シムツーザ®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

Janssen Research & Development, LLC (Janssen;Sponsor) and Gilead Sciences, Inc. (GSI) co-developed a 4-agent, once-daily FDC tablet containing the PI darunavir (DRV [800 mg]; developed by the Sponsor), the pharmacokinetic enhancer (booster) cobicistat (COBI [150 mg]; developed by GSI), the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC [200 mg]; developed by GSI), and the next-generation prodrug of the NRTI tenofovir (TFV), ie, tenofovir alafenamide (TAF [10 mg]; developed by GSI). This FDC tablet, hereafter referred to as the D/C/F/TAF FDC tablet, is the first complete single-tablet, once-daily, PI-based HIV-1 regimen. It offers the additional advantage of including a nucleos(t)ide reverse transcriptase inhibitor (N[t]RTI) backbone that has an improved renal and bone safety profile compared with a tenofovir disoproxil fumarate (TDF)-containing backbone.

GSI conducted the initial development of the D/C/F/TAF FDC tablet (up to and including the Phase 2 study). Janssen Research & Development conducted the Phase 3 studies and is subject to regulatory approval, responsible for manufacturing, registration, distribution and commercialization of the product worldwide.

Darunavir is approved for treatment of HIV-1 in patients aged 3 years and above, either as a twice-daily treatment for antiretroviral treatment (ART)-experienced subjects or as a once-daily treatment (800 mg) for ART-naïve subjects and for ART-experienced subjects without DRV resistance-associated mutations (RAMs).

Cobicistat (COBI) 150 mg is approved as a PK enhancer of DRV 800 mg once daily. Cobicistat is devoid of antiviral activity. COBI is available as a single agent (Tybost®), or as part of the FDCs Evotaz® (ATV/COBI), Genvoya® (E/C/F/TAF), PREZCOBIX® (DRV/COBI) and Stribild® (STB; elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate [E/C/F/TDF]).

Emtricitabine (FTC) is an NRTI approved for use in combination with other agents for the treatment of HIV-1 infection in adults and children (4 months of age or older, and is available as a single agent (Emtriva®) or as part of FDCs (Atripla® [ATR; EFV/F/TDF], Descovy® [F/TAF], Eviplera® [FTC/RPV/TDF], Genvoya® [E/C/F/TAF], Odefsey® [rilpivirine/emtricitabine/tenofovir alafenamide; R/F/TAF], Stribild® [E/C/F/TDF] and Truvada® [TVD; F/TDF]).

Tenofovir alafenamide (TAF), developed by GSI, is a prodrug of tenofovir (TFV) that is predominantly hydrolyzed to TFV and subsequently phosphorylated in target lymphoid cells; thus, the antiviral molecular mechanism of action of TAF reflects that of TFV, as well as of the other TFV prodrug, tenofovir disoproxil fumarate (TDF).

TAF is approved as part of GSI's FDCs Descovy® (F/TAF), Genvoya® (E/C/F/TAF), and Odefsey® (R/F/TAF). TAF is more stable in plasma than TDF. It achieves higher intracellular

levels of the active phosphorylated metabolite TFV DP and approximately 90% lower circulating levels of TFV relative to TDF. This distinct metabolism of TAF offers an improved clinical profile compared with TDF (TDF is associated with an increased risk of nephrotoxicity and with early onset bone demineralization in adults). Moreover, TAF might exhibit a higher barrier to resistance in vivo when compared to TDF, because the level of TFV DP achieved in vivo upon loading with TAF is significantly higher (≥5 times) than with TDF. This FDC tablet, may promote better adherence to bPI-based regimens and represents a new, potent, safe and convenient treatment of HIV-1 infected subjects.

The D/C/F/TAF FDC tablet contains 800 mg of DRV (as 867 mg of DRV ethanolate), 150 mg of COBI (as 288.5 mg of COBI on silicon dioxide), 200 mg of FTC, and 10 mg of TAF (as 11.2 mg of the hemifumarate co-crystal).

The final formulation is a yellow to yellowish-brown, capsule-shaped, immediate release D/C/F/TAF FDC film-coated monolayer tablet manufactured via the co-dry granulation formulation concept. The D/C/F/TAF FDC tablet core contains silicon dioxide, croscarmellose sodium, microcrystalline cellulose and magnesium stearate as inactive ingredients. The tablets are film-coated with polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and yellow ferric oxide. The film coating is non-functional. There are no differences between the D/C/F/TAF FDC that was used in the Phase 3 clinical studies compared to the planned commercial formulation, except for the debossing (tablets without debossing in the double-blind phase of Study TMC114FD2HTX3001). The planned commercial tablet, also used in the 2 Phase 3 pivotal studies TMC114IDF3013, and the open-label phase of Study TMC114FD2HTX3001, is debossed with "8121" on one side and "JG" on the other side.

The recommended dosage of the D/C/F/TAF FDC tablet is one tablet taken orally once daily with food in adults and pediatric patients aged 12 years and older with body weight at least 40 kg.

2 PROPOSED INDICATION

TRADENAME, a fixed dose combination of darunavir, cobicistat, emtricitabine and tenofovir alafenamide, is indicated for the treatment of HIV-1 infection in adult and adolescent subjects aged 12 years and older

3 CLINICAL DEVELOPMENT PROGRAM

The development program of the D/C/F/TAF FDC product is based on 7 clinical studies conducted with the D/C/F/TAF FDC in adults: 2 Phase 3 studies which are still ongoing (TMC114FD2HTX3001 and TMC114IFD3013), 1 completed Phase 2 study (GS-US-299-0102), conducted by Gilead, and 4 completed Phase 1 studies of which 3 (TMC114FD2HTX1001, TMC114FD2HTX1002 and TMC114FD2HTX1004) were conducted by the Sponsor and 1 (GS-US-299-0101) by Gilead.

In order to facilitate intake for subjects that have difficulty swallowing larger tablets, one completed clinical study (TMC114FD2HTX1004) assessed the relative bioavailability of the D/C/F/TAF FDC tablet when split or crushed.

The pharmacokinetic properties of the individual components DRV, COBI, FTC, and TAF have been subject to comprehensive development programs to support their respective drug licenses, alone or in different combinations.

The absorption, distribution, metabolism, and elimination characteristics of the components of the D/C/F/TAF FDC are characterized from the results of studies with the D/C/F/TAF FDC tablet, combined with applicable data from earlier clinical studies with the individual components.

The D/C/F/TAF 800/150/200/10 mg FDC tablet is bioequivalent to combined administration as separate formulations of DRV, COBI, and F/TAF (F/TAF administered as FDC tablet) in healthy subjects as demonstrated in study TMC114FD2HTX1001.

From the D/C/F/TAF development program, the efficacy results (virologic response defined as HIV 1 RNA <50 copies/mL and virologic rebound, respectively) and results from resistance development analyses at Week 48 of the Phase 3 studies with the D/C/F/TAF FDC (TMC114FD2HTX3001 and TMC114IFD3013) were comparable to the efficacy and resistance results from historical studies. Therefore, the D/C/F/TAF FDC is appropriate for the treatment of ART-naïve subjects and ART experienced virologically suppressed subjects. D/C/F/TAF should not be used in PI experienced virologically suppressed subjects with known DRV resistance-associated mutations or with suspected DRV resistance, if no genotype available.

The efficacy and safety of the D/C/F/TAF FDC tablet in ART-experienced, virologically-failing, HIV-1 infected patients can be extrapolated from the D/C/F/TAF Phase 3 studies, and from the historical data on the individual components of D/C/F/TAF. In the Phase 3 studies with the D/C/F/TAF FDC tablet, exposures to DRV (TMC114FD2HTX3001 and TMC114IFD3013) and to TAF (TMC114FD2HTX3001) were consistent with historical pharmacokinetic (PK) data of boosted DRV and TAF administered as single. These D/C/F/TAF FDC PK results permit extrapolation to the durable historical efficacy data for the individual D/C/F/TAF components. The Sponsor therefore concludes that the D/C/F/TAF FDC is appropriate to be used by ART experienced, virologically-failing patients, in line with the DRV once daily indication. DC/C/F/TAF FDC should not be used in PI experienced, virologically failing patients harboring any DRV RAM.

The proposed use of D/C/F/TAF in special populations, such as subjects with renal impairment, relies on data from relevant clinical studies with the individual components that has been previously submitted to the FDA.

The efficacy and safety of the D/C/F/TAF FDC tablet in HIV 1 infected adolescents can be extrapolated from the adult data, given that the exposures of the individual components of the D/C/F/TAF FDC have been shown to be similar in adults and adolescents. The adult doses of

boosted DRV and F/TAF have shown potent efficacy, robust immunological response, and safety and tolerability in HIV 1 infected, ART naïve adolescents, similar to results from studies in HIV 1 infected, ART naïve adults. Furthermore, the exposure to COBI, as well as its capacity as a PK enhancer, have been shown to be similar in adults and adolescents. The Sponsor concludes that D/C/F/TAF FDC is appropriate to be used by adolescents, aged ≥12 to <18 years and weighing ≥40 kg.

4 CLINICAL EFFICACY AND SAFETY OF D/C/F/TAF FDC

Efficacy of D/C/F/TAF FDC

The efficacy results of the Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 provide a robust proof of the efficacy profile of the D/C/F/TAF FDC, with a high genetic barrier to resistance, in both ART-naïve and ART-experienced, virologically-suppressed, HIV-1 infected subjects:

- A comparable (noninferior) efficacy was observed with the D/C/F/TAF FDC versus the reference treatment, on the primary endpoints.
- Results of secondary efficacy, sensitivity, and subgroup analyses all support the primary endpoints observed with the D/C/F/TAF FDC compared to reference treatment.
- No genotypic or phenotypic resistance was observed against DRV and TAF. Development of resistance to FTC was observed in 1 subject.

Results of the Phase 2 Study GS-US-299-0102, in HIV-1 infected, ART-naïve adults showed similar virologic outcomes between the 2 treatment groups (D/C/F/TAF FDC and DRV+COBI+F/TDF) and noninferiority of D/C/F/TAF to DRV+COBI+F/TDF was determined (virologic response rate defined as HIV-1 RNA <50 copies/mL at Week 24, using the FDA snapshot approach.

Phase 3 Study TMC114FD2HTX3001 -- HIV-1 Infected, ART-naïve, Adult Subjects

In the Phase 3 Study TMC114FD2HTX3001, the Week 48 results of this study provide robust proof of efficacy and noninferiority of the D/C/F/TAF FDC compared to reference treatment as determined by the proportion of virologic responders (HIV-1 RNA <50 copies/mL at Week 48; FDA-defined snapshot approach). At Week 48, the virologic response rate (HIV-1 RNA <50 copies/mL; FDA snapshot approach; primary endpoint) was similar in both treatment groups: 91.4% (331/362) in the D/C/F/TAF group versus 88.4% (321/363) in the control group.

The virologic failure rate was low in each treatment group: 4.4% (16/362) in the D/C/F/TAF group compared to 3.3% (12/363) in the control group. The virologic response rate (HIV-1 RNA <50 copies/mL, FDA snapshot approach) in the PP analysis set was 94.0% (327/348) in the

D/C/F/TAF group compared to 92.2% (317/344) in the control group with a difference of (95% CI) 1.5 (-.3; 5.2) between D/C/F/TAF and control.

Phase 3 Study TMC114IFD3013 -- HIV-1 Infected, ART-experienced, Virologically Suppressed, Adult Subjects

The Week 48 results of this study in HIV-1 infected, ART-experienced, virologically-suppressed (HIV-1 RNA <50 copies/mL) subjects provide robust proof of efficacy.

The protocol-defined virologic rebound rate cumulative through Week 48 (primary endpoint) was very low and similar in both treatment groups (2.5% [19/763] with D/C/F/TAF FDC versus 2.1% [8/378] with control).

The results in the PP analysis set confirm the noninferiority of D/C/F/TAF vs control. The protocol-defined virologic rebound rate cumulative through Week 48 was low in both treatment groups for the PP analysis set: 1.9% (14/721) in the D/C/F/TAF group versus 0.8% (3/358) in the control group with a difference (95% CI) between D/C/F/TAF and control of 1.1 (-0.3; 2.5).

The results were consistent across various subgroups. In this treatment-experienced population, results from subgroup analyses also showed that the bPI used at screening (DRV, ATV, or LPV boosted with either rtv or COBI), and the level of ART experience (number of previous ARVs used; or previous ARV, PI, NRTI, or NNRTI virologic failure) did not affect the cumulative rebound rate through Week 48 in either treatment group.

At Week 48, the virologic response rate (HIV 1 RNA <50 copies/mL; FDA snapshot approach; key secondary endpoint) in the D/C/F/TAF group and the control group was similar (94.9% versus 93.7%). The virologic failure rate was very low in each treatment group (0.8% with D/C/F/TAF versus 0.5% with control) with a difference (95% CI) in virologic failure rate at Week 48 between D/C/F/TAF and control of 0.3 (0.7; 1.2).

The protocol-defined virologic rebound rate cumulative through Week 48 (primary endpoint) appeared to be predominantly driven by transient low-level viremia. Most of the protocol-defined rebounders through Week 48 were re-suppressed at Week 48 following continuation of the assigned study treatment.

Efficacy in HIV 1 Infected, Adolescent Subjects

D/C/F/TAF FDC is expected to show the same high level of efficacy in adolescents (aged ≥12 to <18 years) as in adults. This is based on the efficacy results of clinical studies with boosted DRV (TMC114-C230) and E/C/F/TAF (GS-US-292-0106) in adolescents showing similar efficacy profiles of the adult doses of the components in adolescents, and the pharmacokinetic data of boosted DRV and the other individual components of D/C/F/TAF FDC.

These results are further supported by the recent results from a Phase 2/3 switch study (GS-US-216-0128) in HIV-1 infected, virologically-suppressed adolescents (aged ≥12 to <18 years). In this study, subjects switched from DRV plus rtv or ATV plus rtv to DRV plus COBI 150 mg once daily or ATV plus COBI 150 mg once daily in combination with 2 NRTIs. This study showed that high rates of virologic suppression were maintained 48 weeks after switching from rtv to COBI in this adolescent population.

Clinical Resistance Data

Overall, in the Phase 3 studies included in this submission (Studies TMC114FD2HTX3001 and TMC114IFD3013), the following was observed in subjects receiving D/C/F/TAF:

- No DRV or primary PI RAMs were observed in any of the 1,125 subjects treated with D/C/F/TAF.
- No TAF RAMs were observed in any of the 1,125 subjects treated with D/C/F/TAF.
- 1 subject (0.1%) out of the 1,125 subjects treated with D/C/F/TAF developed an FTC RAM M184M/V/I, conferring phenotypic resistance to FTC.

Results from the Phase 2 studies included in this submission are in line with the Phase 3 resistance data. In all Phase 2/3 studies supporting D/C/F/TAF FDC, no genotypic or phenotypic resistance related to DRV was observed. Development of resistance to FTC or TDF/TAF in the background regimen was rare.

Efficacy results at Week 48 (virologic response defined as HIV-1 RNA <50 copies/mL and virologic rebound, respectively) of the Phase 3 studies with the D/C/F/TAF FDC (TMC114FD2HTX3001 and TMC114IFD3013) compare favorably to the efficacy results from historical studies. Furthermore, the low-level development of resistance observed in the studies with the D/C/F/TAF FDC is in line with other studies investigating DRV 800 mg once daily based regimens and studies investigating F/TAF vs F/TDF regimens.

Safety of D/C/F/TAF FDC

Phase 3 Study TMC114FD2HTX3001 in HIV 1 Infected, ART naïve, Adult Subjects

Safety findings from Study TMC114FD2HTX3001 are consistent with the known safety profiles of the individual components of the D/C/F/TAF FDC. In this study, where the only difference between the 2 treatment groups was the use of TAF rather than TDF, showed that D/C/F/TAF compared to DRV/COBI+F/TDF in treatment-naïve subjects has a better bone and renal safety profile and higher rates of abnormal fasting lipids, consistent with the higher lipid-lowering effect of TDF compared to TAF.

No deaths occurred up to the Week-48 visit. During the follow-up period, 1 subject in the control group experienced a fatal grade 4 SAE of sepsis after study drug interruption for a grade 4 sclerosing cholangitis. The event was considered not related to the study drug.

The incidence of SAEs was 4.7% in the D/C/F/TAF group compared to 5.8% in the control group. No SAEs were considered related to the study drug in the D/C/F/TAF group.

The incidence of AEs leading to permanent discontinuation of the study drug was 1.9% in the D/C/F/TAF group compared to 4.4% in the control group. AEs leading to discontinuation were isolated events.

The majority of AEs were grade 1 or 2. Grade 3 or 4 AEs were reported in 5.2% of subjects in the D/C/F/TAF group and in 6.1% of subjects in the control group. The most frequent (>2 (0.6%) subjects in either treatment group) grade 3 AE was low density lipoprotein (LDL) cholesterol increased in 4 subjects in the D/C/F/TAF group, and no subjects in the control group. No grade 4 AE was reported for >1 subject in either treatment group except for suicide attempt in 2 (0.6%) subjects in the control group.

AEs considered at least possibly related to study drug were more frequently reported in the control group compared to the D/C/F/TAF group. In the control group, there was a higher incidence of related AEs, of related SAEs and of AEs leading to discontinuation than in the D/C/F/TAF group. The related AEs in the D/C/F/TAF group were mainly known ADRs for one or more of the individual components of D/C/F/TAF. The most frequently reported related AEs in the D/C/F/TAF group were diarrhea, rash, and nausea (reported in 5.5% to 8.6% of subjects).

Phase 3 Study TMC114IFD3013 in HIV 1 Infected, ART experienced, Virologically suppressed, Adult Subjects

Safety findings from Study TMC114IFD3013 are consistent with the known safety profiles of the individual components of the D/C/F/TAF FDC. This study allowed assessment of whether the renal and bone safety potentially improved following a switch from a bPI+F/TDF based regimen to the D/C/F/TAF regimen. The renal and bone safety profile for D/C/F/TAF compared favorably with the control group, with an improvement of renal parameters and fewer decreases in bone mineral density (BMD), following switch to D/C/F/TAF compared to continuing the current (screening) F/TDF-based regimen.

No deaths occurred up to the Week-48 visit and the incidence of SAEs was low in both treatment groups. SAEs were isolated events. The most frequent SAE in the D/C/F/TAF group was pneumonia, reported in 3 (0.4%) subjects; all other SAEs (by preferred term) were reported in not more than 2 subjects per treatment group.

The incidence of AEs leading to permanent discontinuation of the study drug was low in both treatment groups. AEs leading to discontinuation were all isolated events (by preferred term reported in only 1 subject per treatment group).

Overall, the incidence of AEs was similar in both treatment groups. The incidence of the most frequent AEs (preferred term reported in ≥5% of subjects per treatment group) was also similar in both treatment groups and all AEs were reported in less than 11% of subjects per treatment group.

The majority of AEs were grade 1 or 2. Grade 3 or 4 AEs were reported in 6.8% of subjects in the D/C/F/TAF group and in 8.2% of subjects in the control group.

AEs considered at least possibly related to study drug in this open-label study were more frequently reported in the D/C/F/TAF group compared to the control. The related AEs in the D/C/F/TAF group were mainly known ADRs for one or more of the individual components of D/C/F/TAF. The most frequently reported related AEs in the D/C/F/TAF group were diarrhea, abdominal pain, headache, and nausea (reported in 1.0% to 2.1% of subjects).

Safety in HIV-1 Infected, Adolescent Subjects

Overall, the available safety data showed that the safety profile of the different components of D/C/F/TAF in adolescents is similar to that observed in adults.

Safety in Phase 1 Studies and Supportive Studies

There were no safety signals or unexpected findings in any of these Phase 1 studies with the D/C/F/TAF FDC tablet. No deaths, other SAEs, or AEs of grade 3 have been reported in these studies. In the Phase 1 studies with the D/C/F/TAF FDC tablet, 1 subject (TMC114FD2HTX1004) had a grade 4 AE (the event also led to discontinuation of study medication).

D/C/F/TAF has an Improved Bone Safety Profile Compared to a TDF-based Regimen

Treatment with D/C/F/TAF was associated with an improved bone safety profile, as compared to the TDF-based regimen in the control groups of the Phase 3 studies.

Treatment with D/C/F/TAF resulted in stable BMD at both the hip and spine for ART-naïve subjects (TMC114FD2HTX3001) compared to a decrease in BMD in the control group (differences between treatment groups were statistically significant at Week 48 with $p<0.001$ for hip and $p=0.004$ for spine).

Treatment with D/C/F/TAF resulted in improvements in BMD for subjects who switched from a TDF-based regimen compared to no relevant change in subjects who remained on that regimen (differences in both hip and spine at Week 48 were statistically significant with $p<0.001$ between treatment groups of Study TMC114IFD3013).

In the treatment of adolescents with F/TAF (administered as E/C/F/TAF), there were no notable changes from baseline in height-for-age adjusted spine and total body less head (TBLH) BMD

z-scores indicating that subjects mineralized bone at rates consistent with those of the age-matched normal reference population.

Patients with HIV-1 infection have an increased risk for bone disease and the improved bone mineral density profile observed with D/C/F/TAF represents a clinically meaningful advancement in therapeutic options, particularly for patients with risk factors for osteoporotic bone disease (eg, patients older than 50 years), and for adolescents with risks of delayed growth.

D/C/F/TAF has an Improved Renal Safety Profile Compared to a TDF-based Regimen

Results from the 48-week analysis demonstrated that treatment with D/C/F/TAF is associated with an improved renal safety profile, as compared to the TDF-based regimen in the control group, as demonstrated in Study TMC114FD2HTX3001 in ART-naïve subjects. Treatment with D/C/F/TAF resulted in a larger increase in $eGFR_{cyst}$ compared to the TDF-based control regimen reflecting the improved renal safety of TAF versus TDF.

Consistently, in the D/C/F/TAF group less proteinuria was observed compared to the control group. Treatment with the D/C/F/TAF regimen was also associated with less increases in markers of proximal renal tubulopathy (RBP to creatinine ratio, beta-2-microglobulin, and $FEPO_4$) compared to the TDF-based control regimen. No AEs compatible with PRT, including Fanconi syndrome, were reported.

Similar consistent trends were observed in Study TMC114IFD3013 in ART-experienced, virologically-suppressed subjects. In the D/C/F/TAF group, where subjects came from a regimen consisting of a PI boosted mainly with rtv and combined with F/TDF, there was a more favorable evolution of $eGFR_{cyst}$ (stable in D/C/F/TAF vs decrease in control), and a statistically significant improvement of proteinuria in D/C/F/TAF compared to control (decreased versus increased levels).

Treatment with the D/C/F/TAF regimen was also associated with less increases in markers of tubulopathy in this ART-experienced patient population compared to control (TDF-based regimen). No subjects met the study-defined criteria for potential subclinical proximal renal tubulopathy in the D/C/F/TAF group, versus 2 in the control group. No AEs compatible with PRT, including Fanconi syndrome, were reported.

Few subjects overall discontinued for renal AEs or renal laboratory abnormalities.

Improved Convenience

In the open-label Phase 3 Study TMC114IFD3013 which allowed to compare drug accountability between treatment groups (intake of 1 pill versus 3 pills), there was a trend for better adherence (>95% adherence to ARV intake) in the D/C/F/TAF group (91.6%) compared to the control group (85.3%).

The D/C/F/TAF FDC represents an efficacious and safe simplification to a once-daily, single-tablet, complete ARV regimen. The D/C/F/TAF FDC has a robust and sustained antiviral efficacy and immunologic recovery profile with a high genetic barrier to resistance and an improved patient convenience through fewer pills, which should lead to increased adherence, very low level of resistance development, and improved outcome in these patients. In addition, the D/C/F/TAF FDC has a favorable safety profile and treatment with the D/C/F/TAF FDC leads to modest and manageable lipid increases, and has an improved renal and bone safety profile compared to a regimen with a TDF-containing backbone.