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REMDESIVIER; CLINICAL SIGNIFICANCE, IMPLICATIONS, CHEMISTRY AND, MEDICINAL SYNTHESIS

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ABSTRACT

An outbreak of novel corona-virus (2019-nCoV) that began in Wuhan, China, had spread rapidly, with cases now confirmed in multiple countries. Early data reveal the results outcome that Remdesivir is effective against COVID-19. Social media platforms are inundated with requests for Remdesivir, a critical drug in the treatment of COVID-19 that is in short supply throughout the country, (India). Remdesivier is a broad-sprectrum antiviarl drug used as a medication for the treatment of COVID-19. Remdesivir was approved for medical use in the United States in October 2020. The U.S. Food and Drug Administration (FDA) approved Remdesivir based on the agency's analysis of data from three randomised, controlled clinical trials that included participants hospitalised with mild-to-severe COVID-19. The FDA granted approval and reissued the revised EUA to Gilead Sciences Inc. The FDA approved Remdesivir based primarily on evidence from three clinical trials (NCT04280705, NCT04292899, and NCT04292730) of 2043 hospitalised participants with COVID-19. The trials were conducted at 226 sites in 17 countries including the United States of America. The results and outcomes are been discussed with the significant study for the use of Remdesivier as a therapeutic agent in the curing and mitigation of the disease or infection caused by the SARS-CoV-2 and other similar type of viral affecting the human as well as animal species.

KEYWORDS: COVID-19 pandemic medication, Remdesivier synthesis scheme, Pharmacokinetics of Remdesivier, SARS-Cov-2 treatment Remdesivier, Faith and pharmacology of Remdesivier.

1. INTRODUCTION

Corona-virus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome corona-virus 2 (SARS-CoV-2). The first known case was identified in Wuhan, China, in December 2019. The disease has since spread worldwide, leading to an ongoing pandemic. Severe acute respiratory syndrome corona-virus 2.

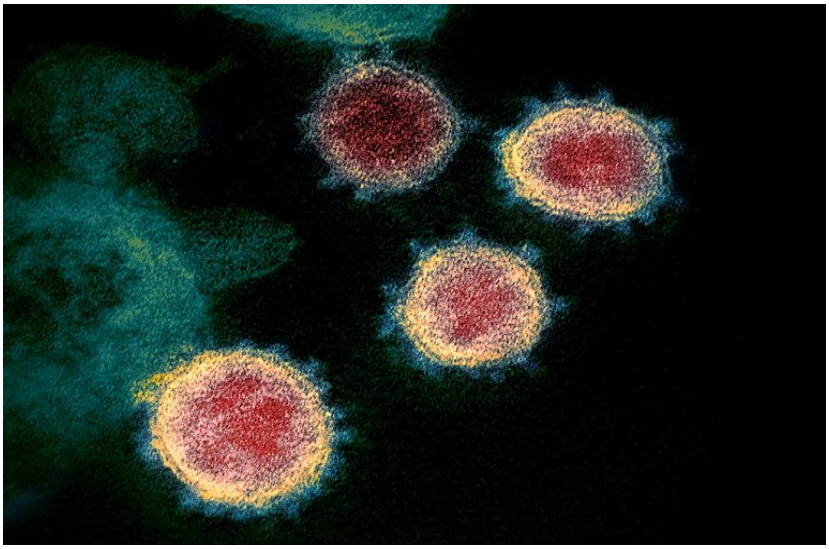


Fig. 1: Transmission electron micrograph of SARS-CoV-2 virions with visible coronae.[12]

During the initial outbreak in Wuhan, China, various names were used for the virus; some names used by different sources included the "corona-virus" or "Wuhan corona-virus". In January 2020, the World Health Organisation recommended ***"2019 novel corona-virus" (2019-nCov)*** as the provisional name for the virus. This was in accordance with WHO's 2015 guidance against using geographical locations, animal species, or groups of people in disease and virus names. On 11th February 2020, the international committee on taxonomy of viruses adopted the official name "severe acute respiratory syndrome corona-virus 2" (SARS-CoV-2). To avoid confusion with the disease SARS, the WHO sometimes refers to SARS-CoV-2 as "the COVID-19 virus" in public health communications and the name HCoV-19 was included in some research articles.

On December 31, 2019, China reported a cluster of cases of pneumonia in people associated with the Huanan seafood wholesale market in Wuhan, Hubei province. On January 7, 2020, Chinese health authorities confirmed that this cluster was associated with a novel corona-virus, 2019-nCoV. Although cases were originally reported to be associated with exposure to

the seafood market in Wuhan, current epidemiologic data indicate that person-to-person transmission of 2019-nCoV is continuous in occurance. As of January 30, 2020, a total of 9976 cases had been reported in at least 21 countries, including the first confirmed case of 2019-nCoV infection in the United States of America, reported on January 20, 2020. Investigations are under way worldwide to better understand transmission dynamics and the spectrum of clinical illness. This report describes the epidemiologic and clinical features of the first case of 2019-nCoV infection confirmed in the United States of America.[17]

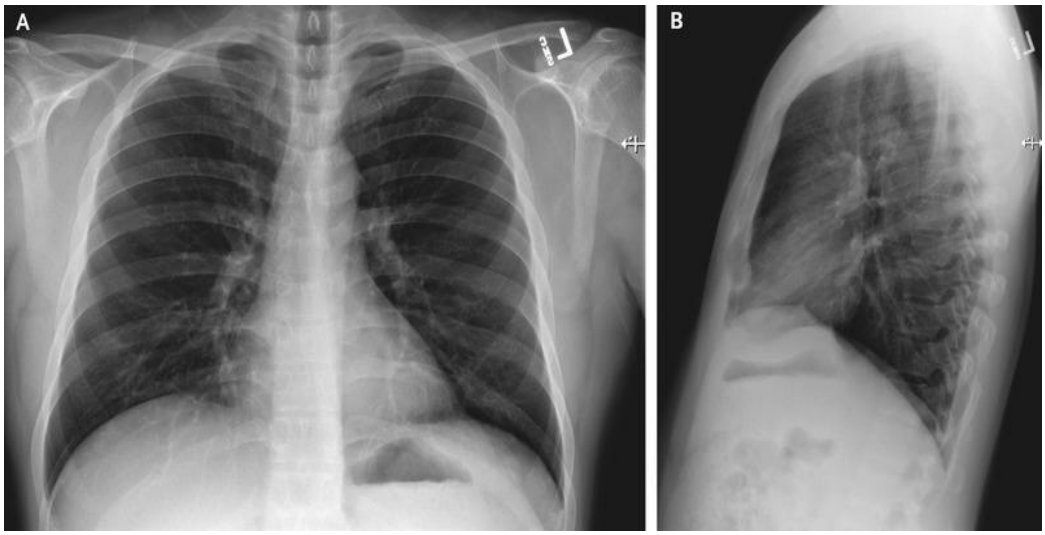
In the COVID-19 pandemic; Remdesivir was originally researched and developed by Gilead Sciences in 2009, to treat hepatitis C and respiratory syncytial virus (RSV) but it did not work against hepatitis C or RSV, but it was then repurposed and studied as a potential treatment for Ebola virus disease and Marburg virus infections. A collaboration of researchers from the Centers for Disease Control and Prevention (CDC) and Gilead Sciences subsequently discovered that Remdesivir had antiviral activity in-vitro against multiple filoviruses, pneumoviruses, paramyxoviruses, and coronaviruses. Preclinical and clinical research and development was done in collaboration between Gilead Sciences and various US government agencies and academic institutions. However; Remdesivir is a prodrug that is intended to allow intracellular delivery of GS-441524 monophosphate and subsequent biotransformation into GS-441524 triphosphate, a ribonucleotide analogue inhibitor of viral RNA polymerase. In November 2020, the World Health Organisation (WHO) updated its guideline on therapeutics for COVID-19 to include a conditional recommendation against the use of Remdesivir, triggered by results from the WHO Solidarity trial. The Solidarity trial for treatments is a multinational Phase III-IV clinical trial organised by the World Health Organisation (WHO) and partners to compare four untested treatments for hospitalised people with severe COVID-19 illness. The trial was announced on 18-March-2020, and as of 6-August-2021, 12,000 patients in 30 countries had been recruited to participate in the trial.[10] Researchers at university of Chicago reported promising results from a small study of Remdesivir in treating people with COVID-19. The study included 125 people with COVID-19, all of whom were treated with the Remdesivir, which is not currently approved in the U.S. for treating any disease. Of the 125 patients in the Chicago study, 113 had severe disease, meaning they had difficulty breathing. Kathleen Mullane, a professor of medicine at the university conducting the trial; stated in report that most of the patient improved their health during the treatment. [16]

Remdesivir, Lopinavir/Ritonavir combined, Lopinavir/Ritonavir combined with interferon-beta, and Hydroxychloroquine or Chloroquine are the treatments being studied. The investigation of Hydroxychloroquine, also known as Chloroquine, was discontinued in June 2020 after it was determined that it gave no benefit. Remdesivir has been able to advance into clinical studies so quickly for two key reasons. 1: It is used for Ebola. 2. Large preclinical evidences.[14] Remdesivir is the international nonproprietary name (INN); while the development code name was GS-5734.

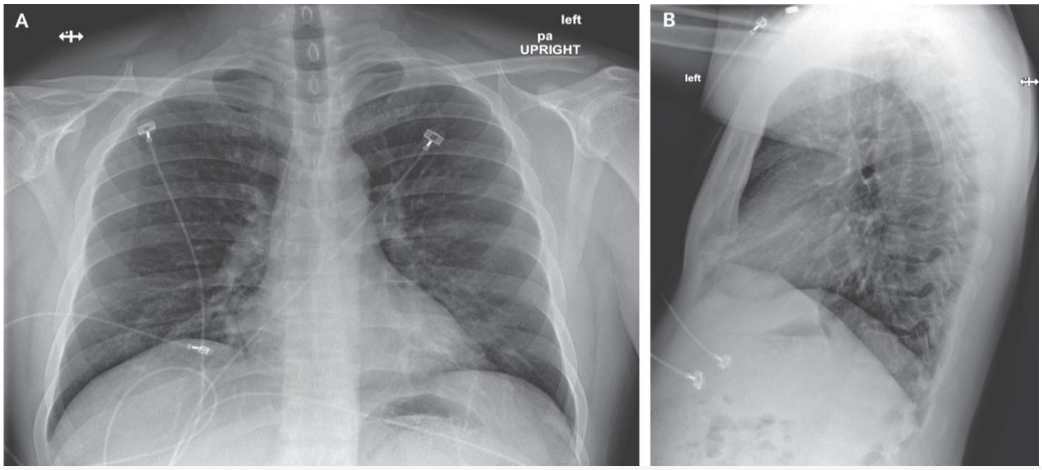
2. Case study

A rapid nucleic acid amplification test (NAAT) for influenza A and B was negative. A nasopharyngeal swab specimen was obtained and sent for detection of viral respiratory pathogens by NAAT; this was reported back within 48 hours as negative for all pathogens tested, including influenza A and B, parainfluenza, respiratory syncytial virus, rhinovirus, adenovirus, and four common corona-virus strains known to cause illness in humans (HKU1, NL63, 229E, and OC43).[17]

2.1 A chest radiograph taken on hospital day: l



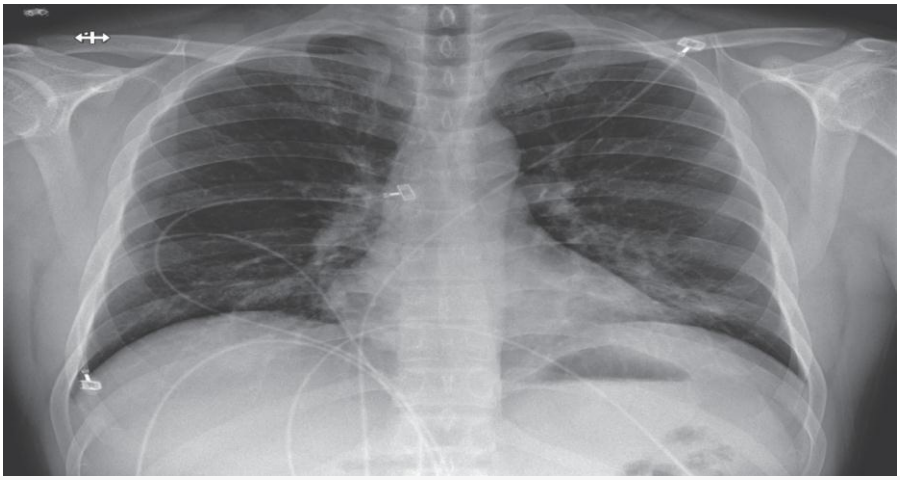
Posteroanterior and Lateral Chest Radiographs, January 19, 2020 (Illness Day 4). Nothoracic abnormalities were noted.



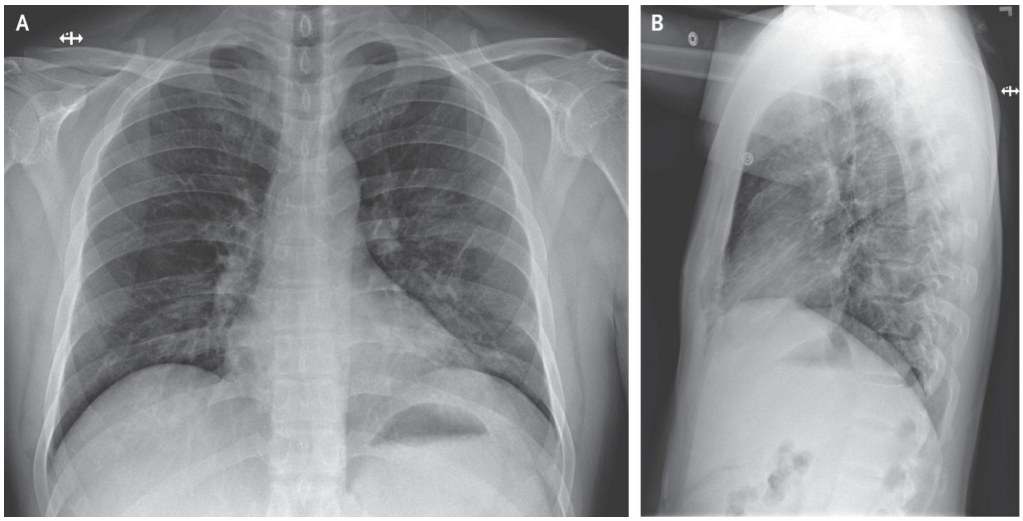
Posteroanterior and Lateral Chest Radiographs, January 22, 2020 (Illness Day 7, Hospital Day 3. No acute intrathoracic plain-film abnormality was noted.

Posteroanterior and Lateral Chest Radiographs, January 22, 2020 (Illness Day 7, Hospital Day No acute intrathoracic plain-film abnormality was noted.

Posteroanterior Chest Radiograph, January 24, 2020 (Illness Day 9, Hospital Day 5).



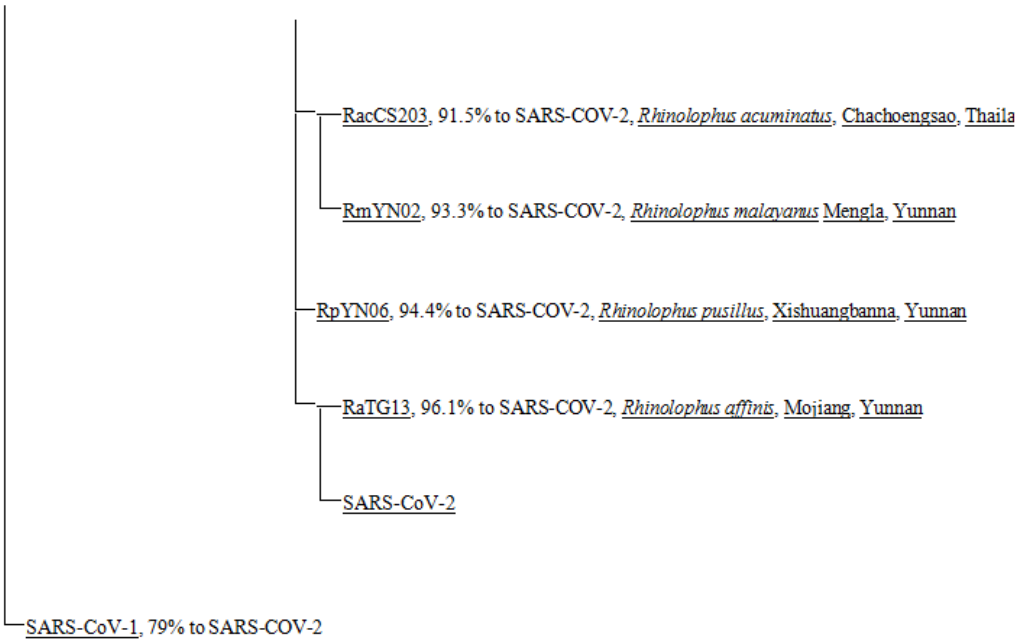
Increasing left basilar opacity was visible, arousing concern about pneumonia



Anteroposterior and Lateral Chest Radiographs, January 26, 2020 (Illness Day 10, Hospital Day 6). Stable streaky opacities in the lung bases were visible, indicating likely atypical pneumonia; the opacities have steadily increased in density over time.[17]

Fig. 2: A chest radiograph taken on hospital day taken from a X-patient with symptoms of COVID-19.(SARS-CoV-2).

3. **A phylogenetic tree based on whole-genome sequences of SARS-CoV-2 and related corona-viruses is:** [8]



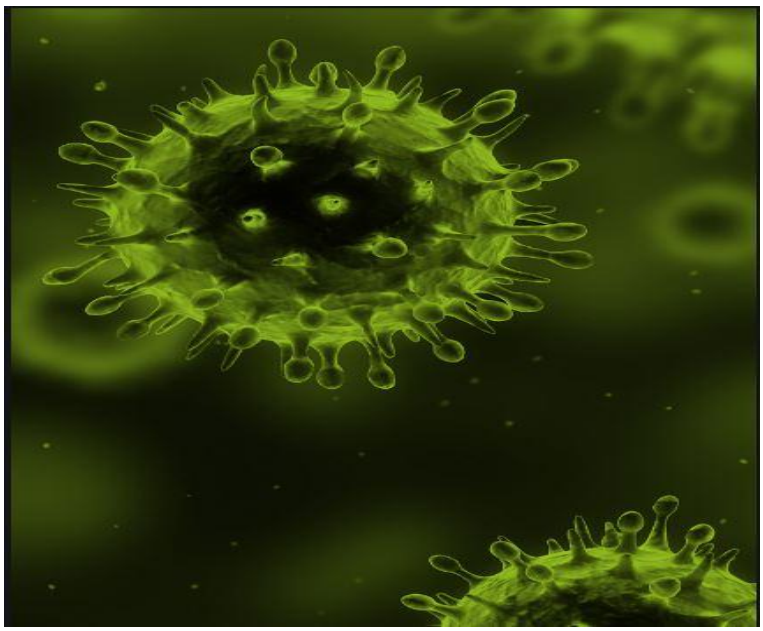


Fig. 3: COVID-19 (disease) SARS-CoV-2 (virus).

4. About emergency use authorisations (EUAs).[6]

The Emergency Use Authorisation (EUA) authority allows FDA to help strengthen the nation's a particular associated countries public health protections against chemical, biological, radiological, and nuclear (CBRN) threats including infectious diseases, by facilitating the availability and use of medical countermeasures (MCMs) needed during public health emergencies. Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), when the secretary of HHS declares that an emergency use authorisation is appropriate, FDA may authorise unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when certain criteria are met, including there are no adequate, approved, and available alternatives.

5. Preparation of brochure for remdesivier

The information in this document reflects emerging data, which is evolving and subject to reassessment.

I. **Requirements:** Quality Single Use Syringes with needle and without needle and single use hypodermic needles and suppliers of disposable gowns, disposable gloves, latex gloves, nitrile gloves, masks and all types of healthcare products.

II. **Remdesivir:** The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorisation (EUA) to permit the emergency use of VEKLURY for treatment of suspected or laboratory confirmed corona-virus disease 2019 (COVID-19), in hospitalised pediatric patients weighing 3.5 kg to less than 40 kg or hospitalised pediatric patients less than 12 years of age weighing at least 3.5 kg. VEKLURY has been authorised by FDA for the emergency uses described above. VEKLURY is not FDA-approved for these uses. VEKLURY is authorised only for the duration of the declaration that circumstances exist justifying the authorisation of the emergency use of VEKLURY under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorisation is terminated or revoked sooner.[5]

III. Product images[2,3,4,13]

Fig. 4: Product marketed Preparation and Information.

IV. Product description

VEKLURY (Remdesivier), contains Remdesivir, a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor. The chemical name for Remdesivir is 2-ethylbutyl *N*-{(*S*)-[2-*C*-(4-

aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2,5-anhydro-d-altrononitril-6-*O*-yl]phenoxyphosphoryl}-L-alaninate. It has a molecular formula of C27H35N6O8P and a molecular weight of 602.6 g/mol. Remdesivir has the following structural formula:

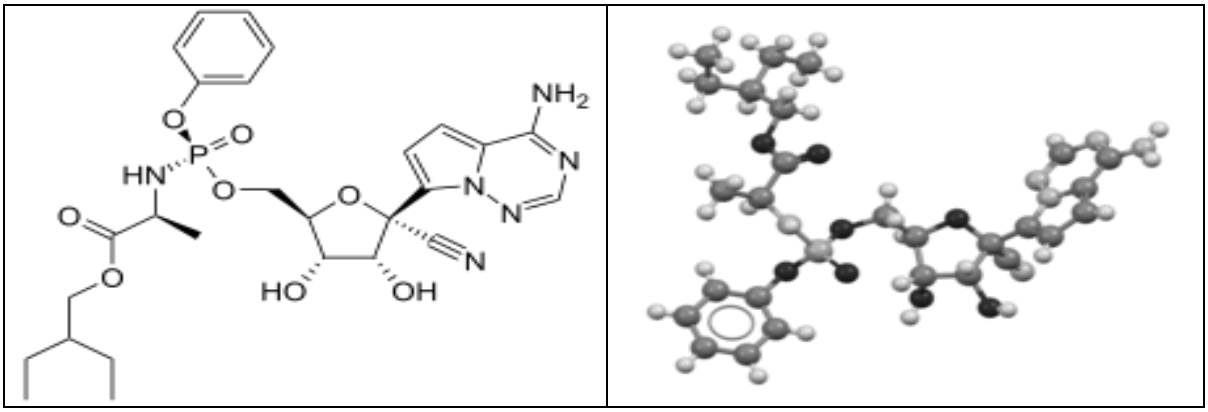


Fig. 5: Structural formula and information for remdesivier.

V. Chemical and physical data[7]

Formula: C27H35N6O8P

Molar mass: 602.585 g·mol^{-1}

Trade names: Veklury.

Other names: GS-5734.

VI. GS-441524

GS-441524 is a nucleoside analogue antiviral drug which was developed by Gilead Sciences. It is the main plasma metabolite of the antiviral prodrug Remdesivir, and has a half-life of around 24 hours in human patients. Remdesivir and GS-441524 were both tested against feline infectious peritonitis (FIP) in cell culture and found to be equivalent. Remdesivir was never tested in cats (though some vets now offer it) but GS-441524 has been found to be effective treatment for FIP, a lethal corona-virus disease which affects domestic cats and is widely used despite no official FDA approval due to Gilead's refusal to license this drug for veterinary use.

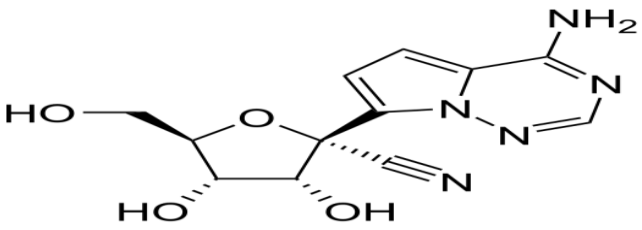


Fig. 6: Structure of GS-441524.

VII. Clinical trials[7]

One randomised, double-blind, placebo-controlled clinical trial (ACTT-1), conducted by the National Institute of Allergy and Infectious Diseases, evaluated how long it took for participants to recover from COVID-19 within 29 days of being treated. The trial looked at 1,062 hospitalised participants with mild, moderate and severe COVID-19 who received Remdesivir (n=541) or placebo (n=521), plus standard of care. Recovery was defined as either being discharged from the hospital or being hospitalised but not requiring supplemental oxygen and no longer requiring ongoing medical care. The median time to recovery from COVID-19 was 10 days for the Remdesivir group compared to 15 days for the placebo group, a statistically significant difference. Overall, the odds of clinical improvement at Day 15 were also statistically significantly higher in the Remdesivir group when compared to the placebo group.

A second randomised, open-label multi-center clinical trial of hospitalised adult participants with moderate COVID-19 compared treatment with Remdesivir for five days (n=191) and treatment with Remdesivir for 10 days (n=193) with the standard of care (n=200). Researchers evaluated the clinical status of participants on day 11. Overall, the odds of a subject's COVID-19 symptoms improving were statistically significantly higher in the five-day Remdesivir group at day 11 when compared to those receiving only standard of care. The odds of improvement with the 10-day treatment group when compared to those receiving only standard of care were numerically favorable, but not statistically significantly different.

A third separate, randomised, open-label multi-center clinical trial of hospitalised adult participants with severe COVID-19 compared treatment with Remdesivir for five days (n= 200) and treatment with Remdesivir for 10 days (n= 197). Researchers evaluated the clinical status of participants on day 14. Overall, the odds of a subject's COVID-19 symptoms improving were similar for those in the five-day Remdesivir group as those in the 10-day Remdesivir group, and there were no statistically significant differences in recovery rates or mortality rates between the two groups.

VIII. Authorised use

There is limited information/little known about the safety and efficacy of using Remdesivir to treat COVID-19. According to some research findings, Remdesivir may help some patients recover faster. VEKLURY is a drug approved in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of corona-virus disease 2019

(COVID-19) requiring hospitalisation. VEKLURY is not approved to treat pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg. VEKLURY is authorised for use under an EUA for treatment of hospitalised pediatric patients weighing 3.5 kg to less than 40 kg or hospitalised pediatric patients less than 12 years of age weighing at least 3.5 kg with suspected or laboratory confirmed corona-virus disease 2019 (COVID-19) for whom use of an intravenous (IV) agent is clinically appropriate.

IX. Contraindications

VEKLURY is not recommended in individuals who have had a history of clinically significant hypersensitivity responses to VEKLURY or any of its components.

X. Renal impairment

VEKLURY is not recommended in pediatric patients (greater than 28 days old) with eGFR less than 30 mL/min or in full-term neonates (at least 7 days to less than or equal to 28 days old) with serum creatinine greater than or equal to 1 mg/dL.

XI. Use in specific population

a. Pregnancy

b. Risk summary

Available data from published case reports and compassionate use of Remdesivir in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In nonclinical reproductive toxicity studies, Remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of Remdesivir (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose (RHD) (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognised pregnancies is 2 to 4% and 15 to 20%, respectively.

XII. Clinical considerations

Disease-associated maternal and/or embryo-fetal risk.

Pregnant women hospitalised with COVID-19 are at risk for serious morbidity and mortality.

a. Lactation

b. Risk summary

There are no available data on the presence of Remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, Remdesivir and metabolites have been detected in the nursing pups of mothers given Remdesivir, likely due to the presence of Remdesivir in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VEKLURY and any potential adverse effects on the breastfed child from VEKLURY or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

XIII. Overdose

There is no human experience of acute over-dosage with VEKLURY. Treatment of overdose with VEKLURY should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with VEKLURY.

XIV. Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details. Please refer to the ASHP Drug Shortages Resource Center for information on shortages of one or more of these preparations.

Healthcare providers should contact the manufacturer or the manufacturer's sole US distributor (AmerisourceBergen) at 800-746-6273 to obtain Remdesivir for use under the FDA-labeled indication or for use under the FDA Emergency Use Authorisation (EUA). The manufacturer has alerted healthcare providers that there are variations in Remdesivir packaging and labeling depending on whether the drug was originally manufactured for use under the EUA or for commercial use. (See General under Dosage and Administration.).

Table 1: Remdesivir.

Routes.	Dosage Forms.	Strengths.	Brand Names.	Manufacturer.
Parenteral.	Powder for injection, for IV infusion only.	100 mg.	Veklury.	Gilead.
	Concentrate for injection, for IV infusion only.	100 mg/20 mL (5 mg/mL).	Veklury.	Gilead.

XV. Compatibility[9]

For information on systemic interactions resulting from concomitant use:

Parenteral: Solution Compatibility: Compatible: 0.9% sodium chloride

XVI. Dose preparation

Prescribing information for complete dosage, preparation, and administration instructions.

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer intravenous medication immediately after preparation when possible. VEKLURY must be administered via intravenous infusion only. Do not administer by any other route. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Prior to dilution in a 0.9% sodium chloride infusion bag, reconstituted VEKLURY for injection should be a clear, colourless to yellow solution, free of visible particles. Discard the vial if the lyophilised powder or reconstituted solution is discoloured or contains particulate matter.

XVII. VEKLURY for injection, 100 mg

Reconstitute VEKLURY for injection lyophilised powder with 19 mL of Sterile Water for Injection and further dilute in 0.9% sodium chloride prior to administration.

Only use Sterile Water for Injection to reconstitute VEKLURY lyophilised powder.

After reconstitution, use vials immediately to prepare diluted solution.

Administer diluted VEKLURY as an intravenous infusion over 30 to 120 minutes.

Discard any remaining reconstituted VEKLURY lyophilised powder and diluted solution.

XVIII. Dosing: Dosage and Administration.

1. VEKLURY can be used at any time after onset of symptoms in hospitalised patients.
2. Pediatric patients (greater than 28 days old) must have an estimated glomerular filtration rate (eGFR) determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before starting VEKLURY and be monitored during treatment as clinically appropriate.
3. Perform hepatic laboratory testing in all patients before starting VEKLURY and during treatment as clinically appropriate.
4. Determine prothrombin time in all patients before starting VEKLURY and monitor during treatment as clinically appropriate.
5. The only authorised dosage form of VEKLURY for pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg is VEKLURY for injection (supplied as 100 mg lyophilised powder in vial).

Table 2: Recommended dosage Form and Dosage in pediatric patients.

Body weight	Recommended dosage form	Loading dose (on Day 1)	Maintenance dose (from Day 2)
3.5 kg to less than 40 kg	VEKLURY for injection, lyophilized powder Only	5 mg/kg	2.5 mg/kg
40 kg and higher		200 mg	100 mg

XIX. Prescribing limits

a. Pediatric patients

Corona-virus Disease 2019 (COVID-19): IV

Treatment duration up to 10 days.

XX. Adult patients

Corona-virus Disease 2019 (COVID-19): IV

Treatment duration up to 10 days.

XXI. Storage and Handling of reconstituted Vial and Diluted solution

After reconstitution, use VEKLURY for injection vial immediately to prepare diluted solution.

Store diluted VEKLURY solution for infusion for no more than 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) prior to administration.

XXII. Stability

a. Storage

b. Parenteral

Powder for Injection, for IV Infusion. Single-dose vials of lyophilised powder (100 mg): <30°C. Should appear as a white to off-white to yellow powder. Reconstituted vials: immediately dilute in 0.9% sodium chloride injection to provide the final solution for IV infusion. (See administration under Dosage and administration.).

Diluted solution: may be stored for up to 24 hours at 20–25°C or for up to 48 hours at 2–8°C after final dilution in IV infusion bag containing 0.9% sodium chloride. Perform dilution for IV infusion on the same day it is administered; whenever possible, administer immediately following dilution. Solution concentrate for injection, for IV infusion. Single-dose vials of solution concentrate (100 mg/20 mL [5 mg/mL]): Refrigerate (2–8°C). Should appear clear and colorless to yellow. After removal from refrigeration, sealed vials may be stored for up to 12 hours at room temperature immediately prior to dilution. Diluted solution: may be stored for up to 24 hours at 20–25°C or for up to 48 hours at 2–8°C after dilution in an IV infusion bag containing 0.9% sodium chloride. Perform dilution for IV infusion within the same day that it is administered; whenever possible, administer immediately following dilution.

XXIII. Warnings

There are limited clinical data available for VEKLURY in patients weighing 3.5 kg to less than 40 kg or patients less than 12 years of age weighing at least 3.5 kg. Serious and unexpected adverse events may occur that have not been previously reported with VEKLURY use.

XXIV. Hypersensitivity including Infusion-related and Anaphylactic reactions

The use of VEKLURY is contraindicated in patients with known hypersensitivity to VEKLURY or any components of the product *[see full EUA Prescribing Information, Contraindications (4), Warnings and Precautions (5.1)]*.

XXV. Increased risk of transaminase elevations

Transaminase elevations have been observed in healthy volunteers who received 200 mg of VEKLURY followed by 100 mg doses up to 10 days; the transaminase elevations were mild (Grade 1) to moderate (Grade 2) in severity and resolved upon discontinuation of VEKLURY. Transaminase elevations have also been reported in patients with COVID-19

who received VEKLURY because transaminase elevations have been reported as a clinical feature of COVID-19, and the incidence was similar in patients receiving placebo versus VEKLURY in clinical trials of VEKLURY, discerning the contribution of VEKLURY to transaminase elevations in patients with COVID-19 can be challenging *[see Full EUA Prescribing Information, Warnings and Precautions (5.2)]*.

Perform hepatic laboratory testing in all patients before starting VEKLURY and during treatment as clinically appropriate.

Consider discontinuing VEKLURY if ALT levels increase to greater than 10 times the upper limit of normal.

Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation.

XXVI. Instruction for healthcare providers

1. The parent/caregiver has the option to accept or refuse VEKLURY.
2. Information on serious adverse events:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalisation or prolongation of existing hospitalisation;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalisation, disability, or congenital anomaly.

XXVII. Administration instructions

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of VEKLURY with IV solutions and medications other than 0.9% sodium chloride injection, USP is not known.

Administer the diluted solution with the infusion rate described in **Table 2.**

Table 3: Recommended rate of infusion—diluted VEKLURY for injection lyophilised powder for pediatric patients weighing 3.5 kg to less than 40 kg.[5]

Infusion volume	Infusion time	Rate of infusion
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min
50 mL	30 min	1.67 mL/min
	60 min	0.83 mL/min
	120 min	0.42 mL/min
25 mL	30 min	0.83 mL/min
	60 min	0.42 mL/min
	120 min	0.21 mL/min
7 mL	30 min	0.23 mL/min
	60 min	0.12 mL/min
	120 min	0.06 mL/min

Table 4: Recommended dilution instructions using reconstituted VEKLURY for injection lyophilised powder in pediatric patients less than 12 years of Age and Weighing 40 kg and higher.[5]

Veklury dose	0.9% sodium chloride infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of reconstituted veklury for injection
Loading dose 200 mg (2 vials)	250 ml	40 ml	40 ml (2 □ 20 ml)
	100 ml	40 ml	40 ml (2 □ 20 ml)
Maintenance dose 100 mg (1 vial)	250 ml	20 ml	20 ml
	100 ml	20 ml	20 ml

Administer the diluted solution with the infusion rate described in **Table 4.**

Table 5: Recommended rate of infusion — Diluted VEKLURY for injection lyophilised powder in pediatric patients less than 12 years of age and weighing 40 kg and higher.[5]

Infusion 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
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min

Table 6: Summary of adverse reaction rates in adult subjects with mild, moderate, or severe COVID-19 in NIAID ACTT-1.[5]

Types of adverse reactions	Veklury N=532 n (%)	Placebo N=516 n (%)
Adverse reactions, Grades ≥3	41 (8%)	46 (9%)
Serious adverse reactions	2 (0.4%)	3 (0.6%)
Adverse reactions leading to treatment discontinuation	11 (2%)	15 (3%)

a. Seizure (n=1), infusion-related reaction (n=1).

b. Seizure (n=1), infusion-related reaction (n=1), transaminases increased (n=3), ALT increased and AST increased (n=1), GFR decreased (n=2), acute kidney injury (n=3).

6. Synthesis of remdesivier

6.1. Synthesis of remdesivir in structural formulae

Remdesivir can be synthesised in multiple steps from ribose derivatives. The figure to the right is one of the synthesis routes of Remdesivir invented by Chun and coauthors from Gilead Sciences. In this method, intermediate a is firstly prepared from L-alanine and phenyl phosphorodichloridate in presence of triethylamine and dichloromethane; triple benzyl-protected ribose is oxidised by dimethyl sulfoxide with acetic anhydride and give the lactone intermediate b; pyrrolo [2,1-f] [1,2,4] triazin-4-amine is brominated, and the amine group is protected by excess trimethylsilyl chloride. n-Butyllithium undergoes a halogen-lithium exchange reaction with the bromide at −78 °C (−108 °F) to yield the intermediate c. The intermediate b is then added to a solution containing intermediate c dropwise. After quenching the reaction in a weakly acidic aqueous solution, a mixture of 1:1 anomers was obtained. It was then reacted with an excess of trimethylsilyl cyanide in dichloromethane at −78 °C (−108 °F) for 10 minutes. Trimethylsilyl triflate was added and reacts for one additional hour, and the mixture was quenched in an aqueous sodium hydrogen carbonate. A nitrile intermediate was obtained. The protective group, benzyl, was then removed with boron trichloride in dichloromethane at −20 °C (−4 °F). The excess of boron trichloride was quenched in a mixture of potassium carbonate and methanol. A benzyl-free intermediate was obtained. The isomers were then separated via reversed-phase HPLC. The optically pure compound and intermediate a are reacted with trimethyl phosphate and methylimidazole to obtain a diastereomer mixture of Remdesivir. In the end, optically pure Remdesivir can be obtained through chiral resolution methods.

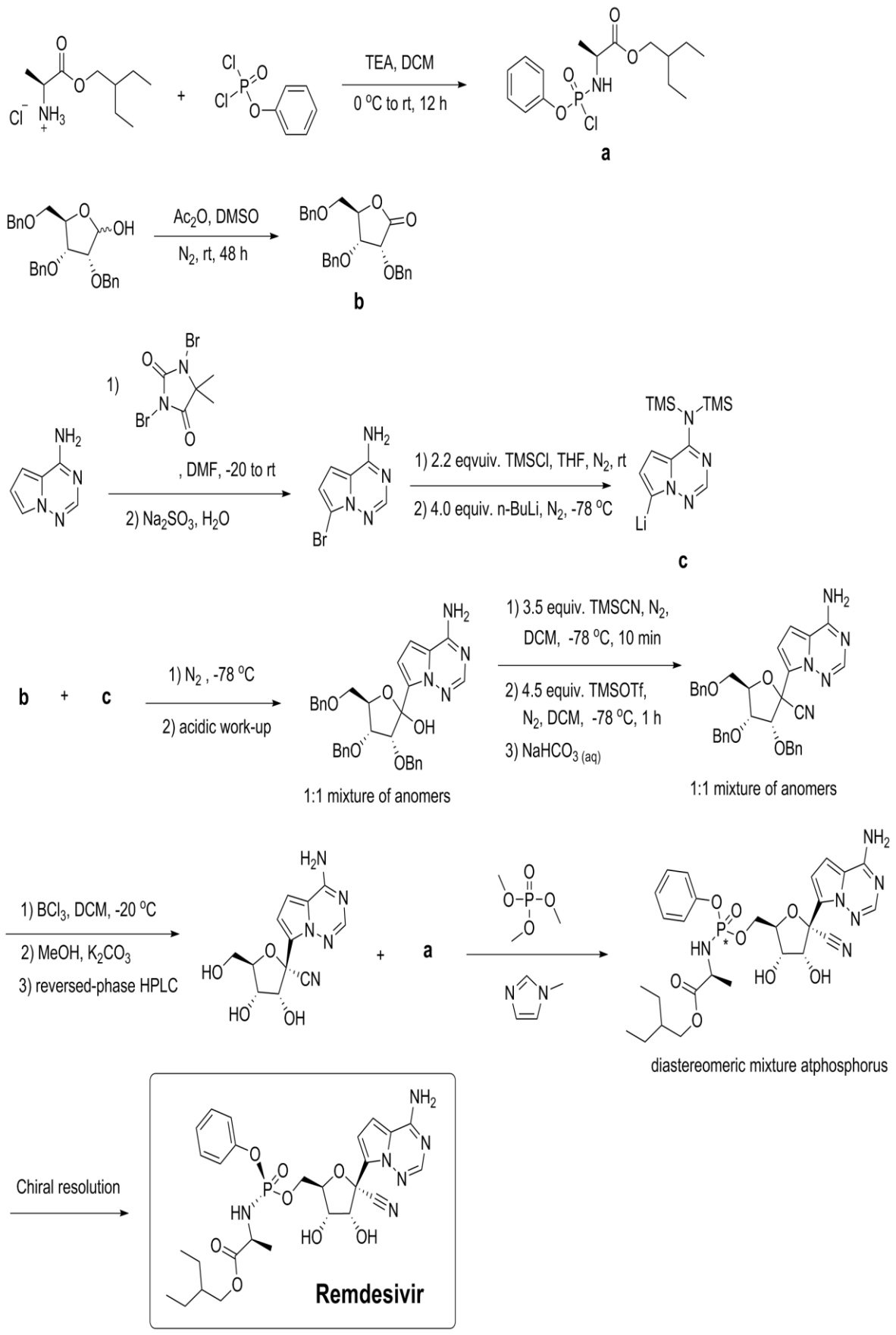


Fig. 7: Synthesis of remdesivier.

7. Clinical pharmacology

7.1. Mechanism of action

Remdesivir is an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication. Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolised to a nucleoside monophosphate intermediate by carboxyesterase 1 and/or cathepsin A, depending upon the cell type. The nucleoside monophosphate is subsequently phosphorylated by cellular kinases to form the pharmacologically active nucleoside triphosphate metabolite (GS-443902). Remdesivir triphosphate (RDV TP) acts as an analog of adenosine triphosphate (ATP) and competes with high selectivity (3.65-fold) over the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination (position i+3) during replication of the viral RNA. In a biochemical assay assessing RDV-TP incorporation by the MERS-CoV RdRp complex, RDV-TP inhibited RNA synthesis with an IC50 value of 0.032 μM. RDV-TP can also inhibit viral RNA synthesis following its incorporation into the template viral RNA as a result of read-through by the viral polymerase that may occur at higher nucleotide concentrations. When Remdesivir nucleotide is present in the viral RNA template, the efficiency of incorporation of the complementary natural nucleotide is compromised, thereby inhibiting viral RNA synthesis. Remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases, including human mitochondrial RNA polymerase.

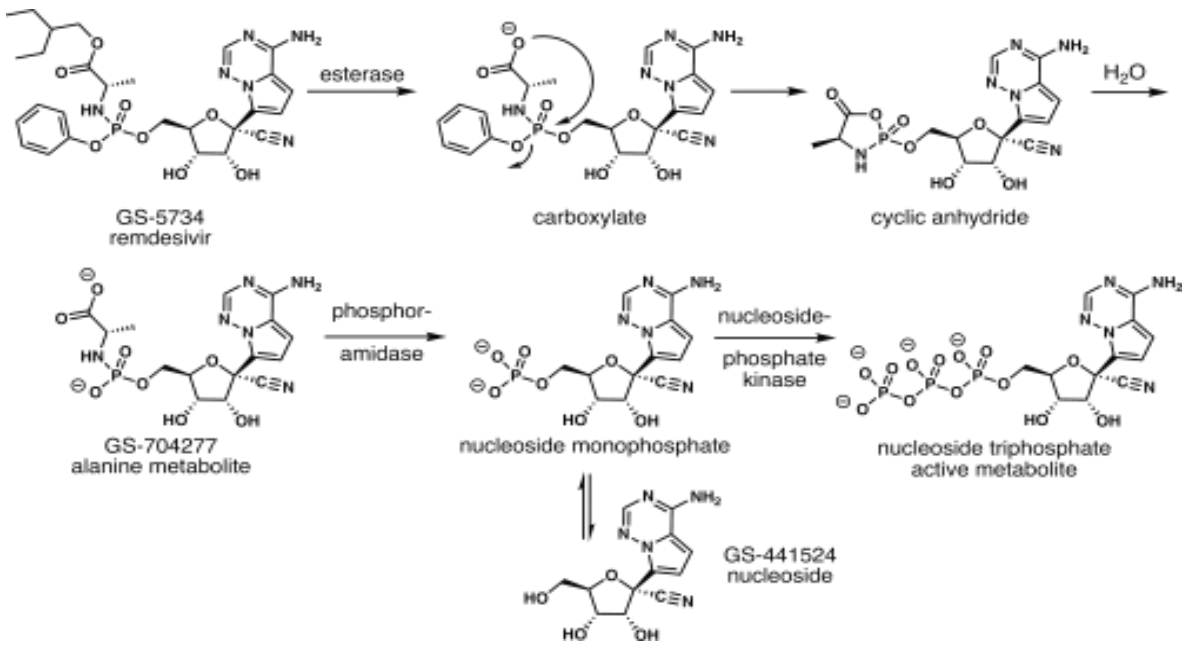


Fig. 8: Mechanism of action.

8. Interactions

Remdesivir is at least partially metabolised by the cytochrome P450 enzymes CYP2C8, CYP2D6, and CYP3A4. Blood plasma concentrations of remdesivir are expected to decrease if it is administered together with cytochrome P450 inducers such as Rifampicin, Carbamazepine, Phenobarbital, Phenytoin, Primidone, and St John's wort.

Using Chloroquine or Hydroxychloroquine with Remdesivir may reduce the antiviral activity of Remdesivir. Coadministration of Remdesivir and Chloroquine Phosphate or Hydroxychloroquine Sulfate is not recommended based on in vitro data demonstrating an antagonistic effect of Chloroquine on the intracellular metabolic activation and antiviral activity of Remdesivir.

9. Pharmacokinetics

The pharmacokinetic (PK) properties of Remdesivir and metabolites have been evaluated in adults in several phase 1 trials and are provided in Table 7. The multiple dose PK parameters of Remdesivir and metabolites in healthy adults are provided in **Table 8.**

Table 7: Pharmacokinetic properties of Remdesivir and Metabolites (GS-441524 and GS-704277) in adults.[5]

	Remdesivir	GS-441524	GS-704277
Absorption			
Tmax (h)	0.67-0.68	1.51-2.00	0.75-0.75
Distribution			
% bound to human plasma proteins	88-93.6	2	1
Blood-to-plasma ratio	0.68-1.0	1.19	0.56
Elimination			
t1/2 (h)	1	27	1.3
Metabolism			
Metabolic pathway(s)	CES1 (80%) Cathepsin A (10%) CYP3A (10%)	Not significantly metabolised	HINT1
Excretion			

ND=not detected

a) Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505); range of median observed on Day 1 and Day 5 or 10.

b) Range of protein binding for Remdesivir from 2 independent experiments show no evidence of concentration-dependent protein binding for Remdesivir.

c) Median (Study GS-US-399-4231).

d) Mean (Study GS-US-399-4231).

Table 8: Multiple dose PK parametersa of Remdesivir and Metabolites (GS-441524 and GS-704277) following IV administration of VEKLURY 100 mg to healthy adults.[5]

Parameter Mean (CV%)	Remdesivir	GS-441524	GS-704277
Cmax (Nanogram per mL)	2229 (19.2)	145 (19.3)	246 (33.9)
AUCtau (Nanogram•h permL)	1585 (16.6)	2229 (18.4)	462 (31.4)
Ctrough (Nanogram per mL)	ND	69.2 (18.2)	ND

CV=Coefficient of Variation; ND=Not detectable (at 24 hours post-dose)

a. Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505).

9.1. Remdesivir pharmacokinetics[9]

Absorption

a. Plasma concentrations

Pharmacokinetics of Remdesivir evaluated in healthy adults in several phase 1 trials.

Prodrug that is initially metabolised to GS-441524 (predominant circulating metabolite) and GS-704277 and is converted intracellularly to the active nucleoside triphosphate metabolite (GS-443902). (See elimination under pharmacokinetics.).

Following IV infusion over 30 minutes in healthy adults, peak plasma concentrations of Remdesivir are attained within 0.7 hours and peak plasma concentrations of GS-441524 and GS-704277 are attained within 1.5–2 and 0.75 hours, respectively.

Data from a single-dose pharmacokinetic study in healthy adults indicate that pharmacokinetics of the lyophilised powder and solution concentrate formulations of Remdesivir are comparable.

b. Distribution

c. Extent

High intracellular concentrations of the active triphosphate metabolite (GS-443902) reported in peripheral blood mononuclear cells (PBMCs) of healthy adults 24 hours after a single dose of Remdesivir given by IV infusion; these concentrations were up to 370-fold higher than the in vitro 50% effective concentration (EC50) of the drug reported for SARS-CoV-2.

d. Plasma protein binding

Remdesivir is 88–94% bound to plasma proteins; GS-441524 and GS-704277 are 2 and 1% bound to plasma proteins, respectively.

10. Animal toxicology and/or pharmacology

Intravenous administration (slow bolus) of Remdesivir to male rhesus monkeys at dosage levels of 5, 10, and 20 mg/kg/day for 7 days resulted, at all dose levels, in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts. Intravenous administration (slow bolus) of Remdesivir to rats at dosage levels of ≥3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction.

Kidney-related effects in rats and monkeys were observed at exposures of the predominant circulating metabolite (GS-441524) that are lower than the exposure in humans at the RHD.

11. Remdesivier drugs intereactions[9]

Interactions for remdesivir

In vitro, Remdesivir is a substrate of CYP3A4, P-glycoprotein (P-gp), and organic anion transporting polypeptide 1B1 (OATP1B1); the predominant circulating metabolite (GS-441524) is a substrate for OATP1B1 and OATP1B3. Remdesivir inhibits CYP3A4, OATP1B1, OATP1B3, and multidrug and toxin extrusion transporter (MATE) 1 in vitro. Clinical relevance of in vitro interaction assessments not established. Drug-drug interaction trials of Remdesivir and concomitant medications not conducted in humans.

12. Specific drugs[9]

Table 9: Specific drugs.

Drug	Interaction	Comments
Chloroquine and Hydroxychloroquine.	In vitro evidence that antiviral activity of Remdesivir is antagonised by Chloroquine and Hydroxychloroquine in dose-dependent manner; in vitro evidence that increasing concentrations reduce formation of active Remdesivir metabolite (GS-443902).	Concomitant use not recommended.
Dexamethasone.	Minimal or no reduction in Remdesivir exposure expected.	
Influenza antivirals (Baloxavir, Oseltamivir).	Clinically important interactions not expected.	

13. Elimination

13.1. Metabolism

Metabolised (10%) by CYP3A4.

13.2. Metabolised intracellularly to a nucleoside monophosphate intermediate (GS-704277) by

Carboxyesterase 1 and/or cathepsin A, depending on the cell type. The nucleoside monophosphate is subsequently phosphorylated by cellular kinases to form the pharmacologically active nucleoside triphosphate metabolite (GS-443902).

13.3. Elimination route

Data from healthy adults indicate that 10% of a Remdesivir dose eliminated in urine as unchanged drug and 49 and 2.9% of the dose eliminated in urine as GS-441524 and GS-704277, respectively.

13.4. Half-life

In healthy adults, Remdesivir has a plasma half-life of 1 hour and GS-441524 and GS-704277 have plasma half-lives of 27 and 1.3 hours, respectively.

GS-441524 has an intracellular half-life in PBMCs of >35 hours; median half-life of pharmacologically active metabolite (GS-443902) in PBMCs reported to be 36–49 hours.

14. Abbreviations

1. **(ECMO):** Extracorporeal membrane oxygenation.	2. **(eGFR):** Estimated glomerular filtration rate.
3. **(CPAP):** Continuous positive airway pressure.	4. **(HFNO):** High flow nasal oxygenation.
5. **(RSV):** Respiratory syncytial virus.	6. **(CDC):** Centers for disease control and prevention.
7. **(NIAID):** National institute of allergy and infectious diseases.	8. **(ACTT):** Adaptive COVID-19 treatment trial.
9. **(PHEIC):** Public health emergency of international concern.	10. **(ARI):** Acute respiratory infection.
11. **(ARDS):** Acute respiratory distress syndrome.	12. **(LRIs):** Lower respiratory tract infections.
13. (URIs): Upper respiratory tract infections.	14. (RBD): Receptor binding domain.

15. Other information on remdesivier drug[1]

Doctors and pharmacy officials have identified irrational drug use. Therefore, pharmacy officials and doctors have raised the concerns about irrational medication usage. Doctors who have been attending and monitoring thousands of critical COVID-19 patients at 'Gandhi Hospital,' on the other hand, have warned of the dangers of irrational usage of the Remdesivir and other anti-viral drugs.

16. Less common adverse reactions[1]

a. Hypersensitivity reactions.
b. Generalised seizure.
c. Rash.

16.1. Problems and Concerns[1]

Mr. Raja Rao, superintendent of Gandhi hospital, which has been reopened as an exclusive COVID-19 care centre; stated that Remdesivir should only be given to moderate and severe COVID-19 patients in the first week, along with convalescent plasma. According to a senior doctor who has been treating corona-virus cases in the Gandhi hospital said that, it should not be given to asymptomatic or mildly symptomatic patients. “Anti-viral drugs are useful when the virus is in the blood,” stated during a press conference at the State Health Campus in Koti.

17. Advice to patients

Advise patients to read the manufacturer's patient information.

Inform patients or parents/caregivers that hypersensitivity reactions have been reported during and after Remdesivir administration. Importance of informing clinicians if signs and symptoms of hypersensitivity (changes in heart rate, fever, shortness of breath, wheezing, rash, nausea, sweating, shivering, or swelling of the lips, face, or throat) occur.

Inform patients or parents/caregivers that Remdesivir may increase the risk of hepatic laboratory abnormalities. Importance of immediately informing clinicians if symptoms of liver inflammation occur.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs and herbal supplements. Importance of informing clinicians if currently taking Chloroquine or Hydroxychloroquine.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed. Inform patients that it is not known whether Remdesivir can cause fetal harm or whether the drug is distributed into milk.

When Remdesivir is used under the EUA in pediatric patients weighing 3.5 to <40 kg or <12 years of age weighing ≥3.5 kg†, the fact sheet for parents and care-givers that is provided with the drug and available at the FDA website ([Web]) must be given to the parent/caregiver prior to administration of the drug. In addition, inform the parent/caregiver (and patient if age-appropriate) that they have the option to accept or refuse Remdesivir, inform them about the important known and potential risks and benefits of Remdesivir and the extent to which risks and benefits are unknown, and provide information on available alternative treatments and the risks and benefits of those alternatives. If providing this information will delay administration of Remdesivir to a degree that would endanger the life of the patient, the information must be provided to the parent/caregiver as soon as feasible after Remdesivir is administered.

18. Clinical significance

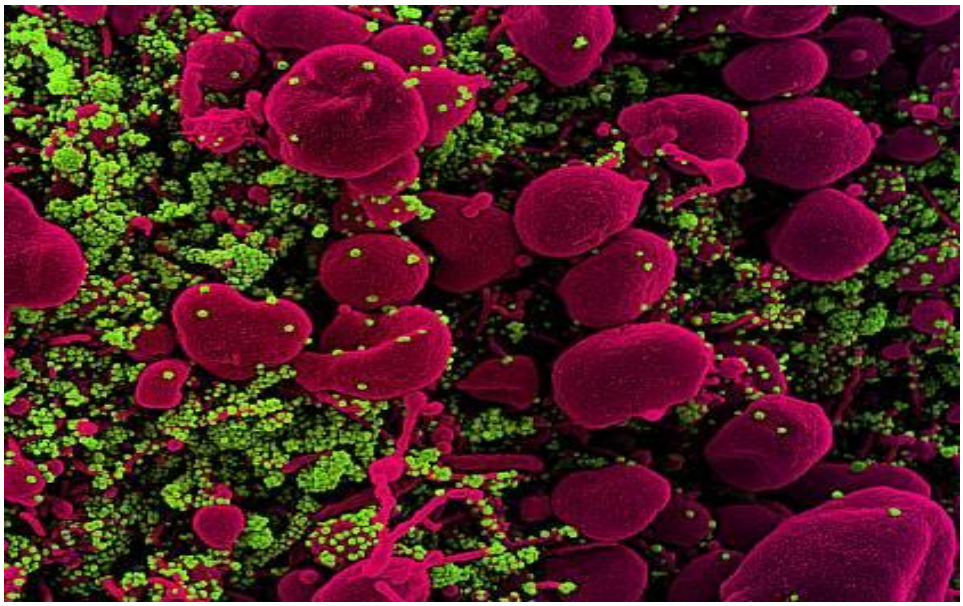


Fig. 9: Colourised scanning electron micrograph of a cell (pink), isolated from a patient sample, that's heavily infected with SARS-COV-2 virus particles (green).

Niaid[15]

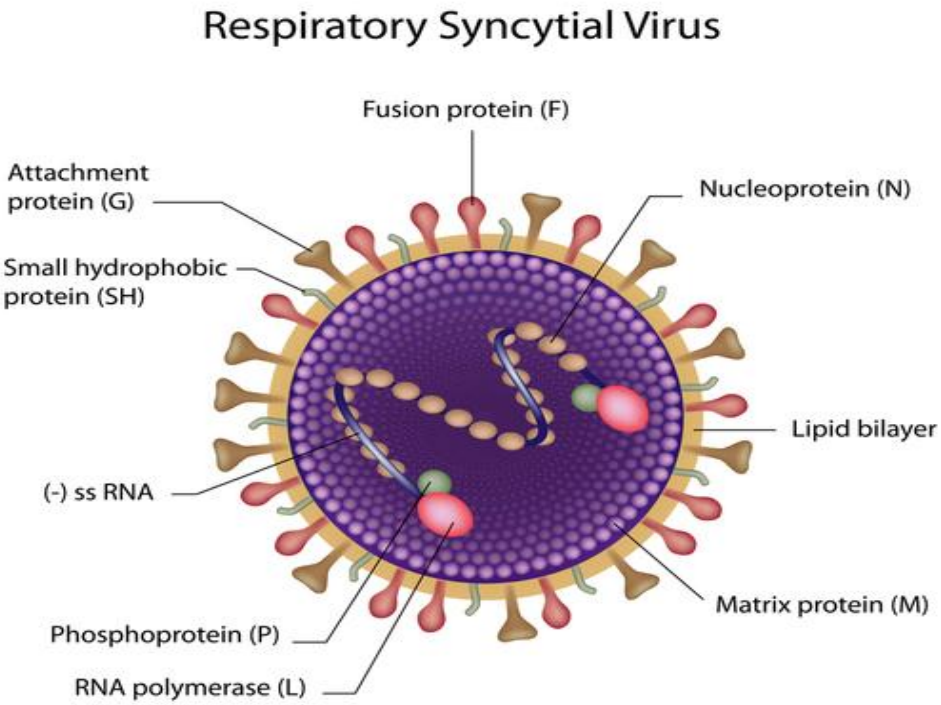


Fig. 10: Respiratory syncytial virus.

19. Authorisations and Deployment of medication for COVID-19

Remdesivir is approved or authorised for emergency use to treat COVID‑19 in around 50 countries. Remdesivir has been authorised for emergency use in the India, Singapore, and approved for use in Japan, the European Union, the United States of America, and Australia for people with severe symptoms. In February 2021, the Committee for medicinal products for human use (CHMP) of the European Medicines Agency (EMA) started an evaluation to decide if the indication for Remdesivir should be modified to include those not requiring supplemental oxygen. Remdesivir is the first treatment for COVID‑19 to be approved by the U.S. Food and Drug Administration (FDA). The approval by the FDA does not include the entire population that had been authorised to use Remdesivir under an Emergency Use Authorisation (EUA) originally issued on 1-May-2020. In order to ensure continued access to the pediatric population previously covered under the EUA, the FDA revised the EUA for Remdesivir to authorise the drug's use for treatment of suspected or laboratory-confirmed COVID-19 in hospitalised pediatric patients weighing 3.5 kilograms (7.7 lb) to less than 40 kilograms (88 lb) or hospitalised pediatric patients less than twelve years of age weighing at least 3.5 kilograms (7.7 lb). Clinical trials assessing the safety and efficacy of Remdesivir in this pediatric patient population are ongoing.

I. Australia

In July 2020, Remdesivir was provisionally approved for use in Australia for use in adults and adolescents with severe COVID-19 symptoms who have been hospitalised. Australia claims to have a sufficient supply of Remdesivir in its national stockpile.

II. Canada

As of 11-April-2020, access in Canada was available only through clinical trials. Health Canada approved requests to treat twelve people with Remdesivir under the department's special-access program (SAP). Additional doses of Remdesivir are not available through the SAP except for pregnant women or children with confirmed COVID‑19 and severe illness.

On June-19-2020, Health Canada received an application from Gilead for the use of Remdesivir for treating COVID‑19. On July-27-2020, Health Canada conditionally approved the application.

On September-22-2020, minister of public services and procurement, announced that Canada had entered into a deal to obtain up to 150,000 vials of Remdesivir from Gilead starting in October. As of 8 October, Remdesivir was still not widely available in Alberta, because Alberta Health Services was undertaking a "formulary review" to be completed by mid-November.

III. Czech republic

On 17-March-2020, the drug was provisionally approved for use for COVID-19 patients in a serious condition as a result of the outbreak in the Czech Republic.

IV. European union

On 17-February-2016, orphan designation (EU/3/16/1615) was granted by the European Commission to Gilead Sciences International Ltd, United Kingdom, for Remdesivir for the treatment of Ebola virus disease.

In April, 2020, the European Medicines Agency (EMA) provided recommendations on compassionate use of Remdesivir for COVID‑19 in the EU.

On 11-May-2020, the Committee for Medicinal Products for Human Use (CHMP) of the EMA recommended expanding the compassionate use of Remdesivir to those not on

mechanical ventilation. In addition to those undergoing invasive mechanical ventilation, the compassionate use recommendations cover the treatment of hospitalised individuals requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices or ECMO (extracorporeal membrane oxygenation). The updated recommendations were based on preliminary results from the NIAID-ACTT study, which suggested a beneficial effect of Remdesivir in the treatment of hospitalised individuals with severe COVID‑19. In addition, a treatment duration of five days was introduced alongside the longer ten-day course, based on preliminary results from another study (GS-US-540-5773) suggesting that for those not requiring mechanical ventilation or ECMO, the treatment course may be shortened from ten to five days without any loss of efficacy. Individuals who receive a five-day treatment course but do not show clinical improvement will be eligible to continue receiving Remdesivir for an additional five days.

On 3-July-2020, the European Union granted a conditional marketing authorisation for Remdesivir with an indication for the treatment of corona-virus disease 2019 (COVID‑19) in adults and adolescents (aged twelve years and older with body weight at least 40 kilograms [88 lb]) with pneumonia requiring supplemental oxygen. At the end of July, the European Union secured a €63 million (US$74 million) contract with Gilead, to make the drug available there in early August 2020.

On 8-October-2020, Gilead Sciences and the European Commission announced they had signed a joint procurement framework contract in which Gilead agreed to provide up to 500,000 Remdesivir treatment courses over the next six months to 37 European countries. Among the contracting countries were all 27 EU member states plus the United Kingdom, "Albania, Bosnia & Herzegovina, Iceland, Kosovo, Montenegro, North Macedonia, Norway, and Serbia". At the time, the price per treatment course was not disclosed; on 13 October, Reuters reported the price was 2,070 Euros, thereby implying the total value of the contract (if all 500,000 courses are ordered) is approximately €1.035 billion. Under the new contract, each participating country will directly place orders with Gilead and pay Gilead directly for its own orders.

V. India

India approves emergency use of Remdesivir to treat Covid-19 patients. The Indian government approved Gilead Sciences Inc's antiviral drug Remdesivir for emergency use in

treating Covid-19 patients. Remdesivir is the first drug to show improvement in Covid-19 patients in formal clinical trials. It was granted emergency use authorisation by the U.S. Food and Drug Administration and had also received approval by Japanese health regulators. Remdesivir was approved on June-1-2020, under emergency use with condition for five dose administration, the drugs controller general of the India stated in an e-mail statement.[11]

VI. Iran

Remdesivir has been also produced in Iran by Barakat; Iran is planning to increase the productions of Remdesivir ampoules from 20,000 to 150,000 ampoules per month. It has also the permission of the "Food and Drug Administration" of MOHME.[9]

VII. Japan

On 7-May-2020, Japan's Ministry of Health, Labour and Welfare approved the drug for use in Japan, in a fast-tracked process, based on the U.S. emergency authorisation.

VIII. Mexico

On 23-October-2020, Deputy Secretary of Prevention and Health Promotion Hugo López-Gatell Ramírez stated at a news conference that Mexico would not necessarily follow the United States in approving the drug for use in Mexico. López-Gatell explained that Cofepris had already twice denied the approval of Remdesivir because, in that agency's view, the evidence does not suggest "sufficient efficacy". On 12-March-2020, Cofepris authorised the drug for emergency cases, advising to give continuous surveillance of the integral health of the patient.

IX. United states of america

On March-20-2020, United States President: sir, Donald Trump announced that Remdesivir was available for "compassionate use" for people with COVID‑19; FDA commissioner Stephen Hahn confirmed the statement at the same press conference. It was later revealed that Gilead had been providing Remdesivir in response to compassionate use requests since 25-January. On March-23-2020, Gilead voluntarily suspended access for compassionate use (excepting cases of critically ill children and pregnant women), for reasons related to supply, citing the need to continue to provide the agent for testing in clinical trials.

On May-1-2020, the U.S. Food and Drug Administration granted Gilead emergency use authorisation (EUA) for Remdesivir to be distributed and used by licensed health care

providers to treat adults and children hospitalised with severe COVID-19. Severe COVID-19 is defined as patients with an oxygen saturation (SpO2) <= 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO), a heart–lung bypass machine. Distribution of Remdesivir under the EUA will be controlled by the U.S. government for use consistent with the terms and conditions of the EUA.

X. Compassionate use of remdesivier

Estonia, Greece, The Netherlands and Romania on 25 and 26 March, 2020 requested from the agency (EMA) a CHMP opinion on the compassionate use of Remdesivier medicinal product in accordance with Article 83 (3) of Regulation (EC) No. 726/2004.[19]

20. Other information

20.1. SARS-CoV-2 variants

A. Delta Variant and Other related variants of SARS-CoV-2

Specific strains of the SARS-CoV-2 virus known as B.1.617.2 that is spreading quickly across the globe in mid-2021. (31-July-2021) δ variant; also known as 20A/S:478K was first detected in India in the late 2020. Carries a number of spike protein mutation including L452R; less suseptable to nutralisation by monoclonal antibodies. United Kingdom (U.K.) reported variant: B.1.1.7 (Alpha); α variant. B.1.1.7: Alpha variant, this SARS-CoV-2 variant – also known as 201/501Y.V1, variant of concern [VOC], 202012/01 – emerged in the U.K. during September 2020. This variant also has a mutation in the receptor binding domain (RBD). Of the spike protein at position 501, where the amino acid asparagine (N) has been replaced with tyrosine (Y). The shorthand for this mutation is N501Y. This variant also has several other mutations including a 69/70 deletion and mutation in the P681H region. Variant is associated with increased transmissibility (i.e., more efficient and rapid transmission). South Africa variant-B.1.351 (Beta); β variant; a SARS-CoV-2 variant -also known as 20H/501Y.V2 shares some mutations with B.1.1.7 but emerged independently in October 2020 in the South Africa. Variant has multiple mutations in the spike protein, including K417N, E484K, N501Y. Unlike the B.1.1.7, lineage detected in the U.K. mRNA vaccine (Pfizer and moderna) has been shown to induce significant neutralising antibodies against B.1.351, but the clinical significance on its effectiveness is yet to be determined. Brazil variant-P.1 (Gamma) γ variant was first identified in four travelers from Brazil, who were

tested during routine screening at Haneda airport outside Tokyo, Japan. This variant has 17 unique mutations, including three in the receptor binding domain of the spike protein.

21. CONCLUSION

Through the entire study it can be concluded that the Remdesiver is beneficial for the purpose of treatment and mitigation from infection caused by: COVID-19. Previous lab studies showed that Remdesivir had stronger antiviral activity against corona-viruses like SARS and MERS than it did against Ebola, so when COVID-19, which is also caused by a corona-virus, emerged, scientists who were aware of the lab data had used the drug to treat the new disease condition on a short trial period. The effectiveness of the Remdesivier for the treatment of the COVID-19 condition caused in the humans can be cured as per the obtained study results which explained its therapeutic usage in treating COVID-19. Remdesivier can be effectively synthesised using the different laboratory techniques. The dosing and therapeutic effective dose have been well distinct and studied. The obtained study explains the safety, use and treatment effectiveness of the Remdesivier as an antiviral against SARS-CoV-2 virus. There are no therapeutic equivalent of Remdesivier in the market and Giled is the first manufacturing company of Remdesiveir for the treatment of the COVID-19 caused by SARS-CoV-2.

22. ACKNOWLEDGEMENT

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