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TO DOCUMENT SAFETY ASPECTS OF REMDESIVIR AND BARICITINIB IN COVID-19 AFFECTED POPULATION

***Sara Shireen, Mirza Misbah Baig, Madiha Maryam, Umaima Faizeen, Humera Farheen and Simrah Mujahed**

Assistant Professor, Dep. of Pharmacy Practice, Deccan School of Pharmacy, Telangana, India.

***Corresponding Author: Sara Shireen**
Assistant Professor, Dep. of Pharmacy Practice, Deccan School of Pharmacy, Telangana, India.

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ABSTRACT
Today, the entire world has come to a standstill, grappling with a common enemy. The novel coronavirus pandemic has undoubtedly proven to be a tougher challenge leading to millions of cases and a staggering number of deaths. Remdesivir is an FDA-approved (and sold under the brand name Veklury) intravenous antiviral drug for use in adult and pediatric patients. Baricitinib is a janus kinase inhibitor, which blocks the activity of one or more of a specific family of enzymes, interfering with the pathway that leads to inflammation. According to the study conducted, it was found that when Remdesivir was given alone in the patient suffering from COVID-19 the mean recovery time was 11.3% and mortality rate was 7.1% Remdesivir significantly reduces the mortality and shows more safety, efficacy and reduced serious adverse effects by absolute 6% and no significant Grade 3 or 4 adverse effects were reported. When Remdesivir was given in combination with Baricitinib was superior to remdesivir alone in reducing recovery time (12.5%) and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or non-invasive ventilation. The mortality rate for baricitinib in combination with remdesivir vs. 7.1% for remdesivir, a relative reduction of 35%. Adverse events and serious adverse events were reported in 41% and 15% of patients treated with baricitinib in combination with remdesivir, respectively, vs. 48% and 20% in patients treated with remdesivir.

KEYWORDS: COVID-19, Remdesivir, Baricitinib.

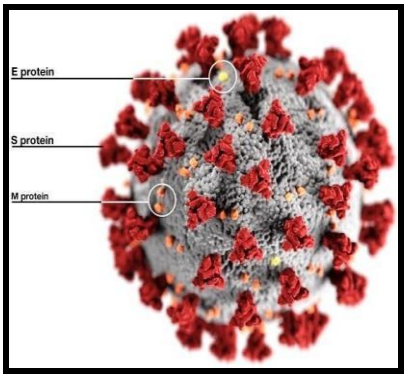
1. INTRODUCTION

BACKGROUND[1]

Today, the entire world has come to a standstill, grappling with a common enemy. Although we have had numerous outbreaks of diseases in the past, including Ebola, cholera, Middle East respiratory syndrome (MERS), the novel coronavirus pandemic has undoubtedly proven to be a tougher challenge leading to millions of cases and a staggering number of deaths. An outbreak that was presumably first detected in a province in China in late December has found its way into almost every part of the world, leading to a global health crisis. Having a better understanding of the virus through various studies will give us an opportunity to hopefully mitigate the severity of this crisis.

SARS-CoV-2 is a single-stranded, positive-sense, enveloped RNA virus whose genome encodes a number of structural proteins, non-structural proteins, and accessory proteins. The nonstructural proteins [3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), helicase, and RNA-dependent RNA polymerase (RdRp)] and the structural protein (spike protein) play an important role in viral pathogenesis and hence they are being recognized as potential targets for drug therapy

Laboratory findings include lymphocytopenia in 83.2% of patients, thrombocytopenia in 36.2%, and leukopenia in 33.7% people



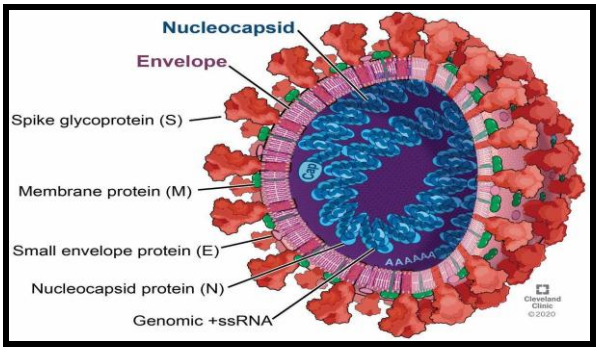


Figure 01: Structure of Coronavirus.

Viral Classification[2]
REALM: Ribovirus
KINGDOM: Orthovirae
PHYLUM: Pisu Ricota
ORDER:Nidovirales
FAMILY: Coronaviridae
SUBFAMILY: Ortho Corona Virinae

Genera
- Alphacoronavirus.
- Betacoronavirus.
- Gammacoronavirus.
- Delta Coronavirus.

Synonym: Coronaviridae.

Classification[2]

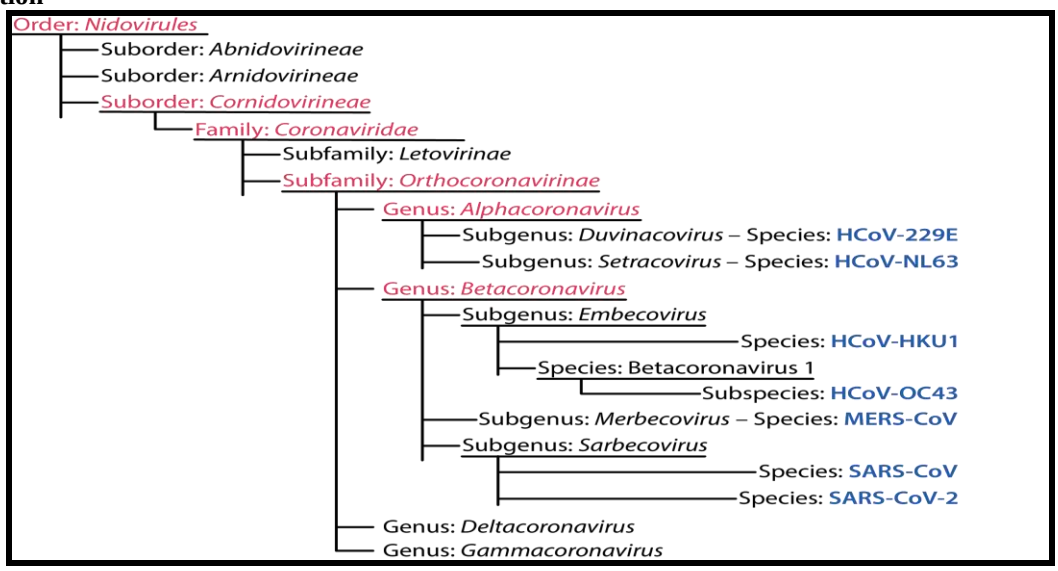


Figure 2: Classification of Coronavirus.

In a clinical trial of hospitalized patients with COVID-19, baricitinib, in combination with remdesivir, was shown to reduce time to recovery within 29 days after initiating treatment compared to patients who received a placebo with ramdev sivir. The safety and effectiveness of this investigational therapy for use in the treatment of COVID-19 continues to be evaluated. Baricitinib is not authorized or approved as a stand-alone treatment for COVID-19.

Remdesivir is an FDA-approved (and sold under the brand name Veklury) intravenous antiviral drug for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization. Remdesivir also remains authorized for emergency use for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg (about 7.7 pounds) to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.[3]

Baricitinib is a janus kinase inhibitor, which blocks the activity of one or more of a specific family of enzymes, interfering with the pathway that leads to inflammation. Baricitinib is a prescription oral tablet medication that is FDA-approved (and sold under the brand name Olumiant) for the treatment of moderately to severely active rheumatoid arthritis. Under today's EUA, the FDA is authorizing the emergency use of baricitinib, in combination with remdesivir, for the treatment of certain hospitalized patients with suspected or laboratory-confirmed COVID-19.[4]

1.2. Remdesivir

1.2..1 General Information[5]

- Remdesivir [chemical name: 2-ethylbutyl N-{(S)-[2-C(4-aminopyrrole[2, 1-f][1,2,4]triazin-7-yl)-2-5-anhydro-d-altrononitril-6-O-yl]phenoxyphosphoryl}-l-alaninate] is a low-molecular-weight (602.6 g/mol) prodrug with the molecular formula C27H35N6O8P Remdesivir is administered by intrave-nous (IV) infusion.

- Remdesivir was developed for IV administration because of poor hepatic stability (extensive first-pass extraction).

Principle Behind Use

RDV has been shown to have activity against varying coronaviruses in the airway epithelial cells in humans. Preliminary results of the Adaptive COVID-19 Treatment Trial (ACTT-1) suggest that a 10-day course of RDV was more effective than a placebo in the treatment of hospitalized patients with COVID-19. The benefit was seen in terms of shortened recovery time (11 days versus 15 days).

Preclinical Pharmacology and Toxicology

Preclinical Trial

- In animal studies, remdesivir has been found effective in protecting rhesus monkeys from MERS-CoV infection, when given prior to infection.[6]
- A randomized, well-marked, controlled animal study with 12 rhesus monkeys infected with SARS-CoV-2 reported that an attenuation of respiratory symptoms and reduction in lung damage with remdesivir administered 12 hours after virus infection.[7]
- SARS-CoV-2 virus enters host cells by binding to and fusing with cell membrane receptor, ACE-2, followed by membrane fusion. Once inside, the virus uses the host cell's machinery to replicate, using the virus's RNA Dependent RNA Polymerase (RdRp) for making genome and transcript copies.[8]
- Among the different strains of the coronavirus, this non-structural protein is unique in structure, and thus making it a potentially useful drug target. Based on these facts, remdesivir was approved by FDA in various clinical trials for the treatment of COVID-19 infected people.However, efficacy of remdesivir in vitro or in animals does not match with the clinical outcomes in humans. Further, remdesivir has some side effects.[9]

Primary Pharmacodynamics

Remdesivir is a nucleoside analog used to inhibit the action of RNA polymerase.[11] The duration of action is moderate, as it is given once daily. Due to much higher selectivity of mammalian DNA and RNA polymerases, including human mitochondrial RNA polymerase, for ATP over remdesivir triphosphate, remdesivir is not a significant inhibitor of these enzymes, which contributes to its overall tolerability and safety profile. Despite this, remdesivir carries risks for hypersensitivity reactions, including anaphylaxis and other infusion-related reactions, elevated transaminase levels, and potential decreased efficacy when combined with hydroxychloroquine or chloroquine.[12]

Safety Pharmacology

- Studies were conducted to examine the potential effects of remdesivir on the respiratory, CNS, and cardiovascular systems after IV administration.[11]
- In a respiratory safety study in rats, remdesivir had no effect on tidal volume or minute volume; however, respiration rates were increased from 0.75 to 6 hours post dose in animals administered ≥ 20 mg/kg.[11]
- Remdesivir had no effect on the CNS of rats and no effect on cardiovascular parameters in monkeys. at dose levels up to 50 and 10 mg/kg, respectively. Resulting in an safety margin at the No-observed-adverse-effect level (NOEL) (50 mg/kg) in rats and in an approximately 2.5-fold safety margin at the NOEL (10 mg/kg) in monkeys at the currently proposed 200-mg maximum clinical dose.[12]

Non-Clinical Pharmacokinetics[11]

- In preclinical species, IV remdesivir is extensively metabolized by hydrolases, resulting in sequential appearance of the intermediate metabolite alanine metabolic and nucleoside metabolite in plasma.
- Remdesivir showed broad tissue distribution and efficient activation to triphosphate in both bone marrow cells and respiratory tissues in monkeys.
- Following IV administration of 10 mg/kg Remdesivir o rats, most of the radioactivity was excreted within 48 h after administration. Means of 63.0% and 27.8% of the administered radioactivity in rats were excreted in urine and feces, respectively.
- In monkeys, means of 33.6% and 25.6% of the administered radioactivity were recovered in urine and feces, respectively, by 168 hours post-dose, indicating that renal and biliary excretion were the major routes of elimination of radioactivity in both species.

Non-Clinical Toxicology[12]

- Nonclinical safety studies were conducted in rats and monkeys for up to 4 weeks. The kidney was identified as the target organ of toxicity in animals.
- Findings included increased serum creatinine, proteinuria, increased kidney weight, and proximal tubular epithelial necrosis.
- Additional adverse effects were noted on appetite, body weight gain, and respiratory rate (increased). The vehicle control for Remdesivir, 12% sulfobutylether-β-cyclodextrin (SBECD), is a known renal toxicant deemed safe for use in patients > 32 kg (250 mg/kg/day).
- It is known to cause vacuolation of the kidney tubular cells without loss/change of kidney function in animals. In monkeys, RDV exacerbated SBECD-related effects at 10 mg/kg where functional changes of the kidney were noted. Exposure at 10 mg/kg in monkeys is 2.7 times the exposure in humans at the recommended human dose (RHD).

Clinical Pharmacology

Mechanism of Action[13]

The mechanism of actions of different drugs against COVID-19. The figure illustrates the probable site of drugs effect during SARS-CoV2 infection including.

- Binding and viral entry via membrane fusion or endocytosis (which are blocked by rhACE2, Bromhexine, Arbidol, Hydroxychloroquine, Ruxolitinib, and Baricitinib),
- Release of the viral genome,
- Translation of viral polymerase protein,
- RNA replication,
- Genomic replication (which is inhibited by Oseltamivir and Emtricitabine),
- Translation of viral structural protein such as main proteases (which is inhibited by Atazanavir, Lopinavir, Darunavir, Danoprevir, and Noscapine),
- Capsidation and RNA-dependent RNA polymerase (which is inhibited by Remdesivir, Favipiravir, and Ribavirin),
- Formation of the mature virion,
- Exocytosis.

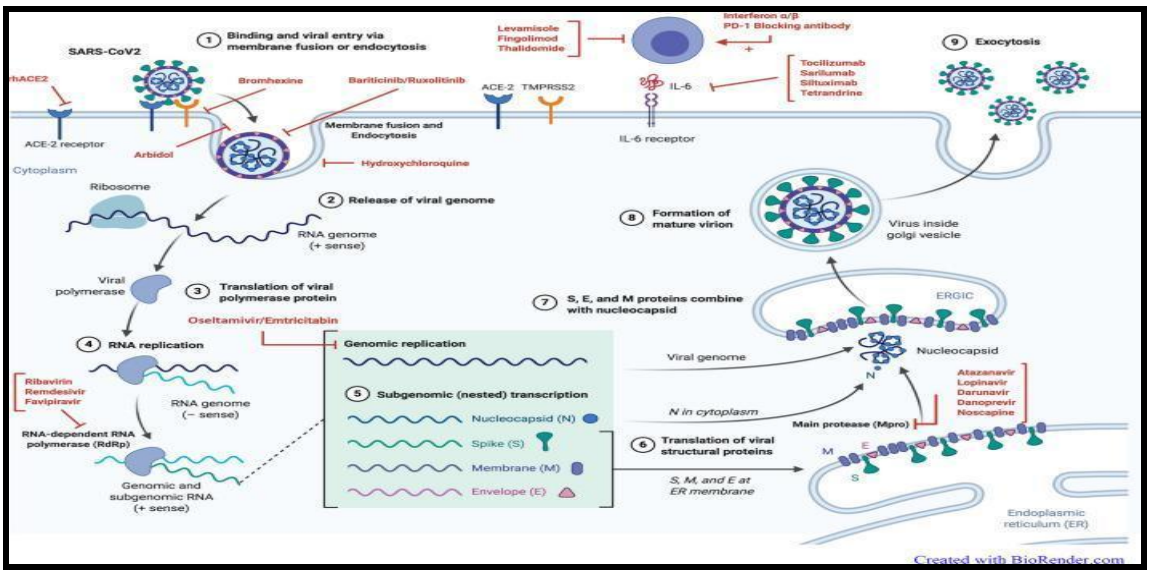


Figure 3: Mechanism of Action of Remdesivir.

Pharmacokinetics[13]

- **Absorption:** Remdesivir is absorbed quickly; maximal plasma concentrations following a single 30-minute intravenous infusion are reached within 0.67-0.68 hours (Tmax).
- **Protein binding:** Remdesivir is 88-93.6% bound to human plasma proteins.
- **Metabolism:** Remdesivir is a phosphoramidate prodrug that must be metabolized within host cells to its triphosphate metabolite to be therapeutically active.
- **Route of elimination:** Remdesivir is 74% eliminated in the urine and 18% eliminated in the feces.
- **Half-life:** Remdesivir has an elimination half-life of 1 hour following a single 30-minute intravenous infusion.

Adverse Effects[14]

- **Cardiovascular**: Hypotension, arrhythmias, and cardiac arrest.
- **Pulmonary**: Dyspnea, Acute respiratory failure, acute respiratory distress, pneumothorax, pulmonary embolism.
- **Hematological**: Anemia, lymphopenia.
- **Endocrine**: Hyperglycemia.
- **Infectious**: Pneumonia, septic shock.
- **Gastrointestinal**: elevated lipase, nausea, vomiting, diarrhea, constipation, poor appetite, gastroparesis, and lower GI bleeding.
- **Hepatic**: Hepatic manifestation characterized by Grade 1-4 increase in serum transaminases (ALT and/or AST) are the most common adverse effects seen in patients treated with remdesivir. Other abnormalities include hyperbilirubinemia.
- **Renal and Metabolic:** Acute kidney injury or worsening of underlying chronic kidney disease, hypernatremia, hypokalemia.
- **Neurological**: Headache, lightheadedness.
- **Skin**: Rash, contact dermatitis, pruritus.
- **Psychiatric**: Delirium.
- **Other adverse effects:** Pyrexia, insomnia, multi-organ dysfunction, DVT, and hypersensitivity/ anaphylactic reactions related to the infusion.

Contraindication[15]

- Patients with alanine aminotransferase (ALT) levels >5-times upper limit of normal or severe hepatic dysfunction.[14]
- Adult and pediatric patients (>28 days old) with severe renal impairment described as eGFR < 30 ml/min.[15]
- Neonates (at least 7 days to ≤ 28 days old) with serum creatinine ≥1 mg/dL.[15]

Drug-Drug Interaction[15]

- **Chloroquine**: May diminish the therapeutic effect of Remdesivir.
- **CYP3A4 Inducers (Strong):** May decrease the serum concentration of Remdesivir

- **Hydroxychloroquine**: May diminish the therapeutic effect of Remdesivir.

Labeling[16]

Indication and Dosage

Remdesivir dosage for FDA-labeled indication for treatment of COVID-19 in adults and pediatric patients ≥12 years of age weighing at least 40 kg (lyophilized powder formula-tion or solution concentrate formulation): Loading dose of 200 mg by IV infusion on day 1, followed by maintenance doses of 100 mg by IV infusion once daily from day 2. For pts not requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 5 days; if pt does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total treatment duration of 10 days). For those requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days.46

Emergency use authorization (EUA) remdesivir dosage for treatment of COVID-19 in pediatric patients weighing 3.5 to <40 kg (lyophilized powder formulation only): Loading dose of 5 mg/kg by IV infusion on day 1, followed by maintenance doses of 2.5 mg/kg by IV infusion once daily from day 2. For pts not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO), recommended total treat-ment duration is 5 days; if pt does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total treatment duration of 10 days). For those requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days. 26 ventilation and/or ECMO, recommended total treatment duration is 5 days; if pt does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total treatment duration of 10 days). For those requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days.26

NIH COVID-19 Treatment Guidelines Panel-recommended duration of remdesivir treatment: [8]
The NIH panel recommends that hospitalized pts who require supplemental oxygen but do not require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, should receive remdesivir for a duration of 5 days or until hospital discharge, whichever comes first. If such pts progress to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO during such treatment, the panel recommends that the remdesivir course be completed. The panel states that there are insufficient data on the optimal duration of remdesivir treatment for pts who have not shown clinical improvement after a 5-day regimen;some experts would extend the total duration of remdesivir treatment to up to 10 days in these patients

Storage and Handling

- Do not reuse or save reconstituted or diluted remdesivir for future use. This product contains no preservative; therefore, partially used vials should be discarded.
- Store injection, 100 mg, vials below 30°C (below 86°F) until required for use.
- After reconstitution, use vials immediately to prepare a diluted solution. Dilute the reconstituted solution in 0.9% sodium chloride injection, USP within the same day as administration.
- The diluted solution in the syringe should be used immediately.
- The diluted solution in the infusion bags can be stored up to 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours.

Clinical Trials[17,18,19]

- The ACTT-1 trial **(NCT04280705)** results showed that remdesivir shortened recovery time by 5 days, and in a subgroup analysis the results showed a mortality benefit in patients requiring supplemental oxygen but not mechanical ventilation.
- A trial **(NCT04292730)** evaluating the use of remdesivir in the setting of moderate COVID-19 (patients with pulmonary infiltrates on chest imaging and oxygen saturation greater than 94%) concluded that 5 days of remdesivir was associated with higher odds of a better clinical status compared with standard of care.
- The phase 3 trial involving 397 hospitalized patients with confirmed SARS-CoV-2 infection, oxygen saturation of 94% or less while they were breathing ambient air, and radiologic evidence of pneumonia **(NCT04292899)**, to receive intravenous remdesivir for either 5 days or 10 days.
- The double-blind, randomized, placebo-controlled trial of intravenous remdesivir in 1062 adults hospitalized with Covid-19 (**NCT04280705)** shows that The rate ratio for recovery was largest among patients with a baseline ordinal score of 5.

Table 01: List of Clinical Trials of Remdesivir.

S.no	CTID	Title	Phase	Status	Date
1.	NCT04640168	Adaptive COVID-19 Treatment Trial 4 (ACTT-4)	3	Active, not recruiting	26-05-2021
2.	NCT04843761	Therapeutics for Severely Ill Inpatients With COVID-19	3	Recruiting	25-05-2021
3.	NCT04745351	Study to Evaluate the Efficacy and Safety of Remdesivir in Participants With Severely Reduced Kidney Function Who Are Hospitalized	3	Recruiting	24-05-2021

		for Coronavirus Disease 2019 (COVID-19)			
4.	NCT04501978	Therapeutics for Inpatients With COVID-19	3	Recruiting	18-05-2021
5.	NCT04315948	Trial of Treatments for COVID-19 in Hospitalized Adults	3	Active,not recruiting	19-05-2021
6.	EudraCT: 2020-005416-22	A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of Remdesivir in Participants with Severely Reduced Kidney Function who are Hospitalized for COVID-19	3	Ongoing	24-03-2021
7.	EudraCT: 2020-002275-34	A phase III, randomized, double blind, multicenter study to evaluate the efficacy and safety of remdesivir	3	Completed	13-11-2020
8.	EudraCT: 2020-003510-12	Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting	3	Ongoing	02-10-2020

Efficacy and Safety Finding[20,21]

- Patients treated with remdesivir had a significant reduction in median time to recovery from 10 to 14 days (11.3% improvement).
- The proportion of patients who progressed to ventilation (non-invasive or invasive) or died by Day 29 with remdesivir 28%.
- The proportion of patients who died by Day 29 was a relative reduction of 35%.
- Remdesivir reduced serious adverse effects by absolute 6% and no significant Grade 3 or 4 adverse effects were reported.
- Infections and venous thromboembolism (VTE) occurred in. 10% and 3% of patients treated with remdesivir.

1.3. Baricitinib

Introduction[22]

Baricitinib(2-[1-ethylsulfonyl-3-[4-(7H-pyrrolo[2,3-d] pyrimidin-4-yl) pyrazol-1-yl] azetidin-3-yl]acetonitrile;phosphoric acid) is an orally available small molecule inhibitor of Janus kinases that is used to treat moderate-to-severe rheumatoid arthritis and in late 2020 was given emergency use authorization as therapy in combination with remdesivir for severe COVID-19. Baricitinib is associated with transient and usually mild elevations in serum aminotransferase levels during therapy but has yet to be linked to cases of clinically apparent acute liver injury.[23]

On November 19, 2020, FDA issued an Emergency Use Authorization (EUA) for the distribution and emergency use of baricitinib to be used in combination with remdesivir in hospitalised adult and pediatric patients two years of age or older with suspected or laboratory confirmed COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[21]

Principle Behind Use.[23]

Due to the anti-inflammatory action of baricitinib, it was independently hypothesized using artificial intelligence (AI)-algorithms to be useful for the treatment of COVID-19 infection via proposed anti-cytokine effects and as an inhibitor of host cell viral propagation. Baricitinib has been found to inhibit IL-6-induced MCP1 production from human peripheral blood mononuclear cells

Mechanism of Action[24]

Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. Janus kinases (JAKs) are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in haematopoiesis, inflammation and immune function. Within the intracellular signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. Baricitinib modulates these signalling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STATs.

Pharmacodynamics[24,25]

- The pharmacodynamics of baricitinib, evaluated by the inhibition of STAT3 phosphorylation following cytokine stimulation in the whole blood ex vivo, was well correlated with baricitinib plasma concentrations.
- Baricitinib was generally safe and well tolerated, with no serious treatment-related adverse events (AEs) reported from either of the studies. An expected rapidly reversible, dose-related decline in absolute neutrophil count noted with baricitinib.

Pharmacokinetics[24]

- **Absorption:** When orally administered, baricitinib is rapidly absorbed with an oral bioavailability of approximately 79 %. It has a median time to reach peak plasma concentration (Tmax) of 1hour.
- **Volume of distribution:** Mean volume of distribution following intravenous infusion administration is 76 L.
- **Protein binding:** Baricitinib is approximately 50 % bound to plasma proteins.

- **Elimination:** Baricitinib was excreted predominantly as the unchanged active substance in urine (69 %) and feces (15 %) and only 4 minor oxidative metabolites were identified (3 in urine; 1 in feces) constituting approximately 5 % and 1 % of the dose, respectively.

Drug-Drug Interaction[26]

Although a small fraction (6%) of baricitinib is metabolized by CYP3A4, co-administration with ketoconazole (a strong CYP3A4 inhibitor) or rifampin (a strong CYP3A4 inducer) did not have a clinically meaningful impact on baricitinib PK.

Warning and Precautions[26]

Serious Infections: The most common serious infections reported with Olumiant included pneumonia, herpes zoster and urinary tract infection.

Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, esophageal candidiasis, pneumocystosis, acute histoplasmosis, cryptococcosis, cytomegalovirus and BK virus were reported with Olumiant. Some patients have presented with disseminated rather than local disease and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids. Avoid Olumiant in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating Olumiant in patients.

- with chronic or recurrent infection.
- who have been exposed to TB?.
- with a history of a serious or an opportunistic infection.
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or.
- with underlying conditions that may predispose them to infection.

Laboratory Abnormalities.[27]

- Neutropenia.
- Lymphopenia.
- Anemia.
- Liver Enzyme Elevations.
- Lipid Elevations.
- Hypersensitivity.

Adverse Reactions[28]

Most common adverse reactions include: upper respiratory tract infections, nausea, herpes simplex (0.8%, 0.7%) and herpes zoster.

Serious Side Effects: serious venous thrombosis, including pulmonary embolism, and serious infections have been observed in COVID-19 patients treated with baricitinib and are known adverse drug reactions of baricitinib.

Labeling[29]

Dosage

The recommended dosage of baricitinib is.

- Adults and pediatric patients 9 years of age and older: 4 mg once daily.
- Pediatric patients 2 years to less than 9 years of age: 2 mg once daily.

Storage and Handling

- Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).
- Keep out of reach of children.

Clinical Trials[30,31]

Table 02: List of Clinical Trials of Baricitinib.

S.NO	CTID	Title	Phase	Status	Date
1.	NCT04373044	Baricitinib, Placebo and Antiviral Therapy for the Treatment of Patients With Moderate and Severe COVID-19	2	Terminated	2021-05-26
2.	NCT04640168	Adaptive COVID-19 Treatment Trial 4 (ACTT-4)	3	Active, not recruiting	2021-05-26
3.	NCT04421027	A Study of Baricitinib (LY3009104) in Participants With COVID-19	3	Active, not recruiting	2021-05-21
4.	NCT04890626	Clinical Trial to Evaluate the Efficacy of Different Treatments in Patients With COVID-19	3	Recruiting	2021-05-20
5.	EudraCT: 2020-001517-21	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Study of Baricitinib in Patients with COVID-19 Infection	3	Ongoing	2020-06-30

1.4. Combination of remdesivir and baricitinib.

Clinical Trial[32,33]

The Adaptive COVID-19 Treatment Trial (ACTT)-2 investigating combination treatment with baricitinib, a Janus kinase inhibitor, and remdesivir for the treatment of COVID-19 in hospitalized adults were published in the New England Journal of Medicine (NEJM) on March 4, 2021. The trial found that a combination of baricitinib and remdesivir was superior to the combination of remdesivir and placebo at shortening recovery time and improving clinical status in adults hospitalized with COVID-19, particularly for those who were receiving high-flow oxygen or noninvasive ventilation.

Table 04: List of Clinical Trials of Combination of Remdesivir And Baricitinib.

S.no	Study Identifier, Protocol Number	IND	Type of Study	Population (N)	Study Design and Type of Control	Test Product(s) Dosing Regimens; Dosage Forms; Routes of Administration, Duration	Study Status
	Key study supporting the EUA request						
1.	Protocol No. 20-0006 (ACTT-2) NCT04401579	147771	Efficacy Safety	1033 Baricitinib + remdesivir (n=515) Placebo + remdesivir (n=518)	Randomized, double-blind, placebo-controlled, parallel group clinical trial in hospitalized COVID-19 patients	Baricitinib 4 mg oral (two 2 mg tablets), dosed 14 days or placebo All patients received Remdesivir (10 days): Remdesivir 200 mg IV Day 1: Followed by 100 mg IV QD Days 2-10	Completed
	Study supporting the baricitinib COVID-19 clinical development program (this study is ongoing as of the time of this review and no data are available to support the EUA request)						
2.	Study 14V-MCKHAA NCT04421027	149279	Efficacy Safety	Planned 1000 to 1400	Randomized, double-blind, placebo-controlled, parallel group clinical trial in hospitalized COVID-19 patients	Baricitinib, 4 mg oral (two 2 mg tablets) dosed for 14 days on standard of care background treatment	Ongoing

Efficacy and Safety Finding[34,35,36]

- Patients treated with baricitinib in combination with remdesivir had a significant reduction in median time to recovery from 8 to 7 days (12.5% improvement) compared to remdesivir.
- Patients treated with baricitinib in combination with remdesivir were more likely to have a better clinical status at Day 15compared to patients treated with remdesivir.
- The proportion of patients who progressed to ventilation (non-invasive or invasive) or died by Day 29 was lower in baricitinib in combination with remdesivir (23%) compared to remdesivir (28%).
- The proportion of patients who died by Day 29 was 4.7% for baricitinib in combination with remdesivir vs. 7.1% for remdesivir, a relative reduction of 35%.
- Adverse events and serious adverse events were reported in 41% and 15% of patients treated with baricitinib in combination with remdesivir, respectively, vs. 48% and 20% in patients treated with remdesivir.
- Infections and venous thromboembolism (VTE) occurred in 6% and 4% of patients treated with

baricitinib in combination with remdesivir, respectively, vs. 10% and 3% of patients treated with remdesivir.

1.5. Adverse Events and Serious Adverse Events[37]

Definition of Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) products. If multiple abnormalities are part of the same clinical syndrome, they can be reported together as one AE under a unifying clinical diagnosis.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing (baseline) medical condition increases above baseline to severity grade 3 or 4, it should be recorded as an AE.

Given the nature of severity of the underlying illness, subjects will have many symptoms and abnormalities in vital signs and laboratory values. Only Grade 3 and 4 AEs will be captured in this trial. In addition, the following AEs will be reported.

- Any Grade 2 or higher suspected drug-related hypersensitivity reactions associated with study product administration will be reported as an AE.
- Any venous thromboembolism at any time during the study.

Unsolicited laboratory values collected as part of standard of care, will need to be reported only if Grade 3 or above and only if clinically significant and/or part of a diagnosis or a clinical syndrome. In this case, if laboratory and vital sign abnormalities are part of the clinical syndrome, they should be reported as one AE under one clinical diagnosis or syndrome. Example: Low oxygen level/arterial blood gases could be part of respiratory failure diagnosis.

Intermittent abnormal laboratory values or vital sign measurements common in the severely ill populations (such as electrolyte abnormalities, low blood pressure, hyperglycemia, etc.) that are part of the same clinical diagnosis (e.g., uncontrolled diabetic) can be recorded once with the worst grade for each adverse event (grade 3 and 4 only for this trial), with the start and stop dates of the intermittent syndrome. If there is clear resolution of the event, and then recurrence, it should be treated as a separate adverse event. Resolution is defined as return to baseline (either normal if was normal at Day 1, or baseline (Day 1) grade if already an abnormality on the toxicity table at Day 1) for > 48 hours.D-dimer and CRP should not be graded. They are collected on the same schedule as the safety laboratory tests (see SOA). However, they will be used in the assessment of study outcomes.

Definition of Serious Adverse Event (SAE)

An AE or suspected adverse reaction is considered serious (i.e., is an SAE) if, in the view of either the investigator or the Sponsor, it results in any of the following outcomes.

- Death.
- A life-threatening AE.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; orA congenital anomaly/birth defect.

Grade 4 AEs (potentially life-threatening events) are not always SAEs unless they are imminently life threatening.

“Life-threatening” refers to an AE that at occurrence represents an immediate risk of death to a subject. An event that may cause death if it occurs in a more severe form is not considered life-threatening.

Suspected Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the Investigator Brochure (IB), Package Insert, and/or Summary of Product Characteristics.

Classification of an Adverse Event

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

Severity of Adverse Events

All AEs and SAEs will be assessed for severity using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

For AEs not included in the Table, the following guidelines will be used to describe severity. In addition, all deaths related to an AE are to be classified as grade 5.

- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living and causes discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe (Grade 3): Events that interrupt usual activities of daily living, or significantly affect clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.
- Potentially life-threatening event (Grade 4): Events that are potentially life threatening.

- Deaths (Grade 5): All deaths related to an AE are classified as grade 5.

Relationship to Study Intervention

For each reported adverse reaction, the PI or designee must assess the relationship of the event to the study product using the following guideline.

- **Related** – There is a temporal relationship between the study intervention and event, and the AE is known to occur with the study intervention or there is a reasonable possibility that the study intervention caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related –** There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Time Period and Frequency for Event Assessment and Follow-Up

For this study, all Grade 3 and 4 AEs, all SAEs occurring from the time the informed consent is signed through the Day 29 visit will be documented, recorded, and reported.

Investigator Reporting of AEs

Information on AEs will be recorded on the appropriate CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

Investigators Reporting of SAEs

Any AE that meets a protocol-defined criterion as an SAE that is judged to be related to either study product must be submitted within 24 hours of site awareness on an SAE form to the DMID Pharmacovigilance Group. Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct. At any time after completion of the study, if the site PI or appropriate sub-investigator becomes aware of an SAE that occurred during the subject's participation in the study, the site PI or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

1.6. Responsibilities[38]

International Council for Harmonization (ICH), in its guideline ICH E6 (R2) defines Good Clinical Practice (GCP) as 'an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The WHO and ICH GCP codes were first issued in 1995 and 1996 respectively [Ethics and IRB applications]). However, it is important to appreciate that these codes have subsequently evolved in response to developments in the field of medical ethics.

The ICH-GCP guideline was developed with reference to clinical practice in the European Union, Japan, USA, Australia, Canada and the Nordic countries. It now provides a unified standard and facilitates the mutual acceptance of clinical data by the regulatory authorities in differing jurisdictions. Compliance with ICH-GCP is now a legal obligation in many countries. Some countries have modified their own GCP guidelines according to the ICH-GCP.

Investigator Responsibilities

Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on HarmoniSation (ICH) guidelines, or with the law and regulations of the country in which the research Is conducted, whichever affords the greater protection to the study subject.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators, 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable sub-investigators will comply with 21 CFR, Part 54, 19 providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any sub-investigator's) participation in the study.The investigator and sub-investigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study complet is defined as the date when the last subject completes the protocol-defined activities.

Institutional Review Board (TRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject

information sheets, or descriptions or tC to obtain informed consent) to an IRB/IEC. The investigator will not begin any study sul activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying information be provided to the subject after initial IRB/IEC approval, with the exception not necessary to reduce immediate risk to study subject

The Principles of Ich-Gcp

- Clinical trials should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- The rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interest of science and society.
- The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
- Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
- A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/ independent ethics committee (IEC) approval/ favorable opinion.
- The medical care given to, and medical decisions made on behalf of participants should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- Freely given informed consent should be obtained from every participant prior to clinical trial participation.
- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
- The confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- Investigational products should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practice (GMP). They should be used in accordance with the approved protocol. Systems with procedures that assure the quality of every aspect of the trial should be implemented.
- Systems with procedures that assure the quality of every aspect of the trial should be implemented.

These core principles can be summarised as follows: All clinical trials should be conducted in accordance with ethical principles, after establishing sound scientific evidence that the benefits expected of the trial clearly outweigh any potential risks. The rights, safety and wellbeing of trial participants are of prime importance. Informed consent and maintenance of confidentiality are mandatory. The study must be conducted by appropriately qualified personnel with sufficient experience. Detailed study protocols should be defined by the researchers and approved by the Institutional Review Boards (IRBs). Records should be properly maintained, easily accessible and retrievable. Investigational products should be manufactured according to Good Manufacturing Practice.

Sponsor

A person, company, institution, group, or organization that oversees or pays for a clinical trial and collects and analyzes the data.

Study sponsor responsibilities

The specific regional requirements for a clinical study sponsor can vary. Generally, a sponsor is responsible for.

Selecting the investigator(s)

- Providing investigator(s) with the necessary information to conduct the clinical trial.
- Ensuring proper monitoring of the clinical study.
- Ensuring all the necessary ethic review(s) and approval(s) are obtained.
- Preparing and submitting clinical trial application(s) and amendment(s) to the appropriate regulatory agencies.
- Ensuring that any reviewing ethics board and regulatory agencies are promptly informed of any significant new information (for example, important findings that affect product safety) in a clinical study.
- Ensuring compliance with labelling, reporting and record-keeping requirements.
- Refraining from engaging in promotional activities and other prohibited activities such as commercializing an investigational medical device.
- Ensuring that the clinical study is conducted in accordance with Good Clinical Practice (GCP).

Study investigator responsibilities

In a clinical trial, the responsibilities of an investigator generally include.

- Protecting the rights, safety and welfare of subjects in the clinical study.
- Ensuring that informed consent is properly obtained from clinical trial subjects.
- Conducting the clinical study (that is, directly overseeing the administration of the test products to the subject). In situations where there is a team of

researchers, the investigator will act as the team leader.
- Ensuring that the clinical trial is conducted in accordance with the signed agreement and the investigational plan.
- Controlling the products under investigation (for example, supervising medical-device use and disposal).
- Ensuring proper record-keeping and reporting requirements are met (for example, mandatory safety reporting).

Sponsor-investigators: Additional considerations

Sponsor-investigators also generally need to manage the following.
- Securing funding for the clinical trial.
- Applying for the appropriate insurance.
- Generating the appropriate clinical trial documentation (for example, informed consent, protocols) and submissions (for example, ethics and/or regulatory submissions).
- Ensuring adequate resources are available for the duration of the trial (for example, experienced staff, investigational and control products, clinical and medical supplies, an analytical laboratory).
- Creating appropriate written procedures (for example, standard operating procedures related to GCP).
- Meeting all the applicable regulatory requirements such as obtaining and maintaining necessary approvals from the relevant ethics review boards and regulatory agencies.

Sponsor-investigators

Getting started with a clinical trial applicationWhile the completion of a clinical trial application involves many tasks and may seem daunting, there are many resources to help. The following approach can assist you.
- Research the regulatory requirements pertaining to the applicable submissions. Make good use of regulatory agency websites and professional organizations as well as related publications, seminars and training.
  Contact the relevant regulatory agency via formal or informal means. Formal means may take the form of a request for a pre-submission meeting with the agency. Informal means may include contacting them with general questions.
- Prepare and submit the application based on the format and content relevant to the specific submission. Make sure that any comments or feedback received at the pre-submission meeting are incorporated in the submission dossier.
- After a submission is approved, ensure that all the post-approval requirements are fulfilled, such as any required safety reporting, annual reporting and amendment submissions relating to significant changes to the products or study plan.
- Make certain that you fulfill your responsibilities as a sponsor as well as an investigator according to applicable regulatory requirements.

Case Report Form

A case report form (or CRF) is a paper or electronic questionnaire specifically used in clinical trial research. The case report form is the tool used by the sponsor of the clinical trial to collect data from each participating patient. All data on each patient participating in a clinical trial are held and/or documented in the CRF, including adverse events.

The sponsor of the clinical trial develops the CRF to collect the specific data they need in order to test their hypotheses or answer their research questions. The size of a CRF can range from a handwritten one-time 'snapshot' of a patient's physical condition to hundreds of pages of electronically captured data obtained over a period of weeks or months. (It can also include required check-up visits months after the patient's treatment has stopped.).
The sponsor is responsible for designing a CRF that accurately represents the protocol of the clinical trial, as well as managing its production, monitoring the data collection and auditing the content of the filled-in CRFs.

Case report forms contain data obtained during the patient's participation in the clinical trial. Before being sent to the sponsor, this data is usually de-identified (not traceable to the patient) by removing the patient's name, medical record number, etc., and giving the patient a unique study number. The supervising Institutional Review Board (IRB) oversees the release of any personally identifiable data to the sponsor.

From the sponsor's point of view, the main logistic goal of a clinical trial is to obtain accurate CRFs. However, because of human and machine error, the data entered in CRFs is rarely completely accurate or entirely readable. To combat these errors monitors are usually hired by the sponsor to audit the CRF to make sure the CRF contains the correct data.

Information Consent Form

Informed consent is a process for getting permission before conducting a healthcare intervention on a person, for conducting some form of research on a person, or for disclosing a person's information. A health care provider may ask a patient to consent to receive therapy before providing it, a clinical researcher may ask a research participant before enrolling that person into a clinical trial, and a researcher may ask a research participant before starting some form of controlled experiment. Informed consent is collected according to guidelines from the fields of medical ethics and research ethics.

An informed consent can be said to have been given based upon a clear appreciation and understanding of the facts, implications, and consequences of an action. To

give informed consent, the individual concerned must have adequate reasoning faculties and be in possession of all relevant facts. Impairments to reasoning and judgment that may prevent informed consent include basic intellectual or emotional immaturity, high levels of stress such as posttraumatic stress disorder (PTSD) or a severe intellectual disability, severe mental disorder, intoxication, severe sleep deprivation, Alzheimer's disease, or being in a coma.

CONCLUSION

According to the study conducted, it was found that when Remdesivir was given alone in the patient suffering from COVID-19 the mean recovery time was 11.3% and mortality rate was 7.1% Remdesivir significantly reduces the mortality and shows more safety, efficacy and reduced serious adverse effects by absolute 6% and no significant Grade 3 or 4 adverse effects were reported

When Remdesivir was given in combination with Baricitinib was superior to remdesivir alone in reducing recovery time (12.5%) and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or non-invasive ventilation. The mortality rate for baricitinib in combination with remdesivir vs. 7.1% for remdesivir, a relative reduction of 35%. Adverse events and serious adverse events were reported in 41% and 15% of patients treated with baricitinib in combination with remdesivir, respectively, vs. 48% and 20% in patients treated with remdesivir.

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