**Supplemental Digital Content**

Supplemental digital content has been provided by the authors to give readers additional information about their work.

Supplement to: **Randomized study evaluating the efficacy and safety of switching from ABC/3TC to a single-tablet regimen of E/C/F/TAF**

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# **Supplemental Digital Content 1.** Full inclusion criteria.

***Inclusion criteria (all must be met for inclusion in study)***

1. The ability to understand and sign a written informed consent form, obtained prior to study procedure initiation.
2. Age ≥18 years.
3. Currently receiving abacavir/lamivudine (ABC/3TC) plus a third antiretroviral agent (Table S1) for ≥6 consecutive months prior to the screening visit. For subjects with three or more antiretroviral therapy (ART) regimens, a regimen history must be provided to the sponsor for approval.

Table S1. Allowable antiretroviral agents of pre-existing HIV regimen.

|  |  |
| --- | --- |
| **Antiretroviral class** | **Agents** |
| Boosted PI | ATV+COBI (or ATV/COBI FDC), DRV+COBI (or DRV/COBI FDC),DRV+RTV, LPV/r, ATV+RTV, FPV+RTV, SQV+RTV, ATV (no booster) |
| NNRTI | EFV, ETR, NVP, RPV |
| INSTI | DTG, RAL |

ATV, atazanavir; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; FDC, fixed-dose combination; FPV, fosamprenavir; INSTI, integrase strand transfer inhibitor; LPV, lopinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; SQV, saquinavir.

1. Documented plasma HIV-1 RNA levels <50 copies/mL for ≥6 months preceding the screening visit (measured at least twice using the same assay).
	1. In the preceding 6 months prior to screening, one episode of “blip” (HIV-1 RNA >50 and <400 copies/mL) is acceptable, only if HIV-1 RNA is <50 copies/mL immediately before and after the “blip”.
	2. To determine virologic suppression in the preceding 6 months prior to screening, the lower limit of quantification (LLOQ) by the local HIV-1 RNA assay may be used, only if its LLOQ is >50 copies/mL (e.g., LLOQ of 75 copies/mL).
2. Plasma HIV-1 RNA level <50 copies/mL at screening visit.
3. All documented historical plasma genotype(s) must not show resistance to tenofovir disoproxil fumarate (TDF) or emtricitabine (FTC), including but not limited to the presence of reverse transcriptase resistance mutants K65R, K70E, M184V/I, or thymidine analog-associated mutations (TAMs) (TAMs are M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R). If historical plasma genotype prior to first ART is not available or subject has three or more ART regimens, subject will have proviral genotype analysis prior to Day 1 to confirm absence of archived resistance to TDF or FTC.
4. Normal electrocardiogram (or if abnormal, determined by the investigator to be not clinically significant).
5. Adequate renal function:

Estimated glomerular filtration rate (GFR) ≥30 mL/min according to the Cockcroft–Gault formula (eGFRCG) for

creatinine clearance (CLcr) [1]:

Male: (140 – age in years) × (weight in kg) = CLcr (mL/min)

 72 × (serum creatinine in mg/dL)

Female: (140 – age in years) × (weight in kg) × 0.85 = CLcr (mL/min)

 72 × (serum creatinine in mg/dL)

1. Hepatic transaminases (aspartate aminotransferase and alanine aminotransferase) ≤5 × upper limit of normal (ULN).
2. Total bilirubin ≤1.5 mg/dL **and** normal direct bilirubin (subjects with documented Gilbert’s syndrome or with atazanavir-associated hyperbilirubinemia may have total bilirubin up to 5 × ULN as long as direct bilirubin is normal).
3. Adequate hematologic function:
	* Absolute neutrophil count ≥1000/mm³
	* Platelets ≥50,000/mm³
	* Hemoglobin ≥8.5 g/dL
4. A female subject is eligible to enter the study if it is confirmed that she is:
	1. Not pregnant, confirmed by a negative serum pregnancy test, which is required for female subjects (unless permanently sterile or >2 years postmenopausal).
	2. Not nursing. Lactating females must agree to discontinue nursing before the study drug is administered.
	3. Of non-childbearing potential (i.e., women who have had a hysterectomy, have had both ovaries removed or medically documented ovarian failure, or are postmenopausal women >54 years of age with cessation for ≥12 months of previously occurring menses).
	4. Of childbearing potential (following the initiation of puberty [Tanner stage 2] until postmenopausal, unless permanently sterile or with medically documented ovarian failure) and agrees to either:
		1. Utilize protocol-specified contraceptive methods (consistent, correct use of one of intrauterine device, tubal sterilization, essure micro-insert system, diaphragm with spermicide and a male condom without spermicide, cervical cap with spermicide and male condom without spermicide, or vasectomy in the sole male partner; or continue hormonal contraceptive method and use a single barrier method) or;
		2. Be non-heterosexually active or;
		3. Practice sexual abstinence from screening throughout the duration of study treatment and for 30 days following the last study drug dose.
5. Male subjects must agree to a specified, highly effective method of contraception (condoms without spermicide) during heterosexual intercourse or be non-heterosexually active, or practice sexual abstinence from first dose throughout the study period and for 30 days following the last study drug dose.

# **Supplemental Digital Content 2.** Full exclusion criteria.

***Exclusion criteria (none must be met for inclusion in study)***

1. Previous use of any approved or experimental integrase strand transfer inhibitor (INSTI) (for any length of time) if the current regimen contains a ritonavir-boosted protease inhibitor (PI/r).
2. Subjects with evidence of previous virologic failure on a PI/r or INSTI-based regimen (with or without resistance to either class of ART).
3. A new AIDS-defining condition diagnosed within the 30 days prior to screening (as defined by [2] except CD4+ cell count and/or percentage criteria).
4. Hepatitis C virus that would require therapy during study.
5. Positive hepatitis B surface antigen (HBsAg).
6. Subjects with clinical evidence of decompensated cirrhosis (ascites, encephalopathy, variceal bleeding).
7. Females who are breastfeeding.
8. Positive serum pregnancy test.
9. Have an implanted defibrillator or pacemaker.
10. Current alcohol or substance use judged by the investigator to potentially interfere with subject study compliance.
11. A history of malignancy within the past 5 years (prior to screening) or ongoing malignancy other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma. Subjects with cutaneous KS are eligible, but must not have received any systemic therapy for KS within 30 days of the Day 1 visit and must not be anticipated to require systemic therapy during the study.
12. Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to Day 1.
13. Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements.
14. Participation in any other clinical trial (including observational trials) without prior approval from the sponsor is prohibited while participating in this trial.
15. Known hypersensitivity to the study drug, the metabolites, or formulation excipients.
16. Subjects receiving ongoing therapy with any of the medications in Table S2, including drugs not to be used due to the potential for interaction with 3TC, cobicistat (COBI), elvitegravir (EVG), FTC, or TAF (for 3TC, COBI, EVG, or FTC refer to the individual agents’ Prescribing Information; for TAF refer to the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) fixed-dose combination (FDC) Investigator’s Brochure); or subjects with any known allergies to the excipients of E/C/F/TAF FDC tablets.

Table S2. Disallowed agents.

|  |  |
| --- | --- |
| **Drug class** | **Agents disalloweda** |
| Alpha adrenergic receptor antagonists | Alfuzosin |
| Calcium channel blockers | Bepridil |
| Anticonvulsants | Phenobarbital, phenytoin, carbamazepine, oxcarbazepine |
| Antihistamines | Astemizole, terfenadine |
| Antimycobacterials | Rifampin, rifapentine, rifabutin |
| Ergot derivatives | Ergotamine, ergonovine, dihydroergotamine, methylergonovine, ergometrine |
| GI motility agents | Cisapride |
| Herbal/natural supplements | St. John’s Wort, echinacea |
| HMG-CoA reductase inhibitors | Simvastatin, lovastatin |
| Inhaled beta agonist | Salmeterol |
| Neuroleptics | Pimozide |
| Phosphodiesterase-5 inhibitors | Sildenafil (for pulmonary arterial hypertension) |
| Sedatives/hypnotics | Orally administered midazolam, triazolam |

aAdministration of any of the above medications must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study.

GI, gastrointestinal; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

# **Supplemental Digital Content 3.** Assessments performed at each study visit.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Procedure** | **Screeninga** | **Day 1b** | **End of weekc** | **30-day follow-upe** | **ESDDf** |
| **4** | **8** | **12** | **24w** | **28d** | **32d** | **36** | **48** |
| Written informed consent | X |  |  |  |  |  |  |  |  |  |  |  |
| Medical history | X |  |  |  |  |  |  |  |  |  |  |  |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete physical examinationg | X | X |  |  |  | X |  |  |  | X |  | X |
| Symptom-directed physical examinationh |  |  | X | X | X |  | X | X | X |  | X |  |
| 12-lead ECG (performed supine) | X |  |  |  |  |  |  |  |  | X |  | X |
| Vital signs & weight | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X |  |  |  |  |  |  |  |  |  |  |  |
| Urinalysis & urine chemistry | X | X | X | X | X | X | X | X | X | X | Xu | X |
| Urine storage sample |  | X | X | X | X | X | X | X | X | X |  | X |
| Urine pregnancy testi |  | X | X | X | X | X | X | X | X | X | X | X |
| Serum pregnancy testi | X |  |  |  |  |  |  |  |  |  |  |  |
| Chemistry profilej | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology profilek | X | X | X | X | X | X | X | X | X | X | X | X |
| Plasma HIV-1 RNAl | X | X | X | X | X | X | X | X | X | X | X | X |
| CD4+ T-cell count | X | X | X | X | X | X | X | X | X | X | X | X |
| Whole blood samplem | X |  |  |  |  |  |  |  |  |  |  |  |
| HBV and HCV serologiesn | X |  |  |  |  |  |  |  |  |  |  |  |
| Metabolic assessmentso |  | X |  |  | X | X |  |  | Xd | X |  |  |
| Cystatin-C |  | X |  |  |  |  |  |  |  |  |  |  |
| Estimated GFRCGp | X | X | X | X | X | X | X | X | X | X |  | X |
| Plasma storage sampleq |  | X | X | X | X | X | X | X | X | X |  | X |
| Optional plasma and serum storage sampleq |  | X | X |  | X | X | X |  | Xd | X |  | X |
| HIV-1 genotype/phenotyper |  |  |  |  |  |  |  |  |  | X |  | X |
| Evaluations of bone & renal safety, inflammation, and platelet and coagulation functions |  | X | X |  | X | X | X |  | Xd | X |  |  |
| Questionnaires: VAS, HIVTSQs, HIVTSQc, EQ-5D, SF-36, and FACIT-Ft |  | X | X | X | X | X | X | X | X | X |  | X |
| Randomization |  | X |  |  |  |  |  |  |  |  |  |  |
| Study drug dispensation & accountabilityt |  | X | X | X | X | X | X | X | X | Xv |  | Xv |

aEvaluations to be completed within 42 days prior to the Day 1 visit.

bSubjects will be dispensed study drug on the Day 1 visit; initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit. E/C/F/TAF FDC will be provided to subjects randomized to Treatment Group 1.

cAll study visits are to be scheduled relative to the Day 1 visit date. Visit windows are ±2 days of the protocol-specified date through Week 12, ±6 days of the protocol-specified date through Week 36. The Week 48 visit window is ±6 weeks of the protocol-specified date. Unless notified by Gilead Sciences, Inc., the Week 48 visit should be completed within ±6 days of the visit date. For Treatment Group 2 subjects, the Weeks 28 and 32 visit windows are ±2 days of the protocol-specified date.

dTreatment Group 2 subjects only.

eOnly required for those subjects who permanently discontinue study drug or their current regimen and refuse to continue study visits through Week 48. For the purpose of scheduling a 30-day follow-up visit, a ±6-day window may be used.

fESDD visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through Week 48 visit even if the subject discontinues study drug.

gComplete physical examination (urogenital/anorectal exams will be performed at the discretion of the investigator).

hSymptom-directed physical examination as needed.

iFemales of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.

jChemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, and sodium. At visits in which metabolic assessments are to be performed, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.

kCBC with differential and platelet count.

lIf the HIV-1 RNA value is ≥50 copies/mL, a re-test should be collected at a scheduled or unscheduled visit, 2–4 weeks after the date of the original test (except for screening and Day 1 results). HIV-1 genotype/phenotype resistance testing only conducted for subjects with confirmed virologic failure with HIV-1 RNA value ≥50 copies/mL.

mWhole blood sample for proviral genotype analysis of archived resistance (if the historical plasma genotype report prior to first ARV is not available or subject has three or more ART regimens).

nHepatitis B virus surface antigen, hepatitis B core antibody, and HCV antibody serologies (reflex HCV RNA is performed in subjects with positive HCV antibody serology).

oMetabolic assessments: fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state.

pEstimated GFRCG for creatinine clearance.

qPlasma sample storage for safety and virology testing (Day 1, Weeks 4–48, and ESDD). Optional plasma and serum samples for exploratory assessments (for subjects who provide additional consent) (Day 1, Weeks 4, 12, 24, 48, and ESDD for all subjects and for Treatment Group 2 subjects only; also at Weeks 28 and 36 for Treatment Group 2 subjects only).

rHIV-1 genotype/phenotype resistance testing for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥50 copies/mL.

sBlood for bone safety, parathyroid hormone, and serum 25-hydroxyvitamin D will be collected; inflammation may include cystatin-C, interleukin-6, high-sensitivity C-reactive protein, soluble CD14, soluble CD163, soluble tumor necrosis factor receptor-1, and lipoprotein-associated phospholipase A2; platelet and coagulation function may include soluble glycoprotein VI, P-selectin, soluble CD40 ligand, and D-dimer. Urine for renal safety, including retinol binding protein, and beta-2-microglobulin, will be collected. Samples will be collected in the fasted state. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state.

tEQ-5D, SF-36, and FACIT-F will be administered at Day 1, Weeks 4, 24, 28 (Treatment Group 2 only), and Week 48. HIVTSQs will be administered on Day 1. HIVTSQc will be administered at Weeks 4, 12, 24, 28 (Treatment Group 2 only), 48 and ESDD. VAS will be administered at the following visits: Day 1 − Week 48 and ESDD.

uUrinalysis only.

vDrug accountability only; study drug will not be dispensed at this visit.

wAt Week 24, subjects randomized to Treatment Group 2 will discontinue their current regimen of ABC/3TC plus a third ARV agent and will switch to E/C/F/TAF FDC; initiation of treatment with the study drug must take place within 24 hours after the Week 24 visit. E/C/F/TAF FDC will be provided to subjects.

ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; ART, antiretroviral therapy; ARV, antiretroviral; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CD, cluster of differentiation; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; ECG, electrocardiogram; EQ-5D, European Quality of Life-five dimensions; ESDD, early study drug discontinuation; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FDC, fixed-dose combination; GFRCG, glomerular filtration rate by Cockcroft–Gault equation; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIVTSQ(c/s), HIV Treatment Satisfaction Questionnaire (change/status); LDL, low-density lipoprotein; SF-36, 36-Item Short-Form; VAS, visual analog scale.

# **Supplemental Digital Content 4.** Week 24 snapshot analysis.

|  |  |  |
| --- | --- | --- |
|  | E/C/F/TAF(n=183) | ABC/3TC + third agent(n=91) |
| **Virologic response** |
| HIV-1 RNA <50 copies/mL, n (%) | 170 (92.9) | 89 (97.8) |
| **Virologic response** |
| HIV-1 RNA ≥50 copies/mL, n (%) | 2 (1.1) | 0 |
| HIV-1 RNA ≥50 copies/mL in Week 24 window | 0 | 0 |
| Discontinued study drug due to lack of efficacy | 0 | 0 |
| Discontinued study drug due to AE/death and last available HIV-1 RNA ≥50 copies/mL | 0 | 0 |
| Discontinued study drug due to other reasonsa and last available HIV-1 RNA ≥50 copies/mL | 2 (1.1) | 0 |
| **No virologic data** |
| No virologic data in Week 24 window, n (%) | 11 (6.0) | 2 (2.2) |
| Discontinued study drug due to AE/death and last available HIV-1 RNA ≥50 copies/mL | 7 (3.8) | 0 |
| Discontinued study drug due to other reasonsa and last available HIV-1 RNA ≥50 copies/mL | 3 (1.6) | 1 (1.1) |
| Missing data during window but still on study drug | 1 (0.5) | 1 (1.1) |

aOne subject in the E/C/F/TAF group withdrew consent after a single dose of E/C/F/TAF and was considered a virologic failure due to detectable baseline HIV-1 RNA (prior to E/C/F/TAF; 133 copies/mL), despite having undetectable HIV-1 RNA (33 copies/mL) at screening. The other subject who discontinued in this group discontinued at the investigator’s discretion at Week 15 due to non-adherence (85% adherence up to Week 15 and 62% adherence from Week 4–8).

ABC/3TC, abacavir/lamivudine; AE, adverse event; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

# **Supplemental Digital Content 5.** Median changes from baseline in serum creatinine and estimated glomerular filtration rate (eGFR) by Cockcroft–Gault equation according to presence or absence of a creatinine secretion inhibitor (CSI) in the screening antiretroviral regimen.

|  |  |  |  |
| --- | --- | --- | --- |
| **Population** | **E/C/F/TAF** | **ABC/3TC + third agent** | **p value** |
| **N** | **Median (Q1, Q3)** | **N** | **Median (Q1, Q3)** |
| **Serum creatinine (mg/dL)** |
| All patients | 171 | 0.04 (–0.03, 0.13) | 89 | –0.02 (–0.09, 0.06) | <0.001 |
| Taking CSI at screening | 85 | 0.00 (–0.07, 0.06) | 47 | –0.04 (–0.11, 0.07) | 0.16 |
| No CSI at screening | 86 | 0.09 (0.02, 0.16) | 42 | –0.01 (–0.08, 0.06) | <0.001 |
| **eGFR (mL/min)** |
| All patients | 170 | –4.8 (–11.4, 4.6) | 89 | 1.8 (–7.8, 8.2) | 0.004 |
| Taking CSI at screening | 84 | 0.3 (–5.3, 9.0) | 47 | 2.4 (–6.6, 9.0) | 0.95 |
| No CSI at screening | 86 | –9.5 (–14.4, −3.0) | 42 | 0.9 (–8.4, 7.8) | <0.001 |

ABC/3TC, abacavir/lamivudine; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; Q, quartile.

# **Supplemental Digital Figure 1.** Disposition of participants.

**Assessed for eligibility, N=346**

Excluded, n=71

Failed eligibility criteria (57)

AE (1)
Withdrew consent (8)

Lost to follow-up (2)

Other reasons (3)

Randomized, N=275

Allocated to ABC/3TC + third agent, n=92

 Received ABC/3TC + third agent, n=91

Allocated to E/C/F/TAF, n=183

 Received E/C/F/TAF, n=183

Completed 24 weeks, n=87

Discontinued study drug, n=3

AE (1)

Subject decision (2)

Completed 24 weeks, n=168

Discontinued E/C/F/TAF, n=15

AE (8)
Subject decision (4)
Investigator’s decision (2)
Non-compliance (1)

ABC/3TC, abacavir/lamivudine; AE, adverse event; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

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