Poster# PE13/20

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

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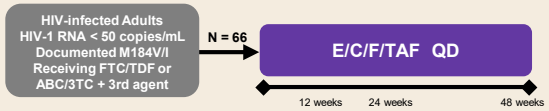
Background and Rationale

- Switches to single-tablet regimens (STR) have demonstrated:
  - Improved adherence
  - Reduced pill burden
  - No risk of partial non-adherence
- M184V/I
  - Most common NRTI mutation in patients failing treatment with 3TC or FTC[1]
  - Occurs in up to 64% of treated patients with prior virologic failure[2]
  - Confers resistance to emtricitabine (FTC), lamivudine (3TC) and ABC, but results in increased susceptibility to tenofovir (TFV)[3]
  - M184V/I mutations may not preclude response to E/C/F/TDF or E/C/F/TAF
  - TAF, with at least 4-fold higher intracellular TFV-DP than TDF, has greater activity against virus with resistance mutations including M184V/I[4]

Methods

Study Design

Ongoing, multicenter, international, open label, single arm study



Part 1: participants with M184V/I only: enrollment closed at 37 participants
Part 2: participants with M184V/I + up to 2 TAMs (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R): enrollment closed.

Primary endpoint:
- HIV HIV-1 RNA < 50 copies/mL at Week 12 using pure virologic response (PVR)

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 NRTI plus third antiretroviral agent regimens
  - 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 of suppression at Weeks 24 and 48 using PVR

Pure Virologic Response Definition

- PVR at Week 12 and Week 24
  - Absence of confirmed virologic failure (HIV-1 RNA ≥ 50 copies/mL on 2 consecutive visits) before Week 24
  - Absence of premature discontinuation with last available HIV-1 RNA ≥ 50 copies/mL
  - E/C/F/TAF discontinuation prior 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 + 3rd 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
  - Lack of exclusionary mutations confirmed by 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

Baseline Characteristics

	Part 1 n=37	Part 2 n=27	Overall n=64
Median age, years (range)	51 (22-76)	55 (33-73)	52 (22-76)
Female	8 (22%)	9 (33%)	17 (27%)
Race/ethnicity			
White	27 (73%)	17 (63%)	44 (67%)
Black or African descent	7 (19%)	8 (30%)	15 (23%)
Hispanic/Latino ethnicity	6 (16%)	4 (15%)	10 (16%)
HIV-1 RNA <50 copies/mL, baseline	37 (100%)	27 (100%)	64 (100%)
Median CD4 count, cells/mm^3 (range)	724 (143-1503)	605 (107-1457)	655 (107-1503)
CD4 <200 cells/mm^3	1 (3%)	2 (7%)	3 (5%)
Median estimated GFR_{CG}, mL/min (range)	94 (36-215)	96 (50-216)	95 (36-216)

Baseline Characteristics

	Part 1 n=37	Part 2 n=27
Screening Regimen*		
NNRTI	11%	11%
INSTI	32%	37%
PI	54%	52%
NRTI backbone was FTC/TDF	54%	48%
Baseline Resistance		
M184V/I only	37	16
M184V/I + 1 TAM	0	8
M41L	0	1
K70R	0	2
T215Y/F	0	4
K219E	0	1
M184V/I + 2 TAMs	0	3
M41L + T215Y/F	0	3

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

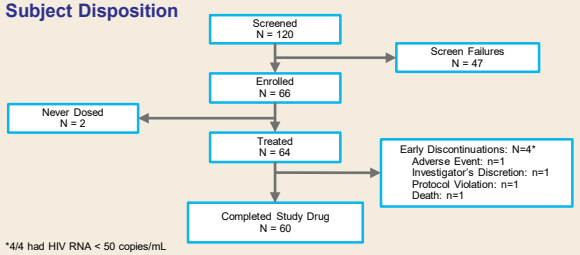
Historical HIV RNA vs. Archival HIV DNA Genotype Reports

- Paired historical & archival data available for all 64 enrolled patients

Genotype	"Historical" (HIV RNA; N=64)		"Archival" or proviral DNA (HIV DNA; N=64)	
M184V	53 (83%)	100%	24 (38%)	44%
M184I	6 (9%)		0 (0%)	
M184V/I	5 (8%)		4 (6%)	
WT	N/A		36 (56%)	

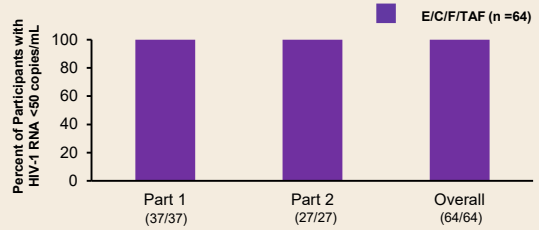
- HIV DNA: M184V/I mutation detected in only 44% of patients

Subject Disposition



*4/4 had HIV RNA < 50 copies/mL

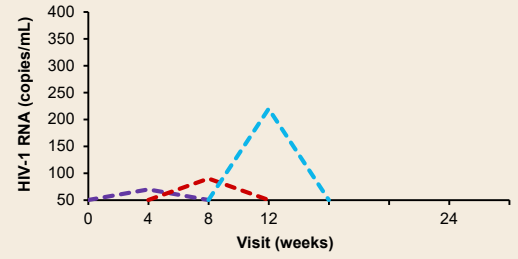
Pure Virologic Response (HIV RNA < 50 copies/mL) at Week 24



Week 12 Primary Analysis:
- No virological failures or emergence of new resistance

Week 24 PVR Analysis:
- No virological failures or emergence of new resistance

Viral Suppression: viral blips > 50 c/mL



- Three subjects experienced a viral blip > 50 but < 400 c/mL
- All viral blips were isolated events.

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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V Abril López de Medrano, M Andreoni, JR Arribas Lopez, L Bernard, M Bickel, M Castaño Carracedo, D Coulston, E DeJesus, A Di Biagio, G Di Perri, C Duvivier, S Esser, J Gallant, M Galli, D Hagins, E Lazaro, A Lazzarin, JM Llibre, J Mallolas, A Mills, C Miralles Alvarez, JM Molina, O Osiyemi, I Pozzi-Martin, T Prazuck, D Prelutsky, P Pugliese, F Pulido, F Raffi, M Ramgopal, G Richmond, D Salmon-Ceron, J Schattenberg, P Sellier, P Shalit, HJ Stellbrink

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Adverse Events (AEs)

AE with E/C/F/TAF (n=64)	All AE n (%)	Drug-related AE n (%)
Any AE	51 (80)	10 (16)*
Any Grade 2, 3 or 4 AE	28 (44)	6 (9)
Any Grade 3 or 4 AE	6 (9)	0 (0)
AEs Leading to Premature Study Drug Discontinuation†	1 (2)	1 (2)

*Diarrhea (1), asthenia (2), fatigue (2), headache (2), skin burning sensation (1), hypertension (1), muscle spasms (1)
† 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.

Serious Adverse Events (SAEs)

	E/C/F/TAF n=64	Related to Study Drug?
SAE†	5 (8%)	None
Tonsillar carcinoma	1	No
Pleural adenocarcinoma	1	No
Proteinuria*	1	No
Acute kidney injury/renal failure†	1	No
Death	1	No

* 47 white male with DM2, dyslipidemia, 2+ proteinuria at baseline: developed 3+ proteinuria at Week 36. Hospitalized for 2 days. †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
‡ Suicide

Grade 3-4 Laboratory Abnormalities

Lab Test	E/C/F/TAF n=64 n
Any Grade 3-4 Laboratory Abnormality	14 (22%)
LDL, fasting	4
Hematuria	4
Glycosuria	3
Hyperglycemia, nonfasting	2
Neutropenia	2
Triglycerides, fasting	1
Hyperglycemia, fasting	1
Creatinine	1
Hyponatremia	1
Hyperbilirubinemia	1
Hypercholesterolemia, fasting	1

- Only 1 Grade 4 laboratory abnormality (fasting triglycerides)

Conclusions

- In this open-label study of participants with HIV RNA < 50 copies/mL harboring the M184V and/or M184I mutation +/- 1-2 TAMs, switching to E/C/F/TAF:
  - Maintained virologic suppression (100%) using the Week 24 PVR analysis
  - Was well tolerated with no study drug related SAE or Grade 3/4 AE and one discontinuation due to adverse events
- Compared to historical genotype, proviral DNA (archive) genotype testing detected M184V/I in less than half of participants
- Switching to E/C/F/TAF may be an effective option for PLWH with pre-existing M184V and/or M184I mutations.

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