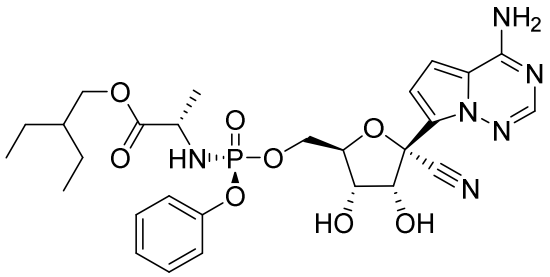
1. INTRODUCTION

Gilead Sciences (Gilead) is submitting this dossier in support of a new marketing application for remdesivir (RDV; GS-5734 ™) for the treatment of coronavirus disease 19 (COVID-19).

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei province, China {Huang 2020}. Sequencing analyses from respiratory tract samples of patients identified a novel coronavirus (CoV), which was named severe acute respiratory syndrome (SARS)-CoV-2 {Zhou 2020}. Cases of the novel infectious disease caused by the SARS-CoV-2 virus, coronavirus disease 2019 (COVID-19), rapidly increased throughout the world. The situation is a major global health emergency, as evident by the International Health Regulations Emergency Committee of the World Health Organization declaration on 30 January 2020 that the SARS-CoV-2 outbreak constitutes a public health emergency of international concern (PHEIC) {World Health Organization (WHO) 2020b}. On 11 March 2020, the World Health Organization declared COVID-19 a pandemic {World Health Organization (WHO) 2020c}. As of 08 July 2020, more than 11,669,000 confirmed cases and 539,000 associated deaths were reported worldwide, including more than 2,923,000 cases and 129,000 deaths in the United States (US) {World Health Organization (WHO) 2020a}. There are currently no approved therapeutic agents available for the treatment of COVID-19 in the US, and the availability of an effective antiviral agent with a favorable benefit-risk profile would address a serious unmet medical need for the treatment of patients with COVID-19.

This marketing application contains administrative, quality, nonclinical, and clinical data supporting RDV for the treatment of COVID-19. Primary safety and efficacy data are presented from a Phase 3, randomized, double-blind, placebo-controlled, multicenter study comparing RDV versus placebo in hospitalized patients with COVID-19 (ACTT-1; Study CO-US-540-5776; sponsored by NIAID), a randomized, open-label part (Part A) of a Phase 3, multicenter study comparing 2 RDV regimens (5 days versus 10 days) in participants with severe COVID-19 (Study GS-US-540-5773), and a randomized open-label part (Part A) of a Phase 3, multicenter study evaluating 2 RDV regimens (5 days and 10 days) versus standard of care (SOC) in participants with moderate COVID-19 (Study GS-US-540-5774). Additional safety data from individuals with COVID-19 are provided from an investigator sponsored Phase 3 study in China (CO-US-540-5758) and the compassionate use program (IN-US-540-5775). Data are also provided from four completed Phase 1 studies in healthy participants (GS-US-399-1812, GS-US-399-4231, GS-US-399-1954, and GS-US-399-5505) and from the Phase 2/3 study (CO-US-399-5366 [PALM]) evaluating various investigational treatments including RDV for the treatment of Ebola virus disease (EVD) {Mulangu 2019}. A tabular summary of studies is presented in Module 2.7.6.

1.1. Chemical Name and Structure

USAN:	Remdesivir
Gilead Product No.:	GS-5734
CAS:	L-Alanine, *N*-[(*S*)-hydroxyphenoxyphosphinyl]-, 2-ethylbutyl ester, 6-ester with 2-*C*-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2, 5-anhydro-D-altrononitrile
IUPAC:	2-Ethylbutyl (2*S*)-2-{[(*S*)-{[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(phenoxy)phosphoryl]amino}propanoate
Molecular Formula:	$C_{27}H_{35}N_6O_8P$
Molecular Weight:	602.6
Chemical Structure:	

1.2. Pharmacological Class

Remdesivir is a novel antiviral drug that has been evaluated for the treatment of COVID-19. Remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad-spectrum activity against members of the CoVs (eg, SARS-CoV-2, SARS-CoV, Middle East respiratory syndrome [MERS]-CoV), filoviruses (eg, Ebola virus [EBOV], Marburg virus), and paramyxoviruses (eg, respiratory syncytial virus, Nipah virus, Hendra virus).

1.3. Route of Administration

Remdesivir is administered intravenously.

1.4. Proposed Indication

The proposed indication statement for remdesivir is as follows:

VEKLURY is indicated for the treatment of adults and pediatric patients 12 years of age and older and weighing at least 40 kg with COVID-19.

2. REFERENCES

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. Lancet 2020;395:497-506.

Mulangu S, Dodd LE, Davey RT, Jr., Tshiani Mbaya O, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med 2019;381 (24):2293-303.

World Health Organization (WHO). Coronavirus Disease (COVID-19) Situation Report – 170. 08 July. 2020a.

World Health Organization (WHO). Statement on the Second Meeting of the International Health Regulations (2005) Emergency Committee Regarding the Outbreak of Novel Coronavirus (2019-nCoV). Available at: https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-%282005%29-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-%282019-ncov%29. Accessed: 10 February. 30 January. 2020b:

World Health Organization (WHO). WHO Director-General's Opening Remarks at the Media Briefing on COVID-19 - 11 March 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed: 16 March 2020. 11 March. 2020c:

Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin. Nature 2020;579:270-3.