVID-19 may be more likely to benefit from treatment with remdesivir in terms of clinical improvement.

Current scientific knowledge based on two randomised comparative trials suggests that the use of remdesivir may reduce the time to recovery for a larger number of patients (≥ 12 years) with COVID-19 whose condition requires hospitalisation. [Level of scientific evidence: Moderate].

Hospitalised patients requiring low-flow supplemental oxygen and patients associated with a severe stage of COVID-19 may be more likely to benefit from treatment with remdesivir in terms of recovery.

Current scientific knowledge based on three randomised comparative trials suggests that the use of remdesivir does not appear to result in a statistically significant difference in the mortality rate of patients (≥ 12 years) with COVID-19 whose condition requires hospitalisation. [Level of scientific evidence: Moderate].

Hospitalised patients requiring low-flow supplemental oxygen may be more likely to benefit from treatment with remdesivir in terms of mortality risk.

Current scientific knowledge based on three randomised comparative trials conducted in the context of COVID-19 in hospitalised patients appears to indicate that the use of remdesivir compared to placebo does not result in additional major adverse effects. [Level of scientific evidence: Low].

Clinical trials are still ongoing in Canada and internationally; these will enable better assessment of the effects of remdesivir alone or in combination with other therapeutic agents in the clinical course of COVID-19 and increase the level of scientific evidence.