SECTION 2.2 – INTRODUCTION

Lenacapavir

Gilead Sciences

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CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.2 – INTRODUCTION....1
TABLE OF CONTENTS....2
LIST OF IN-TEXT TABLES....2
1. INTRODUCTION....3
1.1. Chemical Names and Structure....5
1.2. Pharmacological Class....5
1.3. Route of Administration....6
1.4. Proposed Indication....6
2. REFERENCES....7

LIST OF IN-TEXT TABLES

Table 1. LEN Studies in People with HIV....4

1. INTRODUCTION

Gilead Sciences (Gilead) is submitting a marketing application for lenacapavir (LEN; GS-6207) solution for injection (309 mg/mL) and film-coated tablet (300 mg). Lenacapavir is a new active substance in development by Gilead. It is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function targeted for the treatment of HIV-1 infection. Lenacapavir has potent anti-viral activity and a novel resistance profile. It has low human clearance and is being developed as a long-acting antiretroviral (ARV) treatment. Two dosage forms of LEN are currently in development, a solution for subcutaneous (SC) injection, which is administered once every 6 months and an oral film-coated tablet for initial loading.

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 38 million people infected worldwide and approximately 26 million on antiretroviral (ARV) treatment {UNAIDS 2020}. While combination antiretroviral therapy (ART) for the treatment of HIV–1 infection has been largely successful in reducing the morbidity and mortality previously associated with HIV disease, there remains a significant medical need for new well−tolerated therapies that take into consideration HIV genetic variability, ARV resistance, and new options for regimen simplification, and the desires of people with HIV (PWH) for alternative, longer acting options.

Some treatment–experienced PWH eventually lose virologic, immunologic, or clinical benefit from their current regimens. Heavily–treatment–experienced PWH with multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable HIV viral suppression {Department of Health and Human Services (DHHS) 2013, Thompson 2010, U. S. Department of Health and Human Services 2015, Williams 2014}. These challenges are also relevant for treatment−experienced adolescents who acquired HIV-1 infection via perinatal transmission, given their extensive history of ART, often including suboptimal agents (eg, zidovudine) due to lack of pediatric formulations of more effective and less toxic agents.

Developing safe and effective therapies for PWH with multidrug–resistant HIV remains a priority. Newer treatments that are not impacted by resistance to existing ARV classes are needed to control viral replication, preserve immune function, and prevent clinical progression. Moreover, even without complete virologic suppression, a sustained reduction in HIV-1 RNA ($\geq$ 0.5 log10 copies/mL) can be achieved in HTE individuals by adding, ideally, more than 1 agent; hence, leading to the same benefit but to a lesser degree.

The primary study that supports the safety and efficacy of LEN for the intended indication is a Phase 2/3 study in HTE PWH (Study GS-US-200-4625), which is supported by a Phase 2 study of LEN in treatment−naive PWH (Study GS-US-200-4334). In addition, supportive safety data are also provided from two Phase 1 studies in healthy participants who received LEN at exposures similar to the proposed doses for commercialization (Studies GS-US-200-4538 and GS-US-200-5709). A complete battery of Phase 1 studies also contributed to the characterization of the pharmacokinetic (PK) profiles of LEN and its metabolites, supporting the clinical pharmacology of LEN.

In HTE PWH participants (Study GS-US-200-4625), a higher proportion of participants who received LEN achieved ≥ 0.5 log_{10} reduction from baseline in HIV-1 RNA compared with placebo in the Functional Monotherapy Period (LEN 87.5%, 21 of 24 participants; placebo 16.7%, 2 of 12 participants; proportional difference: 70.8%; 95% CI: 34.9% to 90.0%; $p < 0.0001$). Also, a high rate of virologic suppression was achieved at Week 26 in Cohort 1: 80.6% (29 of 36 participants) had HIV-1 RNA < 50 copies/mL as determined by the United States (US) Food and Drug Administration (FDA)–defined snapshot algorithm.

In treatment-naive PWH participants (Study GS-US-200-4334), a high rate of virologic suppression was achieved at Week 28 in participants receiving LEN (SC or oral formulation): 93.6% (147 of 157 participants) had HIV-1 RNA < 50 copies/mL as determined by the US FDA−defined snapshot algorithm.

In healthy participants (Study GS-US-200-4538; GS-US-200-5709), LEN was generally safe and well tolerated.

Lenacapavir was generally safe and well tolerated in both HTE and treatment-naive PWH participants.

Information on study design and populations for these studies is presented in Table 1.

Table 1. LEN Studies in People with HIV

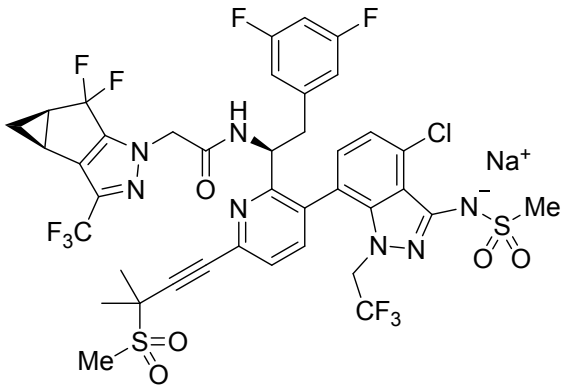
Study Number	Description of Study	Data Cross Reference	Module 2 Cross−Reference
Study in HTE PWH			
GS-US-200-4625	Ongoing, Phase 2/3, randomized, placebo−controlled, multicenter study	GS-US-200-4625 Interim Week 26 CSR	m2.7.3, Section 2.1
Study in Treatment–Naive PWH			
GS-US-200-4334	Ongoing, Phase 2, randomized, open−label, active−controlled, multicenter study	GS-US-200-4334 Interim Week 28 CSR	m2.7.3, Section 2.2
Studies in Healthy Participants			
GS-US-200-4538	Completed, Phase 1, randomized, blinded, placebo-controlled, SAD study	GS-US-200-4538 Final CSR	m2.7.1, Section 2.1.2
GS-US-200-5709	Ongoing, Phase 1, open−label, multiple−cohort, multiple−dose study	GS-US-200-5709 Interim CSR	m2.7.2, Section 2.2.3

CSR = clinical study report; HTE = heavily−treatment experienced; PWH = people with HIV; SAD = single ascending dose

This application contains full administrative, quality, nonclinical, and clinical data supportive of LEN injection and tablets for the proposed indication described in Section 1.4.

1.1. Chemical Names and Structure

Lenacapavir is incorporated into the drug product as lenacapavir sodium. Information on the nomenclature, empirical formula, the relative formula weight, and the chemical structure of the drug substance, lenacapavir sodium, is provided below:

USAN:	Lenacapavir sodium
Gilead Code Number:	GS-6207-02
CAS Registry No:	2283356-12-5
IUPAC	Sodium (4-chloro-7-(2-((*S*)-1-(2-((3b*S*,4a*R*)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1*H*-cyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-1-(2,2,2-trifluoroethyl)-1*H*-indazol-3-yl)(methylsulfonyl)amide
Empirical Formula:	$C_{39}H_{31}ClF_{10}N_7NaO_5S_2$
Formula Weight:	990.3
Chemical Structure:	

1.2. Pharmacological Class

Lenacapavir is a novel, first in class, multistage, selective inhibitor of HIV-1 capsid function. Lenacapavir inhibits HIV at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of preintegration complexes and impairing virion production and proper capsid core formation. Virus produced in the presence of LEN display aberrantly shaped capsids. These malformed virus particles can still infect a new target cell but cannot replicate as they are unable to support reverse transcription without a properly formed capsid core.

Lenacapavir is characterized by potent antiviral activity, a novel resistance profile, low human clearance, and low aqueous solubility. These combined characteristics allow LEN to be well suited for a parenteral formulation that can potentially be used as a novel long-acting ARV for treatment of or prevention for HIV-1 infection administered monthly or less frequently.

Lenacapavir is anticipated to be active against all major types of HIV-1, including those that have developed resistance to existing classes of ARVs (eg, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase strand-transfer inhibitors).

1.3. Route of Administration

Both oral tablets and SC injection formulations of LEN are part of the proposed regimen.

1.4. Proposed Indication

The proposed indication statement for lenacapavir is as follows:

- [TRADENAME], in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 35 kg with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

2. REFERENCES

Department of Health and Human Services (DHHS). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC). Revised 12 February 2013. Available at: http://aidsinfo.nih.gov/guidelines. Accessed: 2013 February 12. 2013.

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Williams I, Churchill D, Anderson J, Boffito M, Bower M, Cairns G, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013. All changed text is cast in yellow highlight.). HIV Med 2014;15 Suppl 1:1-85.