NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY REPORT

Title	Non-Interventional Real-Life Study of Effectiveness, Safety, Adherence, and Health-Related Quality of Life in Adult Patients Receiving Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide (E/C/F/TAF) or Emtricitabine/Tenofovir alafenamide (F/TAF) or Rilpivirine/Emtricitabine/Tenofovir alafenamide (R/F/TAF) for HIV-1 Infection in Germany Protocol ID: GS-DE-292-1912
Version identifier of the final study report	Version 1.0 Final Written by CROMSOURCE
Date of last version of the final study report	09 Sep 2020
EU Post Authorization Study (PAS) register number	ENCEPP/SDPP/11010
Active substance	Elvitegravir Rilpivirine Cobicistat Emtricitabine Tenofovir alafenamide
Medicinal product	Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir alafenamide (E/C/F/TAF) as single tablet formulation Emtricitabine/Tenofovir alafenamide (F/TAF) as single tablet formulation Rilpivirine/Emtricitabine/Tenofovir alafenamide (R/F/TAF) as single tablet formulation
Product reference	EU/1/15/1061/001 EU/1/15/1061/002 EU/1/16/1099/001 EU/1/16/1099/002 EU/1/16/1112/001 EU/1/16/1112/002
Procedure number	Not applicable
Joint Post-Authorization Safety Study (PASS)	No

Research question and objectives	To assess effectiveness, safety, adherence, resource utilization, and patient reported outcomes for quality of life for the use of E/C/F/TAF, F/TAF, and R/F/TAF in routine care.
Country of study	Germany
Marketing Authorization Holder (MAH):	Gilead Sciences Ireland UC Carrigtohill, County Cork, T45 DP77 Ireland
MAH contact person	Name: PPD Telephone: PPD Fax: PPD

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

1. ABSTRACT

1.1. Title

Non-Interventional Real-Life Study of Effectiveness, Safety, Adherence, and Health-Related Quality of Life in Adult Patients Receiving Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide (E/C/F/TAF) or Emtricitabine/Tenofovir alafenamide (F/TAF) or Rilpivirine/Emtricitabine/Tenofovir alafenamide (R/F/TAF) for HIV-1 Infection in Germany

1.2. Keywords

HIV, therapy, regimen, Germany, adult

1.3. Rationale and Background

Tenofovir alafenamide (TAF), a prodrug of tenofovir (TFV) with equal virologic potency of tenofovir disoproxil fumarate (TDF; Viread®) and 91% lower circulating levels of plasma TFV and fewer off-target effects on renal and bone, was approved based on large controlled clinical trials of antiretroviral therapy (ART) naive and experienced patients. As no data are available in patients in routine clinical practice, this study was developed to evaluate the effectiveness and safety of TAF-based regimens in treatment experienced and treatment naive HIV-infected patients.

1.4. Research Question and Objectives

Primary Objective:

- To evaluate HIV-1 RNA and cluster determinant 4 (CD4) cell count changes for patients using E/C/F/TAF, F/TAF, or R/F/TAF within a time period of 24 months

Secondary Objectives:

- Adverse drug reactions (ADR), reason for ART initiation or switch, adherence (number of missed doses), patient persistence, health-related quality of life, health status, treatment satisfaction, and healthcare resource utilization

1.5. Study Design

Prospective, non-interventional, observational cohort study

1.6. Setting

Hospitals and private practitioners, specialized on treating HIV patients, throughout Germany

1.7. Patients and Study Size

Between 2016 and 2018 a total of 767 adults (aged ≥ 18) were enrolled into the study by 37 sites as follows:

- E/C/F/TAF arm: 318 patients (41.4%)
- F/TAF arm: 257 patients (33.5%)
- R/F/TAF arm: 192 patients (25.0%)

Patients were followed for 24 months.

1.8. Variables and Data Sources

Main Variables:

- HIV-1 RNA
- CD4 cell count
- Reason for ART initiation or switch to E/C/F/TAF, F/TAF, or R/F/TAF
- Reason to discontinue E/C/F/TAF, F/TAF, or R/F/TAF
- HIV Symptom Index
- HIV Treatment Satisfaction Questionnaire (only for treatment experienced patients)
- 36-Item Short Form Survey (SF-36)
- ADRs and serious adverse drug reactions (SADRs)
- Healthcare resource utilization

Data Sources:

Collection of routine visit data and questionnaires via electronic case report form (eCRF) using patient chart review by trained personnel at site

1.9. Results

Decreases in HIV-1 RNA viral load were seen in all three arms. In patients taking E/C/F/TAF, mean (95% CI) viral load decreased from 193,180.2 (74264.6, 312095.8) copies/mL at baseline to 83.9 (19.7, 148.1) copies/mL at month 24. In patients taking F/TAF, mean (95% CI) viral load decreased from 369,820.3 (194921.3, 544719.2) copies/mL at baseline to 55.2 (50.3, 60.1) copies/mL at month 24. In patients taking R/F/TAF, mean (95% CI) viral load decreased from 6318.8 (3731.5, 8906.2) copies/mL at baseline to 50.7 (48.6, 52.8) copies/mL at month 24.

Increases in CD4 count were seen in all three arms. Mean (95% CI) change in CD4 count at month 24 was 146.2 (107.3, 185.1) cells/µL in patients taking E/C/F/TAF, 148.8 (105.1, 192.5) cells/µL in patients taking F/TAF, and 123.0 (81.2, 164.8) cells/µL in patients taking R/F/TAF.

Antretroviral regimen persistence was high. The percentage of patients remaining on their initial TAF treatment regimen at study conclusion was 87.7 % in the E/C/F/TAF arm, 61.8% in the F/TAF arm, and 73.6% in the R/F/TAF arm.

Improvements in treatment satisfaction following switch to E/C/F/TAF, F/TAF, or R/F/TAF were observed in treatment experienced patients. The median (IQR) change in HIVTSQc overall treatment satisfaction score at month 12 was 21.5 (8.0, 29.0) in the E/C/F/TAF arm, 15.0 (2.0, 27.0) in the F/TAF arm, and 15.0 (0.5, 27.0) in the R/F/TAF arm.

Substantial changes in SF-36 scores with therapy were not seen in any of the 3 arms and the HIV symptom index was similar for patients in the 3 treatment arms. However, treatment arms were analysed as a whole and no differentiation was done for treatment naive or treatment experienced patients.

Within the 24 months of follow-up, in the E/C/F/TAF arm at least one treatment-emergent adverse drug reaction (TEADR) was reported by 6.6% (21 of 318) of patients and at least one treatment-emergent serious adverse drug reaction (TESADR) was reported by 0.6% (2 of 318) of patients in the All Treated Population (see section 9.3).

In the F/TAF arm, at least one TEADR was reported by only 6.2% (16 of 257) of patients and at least one TESADR was reported by 2.3% (6 of 257) of patients in the All Treated Population.

In the R/F/TAF arm, at least one TEADR was reported by 5.2% (1 of /192) of patients and no TESADRs were reported in the All Treated Population.

In treatment naive patients, the primary driver for therapy start was “early treatment according to guidelines” in all 3 treatment arms.

In the treatment experienced patients, in E/C/F/TAF arm, the primary switch reason was “simplification of ART”; in the F/TAF arm, the primary switch reason was “side effects of current ART”; and in the R/F/TAF arm, the primary switch reason was “side effects of current ART”.

No clinically significant changes in lab parameters were identified.

1.10. Discussion

In this real-life study, E/C/F/TAF, F/TAF and R/F/TAF were associated with substantial reductions in HIV-1 viral load and increases in CD4 count, confirming the efficacy reported in randomized controlled trials. Antiretroviral regimen persistence was generally high. While this study is not powered to make inter-arm comparisons, persistence was numerically higher in patients taking E/C/F/TAF or R/F/TAF compared to those taking F/TAF. Treatment experienced patients who switched to E/C/F/TAF, F/TAF or R/F/TAF reported improvements in treatment satisfaction. No differences were seen in SF-36 scores and HIV symptom index within each arm during the course of the observation looking at all three arms separately. All three regimens were well tolerated, with an adverse drug reaction profile similar to that reported in randomized controlled trials; no new safety signals were identified. No clinically significant changes in laboratory safety parameters were identified. The most common healthcare provider rationale for starting antiretroviral therapy was “early treatment according to guidelines” in all three treatment arms. Healthcare provider rationale for antiretroviral switch differed by arm, with “simplification of ART” being most commonly reported in E/C/F/TAF arm, and “side effects of current ART” being most common in the F/TAF and R/F/TAF arms. These findings demonstrate that E/C/F/TAF, F/TAF and R/F/TAF are safe and effective in a real-life setting demonstrating high treatment persistence and improved patient satisfaction.

1.11. Marketing Authorization Holder (MAH)

The MAH for the study drugs is Gilead Sciences Ireland UC
Carrigtohill, County Cork, T45 DP77, Ireland

1.12. Name and Affiliation of Principal Investigator

PPD

2. LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AMG	German drug act
ANOVA	analysis of variance
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BMD	bone mineral density
CD4	cluster determinant 4
CI	confidence interval
CKD	chronic kidney disease
COBI, C	cobicistat (Tybost®)
CRF	case report form
E/C/F/TAF	elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
EU	European Union
EVG, E	elvitegravir (Vitekta®)
FDC	fixed-dose combination
FTC, F	emtricitabine (Emtriva®)
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
GGT	gamma-glutamyltransferase
GVP	Good Pharmacovigilance Practices
HDL	high-density lipoprotein
HIV	Human immunodeficiency virus
INI	integrase inhibitor
INSTI	integrase strand-transfer inhibitor
LDL	low-density lipoprotein
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measures
NNRTI	nonnucleoside reverse transcriptase inhibitor
N(t)RTI	nucleoside and nucleotide reverse transcriptase inhibitors
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PT	Preferred term

Q1	first quartile
Q3	third quartile
QPPV	qualified person for pharmacovigilance
R/F/TAF	rilpivirine/emtricitabine/tenofovir alafenamide
RNA	ribonucleic acid
RPV, R	rilpivirine
SADR	serious adverse drug reaction
SAP	statistical analysis plan
SF-36	36-Item Short Form Survey
SmPC	summary of product characteristics
SOC	system organ class
Std	standard deviation
TDF	tenofovir disoproxil fumarate
TEADR	treatment-emergent adverse drug reaction
TESADR	treatment-emergent serious adverse drug reaction
TFLs	tables, figures, and listings
TFV	tenofovir
TFV-DP	tenofovir diphosphate
WHO	World Health Organization

DEFINITION OF TERMS

Analytical dataset	The minimum set of data required to perform the statistical analyses leading to the results of the primary objective(s) of the study
Bias	Systemic error in the design, conduct, or analysis of a study that results in a mistaken estimate
Cohort	Group of people characterized by a common experience (eg, occurrence of a specified disease, exposure to a given medication)
End of data collection	The date from which the analytical dataset was completely available
Exposure	A variable whose effect was of interest and was being studied
Outcome	An event (such as disease occurrence or death) that was studied in relation to exposure
Prevalence	Proportion of persons with the exposure/outcome at a specific point in time
Rate	A measure of event occurrence, calculated by dividing the total number of events by the total amount of person-time within an exposure category
Start of data collection	Date from which information on the first study patient was first recorded in the study dataset

3. INVESTIGATORS

Principal investigator:

- PPD

In total 38 sites participated in the study, whereas the data of one site had to be excluded from the analysis PPD

Contact details of all investigators can be made available upon request.

4. OTHER RESPONSIBLE PARTIES

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Medical Manager Gilead	PPD Sen. Dir. Medical Affairs, Gilead Sciences GmbH, Fraunhoferstr. 17, 82152 Martinsried, Germany	Phone: PPD Fax: PPD
Clinical Manager Gilead	PPD Director, Clinical Operations Germany, Gilead Sciences GmbH, Fraunhoferstr. 17, 82152 Martinsried, Germany	Phone: PPD Fax: PPD
Principal Investigator	PPD	Phone: PPD
Global Patient Safety	Global Patient Safety Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA	Phone: PPD

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	04 Jan 2016	04 Jan 2016	Not Applicable
End of data collection	Q4 2019	29 Nov 2019	Not Applicable
Registration in the European Union (EU) Post-Authorization Study (PAS) register (ENCEPP/SDPP/11010)	Q4 2015	05 Oct 2015	Not Applicable
Final report of study results	Q2 2020	Q3 2020	Delay due to delayed data finalization

6. RATIONALE AND BACKGROUND

6.1. Background

HIV-1 infection remains a life-threatening and serious disease of major public health significance. There are now approximately 38 million people infected worldwide{Joint United Nations Programme on HIV/AIDS (UNAIDS) 2013}. Globally, incidence continues to grow, with up to 2.2 million people newly infected with HIV-1 in 2019 alone. The prevalence of people living with HIV-1 infection is also increasing. Patients are being diagnosed earlier and are living longer due to the success of highly active antiretroviral therapy (ART).

Morbidity and mortality for HIV-1 infected patients is increasingly driven by non-AIDS associated comorbidities such as kidney, liver, and heart disease. Even with ART, patients with HIV-1 infection experience more age-related comorbidities, such as renal and bone disease, which manifest earlier than their age-matched HIV-uninfected peers. Moreover, the prevalence and incidence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is expected to rise as the prevalence of HIV-1 infection continues to rise.

Current treatment guidelines recommend that patients initiate therapy earlier, thereby requiring lifelong treatment, potentially for 50 years or more. Accordingly, there is a need for new HIV therapies that improve on the current standard of care so that lifelong ART is more effective, more tolerable, and safer for patients.

Tenofovir (TFV) is a nucleotide analog that inhibits HIV-1 reverse transcription. While tenofovir disoproxil fumarate (TDF), an oral prodrug of tenofovir (TFV), is a preferred nucleoside and nucleotide reverse transcriptase inhibitor (NRTI) for initial therapy, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs. Tenofovir alafenamide (TAF) is also an oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and results in approximately 90% lower circulating levels of TFV relative to TDF at the clinical doses. These characteristics of TAF are associated with effective suppression of viral replication, and an improved tolerability and safety profile of TAF compared to TDF.

Gilead has coformulated TAF with the HIV-1 integrase strand-transfer inhibitor (INSTI) elvitegravir (EVG; E; Vitekta®), the pharmacoenhancer cobicistat (COBI; C; Tybost®), and the NRTI emtricitabine (FTC; F; Emtriva®) into a fixed-dose combination (FDC) tablet that is suitable for once daily use. Thus E/C/F/TAF FDC provides a potent, convenient, tolerable, and practical regimen for the long-term treatment of patients with HIV-1 infection. Findings from two randomized, double-blind, Phase 3 trials of TAF versus TDF, both coformulated with elvitegravir, cobicistat, and emtricitabine, demonstrated non-inferior effectiveness of TAF versus TDF, with a significantly improved effect of TAF compared to TDF on estimated glomerular filtration rate (eGFR), proteinuria, albuminuria, and BMD.

Furthermore, Gilead has coformulated TAF with the NRTI FTC into a FDC tablet for once daily use (in combination with other antiretroviral [ARV] agents) and coformulated TAF with the HIV-1 nonnucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV; R) and the NRTI FTC into a FDC tablet for once daily use.

6.2. Rationale

In this non-interventional, observational, German study we are aiming to describe effectiveness and safety of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) or emtricitabine/tenofovir alafenamide (F/TAF) or rilpivirine/emtricitabine/tenofovir alafenamide (R/F/TAF) in treatment naive and treatment experienced HIV-1 infected adult patients as well as adherence, resource utilization, patient reported outcome data about quality of life, health status and treatment satisfaction of E/C/F/TAF, F/TAF, or R/F/TAF treated patients during daily routine use.

7. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study was as follows:

- To evaluate HIV-1 RNA and cluster determinant 4 (CD4) cell count changes for patients using E/C/F/TAF, F/TAF, or R/F/TAF within a time period of 24 months

The secondary objectives of this study were:

- To describe rates of adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs) for E/C/F/TAF, F/TAF, and R/F/TAF

- To describe the motivation for ART initiation in treatment naive patients (eg, early treatment according to guidelines, treatment as prevention, patient wish) and factors driving the ART switch to E/C/F/TAF, F/T/AF, or R/F/TAF in treatment experienced patients (eg, simplification of ART, patient preference, side effects of current ART)

- To describe adherence (number of missed E/C/F/TAF, F/T/AF, or R/F/TAF doses) and reasons for E/C/F/TAF, F/TAF, or R/F/TAF discontinuation during the study

- To describe physical and mental health-related quality of life, health status, and treatment satisfaction using standardized questionnaires (36-Item Short Form Survey (SF-36), HIV symptom index, and HIV treatment satisfaction questionnaire (only for treatment experienced patients)

- To describe healthcare resource utilization (eg, number of hospitalizations, number of physician visits)

The above parameters were evaluated separately per treatment arm and in various subgroups (eg, treatment naive patients versus treatment experienced patients, age [< 50 years, ≥ 50 years], presence of specific comorbidities, sex).

The collection of ADRs/SADRs reflected the real-life situation, in which the treating physician with best knowledge of his patient assessed whether an observed event could be related to a given treatment. In this way, the study collected safety data reflective of the real-life setting in which it was conducted.

8. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
01	14 April 2016	various	Amendment	Adding 300 patients treated with F/TAF and 300 patients treated with R/F/TAF, adding blood pressure, CD4 nadir, adding historic creatinine and urine parameters, allowing full 24 months documentation even if patients switch therapies, adding cardiovascular and renal risk factors, changes to medical monitor, and updated study timelines
02	12 April 2019	various	Amendment	Addition of product references, update of marketing authorization holder (MAH), update of European Union (EU) qualified person for pharmacovigilance (QPPV) contact details, and update of definitions of special situations

9. RESEARCH METHODS

9.1. Study Design

This was a non-interventional study where enrolled patients had been considered upfront by the investigator as eligible for treatment with E/C/F/TAF, F/TAF, or R/F/TAF in accordance with the approved respective summary of products characteristics (SmPC). This non-interventional study did not influence the treatment decisions made by the participating physicians. All treatments were prescribed according to local treatment guidelines and/or routine clinical practice. The treating physician made all treatment decisions and provided prescriptions for his/her patient. There were no study-specific procedures.

The study was designed as a multicenter, non-interventional, observational cohort study, in accordance with the German Drug Act (§63f AMG). It was planned to enroll a total of 900 adult (aged ≥ 18) HIV-1 infected patients initiating treatment with E/C/F/TAF (N 300), F/TAF (N 300) or R/F/TAF (N 300) in routine care. The study was to enroll approximately 150 treatment naive and 150 treatment experienced patients in each arm, whereas enrollment was planned to occur from January 2016 to December 2017.

Data collection was performed by trained site personnel and by manual entry of data from the patient's medical file and study questionnaires to a computer-based electronic case report form (eCRF). No patient initials were included.

Data were prospectively collected, each enrolled patient was followed for 24 months (irrespective of regimen changes). In case of E/C/F/TAF, F/TAF, or R/F/TAF discontinuation, the date of discontinuation, reasons for discontinuation (eg, patient request, adverse reaction, insufficient effectiveness) and patient's new ART was collected. The patient remained in the study and was continuously documented with the new ART until premature end of documentation (eg, due to lost to follow-up) or until reaching the defined end of documentation 24 months after enrollment.

In total 38 sites participated in the study, whereas the data of one site had to be excluded from the analysis PPD

9.2. Setting

9.2.1. Study Time Period

Data were documented at the following time points:

Baseline (start of E/C/F/TAF, F/TAF, or R/F/TAF therapy) at baseline, the historic data on serum creatinine, quantitative urine parameters, and body weight were documented.

Follow-up: approximately 3 months, 6 months, 12 months, 18 months, and 24 months after E/C/F/TAF, F/TAF, or R/F/TAF therapy initiation (baseline) according to clinical practice.

9.3. Patients

The study was to enroll approximately 900 adult (aged ≥ 18) treatment naive and treatment experienced HIV-1 infected patients initiating treatment with E/C/F/TAF, F/TAF, or R/F/TAF (300 patients per arm) in accordance with the respective SmPC in routine care. Additional inclusion criterion for treatment experienced patients in the F/TAF arm was ≥ 50 years old.

To evenly represent treatment naive and treatment experienced patients, the study was to enroll in each arm approximately 150 treatment naive and 150 treatment experienced patients.

The total study size of 300 patients per arm was chosen to allow the evaluation of collected parameters also within several subgroups per arm (eg, treatment naive patients vs treatment experienced patients, age [< 50 years, ≥ 50 years], presence of specific comorbidities, sex), assuming that such subgroups would be represented in substantial numbers.

All enrolled patients with informed consent who received at least one dose of study medication were included in the All Treated Population, i.e. all enrolled patients with informed consent who received at least one dose of study medication. It was assumed that a patient received at least one dose of study medication if a complete start date was given for E/C/F/TAF, F/TAF, or R/F/TAF on the Study Drug Administration case report form (CRF) page. Patients where “reason for stopping data collection” was given as “Protocol Violation” were excluded from this population. This covered all patients who did not meet the inclusion criteria, including all patients with off-label use.

Population subgroups as described below were analyzed in the study:

Age

- < 50 years of age
- ≥ 50 years of age

Sex at birth

- Male
- Female

Treatment Experience

- Treatment naive patients:

  Treatment-naive patients are defined as patients who answered "No" to "Has the patient previously received treatment for HIV?" on the Previous ARV Medication CRF page.

- Treatment experienced patients:

  Treatment experienced patients are those who answered "Yes" to "Has the patient previously received treatment for HIV?" on the Previous ARV Medication CRF page.

HIV-1-RNA Viral Load at Baseline

- HIV-1-RNA viral load at baseline ≤ 100.000 copies/mL
- HIV-1-RNA viral load at baseline > 100.000 copies/mL

Previous ART

- Previous ART without TDF:

  Patients with previous ART without TDF were treatment experienced patients whose therapy taken immediately prior to initiation of the study drug (as documented on the Previous ARV Medication CRF page), and did not contain TDF. The following medications contain TDF: NRTI/integrase inhibitors (INI): Stribild, NRTI/NNRTI: Atripla and Complera/Eviplera, NRTI: Tenofovir DF and Truvada.

- Previous ART with TDF (not Stribild):

  Patients with previous ART with TDF (not Stribild) were treatment experienced patients whose therapy taken immediately prior to initiation of the study drug (as documented on the previous ARV medication CRF page) did contain TDF but was not Stribild. The following medications contain TDF but are not Stribild: NRTI/NNRTI: Atripla and Complera/Eviplera, NRTI: Tenofovir DF and Truvada.

- Previous ART with Stribild:

  Patients with previous ART with Stribild were treatment experienced patients whose therapy taken immediately prior to initiation of the study drug (as documented on the previous ARV medication CRF page) did contain NRTI/INI Stribild.

9.4. Variables

The main variables were:

- HIV-1 RNA
- CD4 cell count
- Motivation for ART initiation in treatment naive patients and factors driving the ART switch to E/C/F/TAF, F/TAF, or R/F/TAF in treatment experienced patients
- HIV symptom index
- HIV treatment satisfaction questionnaire (only for treatment experienced patients)
- SF 36
- ADRs and SADRs
- Healthcare resource utilization (number and duration of hospitalizations, number of appointments with HIV-treating physician and with other physician types)

9.5. Data Sources and Measurement

According to definition of a "non-interventional study" in terms of guidelines on Good Pharmacovigilance Practices (GVP) Module VIII (Rev 1), the conduct of a non-interventional study requires that the protocol does not stipulate or dictate on the diagnosis, therapeutic decisions, and follow-up of the individual patient. This study only observed and collected the use of drugs and the corresponding descriptive and clinical outcome by the treating physician in the specific indication.

Clinical data was collected from the physician's documentation of the patient's visit in patient medical records that were closest to the prespecified follow up time points (approximately Month 3, 6, 12, 18, and 24). Primary data sources were electronic medical records, where available or paper records at the participating sites. Questionnaires on ART adherence, SF-36, treatment satisfaction, and HIV symptom index were filled in by the patients in paper form and collected by site staff. Data from medical records and from the collected questionnaires were manually transcribed by the investigator or site staff into eCRFs.

9.6. Bias

All decisions on the management of the patient were made solely by the treating physician. Patients may have switched treatment arms at the discretion of the treating physician. Documentation of study variables was not obligatory, and missing data of unpredictable extent could have occurred.

9.7. Study Size

At first 38 sites participated in the study, but 11 patients of one site needed to be excluded from analysis due to withdrawal of this site. In total, 767 adults (aged ≥ 18) were enrolled into the study by 37 sites as follows:

- E/C/F/TAF arm: 159 treatment naive and 159 treatment experienced patients; out of the total of 318 patients, 87 (27.3 %) were ≥ 50 years of age at enrollment.
- F/TAF arm: 100 treatment naive and 157 treatment experienced patients; all 157 (100.0%) treatment experienced patients were ≥ 50 years of age at enrollment.
- R/F/TAF arm: 42 treatment naive and 150 treatment experienced patients; out of the total of 192 patients, 59 (30.8%) were ≥ 50 years of age at enrollment.

9.8. Data Transformation

The study used an electronic data entry system (eCRF); all users received specific access codes to enable them to enter their data. The electronic data entry system contained automatic checks for data completeness and to identify inconsistent data.

ADRs/SADRs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1. Concomitant medications were coded using the World Health Organization (WHO) Drug Dictionary of March 2020. Antiretroviral medication taken alongside F/TAF was not coded.

Timepoints

Visit dates: If a date was needed for the calculation of durations or for the determination of visit windows, the following rules applied:

- If month and year of a date (visit dates, laboratory assessment dates, questionnaire dates or start date of study medication) were given but day was missing, day was set to 15.
- If month and/or year of a date were missing, this date was set to missing.
- In case the date was missing, the corresponding data were excluded from the summary tables and were flagged in the listings.

In listings, all dates appear as documented in the CRF.

Visit windows: For the purpose of all analyses, instead of using the nominal visit months (as reported on the CRF), the visits on and after enrollment were associated with visit months determined from the time since start date of study medication according to the following procedure:

In case the study medication start date was missing or incomplete (incomplete defined as no day and no month and/or no year), the data of the patient appeared only in listings and not in the summary tables.

Visit windows were defined as outlined in Table 1 (days counted from start date of study medication):

Table 1. Visit Window Definition

Months	Visit Window		Visit Day	Labels in Tables	Labels in Listings
	Lower Limit (Days)	Upper Limit (Days)			
0	0	0	0	Baseline	M0
3	46	137	91	Month 3	M3
6	138	274	183	Month 6	M6
12	275	457	365	Month 12	M12
18	458	639	548	Month 18	M18
24	640	822	730	Month 24	M24

Patient visits were assigned to a visit month if their actual visit date fell inside the relevant visit window, irrespective of the CRF assignment of nominal visit month. If for a patient, two or more actual visit dates fell into the same visit window, only data pertaining to the visit date closest to the nominal visit days (and in the event of a tie, the latest) were included in tables.

For the analysis of laboratory data, the same procedure was followed, but visit date was replaced by laboratory analysis date. Laboratory data not included for the summary analyses are flagged in the listings.

9.9. Statistical Methods

All tables, figures, and listings (TFLs) produced concerned the All Treated Population or subgroups thereof (see section 9.3). In the summary tables, the data of these patients were analysed in two ways (where applicable):

- First analysis: up to the point when patients switched/discontinued their initial TAF therapy (E/C/F/TAF, F/TAF, or R/F/TAF) or when they discontinued/completed the study, whichever occurred first. These tables were marked “On Initial TAF Treatment” in the header.

- Second analysis: used all data collected until the end of the observational period, regardless of whether they were collected before or after a regimen switch (if any). These tables were marked “Whole Observational Period” in the header.

9.9.1. Main Summary Measures

HIV-1 RNA viral load values below 50 copies/mL were set to 49 copies/mL for the purpose of the analysis. Of the different available assay methods, this was the largest (worst case) of the lowest levels of quantification.

Binary, categorical, and ordinal variables were described by counts and percentages of each modality (over the total number of responses). The number of missing values is also displayed. Unless otherwise specified, percentages were based on the number of patients with data, and were not calculated for the category of missings.

For continuous variables, mean, standard deviation (Std), minimum, first and third quartile (Q1, Q3), median, and maximum were calculated, together with the total number of observations and the number of missing and nonmissing values.

ADRs, comorbidities and coinfections as well as prior and concomitant medications were reported on a patient basis. For these analyses the percentages were calculated using the number of patients in the All Treated Population of the respective treatment arm as the denominator.

The questionnaire scores were calculated according to the algorithms elaborated for these questionnaires and defined or referred to in the Statistical Analysis Plan (SAP).

P-values and/or 95%-confidence intervals (95%-CI) were calculated when considered relevant. All analyses of this study are of exploratory in nature.

In listings, the visits that were “On Initial TAF Treatment” were marked.

The SAP (supplied in Annex 1, Number 3) describes and expands upon the statistical methods presented in the protocol.

Data were analysed separately per treatment arm (E/C/F/TAF, F/TAF, or R/F/TAF). Separate outputs are provided for the treatment arms.

9.9.2. Main Statistical Methods

All analyses are provided for the All Treated Population.

To assess the influence of relevant factors on the effect of the treatment, certain laboratory parameters (effectiveness and safety) were analysed using a mixed-effect model for repeated measures (MMRM) with the following approach:

For each parameter to be analysed, 3 analyses were provided.

A) The first was performed on the All Treated Population and had age categories (</≥ 50 years of age), sex, and treatment experience categories (treatment naive/treatment experienced) as fixed effects.

B) The second was performed on the subgroup of treatment experienced patients and had age categories, sex, and previous ART (without TDF/with TDF [not Stribild/Stribild]) as fixed effects.

C) The third analysis was performed on the subgroup of treatment naive patients and had age categories, sex, and the HIV-1 RNA viral load at baseline categories (≤/> 100.000 copies/mL) as fixed effects.

For the "Whole Observational Period" approach, the MMRM analysis of variance (ANOVA) included all visits after the baseline visit up to the 24-month visit. For the analysis "On Initial TAF Treatment", visits up to the treatment switch are used (if switch occurred). An autoregressive correlation structure was assumed for this analysis. Restricted maximum likelihood (REML was used to estimate all parameters and was the basis for all hypothesis testing. The hypothesis tests to perform on the fixed effects was type III.

The following parameters were to be analysed this way:

Effectiveness

- HIV viral load
- CD4 cell count

Renal Laboratory Parameters

- Estimated glomerular filtration rate (eGFR) (change from baseline)
- Creatinine clearance (calculated) (change from baseline)

Lipids

- High-density lipoprotein (HDL) (change from baseline)
- Low-density lipoprotein (LDL) (change from baseline)
- Triglycerides (change from baseline)
- Total cholesterol (change from baseline)

Bone Mineral Density (BMD)

- T-score (change from baseline)
- Z-score (change from baseline)

The time to ARV therapy switch was analysed using the Kaplan-Meier method. A patient was regarded as having switched from initial TAF during the observational period, if the stop date of the initial TAF treatment was 3 or more days before the study termination/completion date.

9.9.3. Missing Values

Patients with missing data for one of the parameters were not assigned to a subgroup.

Data of visits not falling inside any visit window were excluded from the summary analysis and flagged in the listings.

Missing values were not imputed.

9.9.4. Sensitivity Analyses

No sensitivity analyses were performed.

9.9.5. Amendments to the Conduct of the Study or Planned Analysis

With Amendment 1 of the protocol, 300 patients initiating F/TAF and 300 patients initiating R/F/TAF were added. Also, the following were added: blood pressure, CD4 nadir, historic creatinine and urine parameters, full 24 months documentation even if patients switch therapies, and cardiovascular and renal risk factors. Study timelines were updated.

Amendment 2 of the protocol introduced the following: addition of product references, update of MAH, update of EU QPPV contact details, and update of definitions of special situations.

Eleven patients (n 5 E/C/F/TAF, n 2 F/TAF, and n 4 R/F/TAF) from PPD had to be excluded from the analysis PPD

9.10. Quality Control

The electronic data entry system contained automatic checks for data completeness and to identify inconsistent data, and respective queries were generated, when necessary. Data and queries were remotely monitored for consistency and completeness.

10. RESULTS

This study was a non-interventional real-life study of effectiveness, safety, adherence, and health-related quality of life in adult patients receiving E/C/F/TAF or F/TAF, or R/F/TAF for HIV-1 infection in Germany.

All analyses are based on the database finalized on 09 June 2020.

In total, 767 adults (aged ≥ 18) were enrolled into the study by 37 sites as follows:

- E/C/F/TAF arm: 318 patients
- F/TAF arm: 257 patients
- R/F/TAF arm: 192 patients

Each treatment arm is discussed separately.

10.1. Participants

10.1.1. E/C/F/TAF Arm

A total of 318 patients provided informed consent, were enrolled into the study, and contributed to data while on therapy.

The number of patients enrolled and completing the study, together with a summary of patient disposition, is shown in Table 2. Overall, 85.5% (272 of 318) of patients completed the study documentation, with 14.5% (46 of 318) not completing study documentation. The main reason for study discontinuation was “Lost to Follow-Up”: with this reason being given for 84.8% (39 of 46) of patients who terminated early.

Table 2. Summary of Patient Disposition - Treatment Arm E/C/F/TAF - All Treated Population (N 318)

		n (%)
All Treated Population		318 (100.0)
Study Completed		272 (85.5)
Early Termination		46 (14.5)
Reason for Early Termination*	Death	1 (2.2)
	Investigator's Discretion	–
	Protocol Violation	–
	Withdrew Consent	3 (6.5)
	Lost to Follow-Up	39 (84.8)
	Study Terminated by Sponsor	–
	Premature Study Drug Discontinuation Prior to Month 24	3 (6.5)

Percentages are based on All Treated Population.
*Percentages of the Reason for Early Termination are based on those patients with early termination.
Patients should only have one reason for not completing study.
Source: Annex 1, Number 4, Table 14.1 1.1 arm 1

10.1.2. F/TAF Arm

A total of 257 patients provided informed consent, were enrolled into the study, and contributed to data while on therapy.

The number of patients enrolled and completing the study, together with a summary of patient disposition, is shown in Table 3. Overall, 86.0% (221 of 257) of patients completed the study documentation, with 14.0% (36 of 257) not completing study documentation. The main reason for study discontinuation was “Lost to Follow-Up”: with this reason being given for 63.9% (23 of 36) of patients who terminated early.

Table 3. Summary of Patient Disposition - Treatment Arm F/TAF - All Treated Population (N 257)

		n (%)
All Treated Population		257 (100.0)
Study Completed		221 (86.0)
Early Termination		36 (14.0)
Reason for Early Termination*	Death	4 (11.1)
	Investigator's Discretion	2 (5.6)
	Protocol Violation	–
	Withdrew Consent	7 (19.4)
	Lost to Follow-Up	23 (63.9)
	Study Terminated by Sponsor	–
	Premature Study Drug Discontinuation Prior to Month 24	–

Percentages based on All Treated Population.
* Percentages of the Reason for Early Termination are based on those patients with early termination.
Patients should only have one reason for not completing study.
Source: Annex 1, Number 4, Table 14.1 1.1 arm 2

10.1.3. R/F/TAF Arm

A total of 192 patients provided informed consent, were enrolled into the study, and contributed to data while on therapy.

The number of patients enrolled and completing the study, together with a summary of patient disposition, is shown in Table 4. Overall, 87.0% (167 of 192) of patients completed the study documentation, with 13.0% (25 of 192) not completing study documentation. The main reason for study discontinuation was “Lost to Follow-Up”: with this reason being given for 84.0% (21 of 25) of patients who terminated early.

Table 4. Summary of Patient Disposition - Treatment Arm R/F/TAF - All Treated Population (N 192)

		n (%)
All Treated Population		192 (100.0)
Study Completed		167 (87.0)
Early Termination		25 (13.0)
Reason for Early Termination*	Death	2 (8.0)
	Investigator's Discretion	–
	Protocol Violation	–
	Withdrew Consent	2 (8.0)
	Lost to Follow-Up	21 (84.0)
	Study Terminated by Sponsor	–
	Premature Study Drug Discontinuation Prior to Month 24	–

Percentages based on All Treated Population.
* Percentages of the Reason for Early Termination are based on those patients with early termination.
Patients should only have one reason for not completing study.
Source: Annex 1, Number 4, Table 14.1 1.1 arm 3

10.2. Descriptive Data

10.2.1. E/C/F/TAF Arm

The demographics for the 318 patients in the E/C/F/TAF arm are summarized in Table 5.

Overall, the mean (SD) age was 41.9 (12.34) years. The median was 40.0. The majority of patients were male: 294 (92.5%) patients were male, with 24 (7.5%) female. The majority of patients were white (91.5%; 291 of 318) followed by 4.4% black (14 of 318).

Table 5. Summary of Demographic Data - Treatment Arm E/C/F/TAF - All Treated Population (N 318)

Variable	Category	Statistic	
Age (years)		n	318
		Mean (SD)	41.9 (12.34)
		95%-CI of Mean	[40.5; 43.3]
		Median	40.0
		Q1, Q3	32.0, 50.0
		Min, Max	19, 85
Age (categories)	≥ 18 years - < 50 years	n (%)	231 (72.6)
	≥ 50 years - < 65 years	n (%)	72 (22.6)
	≥ 65 years	n (%)	15 (4.7)
	Missing	n	–
Sex	Male	n (%)	294 (92.5)
	Female	n (%)	24 (7.5)
	Missing	n	–
Race	American Indian or Alaska Native	n (%)	3 (0.9)
	Asian	n (%)	2 (0.6)
	Black	n (%)	14 (4.4)
	Native Hawaiian or Other Pacific Islander	n (%)	1 (0.3)
	White	n (%)	291 (91.5)
	Not Permitted	n (%)	6 (1.9)
	Other	n (%)	1 (0.3)
	Missing	n	–
Height (cm)		n	300
		Mean (SD)	178.0 (7.79)
		95%-CI of Mean	[177.1; 178.9]
		Median	178.0
		Q1, Q3	173.0, 183.0
		Min, Max	148, 201

Variable	Category	Statistic	
Weight (kg)		n	304
		Mean (SD)	75.9 (12.81)
		95%-CI of Mean	[74.4; 77.3]
		Median	75.0
		Q1, Q3	66.5, 83.0
		Min, Max	47, 156
BMI (kg/m^2)		n	298
		Mean (SD)	24.0 (3.66)
		95%-CI of Mean	[23.5; 24.4]
		Median	23.3
		Q1, Q3	21.5, 25.8
		Min, Max	16, 45
BMI (categories)	< 25 kg/m^2	n (%)	207 (69.5)
	≥ 25 kg/m^2 - < 30 kg/m^2	n (%)	71 (23.8)
	≥ 30 kg/m^2	n (%)	20 (6.7)
	Missing	n	20

Source: Annex 1, Number 4, Table 14.1 3.1 arm 1
BMI: body mass index

The HIV history of the E/C/F/TAF arm was as follows: mean (median) CD4 nadir (cells/µL) was 444.1 (407.5); mean (median) time since diagnosis (years) was 5.3 (3.0). (Source: Annex 1, Number 4, Table 14.1-4.2.1 arm 1)

10.2.2. F/TAF Arm

The demographics for the 257 patients in the F/TAF arm are summarized in Table 6.

Overall, the mean (SD) age was 50.8 (12.23) years. The median was 53.0. The majority of patients were male: 241 (93.8%) patients were male, with 16 (6.2%) female. The majority of patients were white (94.9%; 244 of 257) followed by 3.1% black (8 of 257).

Table 6. Summary of Demographic Data - Treatment Arm F/TAF - All Treated Population (N 257)

Variable	Category	Statistic	
Age (years)		n	257
		Mean (SD)	50.8 (12.23)
		95%-CI of Mean	[49.3; 52.3]
		Median	53.0
		Q1, Q3	45.0, 59.0
		Min, Max	18, 78
Age (categories)	≥ 18 years - < 50 years	n (%)	81 (31.5)
	≥ 50 years - < 65 years	n (%)	151 (58.8)
	≥ 65 years	n (%)	25 (9.7)
	Missing	n	–
Sex	Male	n (%)	241 (93.8)
	Female	n (%)	16 (6.2)
	Missing	n	–
Race	American Indian or Alaska Native	n (%)	–
	Asian	n (%)	4 (1.6)
	Black	n (%)	8 (3.1)
	Native Hawaiian or Other Pacific Islander	n (%)	–
	White	n (%)	244 (94.9)
	Not Permitted	n (%)	1 (0.4)
	Other	n (%)	–
	Missing	n	–
Height (cm)		n	239
		Mean (SD)	177.7 (7.84)
		95%-CI of Mean	[176.7; 178.7]
		Median	178.0
		Q1, Q3	172.0, 183.0
		Min, Max	154, 200

Variable	Category	Statistic	
Weight (kg)		n	239
		Mean (SD)	78.2 (15.80)
		95%-CI of Mean	[76.1; 80.2]
		Median	77.0
		Q1, Q3	68.0, 88.7
		Min, Max	44, 137
BMI (kg/m^2)		n	237
		Mean (SD)	24.7 (4.47)
		95%-CI of Mean	[24.1; 25.3]
		Median	24.0
		Q1, Q3	21.8, 27.2
		Min, Max	14, 43
BMI (categories)	< 25 kg/m^2	n (%)	136 (57.4)
	≥ 25 kg/m^2 - < 30 kg/m^2	n (%)	75 (31.6)
	≥ 30 kg/m^2	n (%)	26 (11.0)
	Missing	n	20

Source: Annex 1, Number 4, Table 14.1 3.1 arm 2
BMI: body mass index

The HIV history of the F/TAF arm was as follows: mean (median) CD4 nadir (cells/µL) was 322.2 (258.0); mean (median) time since diagnosis (years) was 9.3 (7.0). (Source: Annex 1, Number 4, Table 14.1-4.2.1 arm 2)

10.2.3. R/F/TAF Arm

The demographics for the 192 patients in the F/TAF arm are summarized in Table 7.

Overall, the mean (SD) age was 42.9 (12.07) years. The median was 42.5. The majority of patients were male: 171 (89.1%) patients were male, with 21 (10.9%) female. The majority of patients were white (90.6%; 174 of 192) followed by 4.7% black (9 of 192) and 4.7% Asian (9 of 192).

Table 7. Summary of Demographic Data - Treatment Arm R/F/TAF - All Treated Population (N 192)

Variable	Category	Statistic	
Age (years)		n	192
		Mean (SD)	42.9 (12.07)
		95%-CI of Mean	[41.2; 44.6]
		Median	42.5
		Q1, Q3	33.5, 51.0
		Min, Max	18, 79
Age (categories)	≥ 18 years - < 50 years	n (%)	133 (69.3)
	≥ 50 years - < 65 years	n (%)	51 (26.6)
	≥ 65 years	n (%)	8 (4.2)
	Missing	n	–
Sex	Male	n (%)	171 (89.1)
	Female	n (%)	21 (10.9)
	Missing	n	–
Race	American Indian or Alaska Native	n (%)	–
	Asian	n (%)	9 (4.7)
	Black	n (%)	9 (4.7)
	Native Hawaiian or Other Pacific Islander	n (%)	–
	White	n (%)	174 (90.6)
	Not Permitted	n (%)	–
	Other	n (%)	–
	Missing	n	–
Height (cm)		n	180
		Mean (SD)	177.8 (6.79)
		95%-CI of Mean	[176.8; 178.8]
		Median	178.0
		Q1, Q3	173.0, 183.0
		Min, Max	160, 200

Variable	Category	Statistic	
Weight (kg)		n	186
		Mean (SD)	77.9 (15.34)
		95%-CI of Mean	[75.7; 80.2]
		Median	77.0
		Q1, Q3	68.0, 86.0
		Min, Max	46, 152
BMI (kg/m^2)		n	180
		Mean (SD)	24.7 (4.46)
		95%-CI of Mean	[24.0; 25.3]
		Median	24.3
		Q1, Q3	21.7, 27.2
		Min, Max	17, 49
BMI (categories)	< 25 kg/m^2	n (%)	111 (61.7)
	≥ 25 kg/m^2 - < 30 kg/m^2	n (%)	52 (28.9)
	≥ 30 kg/m^2	n (%)	17 (9.4)
	Missing	n	12

Source: Annex 1, Number 4, Table 14.1 3.1 arm 3
BMI: body mass index

The HIV history of the R/F/TAF arm was as follows: mean (median) CD4 nadir (cells/µL) was 405.1 (366.0); mean (median) time since diagnosis (years) was 7.3 (6.0). (Source: Annex 1, Number 4, Table 14.1-4.2.1 arm 3)

10.3. Main Results

The main effectiveness variables were HIV-1 RNA viral load and CD4 cell count.

10.3.1. E/C/F/TAF Arm

10.3.1.1. HIV-1 RNA Viral Load E/C/F/TAF Arm

A summary of HIV-1 viral load at baseline (categorized) is presented in Table 8. In total, 88.9% of patients had an HIV-1 RNA viral load of ≤ 100,000 copies/mL at baseline, while 11.1% had a viral load of > 100,000 copies/mL.

Table 8. Summary of HIV-1 Viral Load at Baseline (Categorized) Treatment Arm E/C/F/TAF - All Treated Population (N 318)

		n (%)
HIV 1 Viral Load at Baseline	≤ 100,000 copies/mL	280 (88.9)
	> 100,000 copies/mL	35 (11.1)
	Missing	3

Source: Annex 1, Number 4, Table 14.2 1.1.1 arm 1

For the analysis "on initial TAF treatment", HIV-1 RNA viral load at each visit and change from baseline for HIV-1 RNA viral load are summarized in Table 9.

At baseline, patients had a mean HIV-1 RNA viral load of 193,180.2 copies/mL. There was a general trend in a reduction of HIV-1 RNA viral load over 24 months, with the lowest level reached at 12 months.

Table 9. Summary of HIV-1 RNA Viral Load - Treatment Arm E/C/F/TAF - All Treated Population (N 318) - On initial TAF treatment

	Visit	Mean	Std	95%-CI of Mean	Q1	Median	Q3	n	Missing	Total
HIV 1 Viral Load (copies/mL)	Baseline	193180.2	1072676.73	[74264.6; 312095.8]	49.0	83.0	21859.0	315	3	318
	Month 3	62.9	126.05	[47.7; 78.2]	49.0	49.0	49.0	266	18	284
	Month 6	57.8	85.51	[47.2; 68.5]	49.0	49.0	49.0	251	24	275
	Month 12	50.9	14.75	[49.1; 52.7]	49.0	49.0	49.0	251	15	266
	Month 18	156.9	1556.66	[42.3; 356.1]	49.0	49.0	49.0	237	16	253
	Month 24	83.9	489.64	[19.7; 148.1]	49.0	49.0	49.0	226	9	235
HIV 1 Viral Load (copies/mL) Change from baseline	Month 3	185579.2	1002706.43	[307325.2; 63833.1]	21551.0	34.0	0.0	263	21	284
	Month 6	194763.6	1031756.59	[323806.1; 65721.1]	21925.5	23.6	0.0	248	27	275
	Month 12	194291.2	1029641.81	[322807.8; 65774.6]	22041.0	1.0	0.0	249	17	266
	Month 18	195855.6	1055080.43	[331453.1; 60258.1]	21551.0	0.0	0.0	235	18	253
	Month 24	194777.3	1069786.59	[335636.3; 53918.3]	20556.0	1.0	0.0	224	11	235

Values below 50 are set to 49 for the purpose of the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.1 arm 1

Overall, 222 (of 318) patients contributed to the MMRM on the initial TAF treatment for the All Treated Population. The results are presented in Table 10. The analysis showed a significant effect for treatment naive versus treatment experienced patients (p-value 0.0136) and a significant p-value (< 0.001) for the interaction between treatment experience and visit.

Table 10. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population (N 222) - On initial TAF treatment

	N	P value
Number of Contributing Patients	222	
Age		0.4295
Sex		0.7036
Treatment Experience		0.0136
Visit		0.4758
Age*Visit		0.6909
Sex*Visit		0.9829
Treatment Experience*Visit		<.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects were not used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.2.1 arm 1

Overall, 114 (of 159) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment experienced patients. The results are presented in Table 11. The analysis shows no significant p-values for any of the factors (age, sex, previous ART, visit and interactions).

Table 11. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population - Subgroup treatment experienced (N 114) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	114	
Age		0.6549
Sex		0.8438
Previous ART Group		0.6658
Visit		0.9984
Age*Visit		0.8113
Sex*Visit		0.9998
Previous ART Group*Visit		0.9855

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.3.1 arm 1

Overall, 107 (of 159) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment naive patients. The results are presented in Table 12. HIV viral load at baseline (≤/> 100,000 copies/mL) showed a significant p-value (< 0.001 for both HIV viral load group and HIV viral load group by visit). The p-value for visit is also significant (0.0022).

Table 12. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population - Subgroup Treatment Naive (N 107) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	107	
Age		0.1560
Sex		0.9544
HIV Viral Load Group		<.0001
Visit		0.0022
Age*Visit		0.0873
Sex*Visit		1.0000
HIV Viral Load Group*Visit		<.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.4.1 arm 1

For the analysis “whole observational period”, HIV-1 RNA viral load at each visit and change from baseline for HIV-1 RNA viral load are summarized in Table 13.

At baseline, patients had a mean HIV-1 RNA viral load of 193,180.2 copies/mL. There was a general trend in a reduction of HIV-1 RNA viral load over 24 months, with the lowest level reached at 12 months.

Table 13. Summary of HIV-1 Viral Load - Treatment Arm E/C/F/TAF - All Treated Population (N 318) – Whole Observational Period

	Visit	Mean	Std	95%-CI of Mean	Q1	Median	Q3	n	Missing	Total
HIV 1 Viral Load (copies/mL)	Baseline	193180.2	1072676.73	[74264.6; 312095.8]	49.0	83.0	21859.0	315	3	318
	Month 3	63.2	125.50	[48.1; 78.3]	49.0	49.0	49.0	269	18	287
	Month 6	57.7	84.52	[47.3; 68.1]	49.0	49.0	49.0	257	25	282
	Month 12	50.8	14.44	[49.1; 52.6]	49.0	49.0	49.0	262	18	280
	Month 18	150.5	1500.77	[34.6; 335.6]	49.0	49.0	49.0	255	18	273
	Month 24	118.2	751.56	[25.0; 211.5]	49.0	49.0	49.0	252	9	261
HIV 1 Viral Load (copies/mL) Change from baseline	Month 3	184812.6	997188.39	[305197.6; 64427.6]	21551.0	54.0	0.0	266	21	287
	Month 6	191536.7	1019853.42	[317560.2; 65513.2]	21810.0	16.1	0.0	254	28	282
	Month 12	190228.1	1010301.46	[313848.8; 66607.4]	22041.0	1.0	0.0	259	21	280
	Month 18	192052.0	1021963.88	[318588.0; 65516.0]	19561.0	0.0	0.0	253	20	273
	Month 24	184277.8	1019991.43	[311589.9; 56965.8]	19561.0	1.0	0.0	249	12	261

Values below 50 are set to 49 for the purpose of the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.5 arm 1

Overall, 248 (of 318) patients contributed to the MMRM on the whole observational period for the All Treated Population. The results are presented in Table 14. Only treatment experience (treatment naive/treatment experienced) showed a significant p-value (0.0087 for treatment experience and < 0.001 for treatment experience by visit).

Table 14. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population (N 248) - Whole Observational Period

	N	P value
Number of Contributing Patients	248	
Age		0.4467
Sex		0.7090
Treatment Experience		0.0087
Visit		0.2803
Age*Visit		0.7237
Sex*Visit		0.9843
Treatment Experience*Visit		<.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, i.e.ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.6.1 arm 1

Overall, 128 (of 159) patients contributed to the MMRM on the whole observational period for the subgroup of treatment experienced patients. The results are presented in Table 15. The analysis shows no significant p-values for any of the factors.

Table 15. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population - Subgroup Treatment Experienced (N 128) - Whole Observational Period

	N	P value
Number of Contributing Patients	128	
Age		0.6324
Sex		0.8124
Previous ART Group		0.6559
Visit		0.9980
Age*Visit		0.7875
Sex*Visit		0.9992
Previous ART Group*Visit		0.9818

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.7.1 arm 1

Overall, 119 (of 159) patients contributed to the MMRM on the whole observational period for the subgroup of treatment naive patients. The results are presented in Table 16. HIV viral load at baseline (≤/> 100,000 copies/mL) showed a significant p-value (< 0.001 for both HIV viral load group and HIV viral load group by visit). The p-value for Visit is also significant (0.0009).

Table 16. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population - Subgroup Treatment Naive (N 119) - Whole Observational Period

	N	P value
Number of Contributing Patients	119	
Age		0.2265
Sex		0.9789
HIV Viral Load Group		<.0001
Visit		0.0009
Age*Visit		0.2181
Sex*Visit		1.0000
HIV Viral Load Group*Visit		<.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.8.1 arm 1

10.3.1.2. CD4 Cell Count E/C/F/TAF Arm

The "on initial TAF treatment" analysis of CD4 cell count and change from baseline of CD4 cell count in the E/C/F/TAF arm is summarized in Table 17 for the All Treated Population. The mean CD4 cell count increased over time.

Table 17. Summary of CD4 Cell Count - Treatment Arm E/C/F/TAF - All Treated Population (N 318) – On Initial TAF Treatment Period

	Visit	Mean	Std	95%-CI of Mean	Q1	Median	Q3	n	Missing	Total
CD4 cell count (cells/µlL)	Baseline	597.3	309.50	[562.9; 631.7]	392.0	560.0	783.0	313	5	318
	Month 3	679.0	314.29	[641.1; 717.0]	460.0	647.0	841.0	266	18	284
	Month 6	703.7	332.86	[661.9; 745.5]	458.0	668.0	900.0	246	29	275
	Month 12	733.5	350.27	[689.6; 777.4]	499.0	686.0	912.0	247	19	266
	Month 18	739.3	335.08	[695.3; 783.3]	500.0	683.0	918.0	225	28	253
	Month 24	756.4	341.36	[710.2; 802.5]	535.0	690.0	953.0	213	22	235
CD4 cell count (cells/µL) Change from baseline	Month 3	82.3	216.69	[55.9; 108.7]	41.0	70.0	187.0	262	22	284
	Month 6	95.5	226.95	[66.9; 124.1]	45.0	85.0	213.5	244	31	275
	Month 12	139.0	255.05	[106.9; 171.1]	14.0	127.0	265.0	245	21	266
	Month 18	131.0	275.36	[94.7; 167.4]	29.0	105.0	303.0	223	30	253
	Month 24	146.2	285.34	[107.3; 185.1]	45.0	118.0	304.0	209	26	235

Source: Annex 1, Number 4, Table 14.2 2.1.1 arm 1

Overall, 204 (of 318) patients contributed to the MMRM on the initial TAF treatment for the All Treated Population. The results are presented in Table 18. The p-values for sex (0.0001), visit (0.0063), and treatment experience by visit interaction (< 0.0001) are significant.

Table 18. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population (N 204) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	204	
Age		0.9888
Sex		0.0001
Treatment Experience		0.5000
Visit		0.0063
Age*Visit		0.3653
Sex*Visit		0.1217
Treatment Experience*Visit		<.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .2.1.1 arm 1

Overall, 104 (of 159) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment experienced patients. The results are presented in Table 19. The p-values for sex (<0.0001), visit (0.0287), and sex by visit interaction (0.0296) are significant.

Table 19. Summary of CD4 cell count, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population - Subgroup Treatment Experienced (N 104) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	104	
Age		0.9061
Sex		<.0001
Previous ART Group		0.6637
Visit		0.0287
Age*Visit		0.7472
Sex*Visit		0.0296
Previous ART Group*Visit		0.8273

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, i.e.ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 2.1.3.1 arm 1

Overall, 99 (of 159) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment naive patients. The results are presented in Table 20. HIV viral load at baseline (≤/> 100,000 copies/mL) has a significant p-value (0.0075) as does visit (0.0012).

Table 20. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population - Subgroup Treatment Naive (N 99) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	99	
Age		0.8851
Sex		0.7815
HIV Viral Load Group		0.0075
Visit		0.0012
Age*Visit		0.1317
Sex*Visit		0.9986
HIV Viral Load Group*Visit		0.0575

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 2.1.4.1 arm 1

For the analysis "whole observational period", CD4 cell counts in the E/C/F/TAF arm, All Treated Population, are summarized in Table 21, as well as changes from baseline for CD4 cell count.

At baseline, patients had a mean (median) CD4 cell count of 597.3 (560.0) cells/µL. The CD4 cell count increased over time.

Table 21. Summary of CD4 Cell Count - Treatment Arm E/C/F/TAF - All Treated Population (N 318) - Whole Observational Period

	Visit	Mean	Std	95%-CI of Mean	Q1	Median	Q3	n	Missing	Total
CD4 cell count (cells/µlL)	Baseline	597.3	309.50	[562.9; 631.7]	392.0	560.0	783.0	313	5	318
	Month 3	679.0	312.61	[641.4; 716.5]	461.0	647.0	840.0	269	18	287
	Month 6	699.7	331.29	[658.5; 740.8]	457.0	658.0	898.0	252	30	282
	Month 12	733.2	347.50	[690.6; 775.7]	502.0	680.0	912.0	259	21	280
	Month 18	740.6	339.00	[697.4; 783.7]	494.5	685.0	919.0	240	33	273
	Month 24	753.9	344.55	[709.9; 797.9]	528.0	690.5	953.0	238	23	261
CD4 cell count (cells/µL) Change from baseline	Month 3	82.7	216.25	[56.6; 108.9]	41.0	70.0	189.0	265	22	287
	Month 6	90.5	233.40	[61.4; 119.6]	46.0	85.0	212.0	250	32	282
	Month 12	133.5	257.74	[101.7; 165.2]	20.5	123.5	267.5	256	24	280
	Month 18	127.7	279.46	[92.0; 163.4]	38.0	106.5	298.0	238	35	273
	Month 24	139.4	288.63	[102.2; 176.7]	45.0	112.0	294.0	233	28	261

Source: Annex 1, Number 4, Table 14.2 2.1.5 arm 1

Overall, 229 (of 318) patients contributed to the MMRM on the whole observational period for the All Treated Population. The results are presented in Table 22. The p-values for sex (0.0058), visit (0.0038), and treatment experience by visit interaction (< 0.0001) are significant.

Table 22. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population (N 229) - Whole Observational Period

	N	P value
Number of Contributing Patients	229	
Age		0.7351
Sex		0.0058
Treatment Experience		0.4752
Visit		0.0038
Age*Visit		0.2211
Sex*Visit		0.1160
Treatment Experience*Visit		<.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .2.1.6.1 arm 1

Overall, 118 (of 159) patients contributed to the MMRM on the whole observational period for the subgroup of treatment experienced patients. The results are presented in Table 23. The p-values for sex (0.0062) and visit (0.0254) are significant.

Table 23. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population - Subgroup Treatment Experienced (N 118) - Whole Observational Period

	N	P value
Number of Contributing Patients	118	
Age		0.8172
Sex		0.0062
Previous ART Group		0.7138
Visit		0.0254
Age*Visit		0.7093
Sex*Visit		0.0529
Previous ART Group*Visit		0.4824

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, i.e. ie,on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 2.1.7.1 arm 1

Overall, 110 (of 159) patients contributed to the MMRM on the whole observational period for the subgroup of treatment naive patients. The results are presented inTable 24. HIV viral load at baseline (0.0085) and the respective interaction (0.0313) have a significant p-value as does visit (0.0011).

Table 24. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm E/C/F/TAF - All Treated Population - Subgroup Treatment Naive (N 110) - Whole Observational Period

	N	P value
Number of Contributing Patients	110	
Age		0.7746
Sex		0.7450
HIV Viral Load Group		0.0085
Visit		0.0011
Age*Visit		0.1009
Sex*Visit		0.9987
HIV Viral Load Group*Visit		0.0313

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 2.1.8.1 arm 1

10.3.2. F/TAF Arm

10.3.2.1. HIV-1 RNA Viral Load F/TAF Arm

A summary of HIV-1 viral load at baseline (categorized) is presented in Table 25. In total, 76.6% of patients had an HIV-1 RNA viral load of ≤ 100,000 copies/mL at baseline, while 23.4% had a viral load of > 100,000 copies/mL.

Table 25. Summary of HIV-1 Viral Load at Baseline (Categorised) Treatment Arm F/TAF - All Treated Population (N 257)

		n (%)
HIV 1 Viral Load at Baseline	≤ 100,000 copies/mL	193 (76.6)
	> 100,000 copies/mL	59 (23.4)
	Missing	5

Source: Annex 1, Number 4, Table 14.2 1.1.1 arm 2

For the analysis "on initial TAF treatment", HIV-1 RNA viral load at each visit and change from baseline for HIV-1 RNA viral load are summarized in Table 26. At baseline, patients had a mean (median) HIV-1 RNA viral load of 369,820.3 (49.0) copies/mL. There was a general trend in a reduction of HIV-1 RNA viral load over 24 months, with the lowest level reached at 18 months.

Table 26. Summary of HIV-1 RNA Viral Load - Treatment Arm F/TAF - All Treated Population (N 257) - On Initial TAF Treatment

	Visit	Mean	Std	95%-CI of Mean	Q1	Median	Q3	n	Missing	Total
HIV 1 Viral Load (copies/mL)	Baseline	369820.3	1409743.86	[194921.3; 544719.2]	49.0	49.0	97936.0	252	5	257
	Month 3	2157.9	20983.99	[669.6; 4985.4]	49.0	49.0	49.0	214	10	224
	Month 6	163.5	1204.23	[4.8; 331.9]	49.0	49.0	49.0	199	20	219
	Month 12	289.6	2750.66	[94.0; 673.1]	49.0	49.0	49.0	200	3	203
	Month 18	52.0	17.72	[49.3; 54.6]	49.0	49.0	49.0	174	9	183
	Month 24	55.2	29.88	[50.3; 60.1]	49.0	49.0	49.0	145	8	153
HIV 1 Viral Load (copies/mL) Change from baseline	Month 3	346456.4	1342642.46	[528668.6; 164244.3]	88370.0	0.0	0.0	211	13	224
	Month 6	364375.4	1415453.63	[563259.7; 165491.1]	29250.0	0.0	0.0	197	22	219
	Month 12	323885.3	1369858.18	[516363.0; 131407.6]	27851.0	0.0	0.0	197	6	203
	Month 18	256686.5	1221428.26	[441618.8; 71754.2]	16451.0	0.0	0.0	170	13	183
	Month 24	276426.5	1251566.33	[484061.9; 68791.2]	34951.0	0.0	0.0	142	11	153

Values below 50 are set to 49 for the purpose of the analysis.
Source:Annex 1, Number 4, Table 14.2 .1.2.1 arm 2

Overall, 145 (of 257) patients contributed to the MMRM on the initial TAF treatment for the All Treated Population. The results are presented in Table 27. A significant p-value (0.0065) is given for age by visit interaction. However, all treatment experienced patients where in the same age group (≥ 50 years) as per inclusion criteria.

Table 27. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population (N 145) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	145	
Age		0.0607
Sex		1.0000
Treatment Experience		0.5164
Visit		0.2441
Age*Visit		0.0065
Sex*Visit		1.0000
Treatment Experience*Visit		0.8710

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source:Annex 1, Number 4, Table 14.2 .1.2.2.1 arm 2

Overall, 96 (of 157) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment experienced patients. The results are presented in Table 28. The analysis shows no significant p-values for the factors sex, previous ART, visit, and respective interactions). Age was not included in the analysis as all treatment experienced patients where in the same age group (≥ 50 years) as per inclusion criteria.

Table 28. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population - Subgroup Treatment Experienced (N 96) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	96	
Sex		0.9442
Previous ART Group		0.6313
Visit		0.9890
Sex*Visit		0.9692
Previous ART Group*Visit		0.9982

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.3.1 arm 2

Overall, 47 (of 100) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment naive patients. The results are presented in Table 29. The analysis shows no significant p-values for the factors of age, visit, and their interaction. HIV viral load at baseline (≤/> 100,000 copies/mL) has a significant p-value (< 0.0196 for HIV viral load group and 0.0001 for HIV viral load group by visit). Since all patients in this analysis were male, sex was not included in this analysis.

Table 29. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population - Subgroup Treatment Naive (N 47) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	47	
Age		0.1801
HIV Viral Load Group		0.0196
Visit		0.2466
Age*Visit		0.1310
HIV Viral Load Group*Visit		0.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.4.1 arm 2

For the analysis "whole observational period", HIV-1 RNA viral load at each visit and change from baseline for HIV-1 RNA viral load are summarized in Table 30. At baseline, patients had a mean (median) HIV-1 RNA viral load of 369,820.3 (49.0) copies/mL. There was a general trend in a reduction of HIV-1 RNA viral load over 24 months, with the lowest level reached at 18 months.

Table 30. Summary of HIV-1 Viral Load - Treatment Arm F/TAF - All Treated Population (N 257) - Whole Observational Period

	Visit	Mean	Std	95% CI of Mean	Q1	Median	Q3	n	Missing	Total
HIV 1 Viral Load (copies/mL)	Baseline	369820.3	1409743.86	[194921.3; 544719.2]	49.0	49.0	97936.0	252	5	257
	Month 3	2091.5	20650.73	[646.2; 4829.2]	49.0	49.0	49.0	221	10	231
	Month 6	156.8	1166.85	[1.1; 314.8]	49.0	49.0	49.0	212	20	232
	Month 12	50.8	2616.98	[78.8; 615.1]	49.0	49.0	49.0	221	4	225
	Month 18	52.1	16.90	[49.8; 54.4]	49.0	49.0	49.0	213	12	225
	Month 24	53.9	25.81	[50.3; 57.5]	49.0	49.0	49.0	202	12	214
HIV 1 Viral Load (copies/mL) Change from baseline	Month 3	388972.0	1476311.48	[586044.8; 191899.1]	97151.0	0.0	0.0	218	13	231
	Month 6	417368.3	1534440.26	[626110.6; 208625.9]	64751.0	0.0	0.0	210	22	232
	Month 12	345945.1	1326787.14	[523470.2; 168420.1]	64751.0	0.0	0.0	217	8	225
	Month 18	305474.6	1210839.78	[470994.3; 139954.9]	32100.5	0.0	0.0	208	17	225
	Month 24	309487.6	1194806.28	[477368.9; 141606.2]	75951.0	0.0	0.0	197	17	214

Values below 50 are set to 49 for the purpose of the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.5 arm 2

Overall, 202 (of 257) patients contributed to the MMRM on the whole observational period for the All Treated Population. The results are presented in Table 31. The analysis shows no significant p-values for the factors of sex and treatment experience. However, a significant p-value is given for age (0.0410 for age and 0.0017 for age by visit interaction). Furthermore, the factor visit also has a significant p-value (< 0.0001).

Table 31. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population (N 202) - Whole Observational Period

	N	P value
Number of Contributing Patients	202	
Age		0.0410
Sex		0.6162
Treatment Experience		0.2992
Visit		<.0001
Age*Visit		0.0017
Sex*Visit		0.9330
Treatment Experience*Visit		0.4217

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.6.1 arm 2

Overall, 130 (of 157) patients contributed to the MMRM on the whole observational period for the subgroup of treatment experienced patients. The results are presented in Table 32. The analysis shows no significant p-values for the factors sex, previous ART, visit, and interactions). Since all patients in this analysis were aged ≥ 50 years, age could not be included in the analysis.

Table 32. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population - Subgroup Treatment Experienced (N 130) - Whole Observational Period

	N	P value
Number of Contributing Patients	130	
Sex		0.8517
Previous ART Group		0.8430
Visit		1.0000
Sex*Visit		0.9993
Previous ART Group*Visit		0.9992

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.7.1 arm 2

Overall, 70 (of 100) patients contributed to the MMRM on the whole observational period for the subgroup of treatment naive patients. The results are presented in Table 33. HIV viral load at baseline (≤/> 100,000 copies/mL) has a significant p-value (0.0042 for HIV viral load group and < 0.0001 for HIV viral load group by visit).

Table 33. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population - Subgroup Treatment Naive (N 70) - Whole Observational Period

	N	P value
Number of Contributing Patients	70	
Age		0.1748
Sex		0.7539
HIV Viral Load Group		0.0042
Visit		0.3051
Age*Visit		0.1218
Sex*Visit		0.9915
HIV Viral Load Group*Visit		<.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, i.e.ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.8.1 arm 2

10.3.2.2. CD4 Cell Count F/TAF Arm

For the analysis “on initial TAF treatment”, CD4 cell counts in the F/TAF arm, all treated population, are summarized in Table 34, as well as changes from baseline for CD4 cell count.

At baseline, patients had a mean (median) CD4 cell count of 530.1 (500.0) cells/µL. There was a general trend to an increase of CD4 over 24 months, with the highest value at month 24.

Table 34. Summary of CD4 Cell Count - Treatment Arm F/TAF - All Treated Population (N 257) – On Initial TAF Treatment

	Visit	Mean	Std	95%-CI of Mean	Q1	Median	Q3	n	Missing	Total
CD4 cell count (cells/µL)	Baseline	530.1	308.95	[491.7; 568.5]	304.0	500.0	716.0	251	6	257
	Month 3	609.9	307.03	[568.6; 651.3]	390.0	592.5	803.0	214	10	224
	Month 6	639.2	304.93	[596.1; 682.2]	421.0	619.0	809.0	195	24	219
	Month 12	678.4	335.86	[630.3; 726.5]	451.0	600.0	866.0	190	13	203
	Month 18	669.3	320.80	[620.0; 718.6]	415.0	611.0	833.0	165	18	183
	Month 24	709.8	344.26	[651.4; 768.2]	451.5	690.0	903.5	136	17	153
CD4 cell count (cells/µL) Change from baseline	Month 3	84.2	191.03	[58.2; 110.3]	-16.0	70.0	176.0	209	15	224
	Month 6	94.8	208.68	[65.0; 124.5]	-40.5	83.0	208.5	192	27	219
	Month 12	122.7	221.58	[90.6; 154.9]	-10.0	96.0	254.0	185	18	203
	Month 18	106.2	218.76	[72.0; 140.4]	-13.0	73.5	208.5	160	23	183
	Month 24	148.8	254.71	[105.1; 192.5]	-14.0	116.0	296.0	133	20	153

Source: Annex 1, Number 4, Table 14.2 2.1.1, arm 2

Overall, 135 (of 257) patients contributed to the MMRM on the initial TAF treatment for the All Treated Population. The results are presented in Table 35. The analysis shows no significant p-values for any of the factors.

Table 35. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population (N 135) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	135	
Age		0.2180
Sex		0.7840
Treatment Experience		0.0658
Visit		0.7420
Age*Visit		0.4493
Sex*Visit		0.5275
Treatment Experience*Visit		0.1212

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2. .2.1.1 arm 2

Overall, 88 (of 157) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment experienced patients. The results are presented in Table 36. The analysis shows no significant p-values for any of the. Age was not included in the analysis as all patients where in the same age group (≥ 50 years).

Table 36. Summary of CD4 cell count, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population - Subgroup Treatment Experienced (N 88) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	88	
Sex		0.8076
Previous ART Group		0.4623
Visit		0.8062
Sex*Visit		0.5214
Previous ART Group*Visit		0.8217

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .2.1.3.1 arm 2

Overall, 45 (of 100) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment naive patients. The results are presented in Table 37. Visit has a significant p-value (< 0.0001). Since all patients contributing to this analysis were male, sex could not be included in the analysis.

Table 37. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population - Subgroup Treatment Naive (N 45) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	45	
Age		0.1051
HIV Viral Load Group		0.0788
Visit		<.0001
Age*Visit		0.4988
HIV Viral Load Group*Visit		0.3264

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .2.1.4.1 arm 2

For the analysis "whole observational period", CD4 cell counts in the F/TAF arm, All Treated Population, are summarized in Table 38, as well as changes from baseline for CD4 cell count. At baseline, patients had a mean (median) CD4 cell count of 530.1 (500.0) cells/µL. There was a general trend to an increase of CD4 over 24 months, with the highest value at Month 12.

Table 38. Summary of CD4 Cell Count - Treatment Arm F/TAF - All Treated Population (N 257) - Whole Observational Period

	Visit	Mean	Std	95%-CI of Mean	Q1	Median	Q3	n	Missing	Total
CD4 cell count (cells/µL)	Baseline	530.1	308.95	[491.7; 568.5]	304.0	500.0	716.0	251	6	257
	Month 3	611.2	306.67	[570.4; 651.9]	390.5	592.5	811.5	220	11	231
	Month 6	699.7	301.51	[602.7; 685.2]	431.0	624.0	809.5	208	24	232
	Month 12	678.9	341.45	[632.5; 725.2]	450.0	600.0	877.0	211	14	225
	Month 18	667.3	314.18	[623.5; 711.1]	422.5	623.5	838.0	200	25	225
	Month 24	667.0	347.18	[646.4; 747.7]	436.0	638.0	897.0	183	31	214
CD4 cell count (cells/µL) Change from baseline	Month 3	89.5	193.56	[63.4; 115.5]	14.0	74.0	180.0	215	16	231
	Month 6	103.0	222.97	[72.3; 133.7]	34.0	88.0	218.0	205	27	232
	Month 12	137.0	244.75	[103.4; 170.6]	8.0	104.0	274.0	206	19	225
	Month 18	117.3	239.95	[83.4; 151.2]	13.0	87.0	226.0	195	30	225
	Month 24	153.4	286.04	[111.2; 195.6]	30.0	114.0	328.0	179	35	214

Source: Annex 1, Number 4, Table 14.2 2.1.5, arm 2

Overall, 182 (of 257) patients contributed to the MMRM on the whole observational period for the All Treated Population. The results are presented in Table 39. The analysis shows no significant p-values for the factors of age, sex, and their respective interaction with visit. The p-values for reatment experience (0.0429), visit (0.0082), and treatment experience by visit interaction (0.0398) are significant.

Table 39. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population (N 182) - Whole Observational Period

	N	P value
Number of Contributing Patients	182	
Age		0.0869
Sex		0.2026
Treatment Experience		0.0429
Visit		0.0082
Age*Visit		0.2004
Sex*Visit		0.4335
Treatment Experience*Visit		0.0398

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .2.1.6.1 arm 2

Overall, 115 (of 157) patients contributed to the MMRM on the whole observational period for the subgroup of treatment experienced patients. The results are presented inTable 40. Age could not be included in the analysis as all treatment experienced patients were in the same age group (≥ 50 years) as per inclusion criteria.

Table 40. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population - Subgroup Treatment Experienced (N 157) - Whole Observational Period

	N	P value
Number of Contributing Patients	115	
Sex		0.7098
Previous ART Group		0.3514
Visit		0.3655
Sex*Visit		0.1330
Previous ART Group*Visit		0.7732

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.7.1 arm 2

Overall, 65 (of 100) patients contributed to the MMRM on the whole observational period for the subgroup of treatment naive patients. The results are presented inTable 41. Age (0.0418) and visit (0.0320) showed a significant p-value.

Table 41. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm F/TAF - All Treated Population - Subgroup Treatment Naive (N 65) - Whole Observational Period

	N	P value
Number of Contributing Patients	65	
Age		0.0418
Sex		0.1119
HIV Viral Load Group		0.1041
Visit		0.0320
Age*Visit		0.2595
Sex*Visit		0.7968
HIV Viral Load Group*Visit		0.1434

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.8.1 arm 2

10.3.3. R/F/TAF

10.3.3.1. HIV-1 RNA Viral Load R/F/TAF Arm

A summary of HIV-1 viral load at baseline (categorized) is presented in Table 42. All patients in this treatment arm (100%) had an HIV-1 RNA viral load of ≤ 100,000 copies/mL at baseline.

Table 42. Summary of HIV-1 Viral Load at Baseline (Categorised) - Treatment Arm R/F/TAF - All Treated Population (N 192)

		n (%)
HIV-1 Viral Load at Baseline	≤ 100,000 copies/mL	185 (100.0)
	> 100,000 copies/mL	–
	Missing	7

Source: Annex 1, Number 4, Table 14.2 1.1.1 arm 3

For the analysis "on initial TAF treatment", HIV-1 RNA viral load at each visit and change from baseline for HIV-1 RNA viral load are summarized in Table 43. At baseline, patients had a mean (median) HIV-1 RNA viral load of 6318.8 (49.0) copies/mL. The mean (median) viral load subsequently was 69.2 (49.0) at Month 3; 82.2 (49.0) at Month 6; 49.7 (49.0) at Month 12; 290.9 (49.0) at Month 18, and 50.7 (49.0) at Month 24.

Table 43. Summary of HIV-1 Viral Load - Treatment Arm R/F/TAF - All Treated Population (N 192) - On Initial TAF Treatment

	Visit	Mean	Std	95%-CI of Mean	Q1	Median	Q3	n	Missing	Total
HIV 1 Viral Load (copies/mL)	Baseline	6318.8	17837.39	[3731.5; 8906.2]	49.0	49.0	97.0	185	7	192
	Month 3	69.2	184.91	[40.9; 97.6]	49.0	49.0	49.0	166	10	176
	Month 6	82.2	391.98	[20.4; 144.0]	49.0	49.0	49.0	157	10	167
	Month 12	49.7	5.92	[48.8; 50.7]	49.0	49.0	49.0	160	3	163
	Month 18	290.9	2966.31	[186.1; 767.8]	49.0	49.0	49.0	151	5	156
	Month 24	50.7	12.46	[48.6; 52.8]	49.0	49.0	49.0	133	6	139
HIV 1 Viral Load (copies/mL) Change from baseline	Month 3	6078.4	17381.65	[8783.7; 3373.0]	103.0	0.0	0.0	161	15	176
	Month 6	6712.5	18953.77	[9729.9; 3695.1]	101.0	0.0	0.0	154	13	167
	Month 12	6547.2	18807.34	[9551.2; 3543.2]	92.0	0.0	0.0	153	10	163
	Month 18	6651.5	19205.48	[9815.1; 3487.9]	124.5	0.0	0.0	144	12	156
	Month 24	5831.0	17620.13	[8937.7; 2724.3]	46.0	0.0	0.0	126	13	139

Values below 50 are set to 49 for the purpose of the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.1 arm 3

Overall, 133 (of 192) patients contributed to the MMRM on the initial TAF treatment for the All Treated Population. The results are presented in Table 44. Treatment experience (naive experienced) has a significant p-value (< 0.0001 for both treatment experience and treatment experience by visit) as does visit (< 0.0001).

Table 44. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm R/F/TAF - All Treated Population (N 133) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	133	
Age		0.2430
Sex		0.6347
Treatment Experience		<.0001
Visit		<.0001
Age*Visit		0.2568
Sex*Visit		0.9565
Treatment Experience*Visit		<.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.2.1 arm 3

Overall, 106 (of 150) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment experienced patients. The results are presented in Table 45. The p-values for sex are significant (0.0057 for sex and < 0.0001 for sex by visit interaction).

Table 45. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm R/F/TAF - All Treated Population - Subgroup treatment experienced (N 106) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	106	
Age		0.3969
Sex		0.0057
Previous ART Group		0.4552
Visit		0.8173
Age*Visit		0.6443
Sex*Visit		<.0001
Previous ART Group*Visit		0.7064

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.3.1 arm 3

Overall, 27 (of 42) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment naive patients. The results are presented in Table 46. All of the contributing patients had an HIV viral load at baseline of ≤ 100,000 copies/mL). Therefore, the HIV viral load group and its interaction with visit could not be included in the analysis. The analysis shows no significant p-values for the factors of age and sex. The p-value for visit is significant (0.0118).

Table 46. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm R/F/TAF - All Treated Population - Subgroup Treatment Naive (N 27) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	27	
Age		0.1780
Sex		0.7921
Visit		0.0118
Age*Visit		0.1221
Sex*Visit		0.9970

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
HIV 1 viral load values < 50 are set to 49 for the purpose of analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.4.1 arm 3

For the analysis "whole observational period", HIV-1 RNA viral load at each visit and change from baseline for HIV-1 RNA viral load are summarized in Table 47. At baseline, patients had a mean (median) HIV-1 RNA viral load of 6318.8 (49.0) copies/mL. The mean (median) viral load subsequently was 68.7 (49.0) at Month 3; 80.7 (49.0) at Month 6; 50.1 (49.0) at Month 12; 280.5 (49.0) at Month 18, and 165.7 (49.0) at Month 24.

Table 47. Summary of HIV-1 Viral Load - Whole Observational Period

	Visit	Mean	Std	95%-CI of Mean	Q1	Median	Q3	n	Missing	Total
HIV 1 Viral Load (copies/mL)	Baseline	6318.8	17837.39	[3731.5; 8906.2]	49.0	49.0	97.0	185	7	192
	Month 3	68.7	182.73	[41.1; 96.4]	49.0	49.0	49.0	170	10	180
	Month 6	80.7	381.21	[22.3; 139.1]	49.0	49.0	49.0	166	10	176
	Month 12	50.1	7.94	[48.9; 51.3]	49.0	49.0	49.0	172	3	175
	Month 18	280.5	2802.71	[143.8; 704.9]	49.0	49.0	49.0	170	5	175
	Month 24	165.7	1371.06	[53.3; 384.7]	49.0	49.0	49.0	153	8	161
HIV 1 Viral Load (copies/mL) Change from baseline	Month 3	6227.7	17510.39	[8919.3; 3536.0]	103.0	0.0	0.0	165	15	180
	Month 6	6644.0	18774.90	[9547.9; 3740.0]	101.0	0.0	0.0	163	13	176
	Month 12	6482.1	18502.75	[9326.3; 3637.9]	46.0	0.0	0.0	165	10	175
	Month 18	6575.7	18601.44	[9452.8; 3698.5]	103.0	0.0	0.0	163	12	175
	Month 24	5743.5	16998.72	[8524.0; 2963.0]	46.0	0.0	0.0	146	15	161

Values below 50 are set to 49 for the purpose of the analysis.
Source: Annex 1, Number 4, Table 14.2 1.2.5 arm 3

Overall, 153 (of 192) patients contributed to the MMRM on the whole observational period for the All Treated Population. The results are presented in Table 48. Treatment experience (naive experienced) has a significant p-value (< 0.0001 for both treatment experience and treatment experience by visit) as does visit (< 0.0001).

Table 48. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm R/F/TAF - All Treated Population (N 153) - Whole Observational Period

	N	P value
Number of Contributing Patients	153	
Age		0.2055
Sex		0.3125
Treatment Experience		<.0001
Visit		<.0001
Age*Visit		0.2440
Sex*Visit		0.3474
Treatment Experience*Visit		<.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.6.1 arm 3

Overall, 121 (of 150) patients contributed to the MMRM on the whole observational period for the subgroup of treatment experienced patients. The results are presented in Table 49. The p-values for sex are significant (0.0017 for sex and < 0.0001 for sex by visit interaction).

Table 49. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm R/F/TAF - All Treated Population - Subgroup Treatment Experienced (N 121) - Whole Observational Period

	N	P value
Number of Contributing Patients	121	
Age		0.3778
Sex		0.0017
Previous ART Group		0.4871
Visit		0.6711
Age*Visit		0.8425
Sex*Visit		<.0001
Previous ART Group*Visit		0.7489

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.7.1 arm 3

Overall, 32 (of 42) patients contributed to the MMRM on the whole observational period for the subgroup of treatment naive patients. The results are presented in Table 50. All contributing patients had an HIV viral load at baseline of ≤ 100,000 copies/mL which was thus not included in the analysis. The p-value for visit is significant (0.0061).

Table 50. Summary of HIV-1 Viral Load, Repeated Measures ANOVA - Treatment Arm R/TAF - All Treated Population - Subgroup Treatment Naive (N 33) - Whole Observational Period

	N	P value
Number of Contributing Patients	32	
Age		0.1781
Sex		0.7191
Visit		0.0061
Age*Visit		0.1571
Sex*Visit		0.9733

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on HIV 1 viral load. Patients with missing values for HIV 1 viral load or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2-.1.2.8.1 arm 3

10.3.3.2. CD4 Cell Count R/F/TAF Arm

For the analysis “on initial TAF treatment”, CD4 cell counts in R/F/TAF arm, All Treated Population, are summarized in Table 51, as well as changes from baseline for CD4 cell count.

At baseline, patients had a mean (median) CD4 cell count of 644.2 (612.5) cells/µL. The CD4 cell count rose following initiation of treatment, with mean (median) CD4 cell count rising to 710.9 (650.5) at Month 3, to 710.4 (695.0) at Month 6, to 721.5 (681.0) at Month 12, to 768.1 (749.5) at Month 18, and to 772.1 (708.0) at Month 24.

Table 51. Summary of CD4 cell count - Treatment Arm R/F/TAF - All Treated Population (N 192) – On Initial TAF Treatment

	Visit	Mean	Std	95%-CI of Mean	Q1	Median	Q3	n	Missing	Total
CD4 cell count (cells/µL)	Baseline	644.2	248.01	[608.3; 680.0]	468.0	612.5	786.0	186	6	192
	Month 3	710.9	301.13	[664.4; 757.3]	499.0	650.5	850.0	164	12	176
	Month 6	710.4	250.07	[670.7; 750.1]	525.0	695.0	881.0	155	12	167
	Month 12	721.5	258.88	[680.2; 762.9]	551.0	681.0	860.0	153	10	163
	Month 18	768.1	274.48	[722.2; 814.0]	563.5	749.5	924.0	140	16	156
	Month 24	772.1	309.45	[717.3; 826.8]	555.0	708.0	888.0	125	14	139
CD4 cell count (cells/µL) Change from baseline	Month 3	72.8	197.45	[41.9; 103.7]	-36.0	64.0	188.0	159	17	176
	Month 6	62.4	203.86	[29.8; 94.9]	-35.0	57.0	160.0	153	14	167
	Month 12	67.4	199.44	[35.1; 99.7]	-65.0	64.0	160.0	149	14	163
	Month 18	110.3	202.27	[76.2; 144.5]	-2.0	88.0	201.0	137	19	156
	Month 24	123.0	232.20	[81.2; 164.8]	-38.0	110.0	228.0	121	18	139

Source: Annex 1, Number 4, Table 14.2 2.1.5, arm 3

Overall, 125 (of 192) patients contributed to the MMRM on the initial TAF treatment for the All Treated Population. The results are presented in Table 52. Only the p-values for visit and treatment experience by visit interaction are significant (both < 0.0001).

Table 52. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm R/F/TAF - All Treated Population (N 125) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	125	
Age		0.2295
Sex		0.5249
Treatment Experience		0.8348
Visit		<.0001
Age*Visit		0.6526
Sex*Visit		0.0946
Treatment Experience*Visit		<.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.2.1 arm 3

Overall, 97 (of 150) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment experienced patients. The results are presented in Table 53. All other factors show significant p-values (age: 0.0152, previous ART: 0.0029, visit: 0.0080, previous ART by visit interaction: 0.0009).

Table 53. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm R/F/TAF - All Treated Population - Subgroup Treatment Experienced (N 97) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	97	
Age		0.0152
Sex		0.1769
Previous ART Group		0.0029
Visit		0.0080
Age*Visit		0.5544
Sex*Visit		0.0747
Previous ART Group*Visit		0.0009

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.3.1 arm 3

Overall, 28 (of 42) patients contributed to the MMRM on the initial TAF treatment for the subgroup of treatment naive patients. The results are presented in Table 54. All of the contributing patients had an HIV viral load at baseline of ≤ 100,000 copies/mL which was thus not included in the analysis. The analysis shows no significant p-values for any of the factors.

Table 54. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm R/F/TAF - All Treated Population - Subgroup Treatment Naive (N 28) - On Initial TAF Treatment

	N	P value
Number of Contributing Patients	28	
Age		0.6935
Sex		0.3465
Visit		0.1411
Age*Visit		0.7899
Sex*Visit		0.4941

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.4.1 arm 3

For the analysis "whole observational period", CD4 cell counts in F/TAF arm, All Treated Population, are summarized in Table 55, as well as changes from baseline for CD4 cell count. At baseline, patients had a mean (median) CD4 cell count of 644.2 (612.5) cells/µL. The CD4 cell count rose following initiation of treatment, with mean (median) CD4 cell count rising to 711.4 (651.5) at Month 3. Further values were 706.8 (696.0) at Month 6, 727.9 (693.0) at Month 12, 772.9 (750.5) at Month 18, and 767.1 (708.0) at Month 24.

Table 55. Summary of CD4 Cell Count - Treatment Arm R/F/TAF - All Treated Population (N 192) - Whole Observational Period

	Visit	Mean	Std	95%-CI of Mean	Q1	Median	Q3	n	Missing	Total
CD4 cell count (cells/µL)	Baseline	644.2	248.01	[608.3; 680.0]	468.0	612.5	786.0	186	6	192
	Month 3	711.4	300.24	[665.6; 757.3]	491.0	651.5	889.0	167	13	180
	Month 6	706.8	252.01	[667.9; 745.7]	527.0	696.0	876.0	164	12	176
	Month 12	727.9	258.56	[688.1; 767.6]	562.0	693.0	873.0	165	10	175
	Month 18	772.9	272.88	[730.2; 815.7]	566.0	750.5	932.0	159	16	175
	Month 24	767.1	314.31	[715.2; 819.1]	553.0	708.0	902.0	143	18	161
CD4 cell count (cells/µL) Change from baseline	Month 3	76.4	198.88	[45.6; 107.3]	35.0	64.0	189.0	162	18	180
	Month 6	63.7	211.20	[30.9; 96.4]	30.0	60.0	167.0	162	14	176
	Month 12	72.0	200.75	[40.7; 103.2]	64.0	66.0	175.0	161	14	175
	Month 18	113.4	208.56	[80.3; 146.5]	12.0	88.0	201.0	155	20	175
	Month 24	114.3	253.77	[71.6; 157.0]	50.0	109.5	228.0	138	23	161

Source:Annex 1, Number 4, Table 14.2 2.1.5, arm 3

Overall, 143 (of 192) patients contributed to the MMRM on the whole observational period for the All Treated Population. The results are presented in Table 56. The p-values for visit and treatment experience by visit interaction were significant (both < 0.0001).

Table 56. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm R/F/TAF - All Treated Population (N 143) - Whole Observational Period

	N	P value
Number of Contributing Patients	143	
Age		0.3161
Sex		0.7390
Treatment Experience		0.9533
Visit		<.0001
Age*Visit		0.5933
Sex*Visit		0.1165
Treatment Experience*Visit		<.0001

Results obtained from a repeated measures ANOVA with age (categories), sex, and treatment experience as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.6.1 arm 3

Overall, 110 (of 150) patients contributed to the MMRM on the whole observational period for the subgroup of treatment experienced patients. The results are presented in Table 57. The p-values for age (0.0375), previous ART (0.0053), and previous ART by visit interaction (0.0347) are significant.

Table 57. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm R/F/TAF - All Treated Population - Subgroup Treatment Experienced (N 110) - Whole Observational Period

	N	P value
Number of Contributing Patients	110	
Age		0.0375
Sex		0.4155
Previous ART Group		0.0053
Visit		0.1127
Age*Visit		0.5909
Sex*Visit		0.1076
Previous ART Group*Visit		0.0347

Results obtained from a repeated measures ANOVA with age (categories), sex, and previous ART group as fixed effects.
P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.7.1 arm 3

Overall, 33 (of 42) patients contributed to the MMRM on the whole observational period for the subgroup of treatment naive patients. The results are presented in Table 58. All contributing patients had an HIV viral load at baseline of ≤ 100,000 copies/mL. Therefore, the HIV viral load group and its interaction with visit could not be included in the analysis. None of the remaining factors (age, sex, their respective interactions with visit, and visit itself) have significant p-values.

Table 58. Summary of CD4 Cell Count, Repeated Measures ANOVA - Treatment Arm R/F/TAF - All Treated Population - Subgroup Treatment Naive (N 33) - Whole Observational Period

	N	P value
Number of Contributing Patients	33	
Age		0.7204
Sex		0.3108
Visit		0.1769
Age*Visit		0.8576
Sex*Visit		0.5358

Results obtained from a repeated measures ANOVA with age (categories), sex, and category of HIV 1 viral load at baseline as fixed effects. P values are to show if the respective parameter has an influence on the modelled parameter, ie, on CD4 cell count. Patients with missing values for CD4 cell count or one of the fixed effects cannot be used in the analysis.
Source: Annex 1, Number 4, Table 14.2 .1.2.8.1 arm 3

10.4. Secondary Objective Analyses

Secondary objective analyses were: motivations for initiation or switch of therapy, patient persistence, treatment adherence questionnaire, HIV treatment satisfaction questionnaire, HIV symptom index, quality of life (SF-36) of the patients, and laboratory values.

10.4.1. E/C/F/TAF Arm

10.4.1.1. Motivations for Initiation or Switch of Therapy

The motivations for initiation of E/C/F/TAF in treatment naive patients (eg, early treatment according to guidelines, treatment as prevention, patient wish) are summarized in Table 59. Factors driving the ART switch to E/C/F/TAF in treatment experienced patients (eg, simplification of ART, patient preference, side effects of current ART) are summarized in Table 60.

Table 59. Summary of ART Initiation Reason – Treatment Arm E/C/F/TAF – All Treated Population – Subgroup Treatment Naive (N 159)

		n (%)
Early Treatment According to Guidelines	Yes	100 (62.9)
Patient's Wish	Yes	70 (44.0)
Treatment as Prevention	Yes	39 (24.5)
Other	Yes	4 (2.5)

Multiple answers are possible. Percentages based on treatment naive patients.
Source: Annex 1, Number 4, Table 14.1 6.1

Table 60. Summary of ART Switch Reason – Treatment Arm E/C/F/TAF – All Treated Population – Subgroup Treatment Experienced (N 159)

		n (%)
Patient's Preference	Yes	55 (34.6)
Side Effects of current ART	Yes	63 (39.6)
Simplification of ART	Yes	66 (41.5)
Other	Yes	23 (14.5)

Multiple answers are possible. Percentages are based on treatmentexperienced patients.
Source: Annex 1, Number 4, Table 14.1 6.2.1

10.4.1.2. Patient Persistence

Overall, 9.7% of patients switched to another anti-HIV therapy during the study (Table 61) with a median time to switch of 405 days for those who switched (Table 62).

Table 61. Summary of ARV Therapy Switch from Initial TAF Therapy - Treatment Arm E/C/F/TAF - All Treated Population (N 318)

ARV Therapy Switch from Initial TAF Therapy		n (%)
	Yes	31 (9.7)
	No	287 (90.3)

For this table, a patient is regarded as having switched from initial TAF during the observational period if the stop date of the initial TAF treatment is 3 or more days before the study termination/completion date.
Source: Annex 1, Number 4, Table 14.2 8.1

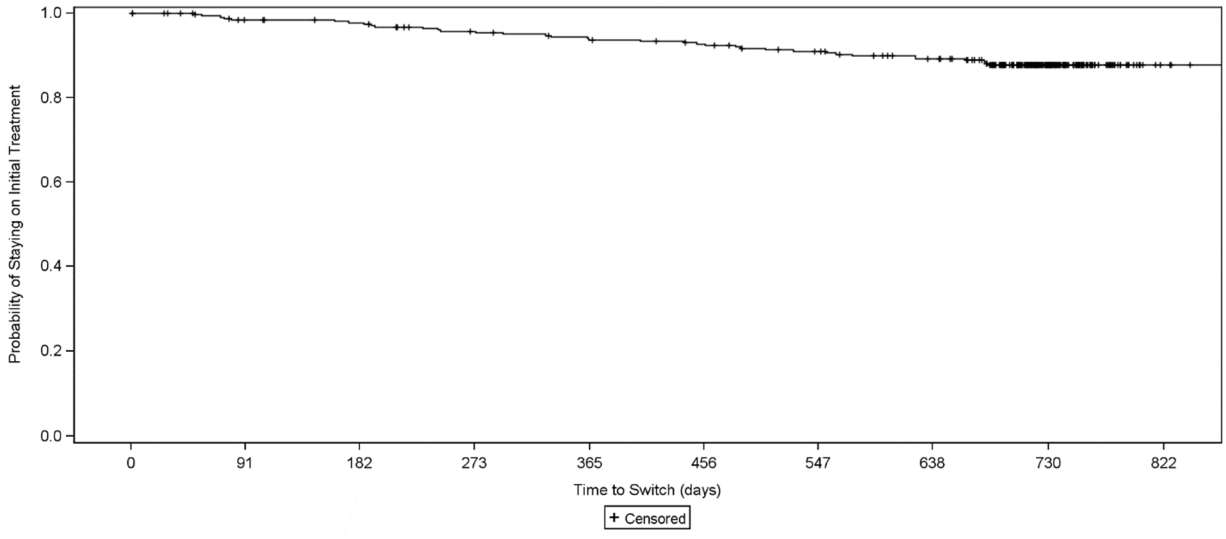
Table 62. Summary of Time to ARV Therapy Switch from Initial TAF Therapy - Treatment Arm E/C/F/TAF - All Treated Population (N 318)

Time to ARV Therapy Switch from Initial TAF Therapy (Days)	Mean	Std	95%-CI of Mean	Q1	Median	Q3	N	Missing	Total
	388.2	203.65	[313.5; 462.9]	232.0	405.0	561.0	31	287	318

For this table, a patient is regarded as having switched from initial TAF during the observational period if the stop date of the initial TAF treatment is 3 or more days before the study termination/completion date.
Source: Annex 1, Number 4, Table 14.2 8.2

The Kaplan-Meier graph and Kaplan-Meier estimator illustrate the percentage of patients still being on the original E/C/F/TAF at the end of the study being 87.7% (Figure 1).

Figure 1. Kaplan-Meier Estimator of Time to ARV Therapy Switch (Days) – Treatment Arm E/C/F/TAF – All Treated Population (N 318)



Source:Annex 1, Number 4, Figure 14.2 8.1 arm 1

10.4.1.3. Treatment Adherence Questionnaire

Results of the treatment adherence questionnaire are summarized in Table 63. As handing out of questionnaires was only implemented with the 1st protocol amendment in June 2016, the return rate of the questionnaire was 55.6% only, but 85.1% of the dispensed questionnaires.

Table 63. Summary of Adherence, Patient Questionnaire - Treatment Arm E/C/F/TAF - All Treated Population (N 318) - On Initial TAF treatment

Visit	Variable	Category	Statistic	
Month 3	Self-assessment of percentage HIV medication taken in past 30 days (VAS)		n	67
			Mean (SD)	98.4 (3.45)
			95%-CI of Mean	[97.5 ; 99.2]
			Median	100.0
			Q1, Q3	98.0, 100.0
			Min, Max	79, 100
	Number of days within the past 30 days in which the HIV Ttherapy was not taken	0	n (%)	44 (65.7)
		1	n (%)	18 (26.9)
		2	n (%)	1 (1.5)
		3	n (%)	2 (3.0)
		4	n (%)	1 (1.5)
		>4	n (%)	1 (1.5)
		Missing	n	212
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	61 (92.4)
		1	n (%)	5 (7.6)
		2	n (%)	–
		3	n (%)	–
		4	n (%)	–
		>4	n (%)	–
		Missing	n	213

Visit	Variable	Category	Statistic	
Month 6	Self-assessment of percentage HIV medication taken in past 30 days (VAS)		n	146
			Mean (SD)	97.7 (8.43)
			95%-CI of Mean	[96.3 ; 99.1]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	30, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	115 (76.7)
		1	n (%)	19 (12.7)
		2	n (%)	5 (3.3)
		3	n (%)	4 (2.7)
		4	n (%)	2 (1.3)
		>4	n (%)	5 (3.3)
		Missing	n	124
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	142 (94.7)
		1	n (%)	4 (2.7)
		2	n (%)	2 (1.3)
		3	n (%)	–
		4	n (%)	2 (1.3)
		>4	n (%)	–
		Missing	n	124
Month 12	Self-assessment of percentage HIV medication taken in past 30 days (VAS)		n	146
			Mean (SD)	98.6 (3.94)
			95%-CI of Mean	[97.9 ; 99.2]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	70, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	110 (75.9)
		1	n (%)	19 (13.1)
		2	n (%)	4 (2.8)
		3	n (%)	8 (5.5)
		4	n (%)	1 (0.7)
		>4	n (%)	3 (2.1)
		Missing	n	120

Visit	Variable	Category	Statistic	
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	136 (95.8)
		1	n (%)	4 (2.8)
		2	n (%)	–
		3	n (%)	–
		4	n (%)	1 (0.7)
		>4	n (%)	1 (0.7)
		Missing	n	123
Month 18	Self-assessment of percentage HIV medication taken in past 30 days (VAS)		n	117
			Mean (SD)	98.9 (2.73)
			95%-CI of Mean	[98.4 ; 99.4]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	84, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	94 (81.7)
		1	n (%)	9 (7.8)
		2	n (%)	7 (6.1)
		3	n (%)	2 (1.7)
		4	n (%)	1 (0.9)
		>4	n (%)	2 (1.7)
		Missing	n	136
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	108 (96.4)
		1	n (%)	4 (3.6)
		2	n (%)	–
		3	n (%)	–
		4	n (%)	–
		>4	n (%)	–
		Missing	n	139

Visit	Variable	Category	Statistic	
Month 24	Self-assessment of percentage HIV medication taken in past 30 days (VAS)		n	98
			Mean (SD)	97.9 (9.06)
			95%-CI of Mean	[96.1 ; 99.7]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	13, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	70 (72.2)
		1	n (%)	11 (11.3)
		2	n (%)	7 (7.2)
		3	n (%)	3 (3.1)
		4	n (%)	3 (3.1)
		>4	n (%)	3 (3.1)
		Missing	n	137
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	90 (94.7)
		1	n (%)	5 (5.3)
		2	n (%)	–
		3	n (%)	–
		4	n (%)	–
		>4	n (%)	–
		Missing	n	139

Source: Annex 1, Number 4, Table 14.1 6.3.1.1 and Table 14.1 6.3.2.1 arm 1
VAS visual analogue scale

10.4.1.4. HIV Treatment Satisfaction Questionnaire (Only for Treatment Experienced Patients)

Median (IQR) change in overall treatment satisfaction score for patients in the treatment experienced subgroup who remained on initial E/C/F/TAF treatment at month 12 was 21.5 (8.0, 29.0) (possible score range -30 to 30). Details including individual item scores can be found in Annex 1, Number 4, Table 14.2-5.2.1. A similar analysis including the “Whole Observational Period” yielded similar results, which are found in Annex 1, Number 4, Table 14.2-5.2.2.

10.4.1.5. HIV Symptom Index

The percentage of symptomatic patients decreased for 14 out of 20 recorded HIV symptom items from Baseline to Month 24 in the "On Initial TAF Treatment" group. The following symptoms showed the highest decline of symptomatic patients comparing Baseline and Month 24: Sadness (BL: 47.8%, M24: 33.3%), Skin Problems (BL: 43.7%, M24: 30.3%), Nervous/anxious (BL: 40.0%, M24: 28.1%). Percentage of patients with "sex problems" decreased from 32.1% to 24.8% from baseline to Month 24 in the "All Treated Population". HIV symptom index results are summarized for all patients in Annex 1, Number 4, Table 14.2-4.1.1, Table 14.2-4.1.2, Table 14.2-4.2.1, and Table 14.2-4.2.2. (arm 1).

10.4.1.6. Quality of Life (SF-36)

Mean Mental Component Score increased from 45.6 (SD 10.9) at Baseline to 49.0 (SD 10.0) at Month 24 for patients in the "On Initial TAF Treatment" group. The mean Physical Compoment Score remained stable (BL: 54.1, SD 8.7; M24: 52.7, SD 7.9). Quality of life was evaluated using the SF-36. Scores are summarized in Annex 1, Number 4, Tables 14.2-3.1 (arm 1). Analysis was also performed for the "Whole Observational Period" showing similar results. Respective values are summarized in Annex 1, Number 4, Tables 14.2-3.2 (arm 1).

10.4.1.7. Laboratory Values

Laboratory and instrumental exams results can be found in Annex 1, Number 4, Tables 14.3-2.1.1 to 14.3-6.2 (arm 1). Creatinine and Uric Acid slightly increased in the "On Initial TAF Treatment" group until Month 24 while aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT) slightly decreased in the study population.

10.4.2. F/TAF Arm

10.4.2.1. Motivations for Initiation or Switch of Therapy

The motivations for initiation of F/TAF in treatment naive patients (eg, early treatment according to guidelines, treatment as prevention, patient wish) are summarized in Table 64. Factors driving the ART switch to F/TAF in treatment experienced patients (eg, simplification of ART, patient preference, side effects of current ART) is summarized in Table 65.

Table 64. Summary of ART Initiation Reason – Treatment Arm F/TAF – All Treated Population – Subgroup Treatment Naive (N 100)

		n (%)
Early Treatment According to Guidelines	Yes	80 (80.0)
Patient's Wish	Yes	28 (28.0)
Treatment as Prevention	Yes	26 (26.0)
Other	Yes	3 (3.0)

Multiple answers are possible. Percentages based on treatment naive patients.
Source: Annex 1, Number 4, Table 14.1 6.1 arm 2.

Table 65. Summary of ART Switch Reason – Treatment Arm F/TAF – All Treated Population – Subgroup Treatment Experienced (N 157)

		n (%)
Patient's Preference	Yes	36 (22.9)
Side Effects of Current ART	Yes	67 (42.7)
Simplification of ART	Yes	34 (21.7)
Other	Yes	34 (21.7)

Multiple answers are possible. Percentages are based on treatment experienced patients.
Source: Annex 1, Number 4, Table 14.1 6.2.1 arm 2.

10.4.2.2. Patient Persistence

The percentage of patients who switched to another anti-HIV therapy during the study was 26.5% (Table 66), with a median time to switch of 425 days for those who switched, according to Table 67.

Table 66. Summary of ARV Therapy Switch from Initial TAF Therapy - Treatment Arm F/TAF - All Treated Population (N 257)

		n (%)
ARV Therapy Switch from Initial TAF Therapy	Yes	68 (26.5)
	No	189 (73.5)

For this table, a patient is regarded as having switched from initial TAF during the observational period if the stop date of the initial TAF treatment is 3 or more days before the study termination/completion date.
Source: Annex 1, Number 4, Table 14.2 8.1 arm 2

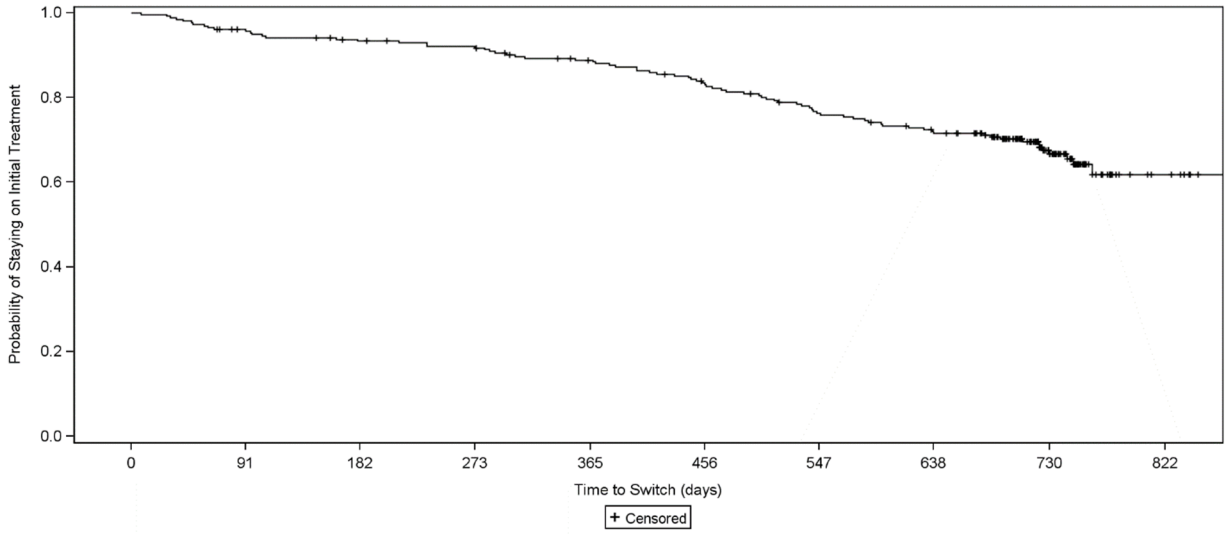
Table 67. Summary of Time to ARV Therapy Switch from Initial TAF Therapy - Treatment Arm F/TAF - All Treated Population (N 257)

Time to ARV Therapy Switch from Initial TAF Therapy (Days)	Mean	Std	95%-CI of Mean	Q1	Median	Q3	N	Missing	Total
Time to ARV Therapy Switch from Initial TAF Therapy	375.0	202.40	[326.0; 423.9]	224.0	425.0	531.0	68	189	257

For this table, a patient is regarded as having switched from initial TAF during the observational period if the stop date of the initial TAF treatment is 3 or more days before the study termination/completion date.
Source: Annex 1, Number 4, Table 14.2 8.2 arm 2

This good persistence can also be seen from the Kaplan-Meier graph and from the Kaplan-Meier estimator of still being on the original F/TAF combination therapy at the end of the study being 61.8% (Figure 2).

Figure 2. Kaplan-Meier Estimator of Time to ARV Therapy Switch (Days) – Treatment Arm F/TAF – All Treated Population (N 318)



Source: Annex 1, Number 4, Figure 14.2 8.1 arm 2

10.4.2.3. Treatment Adherence Questionnaire

Results of the treatment adherence questionnaire are summarized in Annex 1, Number 4, Table 14.1-6.3.1.1, and Table 14.1-6.3.2.1 (arm 2). The return rate of the questionnaire was not satisfactory, and interpretations of the results would be questionable.

Table 68. Summary of Adherence, Patient Questionnaire - Treatment Arm F/TAF - All Treated Population (N 257) - On Initial TAF Treatment

Visit	Variable	Category	Statistic	
Month 3	Self assessment of percentage HIV medication taken in past 30 days (VAS)		n	135
			Mean (SD)	98.2 (8.59)
			95% CI of Mean	[96.8 ; 99.7]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	3, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	99 (76.7)
		1	n (%)	19 (14.7)
		2	n (%)	4 (3.1)
		3	n (%)	3 (2.3)
		4	n (%)	1 (0.8))
		>4	n (%)	3 (2.3)
		Missing	n	92
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	122 (97.6)
		1	n (%)	
		2	n (%)	1 (0.8)
		3	n (%)	1 (0.8)
		4	n (%)	1 (0.8)
		>4	n (%)	
		Missing	n	96
Month 6	Self assessment of percentage HIV medication taken in past 30 days (VAS)		n	126
			Mean (SD)	98.4 (3.73)
			95% CI of Mean	[97.7 ; 99.0]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	75, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	96 (78.2)
		1	n (%)	16 (12.7)
		2	n (%)	9 (7.1)
		3	n (%)	2 (1.6)
		4	n (%)	2 (1.6)
		>4	n (%)	1 (0.8)
		Missing	n	95
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	116 (95.1)
		1	n (%)	6 (4.9)
		2	n (%)	
		3	n (%)	
		4	n (%)	
		>4	n (%)	
		Missing	n	99

Visit	Variable	Category	Statistic	
Month 12	Self assessment of percentage HIV medication taken in past 30 days (VAS)		n	98
			Mean (SD)	98.9 (2.41)
			95% CI of Mean	[98.4 ; 99.4]
			Median	100.0
			Q1, Q3	99.0, 100..0
			Min, Max	88, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	72 (75.0)
		1	n (%)	14 (14.6)
		2	n (%)	5 (5.2)
		3	n (%)	1 (1.0)
		4	n (%)	3 (3.1)
		>4	n (%)	1 (1.0)
		Missing	n	107
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	92 (95.8)
		1	n (%)	2 (2.1)
		2	n (%)	
		3	n (%)	
		4	n (%)	2 (2.1)
		>4	n (%)	
		Missing	n	107
Month 18	Self assessment of percentage HIV medication taken in past 30 days (VAS)		n	92
			Mean (SD)	98.6 (2.83)
			95% CI of Mean	[98 0 ; 99.2]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	88, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	70 (75.3)
		1	n (%)	13 (14.0)
		2	n (%)	5 (5.4)
		3	n (%)	2 (2.2)
		4	n (%)	2 (2.2)
		>4	n (%)	1 (1.1)
		Missing	n	87
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	90 (98.9)
		1	n (%)	
		2	n (%)	1 (1.1)
		3	n (%)	
		4	n (%)	
		>4	n (%)	
		Missing	n	89

Visit	Variable	Category	Statistic	
Month 24	Self assessment of percentage HIV medication taken in past 30 days (VAS)		n	83
			Mean (SD)	98.4 (3.05)
			95% CI of Mean	[97.8 ; 99.1]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	80, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	59 (71.1)
		1	n (%)	12 (14.5)
		2	n (%)	7 (8.4)
		3	n (%)	
		4	n (%)	2 (2.4)
		>4	n (%)	3 (3.6)
		Missing	n	70
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	80 (97.6)
		1	n (%)	2 (2.4)
		2	n (%)	
		3	n (%)	
		4	n (%)	
		>4	n (%)	
		Missing	n	71

10.4.2.4. HIV Treatment Satisfaction Questionnaire

Median (IQR) change in overall treatment satisfaction score for patients in the treatment experienced subgroup who remained on initial F/TAF treatment at month 12 was 15.0 (2.0, 27.0) (possible score range -30 to 30). Details including individual item scores can be found in Annex 1, Number 4, Table 14.2-5.2.1. A similar analysis including the “Whole Observational Period” yielded similar results, which are found in Annex 1, Number 4, Table 14.2-5.2.2.

10.4.2.5. HIV Symptom Index

The percentage of symptomatic patients decreased for 15 out of 20 recorded HIV symptom items from Baseline to Month 24 in the “On Initial TAF Treatment” group. The following symptoms showed the highest decline of symptomatic patients comparing Baseline and Month 24: Nervous/anxious (BL: 44.5%, M24: 30.6%), Appetite Loss (BL: 25.0%, M24: 13.4%), Sleep Trouble (BL: 59.9%, M24: 49.0%). HIV symptom index results are summarized for all patients in Annex 1, Number 4, Tables 14.2-4.1.1, and 14.2-4.2.2 (arm 2).

10.4.2.6. Quality of Life (SF-36)

Mean Mental Component Score increased from 45.2 (mean, SD 11.9) at Baseline to 49.0 (mean, SD 10.6) at Month 24 for patients in the “On Initial TAF Treatment” group. The mean Physical Compoment Score slightly increased from 48.5 (SD 10.2) at Baseline to 50.4 (SD 9.5) at Month

24. Quality of life was evaluated using the SF-36. Scores are summarized in Annex 1, Number 4, Tables 14.2-3.1 (arm 2). Analysis was also performed for the "Whole Observational Period" showing similar results. Respective data are summarized in Annex 1, Number 4, Tables 14.2-3.2 (arm 2).

10.4.2.7. Laboratory Values

Creatinine and Uric Acid slightly increased in the all treated population for patients on initial TAF treatment until Month 24 while aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT) tended to decreased across the population. Laboratory and instrumental exams results can be found in Annex 1, Number 4, Tables 14.3-2.1.1 to 14.3-6.2 (arm 2).

10.4.3. R/F/TAF Arm

10.4.3.1. Motivations for Initiation or Switch of Therapy

The motivations for initiation of R/F/TAF in treatment naive patients (eg, early treatment according to guidelines, treatment as prevention, patient wish) are summarized in Table 69. Factors driving the ART switch to R/F/TAF in treatment experienced patients (eg, simplification of ART, patient preference, side effects of current ART) is summarized in Table 70.

Table 69. Summary of ART Initiation Reason - Treatment Arm R/F/TAF - All Treated Population - Subgroup Treatment Naive (N 42)

		n (%)
Early Treatment According to Guidelines	Yes	27 (64.3)
Patient's Wish	Yes	20 (47.6)
Treatment as Prevention	Yes	19 (45.2)

Multiple answers are possible. Percentages based on treatment naive patients.
Source: Annex 1, Number 4, Table 14.1 6.1 arm 3

Table 70. Summary of ART Switch Reason - Treatment Arm R/F/TAF - All Treated Population - Subgroup Treatment Experienced (N 150)

		n (%)
Patient's Preference	Yes	50 (33.3)
Side Effects of Current ART	Yes	72 (48.0)
Simplification of ART	Yes	33 (22.0)
Other	Yes	26 (17.3)

Multiple answers are possible. Percentages based on treatment experienced patients.
Source: Annex 1, Number 4, Table 14.1 6.2.1 arm 3

10.4.3.2. Patient Persistence

The percentage of patients who switched to another anti-HIV therapy during the study was 14.1% (Table 71), with a median time to switch of 354 days for those who switched, according to Annex 1.

Table 71. Summary of ARV Therapy Switch from Initial TAF Therapy - Treatment Arm R/F/TAF - All Treated Population (N 192)

		n (%)
ARV Therapy Switch from Initial TAF Therapy	Yes	27 (14.1)
	No	165 (85.9)

For this table, a patient is regarded as having switched from initial TAF during the observational period if the stop date of the initial TAF treatment is 3 or more days before the study termination/completion date.
Source: Annex 1, Number 4, Table 14.2 8.1 arm 3

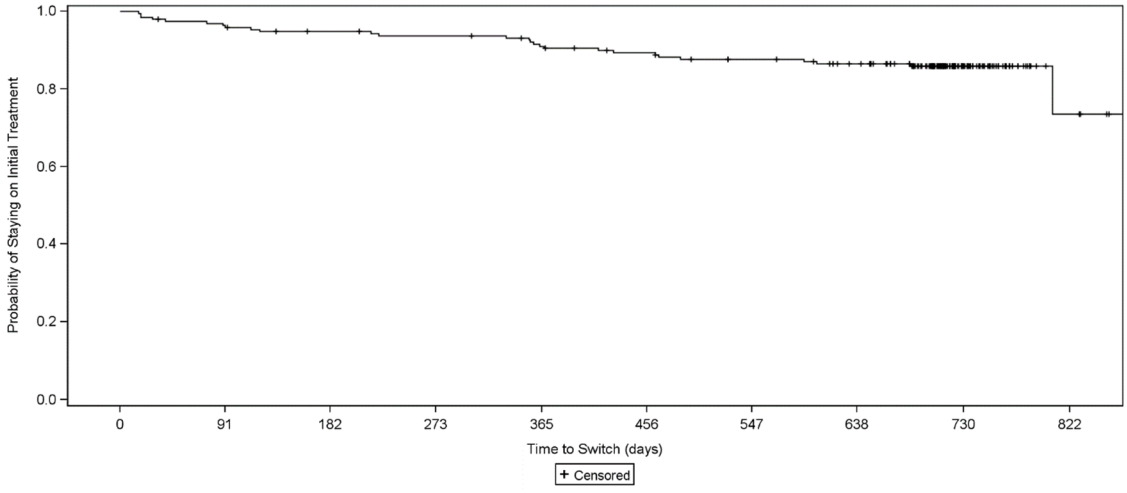
Table 72. Summary of Time to ARV Therapy Switch from Initial TAF Therapy - Treatment Arm R/F/TAF - All Treated Population (N 192)

Time to ARV Therapy Switch from Initial TAF Therapy (days)	Mean	Std	95%-CI of Mean	Q1	Median	Q3	N	Missing	Total
Time to ARV Therapy Switch from Initial TAF Therapy	300.8	225.17	[211.7; 389.9]	89.0	354.0	463.0	27	165	192

For this table, a patient is regarded as having switched from initial TAF during the observational period if the stop date of the initial TAF treatment is 3 or more days before the study termination/completion date
Source: Annex 1, Number 4, Table 14.2 8.2 arm 3

This good persistence can also be seen from the Kaplan-Meier graph and from the Kaplan-Meier estimator of still being on the original R/F/TAF at the end of the study being 73.6% (Figure 3).

Figure 3. Kaplan-Meier Estimator of Time to ARV Therapy Switch (Days) – Treatment Arm R/F/TAF – All Treated Population (N 192)



Source: Annex 1, Number 4, Figure 14.2 8.1 arm 3

10.4.3.3. Treatment Adherence Questionnaire

Results of the treatment adherence questionnaire are summarized in Annex 1 Number 4, Table 14.1-6.3.1.1 and Table 14.1-6.3.1 (arm 3).

The return rate of the questionnaire waslow and interpretation of the results is limited due to the fact that patients needs to remember a long time period.

Table 73. Summary of Adherence, Patient Questionnaire - Treatment Arm R/F/TAF - All Treated Population (N 192) - On Initial TAF Treatment

Visit	Variable	Category	Statistic	
Month 3	Self assessment of percentage HIV medication taken in past 30 days (VAS)		n	118
			Mean (SD)	98.3 (7.95)
			95% CI of Mean	[96.8 ; 99.7]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	20, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	92 (80.7)
		1	n (%)	9 (7.9)
		2	n (%)	6 (5.3)
		3	n (%)	3 (2.6)
		4	n (%)	1 (0.9)
		>4	n (%)	3 (2.6)
		Missing	n	59
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	108 (95.6)
		1	n (%)	3 (2.7)
		2	n (%)	1 (0.9)
		3	n (%)	
		4	n (%)	1 (0.9)
		>4	n (%)	
		Missing	n	60

Visit	Variable	Category	Statistic	
Month 6	Self assessment of percentage HIV medication taken in past 30 days (VAS)		n	113
			Mean (SD)	98.6 (3.98)
			95% CI of Mean	[97.8 ; 99.3]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	65, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	81 (75.7)
		1	n (%)	18 (16.8)
		2	n (%)	5 (4.7)
		3	n (%)	
		4	n (%)	
		>4	n (%)	3 (2.8)
		Missing	n	60
	Number of days within the past 4 days in which the HIV Therapy was not taken	0	n (%)	101 (97.1)
		1	n (%)	3 (2.9)
		2	n (%)	
		3	n (%)	
		4	n (%)	
		>4	n (%)	
		Missing	n	63
Month 12	Self assessment of percentage HIV medication taken in past 30 days (VAS)		n	96
			Mean (SD)	98.4 (3.11)
			95% CI of Mean	[97.8 ; 99.0]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	85, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	65 (70.7)
		1	n (%)	15 (16.3)
		2	n (%)	9 (9.8)
		3	n (%)	1 (1.1)
		4	n (%)	2 (2.2)
		>4	n (%)	
		Missing	n	68
	Number of days within the past 4 days in which the HIV Therapy was not taken	0	n (%)	88 (96.7)
		1	n (%)	3 (3.3)
		2	n (%)	
		3	n (%)	
		4	n (%)	
		>4	n (%)	
		Missing	n	69

Visit	Variable	Category	Statistic	
Month 18	Self assessment of percentage HIV medication taken in past 30 days (VAS)		n	81
			Mean (SD)	98.1 (5.23)
			95% CI of Mean	[96.9 ; 99.2]
			Median	100.0
			Q1, Q3	99.0, 100.0
			Min, Max	60, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	62 (75.6)
		1	n (%)	10 (12.2)
		2	n (%)	6 (7.3)
		3	n (%)	1 (1.2)
		4	n (%)	2 (2.4)
		>4	n (%)	1 (1.2)
		Missing	n	73
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	81 (98.8)
		1	n (%)	
		2	n (%)	
		3	n (%)	
		4	n (%)	1 (1.2)
		>4	n (%)	
		Missing	n	73
Month 24	Self assessment of percentage HIV medication taken in past 30 days (VAS)		n	72
			Mean (SD)	98.2 (4.69)
			95% CI of Mean	[97.1 ; 99.3]
			Median	100.0
			Q1, Q3	98.0, 100.0
			Min, Max	70, 100
	Number of days within the past 30 days in which the HIV therapy was not taken	0	n (%)	48 (66.7)
		1	n (%)	13 (18.1)
		2	n (%)	4 (5.6)
		3	n (%)	3 (4.2)
		4	n (%)	1 (1.4)
		>4	n (%)	3 (4.2)
		Missing	n	66
	Number of days within the past 4 days in which the HIV therapy was not taken	0	n (%)	63 (90.0)
		1	n (%)	6 (8.6)
		2	n (%)	
		3	n (%)	1 (1.4)
		4	n (%)	
		>4	n (%)	
		Missing	n	68

10.4.3.4. HIV Treatment Satisfaction Questionnaire

Median (IQR) change in overall treatment satisfaction score for patients in the treatment experienced subgroup who remained on initial R/F/TAF treatment at month 12 was 15.0 (0.5, 27.0) (possible score range -30 to 30). Details including individual item scores can be found in Annex 1, Number 4, Table 14.2-5.2.1. A similar analysis including the "Whole Observational Period" yielded similar results, which are found in Annex 1, Number 4, Table 14.2-5.2.2.

10.4.3.5. HIV Symptoms Index

The percentage of symptomatic patients decreased for 8 out of 20 recorded HIV symptom items from Baseline to Month 24 in the "On Initial TAF Treatment" group. The following symptoms showed the highest decline of symptomatic patients comparing Baseline and Month 24: Sleep Trouble (BL: 50.8%, M24: 43.2%), Headache (BL: 28.9%, M24: 21.3%), Nervous/anxious (BL: 35.0%, M24: 28.9%). HIV symptom index results are summarized for all patients in Annex 1, Number 4, Table 14.2-4.1.1, Table 14.2-4.1.2, Table 14.2-4.2.1, and Table 14.2-4.2.2 (arm 3).

10.4.3.6. Quality of Life (SF 36)

Both, mean Mental Component Score (48.4 to 49.0) and Physical Component Score (52.4 to 52.7) were stable from Baseline to Month 24 for patients "On Initial TAF Treatment" in the R/F/TAF arm. Quality of life was evaluated using the SF-36. Scores are summarized in Annex 1, Number 4, Tables 14.2-3.1 and 14.2-3.2 (arm 3). Analysis was also performed for the "Whole Observational Period" showing similar results. Respective data are summarized in Annex 1, Number 4, Tables 14.2-3.2 (arm 2).

10.4.3.7. Laboratory Values

Uric Acid slightly increased in the all treated population for patients "On Initial TAF Treatment" until Month 24 while aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT) tended to decreased across the population. A slight decrease was noted in estimated GFR (eGFR). aboratory and instrumental exams results can be found in Annex 1, Number 4, Tables 14-3.2.1.1 to 14.3-6.2 (arm 3).

10.5. Adverse Reactions

10.5.1. E/C/F/TAF Arm

At least one treatment-emergent adverse drug reaction (TEADR) was reported by 6.6% (21 of 318) of patients and at least one treatment-emergent serious adverse drug reaction (TESADR) was reported by 0.6% (2 of 318) of patients in the All Treated Population (Table 74).

TEADRs by system organ class (SOC) and preferred term (PT) are summarized in Table 75. The two most represented SOCs, in terms of patients, were gastrointestinal disorders and nervous system disorders. Six TEADRs were reported in the gastrointestinal disorders SOC, with the

most common PTs in this SOC being “diarrhea”, with 2 events in 2 patients, and “nausea”, with 2 events in 2 patients (0.6% patients for each event). Seven TEADRs were reported in the nervous system disorders SOC, with the most common PT in this SOC being “headache”, with 4 events in 4 patients (1.3%).

TESADR are summarized in Table 76. The only two represented SOCs were cardiac disorders and nervous system disorders. Two TESADRs were reported in the cardiac disorders SOC (“palpitations”; 0.6% of patients) and one in the nervous system disorders (“headache”; 0.3% of patients). The events of palpitations and headache were reported in a male patient of unknown age who received one dose of E/C/F/TAF and subsequently discontinued drug due to these events. No clinical information was provided and these events were reported as resolved 3 months later suggesting alternative non-study drug etiology. The second event of palpitations occurred in a patient who switched treatment from E/C/F/TAF to Triumeq and experienced palpitations assessed as related to Triumeq two months into their new treatment regimen.

Table 74 Summary of TEADRs - Treatment Arm E/C/F/TAF – All Treated Population (N 318)

	Events	Patients n (%)	Rate per 10 Patient Years	95%-CI of Rate
Patients with at least one TEADR	31	21 (6.6)	0.55	[0.38; 0.79]
Patients with at least one TESADR	3	2 (0.6)	0.05	[0.01; 0.16]

Percentages based on All Treated Population.
Rates are Poisson rate estimates with corresponding confidence intervals.
TEADR treatment emergent adverse drug reaction; TESADR treatment emergent serious adverse drug reaction
Source: Annex 1, Number 4, Table 14.3 1.1 arm 1

Table 75. Summary of TEADRs by System Organ Class and Preferred Term-Treatment Arm E/C/F/TAF – All Treated Population

SOC Preferred Term	Events	Patients n (%)	Rate per 10 Patient Years	95%-CI of Rate
Patients with at least one TEADR	31	21 (6.6)	0.55	[0.38; 0.79]
Gastrointestinal disorders	6	6 (1.9)	0.11	[0.04; 0.23]
Diarrhoea	2	2 (0.6)	0.04	[0.00; 0.13]
Nausea	2	2 (0.6)	0.04	[0.00; 0.13]
Dyspepsia	1	1 (0.3)	0.02	[0.00; 0.10]
Flatulence	1	1 (0.3)	0.02	[0.00; 0.10]
Nervous system disorders	7	6 (1.9)	0.13	[0.05; 0.26]
Headache	4	4 (1.3)	0.07	[0.02; 0.18]
Disturbance in attention	1	1 (0.3)	0.02	[0.00; 0.10]
Dizziness	1	1 (0.3)	0.02	[0.00; 0.10]
Migraine	1	1 (0.3)	0.02	[0.00; 0.10]
Skin and subcutaneous tissue disorders	4	4 (1.3)	0.07	[0.02; 0.18]
Pruritus	2	2 (0.6)	0.04	[0.00; 0.13]
Acne	1	1 (0.3)	0.02	[0.00; 0.10]
Hyperhidrosis	1	1 (0.3)	0.02	[0.00; 0.10]
Investigations	3	3 (0.9)	0.05	[0.01; 0.16]
Weight increased	2	2 (0.6)	0.04	[0.00; 0.13]
Blood HIV RNA increased	1	1 (0.3)	0.02	[0.00; 0.10]
Cardiac disorders	2	2 (0.6)	0.04	[0.00; 0.13]
Palpitations	2	2 (0.6)	0.04	[0.00; 0.13]
General disorders and administration site conditions	2	2 (0.6)	0.04	[0.00; 0.13]
Fatigue	1	1 (0.3)	0.02	[0.00; 0.10]
Malaise	1	1 (0.3)	0.02	[0.00; 0.10]
Musculoskeletal and connective tissue disorders	2	2 (0.6)	0.04	[0.00; 0.13]
Pain in extremity	1	1 (0.3)	0.02	[0.00; 0.10]
Pathological fracture	1	1 (0.3)	0.02	[0.00; 0.10]
Psychiatric disorders	2	2 (0.6)	0.04	[0.00; 0.13]
Loss of libido	1	1 (0.3)	0.02	[0.00; 0.10]
Sleep disorder	1	1 (0.3)	0.02	[0.00; 0.10]
Ear and labyrinth disorders	1	1 (0.3)	0.02	[0.00; 0.10]
Vertigo	1	1 (0.3)	0.02	[0.00; 0.10]
Infections and infestations	1	1 (0.3)	0.02	[0.00; 0.10]
Virologic failure	1	1 (0.3)	0.02	[0.00; 0.10]
Reproductive system and breast disorders	1	1 (0.3)	0.02	[0.00; 0.10]
Erectile dysfunction	1	1 (0.3)	0.02	[0.00; 0.10]

Percentages based on All Treated Population.
Rates are Poisson rate estimates with corresponding confidence intervals.
TEADR treatment emergent adverse drug reaction
Source: Annex 1, Number 4, Table 14.3 1.2 arm 1

Table 76. Summary of TESADRs by System Organ Class and Preferred Term-Treatment Arm E/C/F/TAF – All Treated Population

SOC Preferred Term	Events e	Patients n (%)	Rate per 10 Patient Years	95%-CI of Rate
Patients with at least one TESADR	3	2 (0.6)	0.05	[0.01; 0.16]
Cardiac disorders	2	2 (0.6)	0.04	[0.00; 0.13]
Palpitations*	2	2 (0.6)	0.04	[0.00; 0.13]
Nervous system disorders	1	1 (0.3)	0.02	[0.00; 0.10]
Headache	1	1 (0.3)	0.02	[0.00; 0.10]

Percentages based on All Treated Population.
Rates are Poisson rate estimates with corresponding confidence intervals.
TESADR treatment emergent serious adverse drug reaction
* One event was reported to be related to Triumeq
Source: Annex 1, Number 4, Table 14.3 1.3 arm 1

10.5.2. F/TAF Arm

At least one TEADR was reported by 6.2% (16 of 257) of patients and at least one TESADR was reported by 2.3% (6 of 257) of patients in the All Treated Population (Table 77).

TEADRs by SOC and PT are summarized in Table 78. The two most represented SOCs, in terms of patients, were gastrointestinal disorders and psychiatric disorders. Seven TEADRs were reported in the gastrointestinal disorders SOC, with the most common PTs in this SOC being “diarrhea”, with 3 events in 3 patients (1.2%) and “constipation”, with 1 event in 1 patient (0.4%). Four TEADRs were reported in the psychiatric disorders SOC, with the most common PT in this SOC being “sleep disorder”, with 2 events in 2 patients (0.8%). One event of “sleep disorder” was assessed as related to Tivicay and the other one as related to F/TAF, whereas Tivicay was prescribed as 3rd agent also to this patient. The two other TEADRs reported in the psychiatric disorders SOC were “abnormal dreams”, which were considered by the investigator to be related to both, F/TAF and Tivicay, and “suicidal ideation” which was assessed as related to Tivicay.

TESADR are summarized in Table 79. The two most represented SOCs were gastrointestinal disorders and psychiatric disorders. Three TESADRs in 3 patients were reported in the gastrointestinal disorders SOC (“diarrhea”, “gastric dysplasia”, and “oesophageal dysplasia"; 0.4% of patients each) and two in the psychiatric disorders (“sleep disorder” and “suicidal ideation”; 0.4% of patients each).

Table 77. Summary of TEADRs - Treatment Arm F/TAF – All Treated Population (N 257)

	Events	Patients n (%)	Rate per 10 Patient Years	95%-CI of Rate
Patients with at least one TEADR	23	16 (6.2)	0.55	[0.35; 0.82]
Patients with at least one TESADR	8*	6 (2.3)	0.19	[0.08; 0.38]

Percentages based on All Treated Population.
Rates are Poisson rate estimates with corresponding confidence intervals.
TEADR treatment emergent adverse drug reaction; TESADR treatment emergent serious adverse drug reaction
* Four events were reported to be related to Tivicay
Source: Annex 1, Number 4, Table 14.3 1.1 arm 2

Table 78. Summary of TEADRs by System Organ Class and Preferred Term-Treatment Arm F/TAF – All Treated Population

SOC Preferred Term	Events e	Patients n (%)	Rate per 10 Patient Years	95%-CI of Rate
Patients with at least one TEADR	23	16 (6.2)	0.55	[0.35; 0.82]
Gastrointestinal disorders	7	6 (2.3)	0.17	[0.07; 0.34]
Diarrhoea	3	3 (1.2)	0.07	[0.01; 0.21]
Constipation	1	1 (0.4)	0.02	[0.00; 0.13]
Flatulence	1	1 (0.4)	0.02	[0.00; 0.13]
Gastric dysplasia	1	1 (0.4)	0.02	[0.00; 0.13]
Oesophageal dysplasia	1	1 (0.4)	0.02	[0.00; 0.13]
Psychiatric disorders	4	4 (1.6)	0.10	[0.03; 0.24]
Sleep disorder*	2	2 (0.8)	0.05	[0.01; 0.17]
Abnormal dreams	1	1 (0.4)	0.02	[0.00; 0.13]
Suicidal ideation**	1	1 (0.4)	0.02	[0.00; 0.13]
Ear and labyrinth disorders	2	2 (0.8)	0.05	[0.01; 0.17]
Vertigo	2	2 (0.8)	0.05	[0.01; 0.17]
Musculoskeletal and connective tissue disorders	3	2 (0.8)	0.07	[0.01; 0.21]
Arthralgia	1	1 (0.4)	0.02	[0.00; 0.13]
Myalgia	1	1 (0.4)	0.02	[0.00; 0.13]
Periostitis	1	1 (0.4)	0.02	[0.00; 0.13]
General disorders and administration site conditions	1	1 (0.4)	0.02	[0.00; 0.13]
Drug resistance	1	1 (0.4)	0.02	[0.00; 0.13]

SOC Preferred Term	Events e	Patients n (%)	Rate per 10 Patient Years	95%-CI of Rate
Infections and infestations	1	1 (0.4)	0.02	[0.00; 0.13]
Virologic failure	1	1 (0.4)	0.02	[0.00; 0.13]
Metabolism and nutrition disorders	1	1 (0.4)	0.02	[0.00; 0.13]
Hypercholesterolaemia	1	1 (0.4)	0.02	[0.00; 0.13]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (0.4)	0.02	[0.00; 0.13]
Oesophageal carcinoma stage 0	1	1 (0.4)	0.02	[0.00; 0.13]
Nervous system disorders	1	1 (0.4)	0.02	[0.00; 0.13]
Neuropathy peripheral	1	1 (0.4)	0.02	[0.00; 0.13]
Renal and urinary disorders	1	1 (0.4)	0.02	[0.00; 0.13]
Nephropathy toxic***	1	1 (0.4)	0.02	[0.00; 0.13]
Skin and subcutaneous tissue disorders	1	1 (0.4)	0.02	[0.00; 0.13]
Cutaneous symptom	1	1 (0.4)	0.02	[0.00; 0.13]

Percentages based on All Treated Population.
Rates are Poisson rate estimates with corresponding confidence intervals.
TEADR treatment emergent adverse drug reaction
* One event was reported to be related to Tivicay Event was reported to be related to Tivicay
*** An event of non serious toxic nephropathy considered by the investigator to be related to study drug was reported in a 46 year old man. The event was characterized by proteinuria, however there was no evidence of proximal renal tubulopathy and eGFR remained normal throughout the treatment period with study drug.
Source: Annex 1, Number 4, Table 14.3 1.2

Table 79. Summary of TESADRs by System Organ Class and Preferred Term-Treatment Arm F/TAF – All Treated Population

SOC Preferred Term	Events e	Patients n (%)	Rate per 10 Patient Years	95%-CI of Rate
Patients with at least one TESADR	8	6 (2.3)	0.19	[0.08; 0.38]
Gastrointestinal disorders	3	2 (0.8)	0.07	[0.01; 0.21]
Diarrhoea*	1	1 (0.4)	0.02	[0.00; 0.13]
Gastric dysplasia**	1	1 (0.4)	0.02	[0.00; 0.13]
Oesophageal dysplasia**	1	1 (0.4)	0.02	[0.00; 0.13]
Psychiatric disorders	2	2 (0.8)	0.05	[0.01; 0.17]
Sleep disorder	1	1 (0.4)	0.02	[0.00; 0.13]
Suicidal ideation***	1	1 (0.4)	0.02	[0.00; 0.13]
General disorders and administration site conditions	1	1 (0.4)	0.02	[0.00; 0.13]
Drug resistance*	1	1 (0.4)	0.02	[0.00; 0.13]
Infections and infestations	1	1 (0.4)	0.02	[0.00; 0.13]
Virologic failure*	1	1 (0.4)	0.02	[0.00; 0.13]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (0.4)	0.02	[0.00; 0.13]
Oesophageal carcinoma stage 0**	1	1 (0.4)	0.02	[0.00; 0.13]

Percentages based on All Treated Population.
Rates are Poisson rate estimates with corresponding confidence intervals.
TESADR treatment emergent serious adverse drug reaction
* Events were reported to be related to Tivicay
** Gastric dysplasia, oesophageal dysplasia and Oesophageal carcinoma stage 0 were reported in a 57 year old woman with a medical history of Non Hodgkin's lymphoma and COPD 9 months after starting F/TAF. She was reported as experienced worsening dysphagia and was subsequently diagnosed with oesophageal caricinoma in situ. Further clinical details were not provided.
*** This event was reported as related to Tivicay in a 27 year old man with a history of depression. Suicidal ideation particularily in patients with a pre exsiting history of depression is an ADR for Tivicay.
Source: Annex 1, Number 4, Table 14.3 1.3

10.5.3. R/F/TAF Arm

At least one TEADR was reported by 5.2% (10 of 192) of patients in the All Treated Population (Table 80). No TESADR were reported.

TEADRs by SOC and PT are summarized in Table 81. The two most represented SOCs, in terms of patients, were psychiatric disorders and investigations. Five TEADRs were reported in the psychiatric disorders SOC, with the most common PTs in this SOC being "depression", with 2 events in 2 patients (1.0%), followed by "insomnia", "libido decreased", and "nightmare", with 1 event in 1 patient each (0.5%). Three TEADRs were reported in the Investigations SOC, with the only PT in this SOC being "weight increased", with 3 events in 3 patients (1.6%).

Table 80. Summary of TEADRs - Treatment Arm R/F/TAF – All Treated Population (N 192)

	Events e	Patients n (%)	Rate per 10 Patient Years	95%-CI of Rate
Patients with at least one TEADR	11	10 (5.2)	0.33	[0.16; 0.59]

Percentages based on All Treated Population.
Rates are Poisson rate estimates with corresponding confidence intervals.
TEADR treatment emergent adverse drug reaction; TESADR treatment emergent serious adverse drug reaction
Source: Annex 1, Number 4, Table 14.3 1.1 arm 3

Table 81. Summary of TEADRs by System Organ Class and Preferred Term-Treatment Arm R/F/TAF – All Treated Population

SOC Preferred Term	Events e	Patients n (%)	Rate per 10 Patient Years	95%-CI of Rate
Patients with at least one TEADR	11	10 (5.2)	0.33	[0.16; 0.59]
Psychiatric disorders	5	5 (2.6)	0.15	[0.05; 0.35]
Depression	2	2 (1.0)	0.06	[0.01; 0.22]
Insomnia	1	1 (0.5)	0.03	[0.00; 0.17]
Libido decreased	1	1 (0.5)	0.03	[0.00; 0.17]
Nightmare	1	1 (0.5)	0.03	[0.00; 0.17]
Investigations	3	3 (1.6)	0.09	[0.02; 0.26]
Weight increased	3	3 (1.6)	0.09	[0.02; 0.26]
Gastrointestinal disorders	1	1 (0.5)	0.03	[0.00; 0.17]
Abdominal pain upper	1	1 (0.5)	0.03	[0.00; 0.17]
General disorders and administration site conditions	1	1 (0.5)	0.03	[0.00; 0.17]
Fatigue	1	1 (0.5)	0.03	[0.00; 0.17]
Nervous system disorders	1	1 (0.5)	0.03	[0.00; 0.17]
Disturbance in attention	1	1 (0.5)	0.03	[0.00; 0.17]

Percentages based on All Treated Population.
Rates are Poisson rate estimates with corresponding confidence intervals.
TEADR treatment eEmergent adverse drug reaction
Source: Annex 1, Number 4, Table 14.3 1.2 arm 3

11. DISCUSSION

11.1. Key results

This study was a non-interventional study, conducted in Germany in adult patients receiving Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir alafenamide (E/C/F/TAF) or Emtricitabine/Tenofovir alafenamide (F/TAF) or Rilpivirine/Emricitabine/Tenofovir alafenamide (R/F/TAF) for HIV-1 Infection.

In total, 767 patients provided informed consent, were enrolled into the study and contributed to the final analysis: 318 (41.4%, 318/767) were treated with E/C/F/TAF, 257 (33.5%, 257/767) with F/TAF plus third agent (CCR5: 2.3%; INI: 67.7%; NNRTI 12.5%; NRTI 0.8%; PI 27.2% and PKE 0,4%) (see Annex 1, Number 4, Table 14.1-5.3.1, arm 2, for reference) and 192 (25.0%, 192/767) with R/F/TAF.

11.1.1. Primary Outcomes

Some general comments on to the MMRM models used:

In general, those models reflect the nature of the data quite well. When analysed all patients in one model, the majority of the models show significant p-values for treatment experienced versus treatment naive patients and for treatment experience by visit, ie. over time. In other words, treatment experience is statistically associated with lower HIV-1 RNA viral load and also that HIV-1 RNA viral load decreased over time. This was very much influenced by naive patients, which can be seen in naive-patients-only models. Those findings are very much in line with results from clinical trials. Models in treatment experiences patients only showed usually no significant effect on any of the variables.

It has to be mentioned that models in treatment naive patients were often based on small group numbers only. This holds specifically for sex, where only around 6-10% of patients were females.

For the F/TAF arm, inclusion criteria forced all treatment experienced patients to be above the age of 50 years old. Thus, models analyzing all patients together should be interpreted with caution, as no optimal model finding was performed when treatment status and age were analysed together.

This holds true in general, also: Better models might be suitable to the data which were not considered at the time of SAP writing.

Models distinguishing between “On Initial TAF Treatment” and “Whole Observational Period” differed only marginally. The same holds for HIV-1 RNA and CD4 count analyses. However, it has to be said that for the latter, missing values of CD4 count resulted in lower patient numbers for analyses.

11.1.1.1. HIV-1 RNA Viral Load

At baseline, patients in the **E/C/F/TAF** arm had a mean (median) HIV-1 RNA viral load of 193,180.2 (83.0) copies/mL. Viral load was dropping rapidly after starting E/C/F/TAF treatment and reached a median of 49 copies/ml (summarizing viral load below 50 copies/ml; IQR: 49,49) after 3 months for all patients on initial TAF treatment. Same was observed in the "Whole Observational Period" group (see Table 9 and Table 13). These results underline the efficacy findings from randomized clinical trials in a real world setting.

Given the extreme values at baseline, in only one of the subgroups by experience, it is debatable if MMRM is an appropriate model for these data. However, the SAP considered the MMRM if appropriate, but no alternative models were conducted

At baseline, patients in the **F/TAF** arm had a mean (median) HIV-1 RNA viral load of 369,820.23 (49.0) copies/mL. Until Month 3, median viral load had been notably reduced to 49 copies/ml (IQR: 49,49) in both groups, "On Initial TAF Treatment" and "Whole Observational Period", and remained at this level until the end of the observational period (see Table 26 and Table 30).

Baseline mean (median) HIV-1 RNA viral load was 6318.8 (49.0) copies/mL in the **R/F/TAF** arm and thus relatively low compared to the E/C/F/TAF and F/TAF arm due to exclusion of baseline viral load >100,000 copies /ml as per SmPC. Until Month 3, mean (median) viral load declined to 69.2 (49) copies/ml and was about the same level at Month 24 (see Table 43), demonstrating the efficacy of the regimen in the real-world setting. For the "Whole observational period" analysis, median viral load was stable at 49 (IQR: 49,49) and mean viral load slightly increased to 165.7 copies/ml until Month 24 (see Table 47).

11.1.1.2. CD4 Cell Count

At baseline, patients in the **E/C/F/TAF** arm had a mean (median) CD4 cell count of 597.3 (560.0) cells/µL. In both the "On Initial TAF Treatment" and "Whole Observational Period" analysis, CD4 cell count continuesly increased to 750 (mean) and 690 (median) cells/µl until Month 24 (see Table 17 and Table 21).

At baseline, patients in the **F/TAF** arm had a mean (median) CD4 cell count of 530.1 (500.0) cells/µL. In the "On Initial TAF Treatment" analysis, CD4 cell count continuously increased to about 709.8 (mean) and 690 (median) cells/µl whereas CD4 cell count elevation was a little less pronounced in the "Whole Observation Period" group with 667.0 (mean) and 638.0 (median) cell/µl until Month 24 (see Table 34 and Table 38).

At baseline, patients in the **R/F/TAF** arm had a mean (median) CD4 cell count of 644.2 (612.5) cells/µL. Compared to E/C/F/TAF and F/TAF, this arm showed a higher CD4 count at baseline which is in line with the relatively lower baseline viral load compared to arms 1 and 2. In the "On Initial TAF Treatment" analysis, CD4 cell count continuously increased to 722.1 (mean) and 708.0 (median) cells/µl until Month 24. Median CD4 count was comparable at the end of the study in the "Whole Observational Period" group, while mean CD4 count elevation was a little higher with 767.1 cells/µl (see Table 51 and Table 55).

11.1.2. Other Analyses

11.1.2.1. Patient Persistence

Overall 24-month persistence was 87.7% in the E/C/F/TAF arm, 61.8% in the F/TAF arm, and 73.6% in the R/F/TAF arm.

The Persistence of 87.7% in the E/C/F/TAF arm is comparable to the retention rate in phase 3 randomized clinical trials GS-US-292-0104 and -111 with treatment naive patients, which was 89% for E/C/F/TAF after 96 weeks {Wohl 2016}. Discontinuation was mainly due to lost to follow-up (84.8%) in this observational study (Table 2), while no patients discontinued due to TEADRs.

Lower persistence in the F/TAF arm might have been partially driven by switching the patient from MTR to a STR (multi to single tablet regimen) for therapy simplification. Also, a relatively high amount of patients discontinued by withdrawing their consent (19.4%, Table 3).

The Persitence of 73.6% in the R/F/TAF compares to the following retention rates in phase 3 clinical trials with treatment experienced patients after 96 weeks: 88% in GS-US-366-1216, 84% in GS-US-366-1160 {Hagins 2018}. Discontinuation was mainly due to lost to follow-up (84.0%) in this observational study (Table 4), while no patients discontinued to to TEADRs.

11.1.2.2. HIV Treatment Satisfaction Questionnaire

Treatment experienced patients who switched to E/C/F/TAF, F/TAF-based regimen or R/F/TAF reported significant improvements in their treatment satisfaction through 12 months, demonstrating the potential of these newer regimens to improve satisfaction with medication.

11.1.2.3. Quality of Life (SF-36)

SF-36 showed improved Mental Component Scores for E/C/F/TAF and F/TAF from Baseline through Month 24, while the Score was stable for R/F/TAF. Physical Component Score remained stable throughout the study in all three treatment arms.

11.1.2.4. HIV Symptom Index

Switch to E/C/F/TAF and F/TAF-based regimen showed the highest percentage declines in symptomatic patients per item as well as a decline of symptomatic patients in a high number of items (14 and 15 out of 20, respectively). These results demonstrate the high efficacy of E/C/F/TAF in HIV symptom control in a real-world clinical setting.

Compared to E/C/F/TAF, the amount of symptomatic patients at Baseline was relatively high in the F/TAF arm across all items which might be linked to the older age in this population (see Table 5 and Table 6). Interpretability of the F/TAF arm is limited as the drug was always combined with a third agent, so conclusions on the actual F/TAF effect are difficult.

Patients in the R/F/TAF arm showed a decrease in symptomatic patients for 8 out of 20 items Compared to E/C/F/TAF, the percentage of symptomatic patients at Baseline was relatively low in the R/F/TAF arm. This might partly be due to the low number of treatment naive patients in this group (21.9% TN versus 50% in E/C/F/TAF and 38.9% in F/TAF arm), who were additionally restricted to having a viral load of ≤ 100.000 copies/ml correlating with a less advanced disease.

11.1.2.5. Laboratory Values

Reported lab changes did not show clinically significant trends.

11.1.2.6. Adverse Reactions

In the **E/C/F/TAF** arm, at least one TEADR was reported by 6.6% (21 of 318) of patients in the All Treated Population, and the most represented SOC was gastrointestinal and nervous system (mainly headache) disorders. This pattern is in line with the most common adverse events reported in the phase 3 randomized clinical trials GS-US-292-104 and -111 in treatment naive patients until week 96, being nausea, diarrhea, and headache {Wohl 2016}. The amount of patients reporting any TEADR (6.6%) in this real world study is lower than what has been published in the mentioned clinical trials (42.4% reported ADRs) showing the good tolerability of the regimen in clinical routine setting and a broad patient population. No new safety signals were noted in this observational study. At least one TESADR was reported by 0.6% (2 of 318) of patients in the All Treated Population, with the most represented SOC being cardiac disorders (PT palpitations) one case was related to Triumeq and the other case containined insufficient clinical information to determine etiology.

In the **F/TAF** arm, at least one TEADR was reported by 6.2% (16 of 257) of patients in the All Treated Population, and the most represented SOC was gastrointestinal disorders. At least one TESADR was reported by 2.3% (6 of 257) of patients in the All Treated Population, and the most represented SOC was gastrointestinal disorders. The different agents used as a third partner in the F/TAF arm are limiting interpretability of the safety results as the data shown here do not differentiate between F/TAF-related ADRs and ADRs related to the 3rd agent. Given the relatively older age of patients in this treatment arm (67.5% of patients older than 50 years, 27.3% in E/C/F/TAF and 30.8% in R/F/TAF arms) due to inclusion criteria, the regimen showed a high tolerability in this real-world study.

In the **R/F/TAF** arm, at least one TEADR was reported by 5.2% (10 of 192) of patients in the All Treated Population, and the most represented SOC was psychiatric disorders. No TESADR were reported. This translates to an TEADR rate of 0.33 per ten patient years, which highlights the good tolerability of the regimen in this real-world setting.

11.1.2.7. Driver for Therapy Start and Choice of Regimen

The primary driver for starting therapy in treatment naive patients was “early treatment according to guidelines” in all three treatment arms: in 100 (62.9%) E/C/F/TAF patients, in 80 (80.0%) F/TAF patients, and in 27 (64.3%) R/F/TAF patients.

Thus, no differences can be described for the drivers to start the respective TAF treatment.

The primary reason for treatment experienced patients to switch to E/C/F/TAF was “simplification of ART”, in 66 patients (41.5%).

The primary reason for treatment experienced patients to switch to F/TAF was “side effects of current ART”, in 67 patients (42.7%).

The primary reason for treatment experienced patients to switch to R/F/TAF was “side effects of current ART”, in 72 patients (48.0%).

11.2. Limitations

11.2.1. Non-interventional Study

Conducting a non-interventional study presupposes, according to definition of a ‘non-interventional study’ in terms of the EU-guideline 2001/20/EC, that the documentation plan does not dictate or prescribe on diagnosis, therapeutic decision, and follow-up. The study only observes the individual use of a drug by the treating physician in the given indication. No interventional diagnostic or monitoring procedures are applied to the patients included in the study, only those which are applied in the course of current practice. Data are collected only from routine care of patients.

11.3. Generalizability and Interpretation

The rationale of the current non-interventional observational study was to evaluate the real-life outcome of effectiveness, safety, adherence and Health-Related Quality of Life for the use of E/C/F/TAF, F/TAF plus third agent, and R/F/TAF in HIV-1 infected patients in German routine clinical care. Real-life use of the three different F/TAF-based regimens is reflected in the collected data in an unaffected manner. The size of the three arms allowed to describe the different aspects of the study objectives based on data of a considerable number of patients. Interpretability and generalizability of the study results are limited, because, as with all non-interventional studies, the study only observes the use of a drug by the treating physicians in the given indication and data are collected only from routine care of patients. This might also include a certain bias in prescription of a regimen to a particular patient population by the treating physician. Only a small number of women has been enrolled, however this reflects the overall sex distribution in PLWH in Germany.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSION

In routine clinical use, all three antiretroviral regimens - E/C/F/TAF, F/TAF or R/F/TAF - were safe, tolerable and effective. The most common healthcare provider rationale for initiating antiretroviral therapy was “early treatment according to guidelines” in all three treatment arms. Healthcare provider rationale for antiretroviral therapy switch differed by arm, with “simplification of ART” being most commonly reported in E/C/F/TAF arm, and “side effects of current ART” being most commonly reported in the F/TAF and R/F/TAF arms. Treatment persistence was generally high. Treatment experienced patients who switched to E/C/F/TAF, F/TAF or R/F/TAF reported improvements in treatment satisfaction. SF-36 showed improved Mental Component Scores for E/C/F/TAF and F/TAF from Baseline through Month 24, while the Score was stable for R/F/TAF. Physical Component Score remained stable throughout the study in all. HIV symptom index was similar for patients in the three treatment arms. All three regimens were well tolerated, with an adverse event profile similar to that reported in randomized controlled trials; no new safety signals were identified.

14. REFERENCES

Hagins D, Orkin C, Daar ES, Mills A, Brinson C, DeJesus E, et al. Switching to coformulated rilpivirine (RPV), emtricitabine (FTC) and tenofovir alafenamide from either RPV, FTC and tenofovir disoproxil fumarate (TDF) or efavirenz, FTC and TDF: 96-week results from two randomized clinical trials. HIV Med 2018.

Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS report on the global AIDS epidemic. 2013.

Wohl D, Oka S, Clumeck N, Clarke A, Brinson C, Stephens J, et al. Brief Report: A Randomized, Double-Blind Comparison of Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate, Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine for Initial HIV-1 Treatment: Week 96 Results. J Acquir Immune Defic Syndr 2016;72 (1):58-64.

APPENDICES

Annex 1. List of stand-alone documents

The following documents are available upon request.

Number	Date	Title
1	11-Aug-2020	List of Investigators
2	12-Apr-2019	Study Protocol (Amendment 2)
3	17-Aug-2017	Statistical Analysis Plan (Version 2.1)
4	23-Jun-2020	Final Analysis: - Tables 14.1 to 14.4 arm 1 - Tables 14.1 to 14.4 arm 2 - Tables 14.1 to 14.4 arm 3 - Figure 14.2 8.2.1 arm 1 - Figure 14.2 8.2.1 arm 2 - Figure 14.2 8.2.1 arm 3 - Listings 16.2.1-1 to 8-1 arm 1 - Listings 16.2.8-2 arm 1 - Listings 16.2.8-3 arm 1 - Listings 16.2.8-4 arm 1 - Listings 16.2.8-5 to 11-1 arm 1 - Listings 16.2.1-1 to 8-1 arm 2 - Listings 16.2.8-2 arm 2 - Listings 16.2.8-3 arm 2 - Listings 16.2.8-4 arm 2 - Listings 16.2.8-5 to 11-1 arm 2 - Listings 16.2.1-1 to 8-1 arm 3 - Listings 16.2.8-2 arm 3 - Listings 16.2.8-3 arm 3 - Listings 16.2.8-4 arm 3 - Listings 16.2.8-5 to 11-1 arm 3