Poster

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

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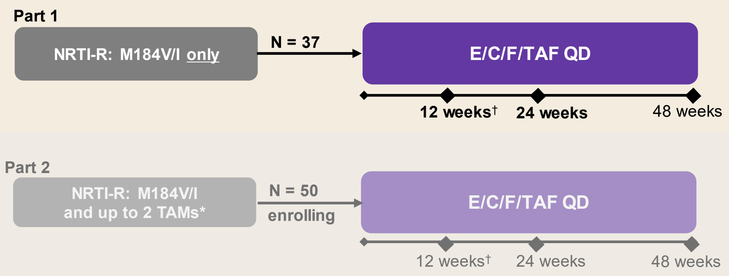
Background and Rationale

- A single-tablet antiretroviral regimen (STR) for switch has demonstrated
  - Improved adherence
  - Reduced pill burden
  - Eliminated risk of partial non-adherence
- M184V/I
  - Most common NRTI mutation in patients treated with 3TC and FTC1
  - Occurs in up to 64% of treated patients with prior virologic failure[2]
  - Confers resistance to FTC and 3TC and decreases susceptibility to ABC, but increases susceptibility to TFV[3]
  - M184 mutations may not preclude response to E/C/F/TDF or E/C/F/TAF
    - TAF, with 4-fold higher intracellular TFV-DP than TDF, may have additional activity against viruses with resistance mutations including M184V/I[4]

3TC, lamivudine; ABC, abacavir; C, cobicistat; E, elvitegravir; FTC or F, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; TFV-DP, tenofovir-diphosphate

Study Design

Ongoing, multicenter, international, open label, single arm study in HIV-1-infected adults with HIV-1 RNA < 50 copies/mL receiving FTC/TDF or ABC/3TC + third agent



*TAMs (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R)
†Primary Endpoint
HIV-1 RNA < 50 copies/mL at Week 12 using PVR (pure virologic response)

Study Objectives

- Primary Objective
  - To evaluate the efficacy of switching to E/C/F/TAF in maintaining HIV-1 RNA < 50 copies/mL at Week 12 in participants with M184V/I using pure virologic response (PVR)
- Secondary Objectives
  - To determine the safety and tolerability of E/C/F/TAF in participants switching from 2 NRTIs + third agent
  - To evaluate the emergence of new resistance mutations in participants who develop virologic failure after switching to E/C/F/TAF
  - To determine the durability at Weeks 24 and 48 in maintaining HIV-1 RNA < 50 copies/mL using PV

Pure Virologic Response Definition

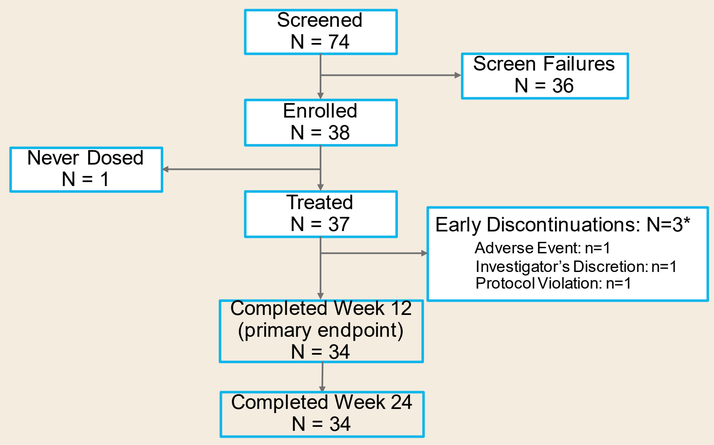
- Pure Virologic Response (PVR) at Week 12 and Week 24
  - Absence of confirmed virologic failure (HIV-1 RNA ≥ 50 copies/mL on 2 consecutive visits) before Week 12 or Week 24
  - Absence of premature discontinuation with last available HIV-1 RNA ≥ 50 copies/mL
  - E/C/F/TAF discontinuation prior to Week 12 or to Week 24 for reasons other than viral rebound (i.e. no data in window and last HIV RNA < 50 copies/mL) are considered to have PVR

Key Inclusion Criteria

- HIV-1 RNA < 50 copies/mL at screening and for at least 6 months
  - One blip (HIV-1 RNA > 50 copies/mL) was acceptable
- Currently receiving FTC/TDF or ABC/3TC + third agent for ≥ 6 months
  - Allowable third agents included NNRTIs, PIs, RAL or DTG
- M184V and/or M184I on historical genotype
  - No exclusionary PI, NRTI or INSTI mutations on historical genotype
  - No additional exclusionary mutations seen on proviral DNA genotype (done at screening on all participants)
- No prior virologic failure on PI or INSTI-based regimen
- Estimated GFR ≥ 30 mL/min (Cockcroft-Gault formula)

Results

Subject Disposition

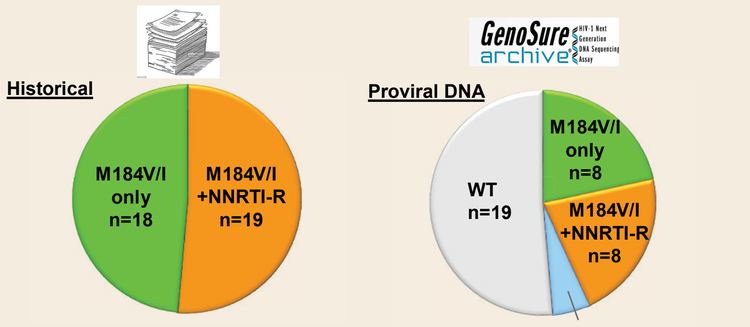


Baseline Characteristics

	E/C/F/TAF n=37
Median age, years (range)	51 (22-76)
Female	8 (22%)
Race/ethnicity	
White	27 (73%)
Black or African descent	7 (19%)
Hispanic/Latino ethnicity	6 (16%)
HIV-1 RNA <50 copies/mL, baseline	37 (100%)
Median CD4 count, cells/mm^3 (range)	724 (143-1503)
CD4 <200 cells/mm^3	1 (3%)
Median estimated GFR_{CG}, mL/min (range)	94 (36-215)
Screening Regimen: Third Agents*	
NNRTI	11%
INSTI	32%
PI	54%
Screening Regimen: FTC/TDF as NRTI backbone	54%

*2 participants included in analyses had non-allowable third agents in screening regimen (E/C/F/TDF and FTC/TDF+ETR+RAL)

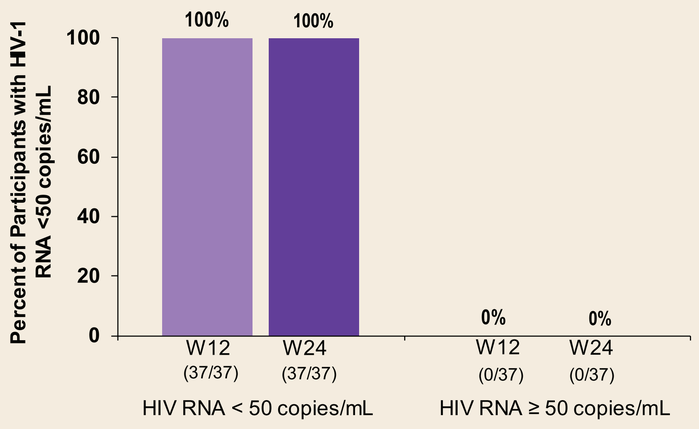
Baseline Resistance (n=37)



- Historical genotype: All participants had M184V/I
  - Approximately half of participants also have NNRTI-R HIV-1
- Proviral DNA: M184V/I detected in less than half of participants

Proviral DNA resistance testing failed to detect known M184V/I and NNRTI-R seen on historical genotype

Pure Virologic Response (HIV RNA < 50 copies/mL) at Week 12 and Week 24



- Two participants each experienced a single viral blip (69 and 93 copies/mL)

Week 12 (Primary) and Week 24 PVR Analyses:

- No virological failures or emergence of new resistance

Adverse Events (AEs)

Adverse Event with E/C/F/TAF (n=37)	All AE n (%)	Drug-related AE n (%)
Any AE	29 (78)	8 (22)*
Any Grade 2, 3 or 4 AE	15 (40)	5 (14)
Any Grade 3 or 4 AE	5 (14)	0 (0)
AEs Leading to Premature Study Drug Discontinuation	1 (3)†	1 (3)†

*Diarrhea (1), asthenia (2), fatigue (2), headache (2), skin burning sensation (1), hypertension (1), muscle spasms (1); participants may report more than 1 AE
†Muscle spasms (G2). 67 year old white male switched from FTC/TDF+ATV+RTV. Muscle cramps, calf, on Day 13. E/C/F/TAF discontinued Day 43, AE resolved Day 52. Electrolytes and other labs normal

Any Serious Adverse Events (SAEs)

	E/C/F/TAF n=37 n (%)	Related to Study Drug
SAE	4 (11%)	0
Tonsillar carcinoma	1	No
Pleural adenocarcinoma	1	No
Proteinuria*	1	No
Acute kidney injury/renal failure†	1	No

*47 white male with DM2, dyslipidemia, 2+ proteinuria at baseline: developed 3+ proteinuria at Week 36. Hospitalized for 2 days. Day 1 serum creatinine was 1.1; At W48, serum creatinine was 0.98. Completed 48 weeks E/C/F/TAF without interruption
† 76 black male with DM2, dyslipidemia, poorly controlled HTN, renal insufficiency: hospitalized Day 57 with hypotension, cough, diarrhea, renal failure requiring dialysis. E/C/F/TAF discontinued as no data on dosing in dialysis. Investigator considered event not related to E/C/F/TAF. As last on-study HIV RNA < 50 copies/ mL, subject was a PVR

Conclusions

- In this open-label study of participants with HIV RNA < 50 copies/mL harboring the M184V and/or M184I mutation, switching to E/C/F/TAF:
  - Maintained virologic suppression (100%) using the Week 12 and Week 24 PVR analyses
  - Was well tolerated with no SAE or Grade 3/4 adverse events that were study-drug related, and one discontinuation due to adverse events
- Compared to historical genotype, proviral DNA resistance testing only detected M184V/I and NNRTI-R in approximately half of participants
- Switching to E/C/F/TAF may be considered for patients with pre-existing M184V and/or M184I mutations
- Part 2 of the study with M184V/I and up to 2 TAMs is currently enrolling

References

1. Miller MD, Antiviral Ther 2012; 17: 993-999.
2. Marconi CID 2008;46:1589.
3. Turner D. Clin Diagn Lab Immunol. 2003;10: 979–981.
4. Margot. Antiviral Res. 2016; 132:50

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