Safety in Subjects With Renal Impairment

Subjects with $eGFR_{CG}$ ≥70 mL/min at screening were allowed to enter this study. Respectively 38 (10.5%) subjects in the D/C/F/TAF group and 31 (8.5%) subjects in the control group had a baseline $eGFR_{CG}$ between 60 and <90 mL/min (CKD stage 2). Data do not suggest any safety concerns in these HIV-1 infected subjects with renal impairment.

6.2.1.2.2. Bone Events/Fractures

Relevant AEs were retrieved under the review category 'Bone events of interest' to search for cases of fracture. The incidence of fractures was low and similar between treatment groups: 1.1% (4/362 subjects) with D/C/F/TAF FDC and 0.6% (2/363 subjects) with control. All fractures were traumatic. No fractures led to permanent discontinuation of the study drugs, none were considered to be related to study drug, and no grade 3 or 4 events were reported. For more information on bone events of interest, refer to Mod2.7.4/Sec3.1.1.1.3.

Bone Mineral Density (BMD)

BMD was measured at baseline and Weeks 24 and 48 by dual-energy X-ray absorptiometry (DXA) scans of the lumbar spine and hip in a substudy consisting of 212 subjects (113 in the D/C/F/TAF group and 99 in the control group).

BMD results from this study showed that the BMD evolution at the hip and spine region from baseline to Week 48 was more favorable in the D/C/F/TAF group compared to the control group:

- At Week 48, there were no clinically relevant percent changes in BMD at the hip and spine region in the D/C/F/TAF group. There were negative percent changes in BMD at the hip and spine region in the control group. The difference between treatment groups was statistically significant at each region (with p<0.001 for difference in hip; and p=0.004 for difference in spine at Week 48).
- 12.5% vs 2.4% (hip) and 12.5% vs 4.7% (spine) of subjects had a **≥3% increase** from baseline BMD at Week 48. Increases in BMD of ≥5% and ≥7% from baseline BMD at Week 48 showed similar results; see Table 11.
- 12.5% vs 44.7% (hip) and 27.1% vs 41.2% (spine) of subjects had a **≥3% decrease** from baseline BMD at Week 48. Decreases in BMD of ≥5% and ≥7% from baseline BMD at Week 48 showed similar results (≥5% decrease: 2.1% vs 25.9% for hip and 15.6% vs 22.4% for spine; and ≥7% decrease: 1.0% vs 7.1% for hip and 4.2% vs 8.2% for spine; see Table 11).
- 5.2% vs 1.2% (hip) and 3.1% vs 1.2% (spine) of subjects had **improvement** of the BMD clinical status from baseline at Week 48 (ie, T-score of osteoporosis to osteopenia, osteoporosis to normal, or osteopenia to normal; see Table 11).
- 3.1% vs 14.1% (hip) and 8.3% vs 15.3% (spine) of subjects had **worsening** of the BMD clinical status from baseline at Week 48 (ie, T-score of normal to osteopenia, normal to osteoporosis, or osteopenia to osteoporosis; see Table 11).

Nine (2.5%) and 16 (4.4%) subjects not taking antiosteoporotic drugs during the screening phase, started a new antiosteoporotic treatment during the treatment phase (see Table 11). These drugs included bisphosphonates, calcium, and vitamin D.

Table 11: Effects of D/C/F/TAF on Bone Mineral Density (BMD) (Study TMC114FD2HTX3001; ITT Population)

	D/C/F/TAF N=113		Control N=99	
	Hip	Spine	Hip	Spine
Bone Mineral Density (g/cm^2), N	113	113	99	99
Percent Change at Week 48, Mean (SE)	0.2107 (0.31503)	-0.6761 (0.41633)	-2.7302 (0.35104)	-2.3809 (0.40702)
Categorical Distribution at Week 48, N	96	96	85	85
<3% increase	32 (33.3%)	30 (31.3%)	18 (21.2%)	15 (17.6%)
≥3% increase	12 (12.5%)	12 (12.5%)	2 (2.4%)	4 (4.7%)
≥5% increase	5 (5.2%)	8 (8.3%)	0	3 (3.5%)
≥7% increase	2 (2.1%)	7 (7.3%)	0	2 (2.4%)
<3% decrease	35 (36.5%)	27 (28.1%)	27 (31.8%)	31 (36.5%)
≥3% decrease	12 (12.5%)	26 (27.1%)	38 (44.7%)	35 (41.2%)
≥5% decrease	2 (2.1%)	15 (15.6%)	22 (25.9%)	19 (22.4%)
≥7% decrease	1 (1.0%)	4 (4.2%)	6 (7.1%)	7 (8.2%)
BMD Clinical Status, N	113	113	99	99
Improvement in T-Score at Week 48[a]	5 (5.2%)	3 (3.1%)	1 (1.2%)	1 (1.2%)
Worsening in T-Score at Week 48[b]	3 (3.1%)	8 (8.3%)	12 (14.1%)	13 (15.3%)
N	362		363	
Subjects starting any antiosteoporotic drug during treatment	9 (2.5%)		16 (4.4%)	

[a] improvement is baseline T-score of osteoporosis to osteopenia at Week 48, osteoporosis to normal, or osteopenia to normal
[b] worsening is baseline T-score of normal to osteopenia at Week 48, normal to osteoporosis, or osteopenia to osteoporosis
BMD = bone mineral density; D/C/F/TAF = D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects.
Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.2.

Bone Biomarkers

Bone biomarkers (ie, including the bone resorption marker C-type collagen sequence [CTX], the bone formation markers procollagen type 1 N-terminal propeptide [P1NP] and alkaline phosphatase [ALP), and other bone biomarkers parathyroid hormone [PTH], and 25-hydroxy vitamin D) suggested less bone turnover in the D/C/F/TAF group than in control, with stable values for all markers in the D/C/F/TAF group and an increase in all markers in the control group.

6.2.1.2.3. Ocular Events

There were no AE reports consistent with posterior uveitis in either treatment group (refer to Mod2.7.4/Sec3.1.1.1.3).

6.2.1.2.4. Severe Skin/Rash Events

Relevant AEs were retrieved under the review category 'Severe skin events of interest' to search for potential cases of severe skin reactions and under 'Rash' to search for potential Rash cases. For more information on severe skin/rash events of interest, refer to Mod2.7.4/Sec3.1.1.1.3.

Severe skin events of interest were reported in 1.7% (6/362 subjects) in the D/C/F/TAF group vs 3.9% (14/363 subjects) in the control group. A medical review of these events concluded that:

- In the D/C/F/TAF group, no subjects experienced a severe skin reaction.
- In the control group, 3 (0.8%) subjects experienced severe skin reactions: 1 grade 4 event of Stevens-Johnson syndrome, 2 events [1 grade 2 and 1 grade 4] of toxic skin eruption. All 3 subjects discontinued study drug and recovered within approximately 2 to 3 weeks. None had a prior history of sulfonamide allergy, 2 of them had a history of allergy to other drugs.

Rash events of interest were reported in 13.0% of subjects in the D/C/F/TAF group and 10.7% of subjects in the control group.

- No subjects in the D/C/F/TAF group had a serious rash event. In the control group, 2 subjects experienced a serious rash event (both considered related); 1 of these subjects had a grade 3 event that led to permanent study drug discontinuation.
- Rash events led to permanent discontinuation of the study drug in 6 (1.7%) subjects in the D/C/F/TAF group vs 5 (1.4%) subjects in the control group. In addition, 1 subject in the control group had a grade 2 nonserious, study drug-related rash morbilliform that led to discontinuation.
- Rash events were considered study drug-related in 27 (7.5%) subjects in the D/C/F/TAF group vs 22 (6.1%) subjects in the control group. All but 1 study drug-related rash event had a worst severity of grade 1 or 2.
- The majority of rash events occurred in subjects without a history of sulfonamide allergy. Only 1 (0.3%) subject in the control group who experienced rash events had a history of sulfonamide allergy; the rash was due to a suspected Bactrim® allergy (overall, 6 [1.7%] subjects in the D/C/F/TAF group and 4 [1.1%] subjects in the control group had a known sulfonamide allergy at baseline).

6.2.1.2.5. Lipid-related Events

Relevant AEs were retrieved under the review category 'Lipid events of interest' to search for the lipid laboratory abnormalities reported as AEs by the investigators. Lipid-related events of interest were reported in 6.6% in the D/C/F/TAF group vs 3.3% in the control group. For more information on lipid-related events of interest, refer to Mod2.7.4/Sec3.1.1.1.3.

At Week 48, median changes (ie, increases) from baseline in fasting lipid parameters showed larger increases in the D/C/F/TAF group than in the control group, with statistically significant differences between the 2 treatment groups. These increases were not reflected in clinically relevant differences between the treatment groups in median changes from baseline in the ratio of total cholesterol (TC)/high density lipoprotein (HDL) cholesterol (median increases from baseline of 0.20 [163.0/41.8 mg/dL at baseline; 196.4/48.0 mg/dL at Week 48] with D/C/F/TAF vs 0.08 [162.4/42.2 mg/dL at baseline; 171.8/43.7 mg/dL at Week 48] with control).

In both treatment groups, the levels of all lipid parameters significantly increased by Week 24 (except for ratio of TC/HDL cholesterol in the control group), with larger changes being observed in the D/C/F/TAF group. These levels remained stable afterwards, through Week 48.

The percentages of subjects with treatment-emergent graded abnormalities in fasting lipid parameters were also higher in the D/C/F/TAF group than in the control group (see also ADRs in Section 6.5.1). Grade 3 or 4 increases in fasting lipid parameters were observed in 1.7% of subjects in the D/C/F/TAF group vs 0.6% of subjects in the control group for TC, 4.9% vs 1.2% of subjects for LDL cholesterol, and 1.2% vs 1.2% of subjects for triglycerides.

Categorical analysis at Week 48 by National Cholesterol Education Program (NCEP) Adult Treatment Panel III classification showed the following (D/C/F/TAF vs control group):

- Changes at Week 48 to a worsened NCEP category than at baseline were observed for 37.5% vs 13.8% of subjects (TC), 5.8% vs 16.2% (HDL cholesterol), 45.5% vs 23.9% (LDL cholesterol), and 28.2% vs 16.5% (triglycerides).
- Changes at Week 48 to an improved NCEP category than at baseline were observed for 1.6% vs 4.0% of subjects (TC), 32.0% vs 18.9% (HDL cholesterol), 6.8% vs 15.5% (LDL cholesterol), and 8.1% vs 7.4% (triglycerides).

No lipid abnormalities-related events led to permanent discontinuation of the study drugs and no serious or grade 4 events were reported. Grade 3 lipid abnormalities-related events of interest were reported in 7 (1.9%) subjects in the D/C/F/TAF FDC group and in 3 (0.8%) subjects in the control group.

Six (1.7%) and 2 (0.6%) subjects not taking lipid-lowering drugs during the screening phase, started a new lipid-lowering treatment during the treatment phase. These drugs included fibrates, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (-statins), nicotinic acid and derivatives, and other lipid-modifying agents (refer to Mod2.7.4/Sec3.1.1.1.3).

Mean changes from baseline at Week 48 in fasting lipid parameters, excluding subjects on lipid-lowering drugs in this study are provided in Appendix 4.

6.2.1.2.6. Liver Events

Relevant AEs were retrieved under the review category ‘Liver events of interest’ to search for possible cases of hepatotoxicity. For more information on liver events of interest, refer to Mod2.7.4/Sec3.1.1.1.3.

There were no cases meeting Hy’s law criteria in the study.

One grade 4 liver event of interest was reported in 1 (0.3%) subject in the control group (considered not related to the study drug and not leading to discontinuation of study drug). Grade 3 liver events of interest were reported in 2 (0.6%) subjects in the D/C/F/TAF group and in 1 (0.3%) subject in the control group. One of the grade 3 AEs in the D/C/F/TAF group was considered study drug-related and was reported as a 'liver injury' consisting of transient unexplained increases of ALT, AST and ALP between Week 4 and Week 12, without associated symptoms. The subject recovered while study drug was continued.

Subjects co-infected with hepatitis B or C were not allowed to participate in this study. During the study, 3 (0.8%) subjects in the D/C/F/TAF group and 3 (0.8%) in the control group developed hepatitis (hepatitis A in 1 subject in each treatment group and hepatitis C in the 4 other subjects [2 in each treatment group]). The medical review does not suggest a different

clinical or laboratory safety profile in the 4 subjects who developed a hepatitis C co-infection during the study.

There were no clinically relevant changes from baseline through Week 48 in median values for the liver-related laboratory tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin [direct, indirect, and total]) (see also ADRs in Table 15). During the treatment phase, elevated liver enzymes were observed for 5.6% of subjects with D/C/F/TAF vs 7.3% with control (ALT), 9.5% vs 10.1% (AST), and 0.6% vs 2.8% (ALP).

6.2.1.2.7. Other Events of Interest

For the other events of interest (hyperglycemia, immune reconstitution inflammatory, coronary artery, pancreas, lipodystrophy, cardiac conduction, convulsion, lactic acidosis, and hemophilia/bleeding events [see Section 4.1.1]), refer to Mod2.7.4/Sec3.1.1.1.3 and Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3. There were no noteworthy findings.

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

The Week-48 results of the Phase 3 Study TMC114IFD3013 demonstrated that the D/C/F/TAF FDC tablet was well tolerated in 763 HIV-1 infected, ART-experienced, virologically-suppressed adults, switching from a bPI+F/TDF-based regimen, over a mean (SD) exposure of 47.2 (6.6) weeks (refer to Mod2.7.4/Sec3.1.1.2.1).

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 BMD, following switch to D/C/F/TAF compared to continuing the current (screening) F/TDF-based regimen.

6.2.2.1. AE Overview in HIV-1 Infected, ART-experienced, Virologically-suppressed Adults

No deaths occurred up to the Week-48 visit and the incidence of SAEs was low in both treatment groups (see Table 12 and refer to Mod2.7.4/Sec3.1.1.2.2). 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. One SAE was considered related to D/C/F/TAF (ie, pancreatitis).

The incidence of AEs leading to permanent discontinuation of the study drug was low in both treatment groups (see Table 12). AEs leading to discontinuation were all isolated events (by preferred term reported in only 1 subject per treatment group).

Table 12: Adverse Events Summary Table (Study TMC114IFD3013; ITT Population)

Number (%) of subjects with:	D/C/F/TAF (N=763)		Control (N=378)	
	Overall	Related	Overall	Related
≥1 AE	625 (81.9%)	138 (18.1%)	311 (82.3%)	28 (7.4%)
≥1 fatal AE	0	0	0	0
≥1 SAE	35 (4.6%)	1 (0.1%)	18 (4.8%)	0
≥1 AE for which study medication was permanently stopped	11 (1.4%)	8 (1.0%)	5 (1.3%)	3 (0.8%)
≥1 worst grade 3 AE	43 (5.6%)	10 (1.3%)	24 (6.3%)	3 (0.8%)
≥1 worst grade 4 AE	9 (1.2%)	0	7 (1.9%)	1 (0.3%)

AE = adverse event, D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects per treatment group; SAE = serious adverse event.

Source: Mod2.7.4/Sec3.1.1.2.2 and Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab29.

Overall, the incidence of AEs was similar in both treatment groups (see Table 12). 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 (refer to Mod2.7.4/Sec3.1.1.2.2 and Mod5.3.5.1/ TMC114IFD3013-W48-CSR/Tab30).

The majority of AEs were grade 1 or 2 (see Table 12 and refer to Mod2.7.4/Sec3.1.1.2.2). 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 group (see Table 12 and refer to Mod2.7.4/Sec3.1.1.2.2). 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).

The ADR profile of D/C/F/TAF based on this study with HIV-1 infected, ART-experienced, virologically-suppressed adults is provide in Section 6.5.

6.2.2.2. Events of Interest in HIV-1 Infected, ART-experienced, Virologically-suppressed Adults

In the D/C/F/TAF group, there was a higher frequency of rash (2.5% difference) and lipid-related events (2.9% difference) which are known ADRs for DRV/COBI (see sections below).

6.2.2.2.1. Renal Events

AEs From Renal System Organ Class (SOC)

Renal and urinary disorders were observed in 3.9% of subjects in the D/C/F/TAF group vs 4.8% in the control group (refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att TSFAE02_EXT). In addition, relevant AEs were retrieved under the review category 'Renal events of interest' to search for potential cases of proximal renal tubulopathy. Renal AEs of interest were reported in 1.7% of subjects in the D/C/F/TAF group and 1.3% of subjects in the control group. Renal AEs of interest consisted mainly of laboratory-related events (1.4% vs 0.8%). Clinical renal AEs of

interest were reported in 0.3% vs 0.5% of subjects, and led to study drug discontinuation in 0.1% (1 subject) vs 0.5% (2 subjects) of subjects. There were no serious renal events of interest. No AEs compatible with PRT, including Fanconi syndrome, were reported. For more information on renal events of interest, refer to Mod2.7.4/Sec3.1.1.2.3.

Glomerular Function

Estimated Glomerular Filtration Rate (eGFR) Based on Serum Cystatin C

- In the D/C/F/TAF group, $eGFR_{cyst}$ (calculated using the CKD-EPI method) remained stable (LS means estimates at Week 48 vs baseline: -0.4 mL/min/1.73 m^2). In the control group, the mean $eGFR_{cyst}$ decreased (LS means estimates at Week 48 vs baseline: -1.8 mL/min/1.73 m^2), but the changes were minimal and not clinically significant. There was a statistically significant difference between the treatment groups in the mean change from baseline at Week 48 of $eGFR_{cyst}$ (p=0.034, ANCOVA).
- Shifts in $eGFR_{cyst}$ CKD stage from baseline to last on-treatment value, were more favorable in the D/C/F/TAF group compared to the control group: 5.3% (D/C/F/TAF) vs 3.7% (control) had an improved $eGFR_{cyst}$ CKD stage and 4.5% vs 7.2% had a worsened $eGFR_{cyst}$ CKD stage.

Serum Creatinine

- In both treatment groups, there was a non-clinically significant increase from baseline in mean serum creatinine (LS means estimates at Week 48 vs baseline: +1.3 µmol/L in the D/C/F/TAF group and +0.7 µmol/L in the control group). There was no statistically significant difference between treatment groups in the mean change from baseline at Week 48 in serum creatinine.

Estimated Glomerular Filtration Rate (eGFR) Based on Serum Creatinine

- Results of $eGFR_{CR}$ ($eGFR_{CG}$ or $eGFR_{CKD\text{-}EPI}$) mirror the findings on serum creatinine.
- In both treatment groups, there was a non-clinically significant decrease from baseline in mean $eGFR_{CG}$ (LS means estimates at Week 48 vs baseline: -0.9 mL/min in the D/C/F/TAF group and -0.2 mL/min in the control group). There was no statistically significant difference between treatment groups in the mean change from baseline at Week 48 of $eGFR_{CG}$.

Proteinuria

In the D/C/F/TAF FDC group, there was an improvement of the proteinuria at Week 48 vs baseline, compared to the control group, as shown by:

- Median levels of UACR decreased at Week 48 in the D/C/F/TAF group (-0.76 mg/g) vs increased levels in the control group (0.40 mg/g). For UPCR, decreases of median values were observed in both treatment groups; the decreases were greater in the D/C/F/TAF group. The difference in median change from baseline in UPCR or UACR between the treatment groups was statistically significant at Week 24 and Week 48.
- At Week 48, compared to baseline, 6.2% vs 14.2% of subjects had clinically significant albuminuria (UACR ≥30 mg/g); 2.1% vs 6.2% of subjects with an UACR <30 mg/g (albuminuria within normal range) at baseline had a worsening to an UACR ≥30 mg/g (clinically significant albuminuria) at Week 48.
- Findings were similar for UPCR.

Proximal Tubular Function

No AEs compatible with PRT, including Fanconi syndrome, were reported.

Clinical renal events of interest were reported in 0.3% (2 subjects) in the D/C/F/TAF group vs 0.5% (2 subjects) in the control group. One renal tubular disorder was reported in the control group (ATV/rtv+F/TDF); the grade 1 AE was nonserious, considered related to the study drug, and led to permanent study drug discontinuation. None of the other 3 clinical renal events of interest reported in this study were suggestive of a potential PRT upon medical review.

Subclinical Proximal Renal Tubulopathy

Renal events of interest consisted mainly of laboratory-related events (1.4% [11 subjects] in the D/C/F/TAF group vs 0.8% [3 subjects] in the control group). Throughout the entire treatment period, none of the subjects in the D/C/F/TAF group and 2 (0.5%) subjects in the control group met the study-defined criteria for a treatment-emergent potential subclinical PRT (ie, confirmed creatinine increase ≥0.4 mg/dL and abnormalities in at least 1 of the 3 other markers of tubular dysfunction [hypophosphatemia, proteinuria, and normoglycemic glycosuria]). None of these 2 control subjects had AEs consistent with PRT reported. In addition, in the D/C/F/TAF group compared to the control group, consistently less subjects presented increases in any of the markers of proximal renal tubular dysfunction during the study.

Tubulopathy Markers

In the D/C/F/TAF FDC group, there were fewer abnormalities than in the control group of other markers of tubulopathy, ie, RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio (refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.1.3.5).

Levels of $FEPO_4$ increased in both treatment groups. There were no statistically significant differences between the treatment groups at Week 24 and Week 48. A similar number of subjects with an $FEPO_4$ ≤20% at baseline in the D/C/F/TAF group (15.8%) and in the control group (13.9%) had a worsening to an $FEPO_4$ >20% at Week 48.

Safety in Subjects With Renal Impairment

Subjects with mild renal impairment ($eGFR_{CG}$ ≥50 and <70 mL/min) were allowed to enter this study. A total of 84 subjects with mild renal impairment ($eGFR_{CG}$ ≥50 and <70 mL/min) were included in this study, of whom 55 subjects received D/C/F/TAF FDC. In addition, 5 subjects with moderate renal impairment ($eGFR_{CG}$ ≥30 and <50 mL/min) were included in this study, of whom 3 subjects received D/C/F/TAF FDC. The available data do not suggest any safety concerns in these HIV-1 infected subjects with renal impairment.

6.2.2.2.2. Bone Events/Fractures

Relevant AEs were retrieved under the review category 'Bone events of interest' to search for cases of fracture. The incidence of fractures was low and similar between treatment groups: 1.2% (9/763 subjects) with D/C/F/TAF FDC and 0.5% (2/378 subjects) with control. All fractures were secondary to a trauma and none were suggestive of an osteoporotic fracture. No fractures led to permanent discontinuation of the study drugs, no fractures were considered to be related to

study drug, and no grade 4 events were reported. For more information on bone events of interest, refer to Mod2.7.4/Sec3.1.1.2.3.

Bone Mineral Density (BMD)

BMD was measured at baseline and Weeks 24 and 48 by DXA scans of the lumbar spine and hip.

BMD results from this study showed that the BMD evolution at the hip and spine region from baseline to Week 48 was more favorable in the D/C/F/TAF group compared to the control group:

- At Week 48, there was a positive percent change in BMD in the D/C/F/TAF group, while in the control group, there were no relevant percent changes. The differences between treatment groups was statistically significant ($p<0.001$ for differences in both hip and spine at Week 48).
- 20.2% with D/C/F/TAF vs 4.1% with control (hip), and 31.8% vs 8.9% (spine) of subjects had a **≥3% increase** from baseline BMD at Week 48. Increases in BMD of ≥5% and ≥7% from baseline BMD at Week 48 showed similar results; see Table 13.
- 2.1% with D/C/F/TAF vs 8.2% with control (hip), and 7.8% vs 19.8% (spine) of subjects had a **≥3% decrease** from baseline BMD at Week 48. Decreases in BMD of ≥5% and ≥7% from baseline BMD at Week 48 showed similar results (≥5% decrease: 0% vs 2.1% for hip and 1.6% vs 8.9% for spine; and ≥7% decrease: 0% vs 0% for hip and 1.0% vs 3.0% for spine; see Table 13).
- 3.2% with D/C/F/TAF vs 1.0% with control (hip), and 8.3% vs 4.0% (spine) of subjects had **improvement** of the BMD clinical status from baseline at Week 48 (ie, T-score of osteoporosis to osteopenia, osteoporosis to normal, or osteopenia to normal; see Table 13).
- 0% with D/C/F/TAF vs 2.1% with control (hip), and 3.6% vs 4.0% (spine) of subjects had **worsening** of the BMD clinical status from baseline at Week 48 (ie, T-score of normal to osteopenia, normal to osteoporosis, or osteopenia to osteoporosis; see Table 13).

Eighteen (2.4%) and 11 (2.9%) subjects not taking antiosteoporotic drugs during the screening phase, started a new antiosteoporotic treatment during the treatment phase (see Table 13). These drugs included bisphosphonates, calcium, and vitamin D.

Table 13: Effects of D/C/F/TAF on Bone Mineral Density (BMD) (Study TMC114IFD3013; ITT Population)

	D/C/F/TAF N=209		Control N=108	
	Hip	Spine	Hip	Spine
Bone Mineral Density (g/cm^2), N	209	209	108	108
Percent Change at Week 48, Mean (SE)	1.4305 (0.17060)	1.4903 (0.24122)	-0.2636 (0.20338)	-0.6275 (0.28453)
Categorical Distribution at Week 48, N	188	192	97	101
<3% increase	106 (56.4%)	70 (36.5%)	42 (43.3%)	33 (32.7%)
≥3% increase	38 (20.2%)	61 (31.8%)	4 (4.1%)	9 (8.9%)
≥5% increase	9 (4.8%)	29 (15.1%)	1 (1.0%)	1 (1.0%)
≥7% increase	4 (2.1%)	6 (3.1%)	0	1 (1.0%)
<3% decrease	37 (19.7%)	45 (23.4%)	43 (44.3%)	38 (37.6%)
≥3% decrease	4 (2.1%)	15 (7.8%)	8 (8.2%)	20 (19.8%)
≥5% decrease	0	3 (1.6%)	2 (2.1%)	9 (8.9%)
≥7% decrease	0	2 (1.0%)	0	3 (3.0%)
BMD Clinical Status, N	209	209	108	108
Improvement in T-Score at Week 48[a]	6 (3.2%)	16 (8.3%)	1 (1.0%)	4 (4.0%)
Worsening in T-Score at Week 48[b]	0 (0%)	7 (3.6%)	2 (2.1%)	4 (4.0%)
N	763		378	
Subjects starting any antiosteoporotic drug during treatment	18 (2.4%)		11 (2.9%)	

[a] Improvement is baseline T-score of osteoporosis to osteopenia at Week 48, osteoporosis to normal, or osteopenia to normal
[b] Worsening is baseline T-score of normal to osteopenia at Week 48, normal to osteoporosis, or osteopenia to osteoporosis.
BMD = bone mineral density; D/C/F/TAF = D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects.
Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.2.

Bone Biomarkers

Bone biomarkers (ie, including CTX, P1NP, ALP, PTH, and 25-hydroxy vitamin D) suggested less bone turnover in the D/C/F/TAF group than in control, with a decrease for all markers in the D/C/F/TAF group and stable values for all markers in the control group.

6.2.2.2.3. Ocular Events

There were no AE reports consistent with posterior uveitis in either treatment group (refer to Mod2.7.4/Sec3.1.1.2.3).

6.2.2.2.4. Severe Skin/Rash Events

Relevant AEs were retrieved under the review category 'Severe skin events of interest' to search for potential cases of severe skin reactions and under 'Rash' to search for potential Rash cases. For more information on severe skin/rash events of interest, refer to Mod2.7.4/Sec3.1.1.2.3.

Severe skin events: There were no AEs reported consistent with a severe skin reaction in either treatment group.

Rash events: The incidence of rash events of interest was low overall, but it was higher in the D/C/F/TAF group compared to the control group, ie, 4.6% (35/763 subjects) with D/C/F/TAF FDC and 2.1% (8/378 subjects) with control. In the D/C/F/TAF group, rash events were reported more frequently in subjects switching at baseline from a regimen not containing DRV as PI or not containing COBI as booster. None of the rash events were of clinical concern as these were at most grade 2 (all drug-related events were grade 1), transient, nonserious, and none led to permanent discontinuation of the study drugs.

6.2.2.2.5. Lipid-related Events

Relevant AEs were retrieved under the review category 'Lipid events of interest' to search for the lipid laboratory abnormalities reported as AEs by the investigators. Lipid-related events of interest were reported in 5.5% in the D/C/F/TAF group vs 2.6% in the control group. For more information on lipid-related events of interest, refer to Mod2.7.4/Sec3.1.1.2.3.

Increases from baseline in median fasting lipid parameters at Week 48 were larger in the D/C/F/TAF group than in the control group (except for triglycerides), with statistically significant differences between the 2 treatment groups. These changes were not reflected in clinically relevant differences between the treatment groups in median changes from baseline in the ratio of TC/HDL cholesterol (0.20 [184.3/47.4 mg/dL at baseline; 205.0/50.3 mg/dL at Week 48] with D/C/F/TAF vs 0.10 [181.4/48.0 mg/dL at baseline; 186.0/47.0 mg/dL at Week 48] with control).

In the D/C/F/TAF group, the levels of all lipid parameters significantly increased by Week 24 and remained stable through Week 48.

The percentages of subjects with treatment-emergent graded abnormalities in fasting lipid parameters were also higher in the D/C/F/TAF group than in the control group (see ADRs in Section 6.5.2). Grade 3 or 4 increases in fasting lipid parameters were observed in 3.8% of subjects in the D/C/F/TAF group vs 1.4% of subjects in the control group for TC, 6.5% vs 1.7% of subjects for LDL cholesterol, and 1.9% vs 2.2% of subjects for triglycerides.

Categorical analysis at Week 48 by NCEP Adult Treatment Panel III classification showed the following (D/C/F/TAF vs control group):

- Worsened NCEP categories at Week 48 vs baseline were observed for 36.4% vs 15.9% of subjects (TC), 7.6% vs 13.2% (HDL cholesterol), 46.3% vs 25.5% (LDL cholesterol), and 16.9% vs 20.7% (triglycerides).
- Improved NCEP categories at Week 48 vs baseline were observed for 7.5% vs 11.4% of subjects (TC), 21.9% vs 12.6% (HDL cholesterol), 10.8% vs 16.8% (LDL cholesterol), and 13.2% vs 12.0% (triglycerides).

No lipid abnormalities-related events led to permanent discontinuation of the study drugs and no serious or grade 4 events were reported. Grade 3 lipid abnormalities-related events of interest were reported in 7 (0.9%) subjects in the D/C/F/TAF FDC group and in 2 (0.5%) subjects in the control group.

Twenty (2.6%) and 7 (1.9%) subjects not taking lipid-lowering drugs during the screening phase, started a new lipid-lowering treatment during the treatment phase. These drugs included fibrates, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (-statins), nicotinic acid and derivatives, and other lipid-modifying agents (refer to Mod2.7.4/Sec3.1.1.1.3).

Mean changes from baseline at Week 48 in fasting lipid parameters, excluding subjects on lipid-lowering drugs in this study are provided in Appendix 4.

6.2.2.2.6. Liver Events

Relevant AEs were retrieved under the review category 'Liver events of interest' to search for possible cases of hepatotoxicity. For more information on liver events of interest, refer to Mod2.7.4/Sec3.1.1.2.3.

There were no cases meeting Hy's law criteria in the study.

One liver event in the D/C/F/TAF group led to permanent discontinuation of the study drug (increased ALT; grade 1; considered related to study drug).

One liver event in the control group was reported as serious (acute hepatitis; grade 4; not related to study drug). Liver events of at least grade 3 were reported in 4 (0.5%) subjects in the D/C/F/TAF group vs 6 (1.6%) subjects in the control group.

Subjects co-infected with hepatitis B or C were not allowed to participate in this study. During the study, 5 (0.7%) subjects in the D/C/F/TAF group and 6 (1.6%) subjects in the control group developed hepatitis (unspecified hepatitis in 1 subject in the control group and hepatitis C in the 10 other subjects). The medical review did not indicate safety concerns in the 10 subjects who developed a viral hepatitis C co-infection during the study.

There were no clinically relevant changes from baseline through Week 48 in median values for the liver-related laboratory tests (AST, ALT, bilirubin [direct, indirect, and total]) (see also ADRs in Table 17). The majority of grade 3 or 4 clinical laboratory abnormalities consisted of increases in AST (1.4% with D/C/F/TAF and 2.7% with control), ALT (1.1% with D/C/F/TAF and 2.4% with control), and total bilirubin (0.1% with D/C/F/TAF and 5.9% with control). The imbalance in bilirubin abnormalities is explained by the subjects on ATV (for which hyperbilirubinemia is a known effect) in the control group. All other grade 3 or 4 abnormalities occurred in less than 1% of subjects.

6.2.2.2.7. Other Events of Interest

For the other events of interest (hyperglycemia, immune reconstitution inflammatory, coronary artery, pancreas, lipodystrophy, cardiac conduction, convulsion, lactic acidosis, and hemophilia/ bleeding events [see Section 4.1.1]), refer to Mod2.7.4/Sec3.1.1.2.3 and Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3. There were no noteworthy findings.

6.3. 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.

Refer to the following sections for more information:

- For an overview of the 2 Phase 2/3 studies in HIV-1 infected, adolescent subjects (including a summary of the study designs), see Table 1.
- For more details on the results of the completed Phase 2 Study TMC114-C230 with DRV/rtv 800/100 mg + AZT/3TC or ABC/3TC once daily, refer to Mod2.7.4/Sec3.2.1.
- For more details on the results of the ongoing Phase 2/3 Study GS-US-292-0106 with E/C/F/TAF FDC (150/150/200/10 mg) once daily, refer to Mod2.7.4/Sec3.2.2.
- For details on recent results from a Phase 2/3 switch study (Study GS-US-216-0128) with DRV+COBI or ATV+COBI + 2 NRTIs once daily, see Section 3.6.[5,20]

In the sections below, a summary is given of the findings for specific safety topics with TAF and DRV in adolescents (ie, renal, bone and lipid-related events).

6.3.1. Renal Events in Adolescents

In adolescents, the effects of TAF on renal toxicity have been assessed in Study GS-US-292-0106 (E/C/F/TAF 150/150/200/10 mg) (Mod2.7.4/Sec3.2.2.3).

Glomerular Function

Changes from baseline in serum creatinine and $eGFR_{CR}$ were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine, and are not considered reflective of changes in actual glomerular filtration rate.

The following changes in serum creatinine and $eGFR_{CR}$ (based on serum creatinine using Schwartz formula) were observed:

- Increases from baseline in median serum creatinine at Week 1, which remained stable through Week 48.
- Decreases from baseline in median $eGFR_{CR}$ at Week 1, which remained stable through Week 48.

There were decreases from baseline in proteinuria, as assessed by UPCR (median percentage change was -27.0% at Week 48).

Proximal Tubular Function

No AEs compatible with PRT, including Fanconi syndrome, were reported.

Other

Urinary retention was reported in a single subject as a serious renal AE.

6.3.2. Bone Events in Adolescents

In adolescents, the effects of TAF on bone toxicity have been assessed in Study GS-US-292-0106 (E/C/F/TAF 150/150/200/10 mg) (Mod2.7.4/Sec3.2.2.3).

Bone Mineral Density

BMD was measured at baseline and Weeks 24 and 48 by DXA scans of 1) the lumbar spine and 2) Total Body Less Head (TBLH).

BMD results from this study with adolescents showed the following:

- Small median changes (increases <5%) were observed in spine and TBLH BMD at Weeks 24 and 48;
- Few subjects had a ≥4% decrease from baseline in spine BMD (3 subjects at Weeks 24 and 1 of these subjects still at Week 48) and no subject had a ≥4% decrease from baseline in TBLH BMD;
- No notable changes from baseline in height-age adjusted spine and TBLH BMD z-scores at Weeks 24 and 48.

These results indicate that subjects mineralized bone at rates consistent with those of the reference population.

6.3.3. Lipid-related Events in Adolescents

In adolescents, the effects of DRV on fasting lipid parameters in the absence of the lipid-protective effect of TDF have been shown in Study TMC114-C230 (DRV/rtv 800/100 mg with AZT/3TC or ABC/3TC as background ARV; refer to Mod2.7.4/Sec3.2.1.3).

In Study TMC114-C230, individual fasting lipid parameters were increased, whereas changes in ratio of TC/HDL cholesterol were minimal (ratio of TC/HDL cholesterol was 0.26 at Week 24 and -0.43 at Week 48).

6.4. Safety in Phase 1 Studies and Supportive Studies for Safety

6.4.1. Phase 1 Biopharmaceutical/Pharmacokinetic Studies With D/C/F/TAF FDC in Healthy Subjects

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 (Study TMC114FD2HTX1004) had a grade 4 AE (asymptomatic increased lipase levels).

For an overview of the Phase 1 studies with a D/C/F/TAF FDC tablet in healthy subjects (including a summary of the study designs), see Mod2.7.4/Tab2.

6.4.2. Phase 1 QT Studies With Individual Components

No thorough QT studies have been performed with the D/C/F/TAF FDC tablet. However, thorough QT studies have been performed with the individual components of the D/C/F/TAF FDC tablet (refer to Mod2.7.4/Sec3.3.1). The results from these studies can be used to assess the CV safety of the D/C/F/TAF FDC.

Results from the thorough QT studies with DRV, COBI, and TAF did not reveal any safety concerns. The thorough QT studies with DRV (Study TMC114-C153 with DRV/rtv 1600/100 mg or 800/100 mg), COBI (Study GS-US-216-0107 with COBI 250 mg or 400 mg) and TAF (Study GS-US-120-0107 with TAF 25 or 125 mg) were interpreted as negative according to the E14 ICH Guidelines, since the results demonstrated that administration of these compounds was not associated with a clinically relevant increase in QT interval. These results do not indicate a safety concern for the D/C/F/TAF FDC tablet.

6.4.3. Studies in Subjects With Renal Impairment

Historical Phase 1 studies and Phase 3 studies with COBI, FTC, or TAF in adult subjects with variable degrees of renal impairment did not raise safety concerns and support the use of these ARTs in subjects with an $eGFR_{CG} \geq 30$ mL/min without the need to adjust the ART dose. Two of these studies are of more specific interest, as they concern DRV with COBI (in combination with 2 NRTIs) in HIV-1 infected subjects with stable, mild to moderate renal impairment ($eGFR_{CG}$ between 50 and <90 mL/min; Study GS-US-236-0118) and TAF (administered as E/C/F/TAF) in HIV-1 infected subjects with mild to moderate renal impairment ($eGFR_{CG}$ between 30 and <70 mL/min; Study GS-US-292-0112). The conclusions of these studies are as follows (refer to Mod2.7.4/Sec3.3.2):

- Results of Study GS-US-236-0118 demonstrated that COBI-boosted PI (DRV) containing treatments do not alter renal function;
- Results of Study GS-US-292-0112 showed that no dose adjustment of E/C/F/TAF is required for subjects with $eGFR_{CG}$ of ≥30 mL/min.

6.5. Summary of the D/C/F/TAF Adverse Drug Reaction Profile

The AEs reported during Studies TMC114FD2HTX3001, TMC114IFD3013, and GS-US-299-0102 were reviewed by internal medical experts for identification of ADRs associated with D/C/F/TAF (refer to Mod2.7.4/Sec2.2.1.2 and Mod2.7.4/App2 for details on this analysis).

An overview of ADRs in the Week-48 analyses of Studies TMC114FD2HTX3001 and TMC114IFD3013 is presented below. Refer to Mod2.7.4/Sec4 for more information. No new ADRs were identified in these studies compared to the known safety profile of DRV/COBI and F/TAF. Overall, the incidence of ADRs is higher in both treatment groups (D/C/F/TAF and control) in Study TMC114FD2HTX3001 (ART-naïve) compared to Study TMC114IFD3013 (ART-experienced, virologically-suppressed), which can be explained by the different populations studied.

6.5.1. Adverse Drug Reactions in ART-naïve Subjects

The proportion of subjects who discontinued treatment with D/C/F/TAF due to ADRs, regardless of severity, was 1.9% (7 subjects). No serious ADRs were reported with D/C/F/TAF. The majority of the ADRs reported during treatment with D/C/F/TAF were mild (grade 1) in severity.

An overview of ADRs of at least grade 2 in severity reported in Study TMC114FD2HTX3001 is presented in Table 14. The most common ADRs for D/C/F/TAF (incidence ≥2%) of at least moderate severity (≥grade 2) were diarrhea (3.9%) and rash (4.4%). There was only 1 grade 3 ADR identified with the D/C/F/TAF FDC (headache), and no grade 4 ADRs.

Laboratory abnormalities, grade 2 to 4, reported in Study TMC114FD2HTX3001 and considered ADRs for D/C/F/TAF are shown in Table 15.

Table 14: Incidence (%) of Adverse Drug Reactions for D/C/F/TAF of at Least Grade 2 Severity in HIV-1 Infected, ART-naïve Subjects (Study TMC114FD2HTX3001; ITT Population)

System Organ Class ADR[a]	D/C/F/TAF (N=362)	Control (N=363)
Any ADR of grade 2, 3 or 4	47 (13.0%)	58 (16.0%)
Gastrointestinal disorders	22 (6.1%)	32 (8.8%)
Diarrhea	14 (3.9%)	18 (5.0%)
Dyspepsia	4 (1.1%)	3 (0.8%)
Nausea	3 (0.8%)	13 (3.6%)
Vomiting	3 (0.8%)	6 (1.7%)
Abdominal pain	2 (0.6%)	3 (0.8%)
Flatulence	1 (0.3%)	0
Skin and subcutaneous tissue disorders	17 (4.7%)	18 (5.0%)
Rash	16 (4.4%)	16 (4.4%)
Pruritus	2 (0.6%)	2 (0.6%)
Angioedema	1 (0.3%)	0
Stevens-Johnson syndrome	0	1 (0.3%)
Nervous system disorders	7 (1.9%)	11 (3.0%)
Headache	7 (1.9%)	11 (3.0%)
General disorders and administration site conditions	5 (1.4%)	7 (1.9%)
Fatigue	5 (1.4%)	6 (1.7%)
Asthenia	0	1 (0.3%)
Musculoskeletal and connective tissue disorders	2 (0.6%)	2 (0.6%)
Myalgia	2 (0.6%)	2 (0.6%)
Metabolism and nutrition disorders	0	2 (0.6%)
Anorexia	0	2 (0.6%)
Psychiatric disorders	0	2 (0.6%)
Abnormal dreams	0	2 (0.6%)

ADR = adverse drug reaction; ART = antiretroviral treatment; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HIV-1 = human immunodeficiency virus type 1; ITT = intent-to-treat (population); N = number of subjects.

[a] ADR terms comprise grouped preferred terms; all individual preferred terms for ADRs are described in Mod2.7.4/App4.

Source: Mod2.7.4/App4

Table 15: Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Drug Reactions for D/C/F/TAF in HIV-1 Infected, ART-naïve Subjects (Study TMC114FD2HTX3001; ITT Population)

Phase = Treatment

	Limits[a]	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N		362	363
Hepatic Parameters			
Alanine aminotransferase (ALT), high, N		358	358
Any treatment emergent grade 2, 3 or 4		6 (1.7%)	9 (2.5%)
Treatment emergent grade 2	2.5 to <5.0x ULN	1 (0.3%)	6 (1.7%)
Treatment emergent grade 3	5.0 to <10.0x ULN	4 (1.1%)	2 (0.6%)
Treatment emergent grade 4	≥10.0x ULN	1 (0.3%)	1 (0.3%)
Aspartate aminotransferase (AST), high, N		358	358
Any treatment emergent grade 2, 3 or 4		7 (2.0%)	10 (2.8%)
Treatment emergent grade 2	2.5 to <5.0x ULN	3 (0.8%)	4 (1.1%)
Treatment emergent grade 3	5.0 to <10.0x ULN	4 (1.1%)	4 (1.1%)
Treatment emergent grade 4	≥10.0x ULN	0	2 (0.6%)
Alkaline phosphatase, high, N		357	358
Any treatment emergent grade 2, 3 or 4		0	3 (0.8%)
Treatment emergent grade 2	2.5 to <5.0x ULN	0	3 (0.8%)
Pancreatic Parameters			
Amylase (total), high, N		357	358
Any treatment emergent grade 2, 3 or 4		8 (2.2%)	17 (4.7%)
Treatment emergent grade 2	1.5 to < 3.0x ULN	7 (2.0%)	17 (4.7%)
Treatment emergent grade 4	≥5.0x ULN	1 (0.3%)	0
Lipase, high, N[b]		13	22
Any treatment emergent grade 2, 3 or 4		1 (7.7%)	6 (27.3%)
Treatment emergent grade 2	1.5 to <3.0x ULN	1 (7.7%)	4 (18.2%)
Treatment emergent grade 3	3.0 to <5.0x ULN	0	2 (9.1%)
Lipid Parameters			
Cholesterol, fasting limits, high, fasting samples only, N		345	338
Any treatment emergent grade 2, 3 or 4		68 (19.7%)	18 (5.3%)
Treatment emergent grade 2	240 to <300 mg/dL	62 (18.0%)	16 (4.7%)
Treatment emergent grade 3	≥300 mg/dL	6 (1.7%)	2 (0.6%)
LDL, fasting limits, high, fasting samples only, N		345	338
Any treatment emergent grade 2, 3 or 4		48 (13.9%)	17 (5.0%)
Treatment emergent grade 2	160 to <190 mg/dL	31 (9.0%)	13 (3.8%)
Treatment emergent grade 3	≥190 mg/dL	17 (4.9%)	4 (1.2%)
Triglycerides, fasting limits, high, fasting samples only, N		345	338
Any treatment emergent grade 2, 3 or 4		28 (8.1%)	17 (5.0%)
Treatment emergent grade 2	>300 to 500 mg/dL	24 (7.0%)	13 (3.8%)
Treatment emergent grade 3	>500 to <1,000 mg/dL	3 (0.9%)	3 (0.9%)
Treatment emergent grade 4	>1,000 mg/dL	1 (0.3%)	1 (0.3%)
Glucose Parameters			
Glucose, serum, fasting limits, high, fasting samples only, N		357	356
Any treatment emergent grade 2, 3 or 4		24 (6.7%)	20 (5.6%)
Treatment emergent grade 2	>125 to 250 mg/dL	23 (6.4%)	20 (5.6%)
Treatment emergent grade 3	>250 to 500 mg/dL	1 (0.3%)	0

Table 15: Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Drug Reactions for D/C/F/TAF in HIV-1 Infected, ART-naïve Subjects (Study TMC114FD2HTX3001; ITT Population)

Phase = Treatment

	Limits[a]	D/C/F/TAF	Control
Renal Parameters			
Creatinine, high, N		358	358
Any treatment emergent grade 2, 3 or 4		16 (4.5%)	49 (13.7%)
Treatment emergent grade 2	>1.3 to 1.8x ULN OR Increase of >0.3 mg/dL above baseline	15 (4.2%)	49 (13.7%)
Treatment emergent grade 4	≥3.5x ULN OR Increase of ≥2.0x above baseline	1 (0.3%)	0

ART = antiretroviral treatment; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HIV-1 = human immunodeficiency virus type 1; ITT = intent-to-treat; LDL = low density lipoprotein; N = number of subjects with data on treatment; ULN = upper limit of normal.

Note: In this table, the percentages are calculated using the number of subjects with data as denominator; percentages based on the total number of subject in the ITT population are provided in Appendix 3.

[a] For details, refer to Mod.2.7.4/Tab33.
[b] Only reflex lipase testing was performed when total amylase >1.5x ULN.

Source: Mod2.7.4/Tab33.

6.5.2. Adverse Drug Reactions in ART-experienced, Virologically-suppressed Subjects Switching From a Boosted PI+F/TDF Regimen to D/C/F/TAF

The proportion of subjects who discontinued treatment with D/C/F/TAF due to ADRs, regardless of severity, was 0.5% (4 subjects). Serious ADRs were reported in 0.5% (4 subjects) with D/C/F/TAF. The majority of the ADRs reported during treatment with D/C/F/TAF were mild (grade 1) in severity.

An overview of ADRs of at least grade 2 in severity reported in Study TMC114IFD3013 is presented in Table 16. The most common ADRs for D/C/F/TAF (incidence ≥2%) of at least moderate severity (≥grade 2) were diarrhea (2.5%), headache (2.4%), and abdominal pain (2.0%). There were only 3 grade 3 ADRs identified with the D/C/F/TAF FDC (abdominal pain, diarrhea, and acute pancreatitis), and no grade 4 ADRs.

Laboratory abnormalities, grade 2 to 4, reported in Study TMC114IFD3013 and considered ADRs for D/C/F/TAF are shown in Table 17.

Table 16: Incidence (%) of Adverse Drug Reactions for D/C/F/TAF of at Least Grade 2 in Severity in HIV-1 Infected, Virologically-suppressed Subjects Switching From a Boosted PI+F/TDF Regimen (Study TMC114IFD3013; ITT Population)

System Organ Class ADR[a]	D/C/F/TAF (N=763)	Control (N=378)
Any ADR of grade 2, 3 or 4	76 (10.0%)	26 (6.9%)
Gastrointestinal disorders	40 (5.2%)	15 (4.0%)
Diarrhea	19 (2.5%)	8 (2.1%)
Abdominal pain	15 (2.0%)	4 (1.1%)
Nausea	4 (0.5%)	3 (0.8%)
Dyspepsia	3 (0.4%)	1 (0.3%)
Vomiting	3 (0.4%)	2 (0.5%)
Abdominal distension	2 (0.3%)	0
Pancreatitis acute	1 (0.1%)	0
Nervous system disorders	18 (2.4%)	1 (0.3%)
Headache	18 (2.4%)	1 (0.3%)
Skin and subcutaneous tissue disorders	9 (1.2%)	3 (0.8%)
Angioedema	4 (0.5%)	2 (0.5%)
Pruritus	2 (0.3%)	0
Rash	2 (0.3%)	1 (0.3%)
Urticaria	2 (0.3%)	0
General disorders and administration site conditions	7 (0.9%)	5 (1.3%)
Fatigue	7 (0.9%)	4 (1.1%)
Asthenia	0	1 (0.3%)
Metabolism and nutrition disorders	7 (0.9%)	2 (0.5%)
Diabetes mellitus	6 (0.8%)	0
Lipodystrophy	1 (0.1%)	1 (0.3%)
Anorexia	0	1 (0.3%)
Musculoskeletal and connective tissue disorders	5 (0.7%)	2 (0.5%)
Myalgia	4 (0.5%)	2 (0.5%)
Osteonecrosis	1 (0.1%)	0
Psychiatric disorders	3 (0.4%)	0
Abnormal dreams	3 (0.4%)	0
Immune system disorders	1 (0.1%)	1 (0.3%)
(Drug) hypersensitivity	1 (0.1%)	1 (0.3%)
Hepatobiliary disorders	0	1 (0.3%)
Acute hepatitis	0	1 (0.3%)

ADR = adverse drug reaction; ART = antiretroviral treatment; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada); HIV-1 = human immunodeficiency virus type 1; ITT = intent-to-treat (population); N = number of subjects; PI = protease inhibitor.

[a] ADR terms comprise grouped preferred terms; all individual preferred terms for ADRs are described in Mod2.7.4/App5.

Source: Mod2.7.4/App5

Table 17: Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Drug Reactions for D/C/F/TAF in HIV-1 Infected, Virologically-suppressed Subjects Switching From a Boosted PI+F/TDF Regimen (Study TMC114IFD3013; ITT Population)

Phase = Treatment

	Limits[a]	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N		763	378
Hepatic Parameters			
Alanine aminotransferase (ALT), high, N		761	376
Any treatment emergent grade 2, 3 or 4		26 (3.4%)	14 (3.7%)
Treatment emergent grade 2	2.5 to <5.0x ULN	18 (2.4%)	5 (1.3%)
Treatment emergent grade 3	5.0 to <10.0x ULN	5 (0.7%)	4 (1.1%)
Treatment emergent grade 4	≥10.0x ULN	3 (0.4%)	5 (1.3%)
Aspartate aminotransferase (AST), high, N		761	376
Any treatment emergent grade 2, 3 or 4		23 (3.0%)	16 (4.3%)
Treatment emergent grade 2	2.5 to <5.0x ULN	12 (1.6%)	6 (1.6%)
Treatment emergent grade 3	5.0 to <10.0x ULN	7 (0.9%)	6 (1.6%)
Treatment emergent grade 4	≥10.0x ULN	4 (0.5%)	4 (1.1%)
Alkaline phosphatase, high, N		761	376
Any treatment emergent grade 2, 3 or 4		2 (0.3%)	0
Treatment emergent grade 2	2.5 to <5.0x ULN	2 (0.3%)	0
Pancreatic Parameters			
Amylase (total), high, N		761	376
Any treatment emergent grade 2, 3 or 4		36 (4.7%)	28 (7.4%)
Treatment emergent grade 2	1.5 to < 3.0x ULN	32 (4.2%)	26 (6.9%)
Treatment emergent grade 3	3.0 to <5.0x ULN	3 (0.4%)	1 (0.3%)
Treatment emergent grade 4	≥5.0x ULN	1 (0.1%)	1 (0.3%)
Lipase, high, N[b]		43	33
Any treatment emergent grade 2, 3 or 4		8 (18.6%)	6 (18.2%)
Treatment emergent grade 2	1.5 to <3.0x ULN	3 (7.0%)	4 (12.1%)
Treatment emergent grade 3	3.0 to <5.0x ULN	3 (7.0%)	0
Treatment emergent grade 4	≥5.0x ULN	2 (4.7%)	2 (6.1%)
Lipid Parameters			
Cholesterol, fasting limits, high, fasting samples only, N		738	363
Any treatment emergent grade 2, 3 or 4		188 (25.5%)	32 (8.8%)
Treatment emergent grade 2	240 to <300 mg/dL	160 (21.7%)	27 (7.4%)
Treatment emergent grade 3	≥300 mg/dL	28 (3.8%)	5 (1.4%)
LDL, fasting limits, high, fasting samples only, N		738	363
Any treatment emergent grade 2, 3 or 4		167 (22.6%)	23 (6.3%)
Treatment emergent grade 2	160 to <190 mg/dL	119 (16.1%)	17 (4.7%)
Treatment emergent grade 3	≥190 mg/dL	48 (6.5%)	6 (1.7%)
Triglycerides, fasting limits, high, fasting samples only, N		738	363
Any treatment emergent grade 2, 3 or 4		55 (7.5%)	31 (8.5%)
Treatment emergent grade 2	>300 to 500 mg/dL	41 (5.6%)	23 (6.3%)
Treatment emergent grade 3	>500 to <1,000 mg/dL	11 (1.5%)	8 (2.2%)
Treatment emergent grade 4	>1,000 mg/dL	3 (0.4%)	0

Table 17: Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Drug Reactions for D/C/F/TAF in HIV-1 Infected, Virologically-suppressed Subjects Switching From a Boosted PI+F/TDF Regimen (Study TMC114IFD3013; ITT Population)

Phase = Treatment

	Limits[a]	D/C/F/TAF	Control
Glucose Parameters			
Glucose, serum, fasting limits, high, fasting samples only, N		761	376
Any treatment emergent grade 2, 3 or 4		61 (8.0%)	23 (6.1%)
Treatment emergent grade 2	>125 to 250 mg/dL	53 (7.0%)	21 (5.6%)
Treatment emergent grade 3	>250 to 500 mg/dL	8 (1.1%)	2 (0.5%)
Renal Parameters			
Creatinine, high, N		761	376
Any treatment emergent grade 2, 3 or 4		43 (5.7%)	25 (6.6%)
Treatment emergent grade 2	>1.3 to 1.8x ULN OR Increase of >0.3 mg/dL above baseline	41 (5.4%)	24 (6.4%)
Treatment emergent grade 3	>1.8 to <3.5x ULN OR Increase of 1.5 to <2.0x above baseline	2 (0.3%)	1 (0.3%)

ART = antiretroviral treatment; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada); HIV-1 = human immunodeficiency virus type 1; ITT = intent-to-treat; LDL = low density lipoprotein; N = number of subjects with data on treatment; PI = protease inhibitor; ULN = upper limit of normal.

Note: In this table, the percentages are calculated using the number of subjects with data as denominator; percentages based on the total number of subject in the ITT population are provided in Appendix 3.

[a] For details, refer to Mod.2.7.4/Tab36.
[b] Only reflex lipase testing was performed when total amylase >1.5x ULN.

Source: Mod2.7.4/Tab36.

6.6. Safety in Ongoing Studies and Programs

There were no new findings in the 2 ongoing Phase 3 studies (TMC114FD2HTX3001 and TMC114IFD3013), from Week 48 up till the safety cut-off date (1 June 2017), that alter the assessments based on the Week-48 analyses (refer to Mod2.7.4/Sec5).

6.7. Safety in Special Groups and Situations

6.7.1. Pediatric Subjects

No clinical studies were performed with the D/C/F/TAF FDC tablet in HIV-1 infected pediatric or adolescent subjects.

Available data for the components of D/C/F/TAF indicate that the overall safety profile in adolescent subjects aged 12 to <18 years and weighing at least 40 kg was similar to that observed in the adult population; see Section 6.3.

Data and doses for co-administration of the components of the D/C/F/TAF FDC in children <12 years are currently not available. The D/C/F/TAF FDC is therefore not recommended for use in pediatric patients <12 years of age.

The D/C/F/TAF FDC should not be used in pediatric patients <3 years of age, in view of the toxicity observed in juvenile rats dosed with DRV.

6.7.2. Elderly Subjects

Limited information is available on the use of the D/C/F/TAF FDC, DRV, or COBI in subjects aged above 65 years of age. Clinical studies with D/C/F/TAF FDC included 35 subjects aged above 65 years of whom 26 subjects received D/C/F/TAF FDC.

No differences in safety or efficacy have been observed between elderly subjects (aged >65 years) and those between 18 and ≤65 years of age (refer to Mod2.7.3/Sec3.1.1.1.2 and Sec3.1.3.1.2.3, and Mod2.7.4/Sec6.1.2). Although no safety issues are expected with D/C/F/TAF in elderly, D/C/F/TAF FDC is to be used with caution in patients above 65 years of age, due to the greater frequency of decreased hepatic function (see Section 6.7.4), concomitant disease(s), and/or polypharmacy.

6.7.3. Renal Impairment

No specific clinical studies have been performed with the D/C/F/TAF FDC in subjects with renal impairment. The Phase 3 studies with D/C/F/TAF allowed the inclusion of subjects with $eGFR_{CG}$ ≥50 mL/min in TMC114IFD3013 and ≥70 mL/min in TMC114FD2HTX3001.

The recommendation for use of D/C/F/TAF FDC in subjects with renal impairment is based on the extrapolation of the available PK and safety data as well as the recommendation for each component of the FDC in this population (see also Section 6.4.3 and Mod2.7.2/ClinPharm/Sec3.3.5).

Based on all available data, as outlined below, the following is recommended:

- No dose adjustment of D/C/F/TAF FDC is required in patients with $eGFR_{CG}$ ≥30 mL/min.
- D/C/F/TAF FDC should not be initiated in patients with $eGFR_{CG}$ <30 mL/min, as there are insufficient data available regarding the use of D/C/F/TAF FDC in this population. D/C/F/TAF FDC should be discontinued in patients with $eGFR_{CG}$ that declines below 30 mL/min during treatment.

The following data support these recommendations (refer to Mod2.7.2/ClinPharm/Sec3.3.5 and Mod2.7.4/Sec6.1.3 for more details):

- Available data from the ongoing Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 provide information on 300 subjects with $eGFR_{CG}$ 70 to <90 mL/min (191 on D/C/F/TAF), 86 subjects with $eGFR_{CG}$ 50 to <70 mL/min (55 on D/C/F/TAF), and 5 subjects with $eGFR_{CG}$ <50 mL/min (3 on D/C/F/TAF). The data do not suggest any safety concerns in these subjects (see Sections 6.2.1.2.1 and 6.2.2.2.1, and refer to Mod2.7.4/Sec6.1.3).
- Available data for the individual components of D/C/F/TAF FDC indicate that there are no safety concerns for the use of D/C/F/TAF in HIV-1 infected subjects with mild to moderate renal impairment (see Section 6.4.3 and refer to Mod2.7.4/Sec6.1.3).
  - The results from Study GS-US-236-0118 in subjects with $eGFR_{CG}$ 50 to <90 mL/min showed that the overall safety profile of DRV in combination with COBI and F/TDF was similar to that observed in the adult population with normal renal function. The results from another study (GS-US-292-0112) in subjects with $eGFR_{CG}$ 30 to <70 mL/min showed

that the safety profile of F/TAF (administered as E/C/F/TAF) was comparable for subjects with $eGFR_{CG}$ <50 mL/min or $eGFR_{CG}$ ≥50 mL/min.

- The renal clearance of DRV is limited and, therefore, a decrease in total body clearance is not expected in patients with renal impairment. Results from clinical studies in HIV-1 infected subjects with DRV/COBI and DRV/rtv showed that creatinine clearance did not have a clinically relevant effect on DRV PK. No PK data for DRV are available in HIV-1 infected patients with severe renal impairment or end stage renal disease.
- In clinical studies with non-HIV infected subjects, no clinically relevant differences in COBI PK were observed between subjects with severe renal impairment ($eGFR_{CG}$ <30 mL/min) or mild to moderate renal impairment and healthy subjects (refer to Mod2.7.2/ClinPharm/Sec3.3.5), consistent with low renal clearance of COBI (see Section 3.4).
- Mean systemic FTC exposure was higher in patients with severe renal impairment ($eGFR_{CG}$ <30 mL/min) than in subjects with normal renal function.
- No clinically relevant differences in TAF or TFV pharmacokinetics were observed between healthy subjects and patients with severe renal impairment ($eGFR_{CG}$ <30 but >15 mL/min) in studies of TAF.
- The PK results from the Phase 3 studies showed that there was no difference in DRV or TAF PK between eGFR subgroups and eGFR was not a significant covariate for the population PK analysis of DRV or TAF (refer to Mod2.7.2/ClinPharm/Sec3.3.5).

6.7.4. Hepatic Impairment

No clinical studies have been performed with the D/C/F/TAF FDC in subjects with hepatic impairment. Also, no subjects with clinically significant functional hepatic impairment (ie, Child-Pugh class A, B, or C) have been included in the 2 Phase 3 studies with D/C/F/TAF FDC, because this was a protocol exclusion criterion in both studies. However, new onset (or flared) acute viral hepatitis or drug-induced liver injury was monitored in these studies.

The recommendation for use of D/C/F/TAF FDC in subjects with hepatic impairment is based on the extrapolation of the available PK and safety data as well as the recommendation for each component of the FDC in this population.

Based on all available data, as outlined below, the following is recommended:

- No dose adjustment of D/C/F/TAF FDC is required in subjects with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment;
- D/C/F/TAF FDC is not recommended for use in subjects with severe hepatic impairment (as the individual components of the FDC have not been studied in this population).

Clinical studies have been performed in subjects with mild to moderate hepatic impairment with the following individual components of the FDC: DRV (in combination with rtv), COBI (in combination with EVG), and TAF (as single agent or as component of a FDC). The results showed the following:

- There were no clinically relevant differences in the DRV pharmacokinetics in subjects with

mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment compared to healthy subjects.

- No clinically relevant differences in COBI PK parameters were observed between subjects with moderate impairment and healthy subjects (refer to Mod2.7.2/ClinPharm/Sec2.1.4.1).
- No clinically relevant changes in TAF or TFV PK parameters were observed between subjects with mild to moderate hepatic impairment and healthy subjects (refer to Mod2.7.2/ClinPharm/Sec2.1.4.1).
- FTC has not been studied in subjects with hepatic impairment; however, because FTC is not significantly metabolized by liver enzymes, the impact of hepatic impairment should be limited (refer to Mod2.7.2/ClinPharm/Sec3.3.4).

6.7.5. Co-infection With HIV-1 and Hepatitis B or C, and Risk of Hepatitis B Flare-up

6.7.5.1. Co-infection With HIV-1 and Hepatitis B or C

The effect of HBV and/or hepatitis C virus (HCV) co-infection on the PK of DRV, COBI, FTC, and TAF when co-administered as the D/C/F/TAF FDC has not been fully evaluated.

Available results from clinical studies with the individual components of the D/C/F/TAF FDC did not show a clinically significant effect of hepatitis B and/or C infection on the PK of DRV and FTC. Refer to the Summary of Clinical Pharmacology for more details (Mod2.7.2/ClinPharm/Sec3.3.4).

Subjects co-infected with HBV or HCV were not allowed to participate in the D/C/F/TAF Phase 3 and 2 studies. The review of the data of the subjects who developed hepatitis B or C co-infection during the Phase 3 studies with D/C/F/TAF did not reveal any concerns for increased hepatic risk (refer to Mod2.7.4/Sec6.1.5).

There is limited experience with DRV (boosted with rtv) in subjects co-infected with HIV-1 and HBV and/or HCV, showing that co-infected subjects were more likely to have baseline and treatment-emergent hepatic transaminase elevations than those without chronic viral hepatitis.[28]

The results of a study in HIV-1 infected subjects with mild to moderate hepatic impairment (Child-Pugh class A or B) showed that the E/C/F/TAF FDC was well tolerated in HIV-1/HBV co-infected adults. No subjects had an ALT flare, and assessments of other liver-related parameters did not reveal any concerns for increased hepatic risk (refer to Mod2.7.4/Sec6.1.5).

Based on these data, it is likely that the safety profile of D/C/F/TAF FDC will be similar in HIV-1 infected subjects and HIV-1/hepatitis B or C co-infected subjects.

6.7.5.2. Risk of Hepatitis B Flare-up After Discontinuation of F/TAF

FTC exhibits clinical activity against HBV. TAF is a HBV nucleoside analog reverse transcriptase inhibitor and is indicated for the treatment of chronic HBV infection in adults with compensated liver disease. Discontinuation of D/C/F/TAF therapy in patients co-infected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC

or TAF components of the D/C/F/TAF FDC. No cases were reported in the ongoing Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 (refer to Mod2.7.4/Sec3.1.1.1.3 and Sec3.1.1.2.3).

Patients co-infected with HIV-1 and HBV who discontinue the D/C/F/TAF FDC should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. The D/C/F/TAF FDC should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate), lamivudine, or adefovir dipivoxil used for the treatment of HBV infection.

6.7.6. Hemophilia/Bleeding Events

No events related to hemophilia/bleeding events were reported in the ongoing Phase 3 Study TMC114FD2HTX3001. In the Phase 3 Study TMC114IFD3013, there were 2 subjects with hemophilia, both in the D/C/F/TAF group. Neither subject experienced a bleeding event (refer to Mod2.7.4/Sec3.1.1.1.3 and Sec3.1.1.2.3).

During the clinical development plan and routine Pharmacovigilance, no safety issues with DRV or DRV/COBI were identified in patients with hemophilia/bleeding events. Therefore, hemophilia/bleeding events are not considered to be a safety concern for treatment with D/C/F/TAF.

6.7.7. Lactic Acidosis/Severe Hepatomegaly With Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other ARVs. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Since TAF and FTC are nucleos(t)ide analogs, treatment with F/TAF should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations) (refer to Mod2.7.4/Sec6.1.6).

No cases were reported in the ongoing Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 (refer to Mod2.7.4/Sec6.1.6).

Clinical study data and nonclinical data for FTC and TAF indicate that the incidences of lactic acidosis/severe hepatomegaly with steatosis in patients being treated with F/TAF are likely to be very low and have minimal impact on public health.

6.7.8. Pregnancy, Lactation, and Fertility

D/C/F/TAF FDC should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Because of both the potential for 1) HIV-1 transmission (in HIV-negative infants), 2) developing viral resistance (in HIV-positive infants), and 3) serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving D/C/F/TAF.

In the studies with D/C/F/TAF FDC:

- 1 subject who received the D/C/F/TAF FDC tablet became pregnant (resulting in an induced abortion) during the follow-up phase of Study TMC114FD2HTX3001;
- 2 pregnancies of partners (1 in the D/C/F/TAF group and 1 in the control group; outcome of both pregnancies unknown) were reported during the follow-up phase of Study TMC114FD2HTX3001;
- 1 subject in the control group had an ectopic pregnancy (leading to a surgical intervention) during the 48-week treatment phase of Study TMC114IFD3013.

For more details and for an overview of pregnancies (and outcomes) reported with the individual components of the D/C/F/TAF FDC tablet, refer to Mod2.7.4/Sec6.4.1.

6.7.9. Overdose

Human experience of acute overdose with the administration of D/C/F/TAF is not available. No study with administration of supratherapeutic doses of D/C/F/TAF has been conducted. Limited clinical experience is available with the components of the D/C/F/TAF FDC at doses higher than the therapeutic doses; refer to Mod2.7.4/Sec6.5 for details.

Increases in exposure when administering the D/C/F/TAF FDC with rtv or COBI are anticipated to be minimal as the inhibition of CYP3A is already near maximal for D/C/F/TAF FDC.

There is no specific antidote for overdose with D/C/F/TAF. Treatment of overdose with D/C/F/TAF consists of general supportive measures. FTC and TFV can be removed by hemodialysis.

6.7.10. Drug Abuse

No systematic examination of the abuse potential of D/C/F/TAF was performed in the preclinical or clinical studies. However, the potential for illegal use is unlikely given that the intracellular target of the D/C/F/TAF FDC is virus-specific.

6.7.11. Withdrawal and Rebound

Clinical studies or systematic analyses to evaluate the potential withdrawal and rebound effects of the D/C/F/TAF FDC have not been conducted. Examination of the safety parameters during washout periods and during follow-up periods after last intake of study drug showed that the overall safety/tolerability profile of the D/C/F/TAF FDC (or of combined treatment with the individual components) was not negatively impacted by interruption or discontinuation of treatment.

For the risk of hepatitis B flare-up after discontinuation of F/TAF, see Section 6.7.5.

6.7.12. Effects on Ability to Drive or Operate Machinery, or Impairment of Mental Ability

No studies have been performed on the effects of the D/C/F/TAF on the ability to drive or use machines. D/C/F/TAF is expected to have no or negligible influence on the ability to drive and

use machines. Patients should be informed that dizziness may occur when treated with D/C/F/TAF.

6.8. Postmarketing Experience

There is no postmarketing experience, as the D/C/F/TAF FDC tablet is not yet marketed in any country.

7. BENEFITS AND RISKS CONCLUSIONS

The benefits and risks of D/F/C/TAF, as summarized below, support the proposed indication of the D/C/F/TAF FDC tablet for the treatment of HIV-1 infection in adult and adolescent subjects aged 12 years and older.

7.1. Summary of Benefits Assessments

The main benefits of the D/C/F/TAF FDC for HIV-1 infected patients are:

- its high efficacy, comparable to control treatment, with a high genetic barrier to resistance development,
- its improved renal and bone safety profile compared to the use of a TDF-based regimen, and
- the convenience it offers by the single-tablet, once-daily formulation, resulting in high adherence rates.

These benefits were demonstrated in the Phase 3 and 2 studies in ART-naïve and ART-experienced, virologically-suppressed, HIV-1 infected subjects.

D/C/F/TAF is a Potent ART With a High Genetic Barrier to Resistance

The results from the Phase 3 studies with the D/C/F/TAF FDC tablet demonstrate the following:

- High response rate (defined as HIV-1 RNA <50 copies/mL; FDA-defined snapshot approach) comparable to a control treatment in the randomized, active-controlled, double-blind, Phase 3 Study TMC114FD2HTX3001 in HIV-1 infected, ART-naïve subjects:
  - In the ITT population, the proportion of virologic responders at Week 48 was 91.4% with the D/C/F/TAF FDC and 88.4% with the control treatment (DRV/COBI FDC co-administered with F/TDF FDC). The stratum-adjusted difference (D/C/F/TAF - control) between the treatment groups (noninferiority margin of -10%) was 2.7% and the lower bound of the 2-sided 95% CI of the difference between treatment groups (D/C/F/TAF - control) was -1.6%, leading to the conclusion of noninferiority of the D/C/F/TAF FDC vs control treatment. Results on the PP population corroborate these findings in the ITT population.
- Very low virologic rebound rate and high response rate comparable to the control treatment in the randomized, active-controlled, open-label, Phase 3 Study TMC114IFD3013 in HIV-1 infected, ART-experienced, virologically-suppressed (HIV-1 RNA <50 copies/mL) subjects:
  - In the ITT population, the proportion of subjects with protocol-defined virologic rebound, cumulative through 48 weeks was 2.5% with the D/C/F/TAF FDC and 2.1% with the control treatment (continuing the current [screening] bPI combined with F/TDF). The difference (D/C/F/TAF - control) in rebound rate between the treatment groups was 0.4% with an upper bound of the 2-sided 95% CI of 2.2%, leading to the conclusion of noninferiority of the D/C/F/TAF FDC vs control treatment (noninferiority margin of 4%). Note that for this study, virologic rebound was assessed cumulatively over the entire treatment period up to Week 48, which is more conservative than the snapshot approach

of virologic rebound (eg, at Week 48) that is generally used in switch studies (see Section 4.1.2).

  - virologic rebound was mainly driven by transient low-level viremia. 12/19 rebounders in the D/C/F/TAF and 4/8 rebounders in the control group were re-suppressed (<50 copies/mL) at Week 48. Using the threshold of ≥200 HIV-1 RNA copies/mL (instead of the ≥50 HIV-1 RNA copies/mL), protocol-defined virologic rebound cumulative through Week 48 was observed in only 3 (0.4%) subjects in the D/C/F/TAF group and in 0 subjects in the control group.

- In the ITT population, the proportion of subjects with virologic response at Week 48 (HIV-1 RNA <50 copies/mL; FDA-defined snapshot approach) was 94.9% with the D/C/F/TAF FDC and 93.7% with the control treatment. Per FDA snapshot approach, virologic failure (HIV-1 RNA ≥50 copies/mL) at Week 48 was 0.8% in the D/C/F/TAF group and 0.5% in the control group.

- Efficacy analyses by subgroups revealed no meaningful differences in virologic outcomes, supporting the FDC as an effective treatment for the treatment of HIV-1 infection, regardless of demographics and disease baseline characteristics. Results were consistent across treatment-naïve subjects and treatment-experienced subjects who were virologically suppressed, and were supported by several sensitivity analyses.

- Immunologic benefits of treatment with the D/C/F/TAF FDC were demonstrated by increases in CD4+ cell counts and were similar to control treatment.

- In the Phase 3 studies with the D/C/F/TAF FDC, no genotypic or phenotypic resistance was observed against DRV and TAF. Development of resistance to FTC was rare (1 subject treated with D/C/F/TAF developed an M184M/I/V mutation, conferring resistance to FTC; see Section 5.3).

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 (see Section 5.5).

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 (refer to the Warnings and Precautions section of the proposed Prescribing Information in Mod1.14.1/Sec5.2).

D/C/F/TAF FDC is Appropriate for ART-experienced, Virologically-failing Patients

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 PK data of boosted DRV 800 mg once daily and TAF administered as single agents (see Section 3.5 and refer to Mod2.7.2/ClinPharm/Sec3.2.2). These D/C/F/TAF FDC PK results permit extrapolation of the durable historical efficacy data of the individual D/C/F/TAF components to the D/C/F/TAF FDC tablet.[10,16,27,28]

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.[27,28] D/C/F/TAF FDC should not be used in PI-experienced, virologically-failing patients harboring any DRV RAM (refer to the Warnings and Precautions section of the proposed Prescribing Information in Mod1.14.1/Sec5.2).

Additional Data Support the Use in Adolescents

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. In addition, doses are generally the same for adults and adolescents; adolescent drug dosing is equivalent for 94.6% (87/92) of the products with adolescent indications concordant with adult indications that were investigated since the FDA Amendments Act of 2007.[22] 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.

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

The results from the Week-48 analyses of the Phase 3 studies demonstrate the following:

- 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 (see Section 6.2.1.2.1):
  - 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 vs TDF. At the same time, a smaller increase in serum creatinine and thus a smaller decrease in eGFR based on serum creatinine were observed, which is attributable to the known COBI effects on the renal tubular creatinine secretion in combination with the improved renal safety of TAF vs TDF. All differences between treatment groups at Week 48 were statistically significant ($p=0.001$ for $eGFR_{cyst}$ and $p<0.001$ for serum creatinine and eGFR based on serum creatinine).
  - Consistently, in the D/C/F/TAF group less proteinuria was observed compared to the control group (with statistically significant differences between treatment groups at Week 48 in median changes from baseline in UPCR and UACR).

- 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 to creatinine ratio, and $FEPO_4$) compared to the TDF-based control regimen. No subjects met the study-defined criteria for potential subclinical proximal renal tubulopathy in the D/C/F/TAF group, vs 2 in the control group. No AEs compatible with PRT, including Fanconi syndrome, were reported.

- Similar consistent trends were observed in Study TMC114IFD3013 in ART-experienced, virologically-suppressed subjects, albeit less pronounced (see Section 6.2.2.2.1).
  - 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). The differences between treatment groups at Week 48 in $eGFR_{cyst}$ were statistically significant. Although the differences between treatment groups in serum creatinine and eGFR based on serum creatinine were not statistically significant, larger increases in serum creatinine and larger decreases in eGFR based on serum creatinine were observed in subjects switching to D/C/F/TAF, likely due to the known effect of COBI on creatinine tubular secretion.
  - Consistently, in the D/C/F/TAF group less proteinuria was observed compared to the control group (with statistically significant differences between treatment groups at Week 48 in median changes from baseline in UPCR and UACR [decreases in the D/C/F/TAF group vs increases in the control group]).
  - Treatment with the D/C/F/TAF regimen was also associated with less increases in markers of proximal renal 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, vs 2 in the control group. No AEs compatible with PRT, including Fanconi syndrome, were reported. These findings are attributable to TAF vs TDF effects.
- Few subjects overall discontinued for renal AEs or renal laboratory abnormalities:
  - 0 with D/C/F/TAF vs 1 subject with control (for increased beta-2-microglobulinemia) discontinued in Study TMC114FD2HTX3001; 1 subject with D/C/F/TAF (for chronic kidney disease) vs 2 subjects with control (1 for renal tubular disorder and 1 for toxic nephropathy) discontinued in Study TMC114IFD3013.

D/C/F/TAF can be Used by Subjects With Baseline $eGFR_{CG}$ 30 to <70 mL/min

No dose adjustment of the D/C/F/TAF FDC is required in patients with $eGFR_{CG}$ ≥30 mL/min (see Section 6.7.3). Data from historical studies with DRV, COBI, FTC, or TAF in adult subjects with variable degrees of renal impairment did not raise any safety concerns and supported the use of these ARTs in subjects with an $eGFR_{CG}$ ≥30 mL/min without the need to adjust the ART dose. In the Phase 3 population PK analysis, eGFR was not found to be a significant covariate for the pharmacokinetics of DRV and TAF (Mod2.7.2/ClinPharm/Sec3.3.5).

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

The results from the Week-48 analyses of the Phase 3 studies demonstrated the following:

- 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 vs a decrease in BMD in the control group (differences between treatment groups of Study TMC114FD2HTX3001 were statistically significant at Week 48 with $p<0.001$ for hip and $p=0.004$ for spine; see Section 6.2.1.2.2).
  - Treatment with D/C/F/TAF resulted in improvements in BMD for subjects who switched from a TDF-based regimen vs 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; see Section 6.2.2.2.2).
  - In the treatment of adolescents with F/TAF (administered as E/C/F/TAF), there were no notable changes from baseline in height-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 (see Section 6.3.2).

  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.

Improved Convenience

In the open-label Phase 3 Study TMC114IFD3013 which allowed to compare drug accountability between treatment groups (intake of 1 pill vs 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%).

7.2. Summary of Risks Assessments

The clinical safety database is robust and includes data originating from the individual components of the D/C/F/TAF FDC as well as the clinical development program with D/C/F/TAF. In the Phase 3 and 2 studies with the D/C/F/TAF FDC, 2,019 HIV-1 infected adult subjects were included. In these studies, a total of 1,228 subjects were treated with the D/C/F/TAF FDC up to 48 weeks. Of those subjects treated with D/C/F/TAF in the Phase 3 studies (N=1,125), 184 (16.4%) were females, 292 (26.0%) subjects were above 50 years of age and 25 (2.2%) above 65 years, and 58 (5.2%) had an $eGFR_{CG}$ below 70 mL/min.

ADR Profile of D/C/F/TAF is Consistent With the Known ADRs of the Components

The results from the Week-48 analyses of the Phase 3 studies demonstrate that treatment with the D/C/F/TAF FDC was well tolerated across all patient populations evaluated (see Section 6.5 for the ADR profile of D/C/F/TAF):

- No new ADRs were identified compared to the known ADRs with the individual components of D/C/F/TAF.
- The proportion of subjects in the D/C/F/TAF group who had a serious ADR was 0% in Study TMC114FD2HTX3001 and 0.5% in Study TMC114IFD3013;
- The number of subjects in the D/C/F/TAF group who discontinued study drug due to ADRs was 1.9% in Study TMC114FD2HTX3001 and 0.5% in Study TMC114IFD3013;
- The only ADRs with a frequency of ≥2% and at least moderate severity (≥grade 2) with D/C/F/TAF were:
  - diarrhea (3.9%) and rash (4.4%) in Study TMC114FD2HTX3001 (ART-naïve subjects); and
  - diarrhea (2.5%), headache (2.4%), and abdominal pain (2.0%) in Study TMC114IFD3013 (ART-experienced, virologically-suppressed subjects).

Most Relevant Risks of Treatment With D/C/F/TAF

Based on the safety profiles of the individual components, the most relevant risks with the treatment of D/C/F/TAF FDC include:

- severe skin reactions/rashes and lipid increases associated with the DRV component of the FDC;
- renal effects associated with the TAF component of the FDC; and
- drug-drug interactions associated with the DRV/COBI component of the FDC.

With the D/C/F/TAF FDC, the incidence of rash (grouped as ADR) was 12.2% in Study TMC114FD2HTX3001 and 3.7% in Study TMC114IFD3013. No severe skin reactions were reported with D/C/F/TAF in either Phase 3 study; 3 severe skin reactions (1 Stevens-Johnson syndrome and 2 toxic skin eruption) were reported in the control group of Study TMC114FD2HTX3001. These findings are consistent with historical data for DRV.[28]

The results from the Week-48 analyses of the Phase 3 Study TMC114FD2HTX3001 with the D/C/F/TAF FDC showed that, compared to a F/TDF-based regimen, treatment with D/C/F/TAF FDC has less renal effects. This was supported by the results from study TMC114IFD3013 (see Section 6.2 and Section 7.1).

With the D/C/F/TAF FDC, compared to a F/TDF-based regimen, higher rates of abnormal fasting lipids were observed (see Section 6.2). These differences between treatment groups in changes from baseline were similar to those observed with E/C/F/TAF vs E/C/F/TDF.[16,17] The higher rates of abnormal fasting lipids with D/C/F/TAF vs control are mitigated by the lack of significant impact on the ratio of TC/HDL cholesterol, and by evidence that the cardiovascular benefits of treating the HIV-1 infection effectively outweigh the risks of ARV therapy.[18,19] It is

known that HIV-1 infection itself is an independent risk factor for CV disease when left untreated, in both adult and pediatric patients.[3,11] Literature data on the impact of ARV drugs on lipid parameters and on CV risk in HIV-1 infected adolescents are scarce; however, based on the information available, the CV benefit/risk ratio in adolescents is expected to be similar to this ratio in adults.

The D/C/F/TAF drug-drug interaction potential is based on that of the individual components, which is well defined and described in the proposed D/C/F/TAF Prescribing Information (see Section 3.7). Overall, these interactions will be addressed in the product labeling and risks will be monitored through pharmacovigilance activities.

Furthermore, the Prescribing Information contains appropriate precautionary language:

- to warn:
  - for the risk of severe acute exacerbations of hepatitis in patients co-infected with HIV-1 and HBV (see Section 6.7.5);
  - for the class effects for NRTIs of lactic acidosis/severe hepatomegaly with steatosis (see Section 6.7.7);
- to ensure the correct use of the D/C/F/TAF FDC tablet:
  - In pregnant and breastfeeding women (see Section 6.7.8);
  - In pediatric patients aged 3 to <12 years, and in pediatric patients below 3 years of age (see Section 6.7.1);
  - In patients above 65 years of age (see Section 6.7.2);
  - In patients with mild to moderate hepatic impairment and patients with severe hepatic impairment (see Section 6.7.4);
  - In patients with an $eGFR_{CG}$ <30 mL/min (see Section 6.7.3).

7.3. Overall Benefits/Risks Conclusions

The data included in this Clinical Overview support the positive benefit-risk profile for the use of the D/C/F/TAF 800/150/200/10 mg FDC once-daily tablet taken with food, for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older and with body weight at least 40 kg), as described in the proposed indication of the Prescribing Information in Mod1.14.1.

The D/C/F/TAF FDC represents an efficacious and safe simplification to a once-daily, single-tablet, complete ARV regimen. 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 as shown by the improved renal and bone safety data compared to a regimen with a TDF-containing backbone. Lipid increases seen during treatment with the DCFTAF FDC were modest and manageable.

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APPENDICES

Appendix 1: Overview of Clinical Studies with D/C/F/TAF FDC Tablet

Phase 3 Studies With D/C/F/TAF FDC Tablet

- Study TMC114FD2HTX3001 (725 subjects enrolled) is an ongoing, randomized, active-controlled, double-blind study to evaluate efficacy and safety of D/C/F/TAF FDC once daily, single-tablet regimen versus a regimen consisting of DRV/COBI FDC co-administered with F/TDF FDC in ART-naïve, HIV-1 infected subjects over a 48-week treatment period. Subjects were randomly assigned (1:1 ratio) to one of the two treatment groups.

  The primary objective of this study was to demonstrate noninferiority in efficacy of a D/C/F/TAF FDC tablet versus DRV/COBI FDC co-administered with F/TDF FDC in HIV-1 infected, ART-naïve adult subjects, as determined by the proportion of virologic responders defined as having HIV-1 ribonucleic acid (RNA) <50 copies/mL at Week 48 (US FDA-defined snapshot approach), with a maximum allowable difference of 10%.

- Study TMC114IFD3013 (1,149 subjects enrolled) is an ongoing, randomized active-controlled, open-label study to evaluate the efficacy, safety, and tolerability of switching to a D/C/F/TAF FDC once-daily, single-tablet regimen versus continuing their screening regimen consisting of a bPI combined with F/TDF in ART-experienced, virologically-suppressed (HIV-1 RNA <50 copies/mL), HIV-1 infected subjects over a 48-week treatment period. Subjects were randomized in a 2:1 ratio to the D/C/F/TAF group (switching) or the control group (continuing screening regimen).

  The primary objective of this study was to demonstrate noninferiority in efficacy of a D/C/F/TAF once-daily single-tablet regimen relative to continuing the bPI combined with F/TDF in these subjects, in regard to the proportion of virologic rebounders (defined as either having confirmed HIV-1 RNA ≥50 copies/mL through Week 48, or in case of early discontinuation a last single viral load of HIV-1 RNA ≥50 copies/mL), with a maximum allowable difference of 4%.

Phase 2 Studies With D/C/F/TAF FDC Tablet

- Study GS-US-299-0102 is a completed, randomized, double-blinded, multicenter, active-controlled study which evaluated the safety and efficacy of a D/C/F/TAF FDC tablet (N=103) versus COBI-boosted DRV (DRV plus COBI) plus F/TDF (N=50) in HIV-1 infected, ART-naïve subjects.

Phase 1 Studies With D/C/F/TAF FDC Tablet

- Study TMC114FD2HTX1001 is a completed, randomized, open-label, single-dose, crossover study in healthy subjects (N=96) which assessed the bioequivalence of plasma concentrations of DRV, FTC, and TAF, in the presence of COBI, administered as either a D/C/F/TAF FDC tablet or as separate agents (ie, DRV plus COBI plus F/TAF) under fed conditions.

- Study TMC114FD2HTX1002 is a completed, randomized, 3-panel, open-label, single-dose, 2-way crossover study in healthy subjects (N=72; 24 in each panel) which evaluated the relative oral bioavailability of the different components after single-dose administration of a D/C/F/TAF FDC tablet compared to the separate agents (DRV plus COBI plus F/TAF) under fed conditions. This study also evaluated the relative oral bioavailability of TAF and FTC after single-dose administration of a DRV-containing FDC tablet (D/C/F/TAF) compared to an EVG-containing FDC tablet (E/C/F/TAF) under fed conditions. In addition, this study assessed the effect of food on the bioavailability of DRV, COBI, FTC, and TAF following single dose administration of a D/C/F/TAF FDC tablet.

- Study TMC114FD2HTX1004 is a completed, open-label, randomized, crossover study in healthy subjects (N=30) which assessed the relative bioavailability of DRV, COBI, FTC, and TAF when administered either as a whole D/C/F/TAF FDC tablet, as a split tablet or as a crushed tablet mixed in applesauce, under fed conditions in healthy subjects.

- Study GS-US-299-0101 is a completed, adaptive-design, randomized, open-label, multiple-dose, 3-part, multiple-cohort study in healthy subjects (N=102; 66 subjects received D/C/F/TAF) which evaluated:
  - the PK of DRV, COBI, FTC, and TFV after administration (once-daily for 21 days) of 3 different D/C/F/TAF FDC formulations (Part 1; N=30);
  - the PK of DRV, COBI, FTC, and TFV after administration (once-daily for 10 days in each cohort, ie, 20 days in total) of DRV/COBI plus TVD relative to administration of the individual components DRV/COBI or TVD (Part 2; N=36); and
  - the PK of DRV, COBI, FTC, TAF, and TFV after administration (once-daily for 12 days in each cohort, ie, 24 days in total) of the selected D/C/F/TAF FDC formulation relative to the administration of the individual components DRV/COBI or FTC, plus TAF (Part 3; N=36).

Appendix 2: Overview of Commercially Available Different Combinations Including Darunavir, Cobicistat, Emtricitabine, or Tenofovir

Darunavir is approved for treatment of HIV-1 in patients aged 3 years and above, either as a twice-daily treatment for ART-experienced subjects or as a once-daily treatment (800 mg) for ART-naïve subjects and for ART-experienced subjects without DRV RAMs. DRV is available as a single agent (Prezista®)[28] or as part of the FDC Prezcobix (DRV/COBI).[27]

Cobicistat 150 mg has been developed by GSI and is approved as a PK enhancer of DRV 800 mg once daily. COBI is available as a single agent (Tybost®)[33] or as part of the FDCs Evotaz® (ATV/COBI)[13], Genvoya (E/C/F/TAF)[16], Prezcobix (DRV/COBI) and Stribild® (STB; elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate [E/C/F/TDF][31]). COBI is devoid of antiviral activity.

Emtricitabine 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). FTC (200 mg) is indicated for use in adults and in pediatric subjects weighing at least 33 kg, and is available as a single agent (Emtriva®)[12] or as part of FDCs (Atripla® [ATR; EFV/F/TDF][2], Descovy [F/TAF][10], Eviplera® [FTC/RPV/TDF], Genvoya [E/C/F/TAF][16], Odefsey® [rilpivirine/emtricitabine/tenofovir alafenamide; R/F/TAF][23], STB [E/C/F/TDF][31] and TVD [F/TDF][32]).

Tenofovir is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription.

Tenofovir disoproxil fumarate (Viread®) is an oral prodrug of TFV and, in combination with FTC, is a guideline-recommended N(t)RTI backbone for ART-naïve patients.[35] The combination of FTC and TDF is used within several once-daily FDCs (TVD [F/TDF], ATR [EFV/F/TDF], Eviplera [FTC/RPV/TDF], and STB [E/C/F/TDF]).

Tenofovir alafenamide, developed by GSI, is a prodrug of 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, TDF. It is approved as part of the 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 to TDF (TDF is associated with an increased risk of nephrotoxicity and with early onset bone demineralization in adults[30,35]). 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.

The F/TAF FDC (Descovy) has been developed by GSI and is a once-daily treatment approved for use in combination with other ARV agents, including DRV/COBI, for treatment of HIV-1 infected adults and adolescents (aged 12 years and older). Two dosage strengths of Descovy are available: F/TAF 200/10 mg and F/TAF 200/25 mg; the TAF dose used depends on the other co-administered medications. The TAF dose used in the approved FDC tablet (from GSI) containing E/C/F/TAF tablet is 10 mg (E/C/F/TAF 150/150/200/10 mg).

TAF 25 mg alone (Vemlidy®) is approved for the treatment of chronic hepatitis B virus infection in adults with compensated liver disease.[34]

Appendix 3: Treatment-emergent Laboratory Abnormalities, Grade 2 to 4 , Considered Adverse Drug Reactions for D/C/F/TAF

Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Drug Reactions for D/C/F/TAF in HIV-1 Infected, ART-naïve Subjects (Study TMC114FD2HTX3001; ITT Population)

Phase = Treatment

	Limits[a]	D/C/F/TAF	Control
Analysis set: intent-to-treat, N		362	363
Hepatic Parameters			
Alanine aminotransferase (ALT), high			
Any treatment emergent grade 2, 3 or 4		6 (1.7%)	9 (2.5%)
Any treatment emergent grade 3 or 4		5 (1.4%)	3 (0.8%)
Treatment emergent grade 2	2.5 to <5.0x ULN	1 (0.3%)	6 (1.7%)
Treatment emergent grade 3	5.0 to <10.0x ULN	4 (1.1%)	2 (0.6%)
Treatment emergent grade 4	≥10.0x ULN	1 (0.3%)	1 (0.3%)
Aspartate aminotransferase (AST), high			
Any treatment emergent grade 2, 3 or 4		7 (1.9%)	10 (2.8%)
Any treatment emergent grade 3 or 4		4 (1.1%)	6 (1.7%)
Treatment emergent grade 2	2.5 to <5.0x ULN	3 (0.8%)	4 (1.1%)
Treatment emergent grade 3	5.0 to <10.0x ULN	4 (1.1%)	4 (1.1%)
Treatment emergent grade 4	≥10.0x ULN	0	2 (0.6%)
Alkaline phosphatase, high			
Any treatment emergent grade 2, 3 or 4		0	3 (0.8%)
Any treatment emergent grade 3 or 4		0	0
Treatment emergent grade 2	2.5 to <5.0x ULN	0	3 (0.8%)
Treatment emergent grade 3	5.0 to <10.0x ULN	0	0
Treatment emergent grade 4	≥10.0x ULN	0	0
Pancreatic Parameters			
Amylase (total), high			
Any treatment emergent grade 2, 3 or 4		8 (2.2%)	17 (4.7%)
Any treatment emergent grade 3 or 4		1 (0.3%)	0
Treatment emergent grade 2	1.5 to < 3.0x ULN	7 (1.9%)	17 (4.7%)
Treatment emergent grade 3	3.0 to <5.0x ULN	0	0
Treatment emergent grade 4	≥5.0x ULN	1 (0.3%)	0
Lipase, high[b]			
Any treatment emergent grade 2, 3 or 4		1 (0.3%)	6 (1.7%)
Any treatment emergent grade 3 or 4		0	2 (0.6%)
Treatment emergent grade 2	1.5 to <3.0x ULN	1 (0.3%)	4 (1.1%)
Treatment emergent grade 3	3.0 to <5.0x ULN	0	2 (0.6%)
Treatment emergent grade 4	≥5.0x ULN	0	0
Lipid Parameters			
Cholesterol, fasting limits, high, fasting samples only			
Any treatment emergent grade 2, 3 or 4		68 (18.8%)	18 (5%)
Any treatment emergent grade 3 or 4		6 (1.7%)	2 (0.6%)
Treatment emergent grade 2	240 to <300 mg/dL	62 (17.1%)	16 (4.4%)
Treatment emergent grade 3	≥300 mg/dL	6 (1.7%)	2 (0.6%)
Treatment emergent grade 4	NA	0	0
LDL, fasting limits, high, fasting samples only			
Any treatment emergent grade 2, 3 or 4		48 (13.3%)	17 (4.7%)
Any treatment emergent grade 3 or 4		17 (4.7%)	4 (1.1%)
Treatment emergent grade 2	160 to <190 mg/dL	31 (8.6%)	13 (3.6%)
Treatment emergent grade 3	≥190 mg/dL	17 (4.7%)	4 (1.1%)
Treatment emergent grade 4	NA	0	0

Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Drug Reactions for D/C/F/TAF in HIV-1 Infected, ART-naïve Subjects (Study TMC114FD2HTX3001; ITT Population)

Phase = Treatment

	Limits[a]	D/C/F/TAF	Control
Triglycerides, fasting limits, high, fasting samples only			
Any treatment emergent grade 2, 3 or 4		28 (7.7%)	17 (4.7%)
Any treatment emergent grade 3 or 4		4 (1.1%)	4 (1.1%)
Treatment emergent grade 2	>300 to 500 mg/dL	24 (6.6%)	13 (3.6%)
Treatment emergent grade 3	>500 to <1,000 mg/dL	3 (0.8%)	3 (0.8%)
Treatment emergent grade 4	>1,000 mg/dL	1 (0.3%)	1 (0.3%)
Glucose Parameters			
Glucose, serum, fasting limits, high, fasting samples only			
Any treatment emergent grade 2, 3 or 4		24 (6.6%)	20 (5.5%)
Any treatment emergent grade 3 or 4		1 (0.3%)	0
Treatment emergent grade 2	>125 to 250 mg/dL	23 (6.4%)	20 (5.5%)
Treatment emergent grade 3	>250 to 500 mg/dL	1 (0.3%)	0
Treatment emergent grade 4	>500 mg/dL	0	0
Renal Parameters			
Creatinine, high			
Any treatment emergent grade 2, 3 or 4		16 (4.4%)	49 (13.5%)
Any treatment emergent grade 3 or 4		1 (0.3%)	0
Treatment emergent grade 2	>1.3 to 1.8x ULN OR Increase of >0.3 mg/dL above baseline	15 (4.1%)	49 (13.5%)
Treatment emergent grade 3	>1.8 to <3.5x ULN OR Increase of 1.5 to <2.0x above baseline	0	0
Treatment emergent grade 4	≥3.5x ULN OR Increase of ≥2.0x above baseline	1 (0.3%)	0

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; LDL = low-density lipoprotein; N = number of subjects with data on treatment, ULN = upper limit of normal.
[a] For details, refer to Mod2.7.4/Tab33.
[b] Only reflex lipase testing was performed when total amylase >1.5x ULN.
Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/TSFAE50_EXT.

Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Drug Reactions for D/C/F/TAF in HIV-1 Infected, Virologically-suppressed Subjects Switching From a Boosted PI+F/TDF Regimen (Study TMC114IFD3013; ITT Population)

Phase = Treatment

	Limits[a]	D/C/F/TAF	Control
Analysis set: intent-to-treat, N		763	378
Hepatic Parameters			
Alanine aminotransferase (ALT), high			
Any treatment emergent grade 2, 3 or 4		26 (3.4%)	14 (3.7%)
Any treatment emergent grade 3 or 4		8 (1%)	9 (2.4%)
Treatment emergent grade 2	2.5 to <5.0x ULN	18 (2.4%)	5 (1.3%)
Treatment emergent grade 3	5.0 to <10.0x ULN	5 (0.7%)	4 (1.1%)
Treatment emergent grade 4	≥10.0x ULN	3 (0.4%)	5 (1.3%)
Aspartate aminotransferase (AST), high			
Any treatment emergent grade 2, 3 or 4		23 (3%)	16 (4.2%)
Any treatment emergent grade 3 or 4		11 (1.4%)	10 (2.6%)
Treatment emergent grade 2	2.5 to <5.0x ULN	12 (1.6%)	6 (1.6%)
Treatment emergent grade 3	5.0 to <10.0x ULN	7 (0.9%)	6 (1.6%)
Treatment emergent grade 4	≥10.0x ULN	4 (0.5%)	4 (1.1%)
Alkaline phosphatase, high			
Any treatment emergent grade 2, 3 or 4		2 (0.3%)	0
Any treatment emergent grade 3 or 4		0	0
Treatment emergent grade 2	2.5 to <5.0x ULN	2 (0.3%)	0
Treatment emergent grade 3	5.0 to <10.0x ULN	0	0
Treatment emergent grade 4	≥10.0x ULN	0	0
Pancreatic Parameters			
Amylase (total), high			
Any treatment emergent grade 2, 3 or 4		36 (4.7%)	28 (7.4%)
Any treatment emergent grade 3 or 4		4 (0.5%)	2 (0.5%)
Treatment emergent grade 2	1.5 to < 3.0x ULN	32 (4.2%)	26 (6.9%)
Treatment emergent grade 3	3.0 to <5.0x ULN	3 (0.4%)	1 (0.3%)
Treatment emergent grade 4	≥5.0x ULN	1 (0.1%)	1 (0.3%)
Lipase, high[b]			
Any treatment emergent grade 2, 3 or 4		8 (1%)	6 (1.6%)
Any treatment emergent grade 3 or 4		5 (0.7%)	2 (0.5%)
Treatment emergent grade 2	1.5 to <3.0x ULN	3 (0.4%)	4 (1.1%)
Treatment emergent grade 3	3.0 to <5.0x ULN	3 (0.4%)	0
Treatment emergent grade 4	≥5.0x ULN	2 (0.3%)	2 (0.5%)
Lipid Parameters			
Cholesterol, fasting limits, high, fasting samples only			
Any treatment emergent grade 2, 3 or 4		188 (24.6%)	32 (8.5%)
Any treatment emergent grade 3 or 4		28 (3.7%)	5 (1.3%)
Treatment emergent grade 2	240 to <300 mg/dL	160 (21%)	27 (7.1%)
Treatment emergent grade 3	≥300 mg/dL	28 (3.7%)	5 (1.3%)
Treatment emergent grade 4	NA	0	0
LDL, fasting limits, high, fasting samples only			
Any treatment emergent grade 2, 3 or 4		167 (21.9%)	23 (6.1%)
Any treatment emergent grade 3 or 4		48 (6.3%)	6 (1.6%)
Treatment emergent grade 2	160 to <190 mg/dL	119 (15.6%)	17 (4.5%)
Treatment emergent grade 3	≥190 mg/dL	48 (6.3%)	6 (1.6%)
Treatment emergent grade 4	NA	0	0
Triglycerides, fasting limits, high, fasting samples only			

Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Drug Reactions for D/C/F/TAF in HIV-1 Infected, Virologically-suppressed Subjects Switching From a Boosted PI+F/TDF Regimen (Study TMC114IFD3013; ITT Population)

Phase = Treatment

	Limits[a]	D/C/F/TAF	Control
Any treatment emergent grade 2, 3 or 4		55 (7.2%)	31 (8.2%)
Any treatment emergent grade 3 or 4		14 (1.8%)	8 (2.1%)
Treatment emergent grade 2	>300 to 500 mg/dL	41 (5.4%)	23 (6.1%)
Treatment emergent grade 3	>500 to <1,000 mg/dL	11 (1.4%)	8 (2.1%)
Treatment emergent grade 4	>1,000 mg/dL	3 (0.4%)	0
Glucose Parameters			
Glucose, serum, fasting limits, high, fasting samples only			
Any treatment emergent grade 2, 3 or 4		61 (8%)	23 (6.1%)
Any treatment emergent grade 3 or 4		8 (1%)	2 (0.5%)
Treatment emergent grade 2	>125 to 250 mg/dL	53 (6.9%)	21 (5.6%)
Treatment emergent grade 3	>250 to 500 mg/dL	8 (1%)	2 (0.5%)
Treatment emergent grade 4	>500 mg/dL	0	0
Renal Parameters			
Creatinine, high			
Any treatment emergent grade 2, 3 or 4		43 (5.6%)	25 (6.6%)
Any treatment emergent grade 3 or 4		2 (0.3%)	1 (0.3%)
Treatment emergent grade 2	>1.3 to 1.8x ULN OR Increase of >0.3 mg/dL above baseline	41 (5.4%)	24 (6.3%)
Treatment emergent grade 3	>1.8 to <3.5x ULN OR Increase of 1.5 to <2.0x above baseline	2 (0.3%)	1 (0.3%)
Treatment emergent grade 4	≥3.5x ULN OR Increase of ≥2.0x above baseline	0	0

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; LDL = low-density lipoprotein; N = number of subjects with data on treatment, ULN = upper limit of normal.
[a] For details, refer to Mod2.7.4/Tab36.
[b] Only reflex lipase testing was performed when total amylase >1.5x ULN.
Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/TSFAE50_EXT.

Appendix 4: Mean Changes From Baseline at Week 48 in Fasting Lipid Parameters, Excluding Subjects on Lipid-lowering Drugs, in the Phase 3 Studies with D/C/F/TAF

Mean Change From Baseline at Week 48 in Fasting Lipid Parameters, Excluding Subjects on Lipid-lowering Drugs[a], in HIV-1 Infected, ART-naïve Subjects (Study TMC114FD2HTX3001)

Lipid Parameter (mg/dL), Fasted	D/C/F/TAF (N=350)		Control (N=353)	
	Baseline	Mean Change at Week 48	Baseline	Mean Change at Week 48
Total Cholesterol	167 (n=331)	+30 (n=298)	163 (n=323)	+11 (n=288)
HDL-cholesterol	44 (n=331)	+6 (n=298)	44 (n=323)	+2 (n=288)
LDL-cholesterol	99 (n=331)	+19 (n=297)	98 (n=323)	+5 (n=288)
Triglycerides	117 (n=331)	+34 (n=298)	111 (n=323)	+21 (n=288)
Total Cholesterol to HDL ratio	4.1 (n=331)	0.2 (n=298)	4.0 (n=323)	0.1 (n=288)

[a] Subjects who used lipid-lowering drugs at screening/baseline or during the 48-week study period were excluded.
D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HDL = high density lipoprotein; LDL = low density lipoprotein.
Source: Ad hoc analysis.

Mean Change From Baseline at Week 48 in Fasting Lipid Parameters, Excluding Subjects on Lipid-lowering Drugs[a], in HIV-1 Infected, Virologically-suppressed Subjects Switching From a Boosted PI+F/TDF Regimen (Study TMC114IFD3013)

Lipid Parameter (mg/dL), Fasted	D/C/F/TAF (N=614)		Control (N=308)	
	Baseline	Mean Change at Week 48	Baseline	Mean Change at Week 48
Total Cholesterol	185 (n=594)	+22 (n=552)	184 (n=295)	+1 (n=270)
HDL-cholesterol	50 (n=594)	+3 (n=549)	50 (n=295)	-1 (n=269)
LDL-cholesterol	109 (n=592)	+18 (n=547)	107 (n=295)	+1 (n=269)
Triglycerides	137 (n=593)	+8 (n=550)	138 (n=295)	+8 (n=270)
Total Cholesterol to HDL ratio	4.0 (n=594)	0.2 (n=549)	3.9 (n=295)	0.1 (n=269)

[a] Subjects who used lipid-lowering drugs at screening/baseline or during the 48-week study period were excluded.
D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HDL = high density lipoprotein; LDL = low density lipoprotein.
Source: Ad hoc analysis.