FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3b Open-Label Pilot Study to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed Dose Combination (FDC) in Virologically Suppressed HIV-1 Infected Adult Subjects Harboring the Archived Isolated NRTI Resistance Mutation M184V/M184I
Name of Test Drug:	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/COBI/FTC/TAF [E/C/F/TAF]; Genvoya® [GEN])
Dose and Formulation:	Fixed-dose combination tablet of E/C/F/TAF (150/150/200/10 mg)
Indication:	Human immunodeficiency virus type 1 (HIV-1) infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-292-1824
Phase of Development:	Phase 3b
IND No.:	111,007
EudraCT No.:	2015-002710-74
ClinicalTrials.gov Identifier:	NCT02616029
Study Start Date:	17 December 2015 (First Subject Screened)
Study End Date:	11 October 2018 (Last Subject Last Observation for the Primary Endpoint) 11 July 2019 (Last Subject Last Visit)
Principal or Coordinating Investigator:	Name: PPD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
Gilead Study Director:	Name: PPD Telephone: PPD
Report Date:	03 March 2020

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS
Study GS-US-292-1824
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3b Open-Label Pilot Study to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed Dose Combination (FDC) in Virologically Suppressed HIV-1 Infected Adult Subjects Harboring the Archived Isolated NRTI Resistance Mutation M184V/M184I

Investigators: Multicenter study

Study Centers: 7 sites (8 Principal Investigators) in France, 4 sites in Italy, 4 sites in Spain, 3 sites in Germany, and 3 sites in the United States

Publications:

Perez-Valero I, Llibre JM, Lazzarin A, di Perri G, Pulido F, Molina JM, Esser S, Margot N, Shao Y, Piontkowsky D, Das M, McNicholl IR, Haubrich R. A Phase 3b Open-Label Pilot Study to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) in Virologically-Suppressed HIV-1 Infected Adults Harboring the NRTI Resistance Mutation M184V/I (GS-US-292-1824): Week 24 Results [Poster PE13/20]. 17th European AIDS Conference (EACS), 6-9 November 2019, Basel, Switzerland.

Perez-Valero I, Llibre JM, Lazzarin A, di Perri G, Pulido F, Molina JM, Esser S, McNicholl IR, Lorgeoux RP, Margot N, Shao Y, Piontkowsky D, Das M, Haubrich R. A Phase 3b Open-Label Pilot Study to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single-Tablet Regimen in Virologically-Suppressed HIV-1 Infected Adults Harboring the NRTI Resistance Mutation M184V and/or M184I (GS-US-292-1824): Week 24 Results [Oral abstract]. 22nd International AIDS Conference, 23-27 July 2018, Amsterdam, The Netherlands.

Perez-Valero I, Llibre JM, Lazzarin A, di Perri G, Pulido F, Molina JM, Esser S, McNicholl IR, Lorgeoux RP, Margot N, Shao Y, Piontkowsky D, Das M, Haubrich R. A Phase 3b Open-Label Pilot Study to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen in Virologically-Suppressed HIV-1 Infected Adults Harboring the NRTI Resistance Mutation M184V and/or M184I (GS-US-292-1824): Week 12 Results [Poster]. XXVI International Workshop on HIV Drug Resistance and Treatment Strategies, 6-8 November 2017, Johannesburg, South Africa.

Study Period:

17 December 2015 (First Subject Screened)
11 October 2018 (Last Subject Last Observation for the Primary Endpoint)
11 July 2019 (Last Subject Last Visit)

Phase of Development: Phase 3b

Objectives:

The primary objective of this study was as follows:

- To evaluate the efficacy of elvitegravir (EVG; E)/cobicistat (COBI; C)/emtricitabine (FTC; F)/tenofovir alafenamide (TAF) (Genvoya, hereafter referred to as "GEN") FDC after switching from a stable regimen consisting of FTC/tenofovir disoproxil fumarate (TDF) or abacavir (ABC)/lamivudine (3TC) plus a third antiretroviral agent in maintaining HIV-1 RNA < 50 copies/mL at Week 12 (using pure virologic response [PVR]) in subjects harboring the archived nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) resistance mutation M184V and/or M184I in HIV-1 reverse transcriptase

The secondary objectives of this study were as follows:

- To determine the safety and tolerability of GEN FDC in subjects switching from 2 NRTI plus third antiretroviral agent regimens
- To evaluate the development of new resistance mutations in subjects who developed virologic failure after switching to GEN FDC
- To determine the durability of efficacy at Weeks 24 and 48 in maintaining HIV-1 RNA < 50 copies/mL using PVR

Methodology: This was an open-label, single arm, multicenter study to evaluate the efficacy and safety of switching to GEN FDC in HIV-1 infected adult subjects with HIV-1 RNA < 50 copies/mL harboring an archived isolated M184V and/or M184I mutation associated with NRTI resistance.

Part 1: 50 subjects with M184V and/or M184I in HIV-1 reverse transcriptase WITHOUT any other NRTI resistance mutation were planned to enter the study. Subjects switched from their current regimen consisting of FTC/TDF or ABC/3TC plus a third antiretroviral agent to E/C/F/TAF FDC on Day 1.

After these subjects had undergone their Week 12 visit, an interim efficacy review was done by an Internal Data Monitoring Committee (IDMC) that was independent of the study team and the study conduct activities, to ensure the rate of virologic failure was not unacceptably high. A PVR of < 80% was considered unacceptable; safety monitoring was designed to assure that the true value of PVR was above 80%.

Part 2: Based on the analysis of the primary efficacy variable (HIV-1 RNA < 50 copies/mL) using PVR, the IDMC recommended continuing to Part 2 of the study as planned, with the entry criteria expanded to include subjects with 1 or 2 thymidine analogue-associated mutations (TAMs) (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R).

A further 50 subjects with M184V and/or M184I in HIV-1 reverse transcriptase WITH or WITHOUT 1 or 2 TAMs were therefore planned to enter the study.

After Screening, study visits occurred at Day 1 and Weeks 4, 8, 12, 16, 24, 36, and 48. After the 48 week visit, subjects stopped study drug and completed a 30-Day Follow-up visit to complete their participation in the study.

Adverse events (AEs) and concomitant medications were assessed at each visit.

A whole blood sample for proviral genotype analysis of archived resistance was collected at Screening.

Laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, CD4+ cell count, complete or symptom directed physical examinations, and vital signs were performed at Screening, Day 1 and specific subsequent study visits. Metabolic assessments were performed at Day 1, and Weeks 24 and 48. Electrocardiograms (ECG) were performed at Screening and Week 48.

Safety Monitoring of Virologic Failures

All HIV-1 RNA values were reviewed on an ongoing basis. Any post-Day 1 HIV-1 RNA ≥ 50 copies/mL were repeated within 2 to 4 weeks. Subjects with confirmed HIV-1 RNA ≥ 50 copies/mL were managed in discussion with the Medical Monitor in accordance with guidelines developed for the GEN Phase 3 program.

Number of Subjects (Planned and Analyzed):

Planned:

Approximately 100

Analyzed:

Subjects Enrolled:	66 (Part 1, 38 subjects; Part 2, 28 subjects)
Safety Analysis Set:	64 (Part 1, 37 subjects; Part 2, 27 subjects)
Full Analysis Set:	62 (Part 1, 36 subjects; Part 2, 26 subjects)

Diagnosis and Main Criteria for Inclusion: Subjects were HIV-1 infected adults (≥ 18 years) with documented HIV-1 RNA < 50 copies/mL for ≥ 6 months preceding and at the Screening visit (measured at least twice using the same assay). One unconfirmed virologic elevation or "blip" of ≥ 50 and < 400 copies/mL after previously reaching viral suppression was acceptable.

Subjects had to have been on a stable antiretroviral (ARV) regimen containing FTC/TDF or ABC/3TC plus an allowed third antiretroviral agent for ≥ 6 consecutive months prior to screening. Allowed third agents were: lopinavir/ritonavir (LPV/r), atazanavir (ATV)+ritonavir (RTV), ATV+COBI (or ATV/COBI FDC), darunavir (DRV)+RTV, DRV+COBI (or DRV/COBI FDC), efavirenz (EFV), rilpivirine (RPV), nevirapine (NVP), etravirine (ETR), raltegravir (RAL), and dolutegravir (DTG). As of Protocol Amendment 1, fosamprenavir (FPV) + RTV, saquinavir (SQV) + RTV, and ATV (no booster) were added as allowed third agents.

Subjects had to have a documented presence of NRTI resistance mutation M184V and/or M184I in HIV-1 reverse transcriptase, WITHOUT TAMs (Part 1) and WITH or WITHOUT 1 or 2 TAMs (Part 2). Subjects were not allowed to have any of the following NRTI resistance mutations: K65R, T69 insertion and Q151M mutation complex [A62V, V75I, F77L, F116Y, Q151M]. Subjects were not allowed to have any primary integrase strand transfer inhibitor (INSTI) or primary protease inhibitor (PI) resistance mutations. Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) mutations were allowed. As of Protocol Amendment 1, the NRTI resistance mutation K70E was also not allowed.

Subjects had to have no evidence of previous virologic failure on a PI/r or INSTI-based regimen (with or without resistance to either class of ARV). Subjects could have evidence of prior virologic failure on an NNRTI plus 2 NRTI-based regimen. Prior treatment changes due to

tolerability were allowed as long as virologic failure was not the reason for treatment change and the subject remained continuously suppressed.

Previous use of any approved or experimental INSTI (for any length of time) was not allowed if the current regimen contained a PI/r.

Subjects had to have an estimated glomerular filtration rate according to the Cockcroft-Gault formula for creatinine clearance ($eGFR_{CG}$) of ≥ 30 mL/min.

Duration of Treatment: A 42 day screening period followed by 48 weeks of treatment and a 30 Day Follow-Up visit after completion of study drug. Subjects who developed virologic failure were to have been followed for the duration of the study or longer to document virologic suppression on a revised regimen.

Test Product, Dose, Mode of Administration, and Batch No.:
Elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg (E/C/F/TAF; GEN) FDC, administered orally, once daily, with food.

Batch numbers: CP1503B1, CP1505B1, CP1604B1, and CP1701B1

Reference Therapy, Dose, Mode of Administration, and Batch No.: None

Criteria for Evaluation:
Efficacy of switch from the current regimen to GEN FDC was evaluated using HIV-1 RNA values; safety was assessed with adverse events and clinical laboratory tests.

Efficacy:
Primary Endpoint:

- HIV-1 RNA < 50 copies/mL at Week 12 using PVR

Secondary Endpoints:

- Emergence of new mutations in HIV-1 reverse transcriptase and integrase (attempted on any post Day 1 sample with HIV-1 RNA ≥ 50 copies/mL)
- HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 using PVR
- HIV-1 RNA < 50 copies/mL at Weeks 12, 24 and 48 using the FDA snapshot analysis (sensitivity analysis)
- CD4+ cell count change from Day 1 at Weeks 12, 24 and 48

Pharmacokinetics/Pharmacodynamics: No pharmacokinetics (PK) or pharmacodynamics (PD) assessments were performed for this report.

Safety: Clinical laboratory tests, including metabolic parameters; $eGFR_{CG}$; and AEs.

Other: Health related questionnaires, including the 3-level version of the EuroQol (5 domains) (EQ-5D-3L), Medical Outcome Study Short Form-36 (SF-36), Visual Analogue Scale (VAS), HIV Treatment Satisfaction Questionnaire (HIVTSQ) and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) were completed at specified visits.

Statistical Methods:

Efficacy: The Full Analysis Set (FAS) included all subjects who were enrolled and received at least 1 dose of study drug. For the FAS, all efficacy data were included, unless specified otherwise. The FAS excluded subjects who took Stribild (EVG/COBI/FTC/TDF) or Descovy (FTC/TAF) as part of the baseline antiretroviral regimen (and thus violated the inclusion criteria). The FAS was the primary analysis set for the efficacy analyses.

The primary endpoint of PVR with HIV-1 RNA < 50 copies/mL at Week 12 was computed. Subjects were classified as a pure virologic responder at Week 12 if they met the following criteria:

- Remained on study treatment
- No confirmed virologic rebound as defined by:
  - HIV-1 RNA ≥ 50 copies/mL on 2 consecutive visits
  - HIV-1 RNA ≥ 50 copies/mL during study followed by premature discontinuation of study

  Note: For confirmation of viral rebound, the first HIV-1 RNA sample had to have been obtained on or before the upper limit of the Week 12 analysis window; the confirming event (ie, the second consecutive HIV-1 RNA sample, or premature study discontinuation) could occur after the upper limit of the Week 12 analysis window.

Subjects who met these criteria were pure virologic responders at Week 12; otherwise subjects were pure virologic failures (PVF) at Week 12.

Similar definitions were used for PVR at Weeks 24 and 48.

Sensitivity analyses of virologic failure used the FDA snapshot analysis (and other sensitivity analyses such as missing equal failure) at Weeks 12, 24 and 48.

For the primary efficacy endpoint, PVR at Week 12, 95% CIs were generated using both the normal approximation method and the exact method.

Descriptive statistics were used to summarize the efficacy endpoints.

Pharmacokinetics/Pharmacodynamics: No PK/PD assessments were performed for this report.

Safety: The primary analysis set for safety analyses was defined as all subjects who received at least one dose of study drug. All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug plus 30 days was summarized. Data for the pretreatment period were included in data listings.

Clinical and laboratory adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 22.0).

Patient Reported Outcomes:
The VAS (%) absolute value and its change from baseline at each visit were summarized overall and by Parts 1 and 2 using descriptive statistics. Number of days with missed doses in the past 30 days and past 4 days were summarized categorically at each visit.

For the SF-36, HIVTSQ, and FACIT-F, scores were summarized overall and by Parts 1 and 2 for each visit using descriptive statistics.

For the EQ-5D-3L, for the 5 descriptive scores, the number and percentage of subjects with each response was summarized overall and by Parts 1 and 2 for each visit. For the index score and VAS score, change from baseline was summarized overall and by Parts 1 and 2 for each visit. In addition, responder analysis was performed based on the index score to determine the proportion of subjects with health worsening or improvement by visit.

SUMMARY OF RESULTS:

Subject Disposition:

A total of 66 subjects were enrolled, of which 64 subjects received at least 1 dose of the study drug (Part 1, 37 subjects; Part 2, 27 subjects); 2 subjects did not receive study drug. A total of 62 subjects (Part 1, 36 subjects; Part 2, 26 subjects) were included in the FAS and analyzed for the primary endpoint. A total of 60 subjects completed study drug treatment (Part 1, 34 subjects; Part 2, 26 subjects) (Table 15.8.2). Fewer than the planned number of subjects were enrolled due to the low prevalence of subjects with documented M184V and/or M184I mutation.

Of the 3 subjects who prematurely discontinued study drug in Part 1, 1 subject discontinued study drug due to an AE (nonserious muscle spasms), 1 subject discontinued study drug at the investigator's discretion (serious adverse event [SAE] of renal failure led the investigator to make this decision), and 1 subject discontinued study drug due to a protocol violation (the subject was not using protocol specified method of contraception). One subject prematurely discontinued study drug in Part 2 because the subject died (no information could be obtained regarding the cause of death).

Subject Demographics and Baseline Disease Characteristics:

The majority of subjects were male (47 subjects, 73.4%), with a mean age of 51 years (range 22 to 76 years) (Table 15.8.3.1). Most subjects were white (44 subjects, 68.8%) and not Hispanic or Latino (48 subjects, 75.0%); 15 subjects (23.4%) were black. The mean (SD) baseline body mass index was 26.2 (5.57) kg/m^2.

All subjects had baseline HIV-1 RNA < 50 copies/mL (64 subjects, 100%). The mean (SD) baseline CD4 cell count was 708 (316.4) cells/μL. The majority of subjects had a baseline CD4 cell count ≥ 500 cells/μL (48 subjects, 75.0%) (Table 15.8.3.2).

The most common HIV risk factor categories were homosexual sex and heterosexual sex (each 28 subjects, 43.8%). Most subjects had asymptomatic HIV disease status (53 subjects, 82.8%), and negative hepatitis C virus (HCV) antibody (54 subjects, 84.4%). The mean (SD) $eGFR_{CG}$ value was 102.0 (35.99) mL/min (Table 15.8.3.2).

Efficacy Results:

All subjects (62 subjects, 100%) in the FAS maintained a PVR (HIV-1 RNA < 50 copies/mL) through Week 12 (primary endpoint), and also through Weeks 24 and 48 (Table 15.9.1.1).

The number of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 12, as determined by the US FDA-defined snapshot algorithm (sensitivity analysis), was 58 subjects (93.5%). One subject in Part 2 (1 of 62, 1.6%) had HIV-1 RNA ≥ 50 copies/mL (217 copies/mL) at Week 12;

HIV-1 RNA was < 50 copies/mL at all subsequent visits. Three subjects in Part 1 (3 of 62, 4.8%) did not have any virologic data in the Week 12 window because they had discontinued study drug (1 subject due to an AE [muscle spasms], 2 subjects for other reasons [investigator's discretion, protocol violation]), but their last available HIV-1 RNA was < 50 copies/mL (Table 15.9.2.1, Listings 16.2.6.2, 16.2.6.1, and 16.2.7.5).

The number of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 24, as determined by the US FDA-defined snapshot algorithm, was 59 subjects (95.2%). No subjects had HIV-1 RNA ≥ 50 copies/mL at Week 24. Three subjects in Part 1 (3 of 62, 4.8%) did not have any virologic data in the Week 24 window because they had discontinued study drug (same as Week 12) (Table 15.9.2.2 and Listing 16.2.6.2).

The number of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48, as determined by the US FDA-defined snapshot algorithm, was 57 subjects (91.9%). No subjects had HIV-1 RNA ≥ 50 copies/mL at Week 48. Five subjects (5 of 62, 8.1%) (4 in Part 1, 1 in Part 2) did not have any virologic data in the Week 48 window; of these, 4 subjects had discontinued study drug (2 subjects due to an AE [muscle spasms; death (unknown cause)], 2 subjects for other reasons [investigator's discretion, protocol violation], but their last available HIV-1 RNA was < 50 copies/mL), and 1 subject was still on study drug but had missing data during the Week 48 window (Table 15.9.2.3, Listing 16.2.6.2, and 16.2.6.1).

The percentage of subjects with HIV-1 RNA < 50 copies/mL using the missing = failure (M = F) and missing = excluded (M = E) methods at Weeks 12, 24, and 48 were as follows:

- M = F: Week 12: 96.8% (60/62 subjects); Week 24: 95.2% (59/62 subjects); Week 48: 93.5% (58/62 subjects) (Table 15.9.3.2.1)
- M = E: Week 12: 98.4% (60/61 subjects); Week 24: 100% (59/59 subjects); Week 48: 100% (58/58 subjects) (Table 15.9.3.2.2)

The mean (SD) baseline CD4 cell count was 715 (314.2) cells/μL. A mean (SD) decrease from baseline was observed at Week 4 (−27 [161.1] cells/μL), which was stable through Weeks 12 (−30 [165.1] cells/μL) and 24 (−10 [187.4] cells/μL). At Week 48, the mean (SD) change from baseline in CD4 cell count was 9 (126.8) cells/μL (Table 15.9.4.1).

Virology Analyses:

None of the subjects in the study met the resistance analysis criteria (2 consecutive visits with HIV-1 RNA ≥ 50 copies/mL at any point in the study or with HIV-1 RNA ≥ 50 copies/mL at last visit). No resistance emergence was observed through 48 weeks of study.

Pharmacokinetics/Pharmacodynamics Results:

No PK/PD assessments were performed for this report.

Safety Results:

Overall, GEN was generally well tolerated by subjects in the study. The median (Q1, Q3) exposure was 48.0 (47.7, 48.1) weeks (Table 15.11.1.1).

Adverse Events

The percentage of subjects who had any AEs while receiving study drug was 79.7% (51 of

64) subjects (Table 15.11.2.1.1). The percentage of subjects who had AEs considered related to study drug by the investigator was 15.6% (10 subjects). The majority of the AEs were Grade 1 or 2 in severity. The percentage of subjects who had Grade 3 or 4 AEs was 9.4% (6 subjects). There were no Grade 3 or 4 AEs considered related to study drug by the investigator. A total of 7.8% (5 subjects) had SAEs; none of the SAEs was considered related to study drug by the investigator and none of the SAEs was reported for more than 1 subject. One subject (1.6%) had an AE that led to study drug discontinuation (nonserious muscle spasms) (Table 15.11.5). One subject (1.6%) died during the study; the cause of death was unknown, although the subject had been hospitalized for ablation of a prostate adenoma (which had been diagnosed 5 years prior to study entry) during the study (Listing 16.2.7.3).

The 3 most common AEs reported were asthenia, bronchitis, and nasopharyngitis, each occurring in 10.9% (7 subjects) (Table 15.11.2.1.3). The 3 most common AEs considered related to study drug by the investigator were asthenia (4.7%, 3 subjects), and fatigue and headache (3.1%, 2 subjects each) (Table 15.11.2.3.2).

No subject experienced any CDC Class C AIDS-defining events during the study (Listing 16.2.7.6).

Subject narratives for AEs that led to study drug withdrawal and SAEs are provided in Section 15.2.

Bone Safety

No subject experienced any treatment-emergent fracture adverse event during the study (Table 15.11.2.4).

Renal Safety

Renal Events

The renal and urinary disorders or associated investigation AEs reported during the study were as follows: polyuria (3.1%, 2 subjects), acute kidney injury, haematuria, micturition urgency, nephroangiosclerosis, proteinuria, renal cyst, and renal failure (1.6%, 1 subject each) (Table 15.11.2.1.2). None of these was considered related to study drug by the investigator (Table 15.11.2.3.1). The AEs of acute kidney injury, renal failure, and proteinuria were serious. The acute kidney injury and renal failure occurred in the same subject; this subject had a medical history of type 2 diabetes mellitus and hypertension, and had Grade 2 elevated serum creatinine and low $eGFR_{CG}$ at baseline (Listing 16.2.8.1.2.3). The subject with proteinuria had a medical history that included type 2 diabetes mellitus; he had +2 (Grade 2) urine protein at baseline, which increased to +3 (Grade 2) at Week 24 and remained high (Listing 16.2.8.1.4.1). All 3 SAEs resolved, and the subjects continued with study drug at the time of the SAEs (Listing 16.2.7.3). The narratives for these SAEs are provided in Section 15.2.

There were no cases of proximal renal tubulopathy (including Fanconi syndrome) reported during the study, and no subject discontinued study drug due to a renal AE that was evaluated as related to study drug by the investigator.

Serum Creatinine and $eGFR_{CG}$

There were no notable changes from baseline during the study in median serum creatinine (baseline 0.93 mg/dL; median change 0.00 mg/dL at Weeks 24 and 48) (Table 15.11.6.2.8) or

eGFR (baseline 94.8 mL/min; median change -0.3 mL/min at Week 24, 0.9 mL/min at Week 48) (Table 15.11.6.2.9).

Proteinuria by Urinalysis (Dipstick)

The majority of proteinuria measurements during the study were ungraded or Grade 1 toxicity, as assessed by dipstick analysis. No subjects had ≥ Grade 3 proteinuria (Listing 16.2.8.1.4.1). One subject had Grade 2 proteinuria at baseline. One subject who had Grade 0 proteinuria at baseline had a shift to Grade 2 at Week 48 (Table 15.11.6.7.1).

Proteinuria by Quantitative Assessment

The majority of urine protein to creatinine ratio (UPCR) measurements during the study were ≤ 200 mg/g; 5 subjects had baseline UPCR > 200 mg/g. Three subjects who had UPCR ≤ 200 mg/g at baseline had a shift to > 200 mg/g at Week 48 (Table 15.11.6.7.2.3).

There were no consistent changes over time in the median percentage change from baseline UPCR (Table 15.11.6.7.2.1). The overall median (Q1, Q3) percentage change from baseline in UPCR at Week 48 was 2.0% (−39.7%, 45.8%).

The majority of urine albumin to creatinine ratio (UACR) measurements during the study were < 30 mg/g. There was a shift from UACR < 30 mg/g at baseline to ≥ 30 mg/g in 4 subjects (7.5%) at Week 12, 5 subjects (9.6%) at Week 24, and 5 subjects (9.4%) at Week 48 (Table 15.11.6.7.2.4).

There were no consistent changes over time in the median percentage change from baseline UACR (Table 15.11.6.7.2.2). The overall median (Q1, Q3) percentage change from baseline in UACR at Week 48 was 1.1% (−38.8%, 82.4%).

Laboratory Abnormalities

There were no clinically relevant changes from baseline in median values for hematology or clinical chemistry parameters during the study, and the median values were within the normal ranges (Table 15.11.6.1.1 to 15.11.6.2.16).

The majority of subjects (87.5%, 56 of 64 subjects) had at least 1 laboratory abnormality reported during the study (Table 15.11.6.5.1). Most of the reported abnormalities were Grade 1 or 2. Fourteen subjects had Grade 3 or 4 laboratory abnormalities; of these, 13 subjects (20.3%) had Grade 3 laboratory abnormalities. The most commonly reported Grade 3 laboratory abnormalities were elevated fasting low density lipoprotein (LDL) cholesterol, urine red blood cells (4 subjects, 6.6% each), and urine glucose (3 subjects, 4.7%) (Table 15.11.6.5.2). One subject (1.6%) had Grade 4 high fasting triglycerides (1477 mg/dL) at Week 48; the subject had high Grade 2 triglycerides (614 mg/dL) at baseline (Listing 16.2.8.1.3).

Liver-related Laboratory Evaluations

During the study, 1 subject (1.6%) had aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) (this subject had Grade 1 alanine aminotransferase (ALT) and Grade 2 AST elevation at Week 48; AST and ALT were within normal limits approximately 1 month later), 5 subjects (7.8%) had bilirubin > 1 × ULN, and 1 subject (1.6%) had bilirubin > 2 × ULN. No subject had AST or ALT > 3 × ULN in combination with bilirubin > 1.5 × ULN (Table 15.11.6.6, Listing 16.2.8.1.2.4).

Metabolic Laboratory Parameters

There were changes from baseline in fasting total cholesterol (median baseline 192 mg/dL; median increase of 14 mg/dL at Week 24 and 18 mg/dL at Week 48), fasting direct LDL (median baseline 123 mg/dL; median increase of 14 mg/dL at both Weeks 24 and 48), and fasting high density lipoprotein (HDL) (median baseline 44 mg/dL; median increase of 4 mg/dL at Week 24 and 5 mg/dL at Week 48). These changes were not considered to be clinically relevant. There were no notable changes in median fasting total cholesterol to HDL ratio, fasting triglycerides, or fasting glucose (Table 15.11.6.3.1 to Table 15.11.6.3.6).

A total of 17.2% (11 of 64 subjects) were taking lipid modifying medications at study entry (Table 15.11.6.3.7), and 3.1% (2 of 64 subjects) initiated lipid modifying medications during the study (Table 15.11.6.3.8). Similar results were observed for the metabolic assessments when subjects taking any lipid modifying medication were excluded (Table 15.11.6.3.9 to Table 15.11.6.3.13).

Other safety measurements

There were no clinically significant ECG abnormal findings (Table 15.11.8, Listing 16.2.8.5) during the study. There were no clinically significant vital signs (Listing 16.2.8.2.1), and no notable changes in median vital signs parameters (Table 15.11.7.1.1 to Table 15.11.7.1.5) or median body weight (Table 15.11.7.2).

There were no pregnancies reported during the study (Listing 16.2.8.6).

Patient Reported Outcomes:

Self-reported adherence was high throughout the study: mean adherence on the VAS was reported as ≥ 96% at all visits (Table 15.12.1.1), and at each visit the majority of subjects reported fewer than 2 days of missed doses in the previous 30 days (Table 15.12.1.2).

There were increases in the mean score for the following SF-36 parameters at Week 24 and Week 48, indicating a better quality of life (QoL) outcome: physical functioning (change at Week 24: 5.2; Week 48: 0.9), role physical (5.0; 1.5), general health (1.9; 0.3), vitality (2.9; 2.0), social functioning (1.9; 0.2), role emotional (6.0; 2.3), mental health (2.6; 2.9), and mental component summary (1.1; 1.2). There was a mean increase in the score at Week 24, but a decrease at Week 48 for bodily pain (change at Week 24: 4.8; Week 48: −0.8) and the physical component summary (1.4; −0.3) (Table 15.12.2).

Through Week 48, subjects reported improvements on the HIV treatment satisfaction questionnaire (HIVTSQ) change forms, compared with their HIVTSQ baseline status. The mean (SD) baseline score (total score of 10 items) on the HIVTSQ was 51.2 (11.21); the scores for the change forms at Weeks 24 and 48 were 23.2 (9.30) and 24.5 (7.42) (Table 15.12.3). The mean (SD) baseline score for the subscale total score of general satisfaction was 25.8 (5.89), and the scores for the change forms at Weeks 24 and 48 were 11.6 (4.77) and 12.2 (3.82) (Table 15.12.3). The mean (SD) baseline score for the subscale total score of lifestyle was 25.3 (5.54), and the scores for the change forms at Weeks 24 and 48 were 11.6 (4.76) and 12.3 (3.80) (Table 15.12.3).

There were variable changes from baseline in the mean score for the different FACIT-F parameters through Weeks 24 and 48, with small increases (indicating better QoL) in the scores

for physical well-being, emotional well-being, trial outcome index, Functional Assessment of Cancer Therapy – General (FACT-G) total score, and FACIT-F total score, while there were decreases (indicating reduced QoL) in the scores for social/family well-being, functional well-being, and additional concerns (Table 15.12.4).

The majority of subjects had a baseline score of 1 (on the scale of 1 to 3, a lower value indicates better QoL outcome) in the individual EQ-5D-3L questions (Tables 15.12.5.1.1 to 15.12.5.1.5). One subject with a baseline score of 2, gave a score 3 on the anxiety/depression question at Week 48 (Table 15.12.5.1.5). The mean (SD) baseline EQ-5D-3L index score was 0.852 (0.1843) (a maximum score of 1 indicates the best health state); there were increases of 0.031 at Week 24 and 0.016 at Week 48, indicating improved health status (Table 15.12.5.2).

In total, 29.4% (15 of 51 subjects) showed improvement in the EQ-5D-3L index score at Week 24, 60.8% (31 of 51 subjects) had no change, and 9.8% (5 of 51 subjects) showed worsening. At Week 48, 29.1% (16 of 55 subjects) showed improvement in the EQ-5D-3L index score, 50.9% (28 of 55 subjects) had no change, and 20.0% (11 of 55 subjects) showed worsening (Table 15.12.5.3).

The mean (SD) baseline EQ VAS score was 83 (20.5); there were increases of 6 at Week 24 and 5 at Week 48, indicating improved health status (Table 15.12.5.4).

CONCLUSIONS: The conclusions from this study are as follows:

In subjects harboring HIV with the NRTI resistance mutation M184V and/or M184I (alone or plus 1 or 2 TAMS) who switched to GEN from a stable regimen consisting of FTC/TDF or ABC/3TC plus a third antiretroviral agent:

- High rates of virologic suppression were maintained through Week 12 of treatment with GEN FDC, with 100% of subjects maintaining HIV-1 RNA < 50 copies/mL using PVR.
- The efficacy of GEN was durable, with 100% of subjects maintaining HIV-1 RNA < 50 copies/mL using PVR through Weeks 24 and 48.
- GEN was well tolerated as demonstrated by the low incidence of SAEs and AEs leading to discontinuation of study drug. None of the reported SAEs were study drug related. Adverse events reported were consistent with the safety profile of GEN.
- No cases of proximal renal tubulopathy (including Fanconi syndrome) were reported after subjects had switched to GEN and none of the renal and urinary disorder or associated investigation AEs that were evaluated as related to study drug by the investigator led to discontinuation of study drug.
- There were no notable changes from baseline in median serum creatinine, eGFR, or renal biomarkers (proteinuria by urinalysis, and proteinuria by quantitative assessments [UPCR, UACR]) through Week 48.
- Changes seen in fasting total cholesterol, direct LDL and HDL were not clinically significant.
- No subject experienced virologic failure, and therefore no subject had emergence of new resistance mutations.