プレジコビックス®配合錠

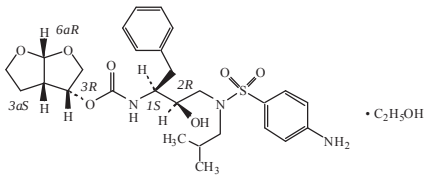
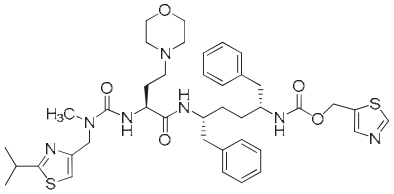
第 2 部：CTD の概要

ヤンセンファーマ株式会社

Module 2.2 – Introduction

1 PRODUCT BACKGROUND

The darunavir/cobicistat (DRV/COBI) fixed dose combination (FDC) tablet contains 800 mg of the medicinal product DRV and 150 mg of the medicinal product COBI and is developed by the Applicant in collaboration with Gilead Sciences Inc (Gilead).

	Darunavir (DRV) ethanolate	**Cobicistat (COBI)**
Structural Formula:		
Molecular Formula:	$C_{27}H_{37}N_3O_7S.C_2H_5OH$	$C_{40}H_{53}N_7O_5S_2$
Molecular Weight:	DRV ethanolate: 547.66 (active moiety) + 46.07 (ethanol, EtOH) = 593.73	776.02 (free form)
Chemical Name:	[(1*S*,2*R*)-3-[[(4-aminophenyl) sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3aS,6a*R*)-hexahydrofuro[2,3-*b*] furan-3-yl ester monoethanolate	1,3-thiazol-5-ylmethyl (2*R*,5*R*)-(5-{[(2*S*)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl} carbamoyl)amino]]-4-(morpholin-4-yl)butanamido}-1,6-diphenylhexan-2-yl)carbamate

Darunavir (PREZISTA®, also known as TMC114), is an HIV-1 protease inhibitor (PI), developed by Janssen Research and Development (formerly Tibotec). It is currently indicated for the treatment of HIV-1 infection in adults and in pediatric patients of 3 years of age and above, in combination with ritonavir (rtv) and with other antiretrovirals (ARVs). Low-dose rtv is coadministered with DRV (as single agent) for its CYP3A inhibitor properties, in order to enhance (boost) DRV concentrations. Darunavir obtained marketing authorization in Europe in February 2007, and is currently registered in more than 100 countries. Once daily and twice daily dosing recommendations of DRV/rtv are available. In adults, the DRV/rtv 800/100 mg once daily dose regimen is recommended in ART-naïve patients and ART-experienced patients with no DRV RAMs,[1] who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L.

[1] DRV RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

In ART-naïve HIV-1 infected subjects this dosing recommendation was registered based on the demonstration of noninferiority in virologic response of the regimen when compared with lopinavir (LPV)/rtv 800/200 mg total daily dose (either 400/100 mg twice daily or 800/200 mg once daily) in the registrational study TMC114-C211 (also referred to as ARTEMIS). In this study, 343 subjects received DRV/rtv 800/100 mg once daily and 346 subjects received a daily dose of LPV/rtv 800/200 mg, both in combination with a fixed background regimen of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC); data up to Week 192 are available. In the ART-experienced HIV-1 infected subjects with no DRV RAMs, noninferiority in virologic response of DRV/rtv 800/100 mg once daily coadministered as single agents was shown in comparison to DRV/rtv 600/100 mg twice daily coadministered as single agents, in the registrational study TMC114-C229 (also referred to as ODIN). In this study, 294 subjects with a viral load >1,000 HIV-1 RNA copies/mL and a CD4+ cell count >50x10^6 cells/L at screening received DRV/rtv 800/100 mg once daily and 296 subjects received DRV/rtv 600/100 mg twice daily, both in combination with an investigator-selected optimized background regimen of ≥2 NRTIs. The results of both studies confirmed that DRV/rtv 800/100 mg once daily is generally safe and well tolerated and provides substantial and durable efficacy benefits.

Cobicistat (COBI, formerly known as GS-9350) is a new chemical entity developed by Gilead for use as a PK enhancer to increase systemic exposure of coadministered drugs metabolized by CYP3A enzymes, including the HIV-1 InSTI elvitegravir (EVG), and the HIV PIs atazanavir (ATV) and DRV. In the European Union, COBI has recently been registered as a pharmacokinetic (PK) enhancer of DRV and atazanavir (ATV). It is a structural analog of rtv and a potent, mechanism-based inhibitor of CYP3A. Inhibition of CYP3A-mediated metabolism by COBI enhances the systemic exposure of CYP3A substrates, such as DRV; this is useful in situations where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism. Cobicistat itself has no detectable antiviral activity against HIV-1 in vitro and does not directly contribute to the efficacy of an ARV regimen. Its primary pharmacodynamic activity is to enhance the exposure of drugs that are metabolized by CYP3A in order to achieve appropriate therapeutic exposures

2 PROPOSED CLINICAL USE

The DRV/COBI FDC 800/150-mg tablet is to be administered once daily and is dosed according to the same once-daily dosage regimen as the single agents.

This tablet is intended to be used in the same adult population for which DRV/low-dose ritonavir (rtv) 800/100 mg once daily (coadministered as single agents) is registered, ie, antiretroviral therapy (ART)-naïve adults and ART-experienced adults with no DRV resistance associated mutations (RAMs) and who have plasma HIV-1 ribonucleic acid (RNA) <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L. The intended indication for the FDC of DRV/COBI 800/150 mg does not represent a new combination regimen but is a so called 'substitution indication' of an already approved regimen, ie, the single agents have already been licensed for combined use at the same dose levels as in the FDC.

The development of a FDC of DRV providing 1 tablet of DRV with its pharmacokinetic enhancer in a once-daily regimen, offers the option to simplify DRV-containing ARV regimens by reducing pill burden. It therefore offers patients increased convenience as well as the potential for improved adherence and reduced risk of medication errors. The DRV/COBI FDC formulation would be the first coformulation of DRV and a pharmacokinetic enhancer. It is also notable that the DRV/COBI FDC formulation would potentially be the first FDC of a PI not containing rtv and could therefore be used in patients who are intolerant to rtv.

3 DEVELOPMENT PROGRAM OF THE DRV/COBI FDC

The development of the DRV/COBI FDC tablet has been built on the information accrued from the development program for DRV in combination with rtv (conducted by the Applicant) and on the development program for COBI (conducted by Gilead).

No non-clinical studies were performed with DRV in combination with COBI.

The FDC clinical program aimed at generating PK data that support the development of a FDC formulation and bridge the comprehensive datasets of the individual agents to the FDC formulation.

Gilead demonstrated that a 150-mg dose of COBI led to similar DRV exposures as a 100-mg dose of rtv, in each case when coadministered with DRV 800 mg once daily (GS-US-216-0115). The PK data for DRV with the proposed DRV/COBI FDC 800/150-mg tablet were bridged with the existing data for DRV/rtv coadministered as single agents by conducting 2 Phase 1 studies in healthy subjects (relative bioavailability study TMC114IFD1001 and bioequivalence study TMC114IFD1003). The PK results for study TMC114IFD1001 were consistent with those of study GS-US-216-0115. Altogether, these 3 Phase 1 studies showed that DRV exposures

achieved with the DRV/COBI FDC are similar to those observed with the rtv- or COBI-boosted DRV single agent. The results allowed the selection of an appropriate DRV/COBI FDC 800/150-mg tablet formulation for the intended commercial use (G006).

The FDC clinical development plan was complemented by an ongoing Phase 3b, open-label, single-arm study (GS-US-216-0130) conducted by Gilead in collaboration with the Applicant. This Phase 3b study is conducted primarily to generate additional safety data on treatment with DRV/COBI 800/150 mg once daily coadministered as single agents in combination with 2 NRTIs, but also further provides supportive evidence of the efficacy and pharmacokinetic profile of DRV/COBI in the targeted population.