Bictegravir/Emtricitabine/Tenofovir Alafenamide Efficacy in Participants With Preexisting Primary Integrase Inhibitor Resistance Through 48 Weeks of Phase 3 Clinical Trials

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Introduction

- Preexisting drug resistance can affect the efficacy of antiretroviral therapy (ART)
- Although transmitted integrase (IN) strand transfer inhibitor (INSTI)–resistance (INSTI-R) rates are low in comparison to nucleoside/tide reverse transcriptase (RT) inhibitor (NRTI)–R and non-NRTI (NNRTI)–R,[1,2] studying INSTI-R remains important and relevant as INSTIs are the backbone for initial regimens in treatment guidelines for most people with HIV
- Studies in both treatment-naïve and virologically suppressed participants have demonstrated the safety and efficacy of bictegravir (BIC)/emtricitabine/tenofovir alafenamide (B/F/TAF), a potent, once-daily, INSTI-containing, single-tablet regimen for treatment of HIV-1 infection[3,4]
  - This efficacy also extends to virologically suppressed participants with certain NRTI mutations, including M184V/I and thymidine analog mutations[5]

Objective

- To investigate virologic outcomes after 48 weeks of B/F/TAF treatment in a pooled analysis of individuals with preexisting INSTI-R

Methods

Overview of B/F/TAF Studies in Pooled Analysis

Study*	Study Design	Participant Status	Age, y	B/F/TAF Participants, n
1489	Phase 3, randomized, active controlled, double blind	ART naïve	≥18	314
1490	Phase 3, randomized, active controlled, double blind	ART naïve	≥18	320
1844	Phase 3, randomized, double blind	Virologically suppressed	≥18	282
1878	Phase 3, randomized, open label	Virologically suppressed	≥18	290
4580	Phase 3b, open label	Virologically suppressed	≥18	330
4449	Phase 3, single arm, open label	Virologically suppressed	≥65	86

*GS-US-380-1489: NCT02607930; GS-US-380-1490: NCT02607956; GS-US-380-1844: NCT02603120; GS-US-380-1878: NCT02603107; GS-US-380-4580: NCT03631732; GS-US-380-4030: NCT03110380; and GS-US-380-4449: NCT03405935.

- Although known INSTI-R was exclusionary per study entry criteria if known before randomization, preexisting INSTI-R identified after enrollment was not excluded

Baseline Genotypic Analysis

- Historical HIV-1 genotype reports were collected, if available, at or after enrollment
- HIV-1 IN, protease (PR), and RT genotyping and phenotyping were conducted prospectively at screening or retrospectively on baseline samples
  - Naïve studies: screening plasma RNA genotyping for RT/PR was done for all participants, followed by retrospective genotyping and phenotyping of IN and RT/PR performed by next-generation sequencing using DeepType HIV assay (Seq-IT GmbH & Co. KG, Kaiserslautern, Germany) with a mutation frequency cutoff ≥15% and/or by population sequencing using the PhenoSense® GT, Genosure® MG, and PhenoSense® Integrase assays (Monogram Biosciences, South San Francisco, CA)
  - Virologically suppressed studies: retrospective baseline proviral DNA genotyping was performed using GenoSure Archive® (Monogram Biosciences)
    - Bioinformatic filters removed APOBEC-mediated, hypermutated deep-sequence reads from GenoSure Archive results to prevent overreporting of E138K, M184I, and M230I in RT and G163R in IN

HIV-1 Drug-Resistance Substitutions (based on IAS-USA)[6]

Primary INSTI-R	T66I/A/K, E92Q/G, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K
Secondary INSTI-R	M50I, H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, T97A, G118R, S119P/R/T, F121C, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151A/L, S153A/F/Y, E157K/Q, G163K/R, E170A
Primary NRTI-R	K65R/E/N, T69 insertions, K70E, L74V/I, Y115F, Q151M, M184V/I, TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219E/N/Q/R)
Primary NNRTI-R	L100I, K101E/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230I/L
Primary PI-R	D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M

PI, PR inhibitor.

B/F/TAF Efficacy Analysis

- Virologic outcomes were defined by the last on-treatment observation carried forward (LOCF) method: HIV-1 RNA <50 copies/mL (success) or ≥50 copies/mL (failure)

Results

Clinical and Demographic Characteristics of Participants With Preexisting INSTI-R

Participant ID	Study/Status	Country	Age, y	Gender	Race	HIV Subtype	CD4 Count at Baseline
1	1489/naïve	USA	58	M	Black	B	722
2	1878/VS	USA	44	M	White	B	187
3	4580/VS	USA	71	M	Black	B	464
4	4580/VS	USA	37	M	Black	B	701
5	4580/VS	USA	52	M	Other	B	74
6	4580/VS	USA	48	M	Black	B	777
7	1844/VS	USA	59	M	White	B	941
8	4580/VS	USA	63	F	Black	B	895
9	4030/VS	USA	51	M	White	B	507
10	4030/VS	CAN	35	M	White	B	722
11	1878/VS	USA	20	M	Black	B	552
12	4030/VS	FRA	59	M	White	B	641
13	1844/VS	CAN	41	F	Black	AG	124
14	4580/VS	USA	60	F	Black	B	1394
15	4030/VS	USA	64	M	Black	B	547
16	4580/VS	USA	44	M	Black	B	465
17	4580/VS	USA	57	F	Black	B	921
18	4030/VS	USA	31	M	White	B	820
19	4030/VS	USA	48	M	Black	C	188
20	4030/VS	CAN	53	F	Black	C	588

CAN, Canada; FRA, France; VS, virologically suppressed.

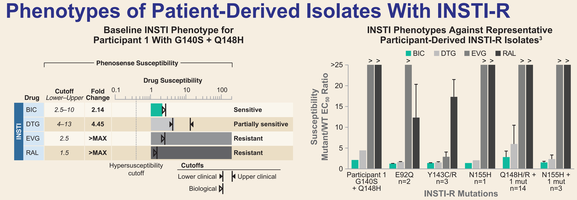
- Preexisting primary INSTI-R substitutions were detected in 20/1906 participants (1%) after enrollment
- Of the 20 participants, 75% were male and 65% Black, and 85% had HIV-1 subtype B, baseline median CD4 counts of 641 (interquartile range [IQR] 527, 771), and median age of 52 y (IQR 43, 59)

Resistance Profile of Participants With Preexisting INSTI-R

Participant ID	Primary INSTI-R	Secondary INSTI-R	NRTI-R	NNRTI-R	PI-R	Viral Load, Copies/mL	
						Baseline	Week 48 LOCF
1	Q148H	M50I, G140S	K70R	K103N	None	30,000	<20
2	E92G	S119T	None	K103N	None	No HIV-1 RNA	No HIV-1 RNA
3	E92G	None	K70R, M184V	None	None	No HIV-1 RNA	<20
4	E92G	None	None	E138A	None	No HIV-1 RNA	No HIV-1 RNA
5	Y143C	None	None	H221Y	None	No HIV-1 RNA	<20
6	Y143C	M50I	None	None	None	No HIV-1 RNA	No HIV-1 RNA
7	Y143H	S119R	None	None	None	No HIV-1 RNA	No HIV-1 RNA
8	Y143H	None	None	None	None	No HIV-1 RNA	No HIV-1 RNA
9	Y143H	None	D67N, K70E/G/R, L74V, M184V, K219Q	L100I, K103N	M46I, N88S	No HIV-1 RNA	No HIV-1 RNA
10	Y143H	None	None	K103N	None	<20	No HIV-1 RNA
11	S147G	None	None	None	V82A	<20	<20
12	S147G	None	None	None	M46I	No HIV-1 RNA	No HIV-1 RNA
13	Q148H	None	None	None	None	<20	No HIV-1 RNA
14	Q148H	S119P	None	None	None	<20	No HIV-1 RNA
15	Q148H	G140S	M184V	K101P/Q/T, Y181C, H221Y	None	<20	<20
16	Q148K	L74I/M, M50I, S119P	None	None	D30D/N	<20	No HIV-1 RNA
17	Q148R	S119T	None	K103N, G190E	Q58E	No HIV-1 RNA	No HIV-1 RNA
18	N155S	S119R	None	None	None	No HIV-1 RNA	No HIV-1 RNA
19	R263K	M50I, L68V	None	None	None	No HIV-1 RNA	No HIV-1 RNA
20	R263K	None	None	None	None	No HIV-1 RNA	No HIV-1 RNA

- Primary INSTI-R mutations were E92G (n=3; 15%), Y143C/H (n=6; 30%), S147G (n=2; 10%), Q148H/K/R (n=6; 30%), N155S (n=1; 5%), and R263K (n=2; 10%)
- NRTI-R, NNRTI-R, and PI-R were detected in 4 (20%), 8 (40%), and 5 (25%) participants, respectively

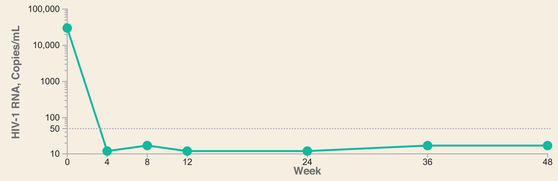
Phenotypes of Patient-Derived Isolates With INSTI-R



DTG, dolutegravir; EC_{50}, half-maximal effective concentration; EVG, elvitegravir; MAX, EC_{50} was higher than maximal drug concentration tested; RAL, raltegravir; WT, wild-type.

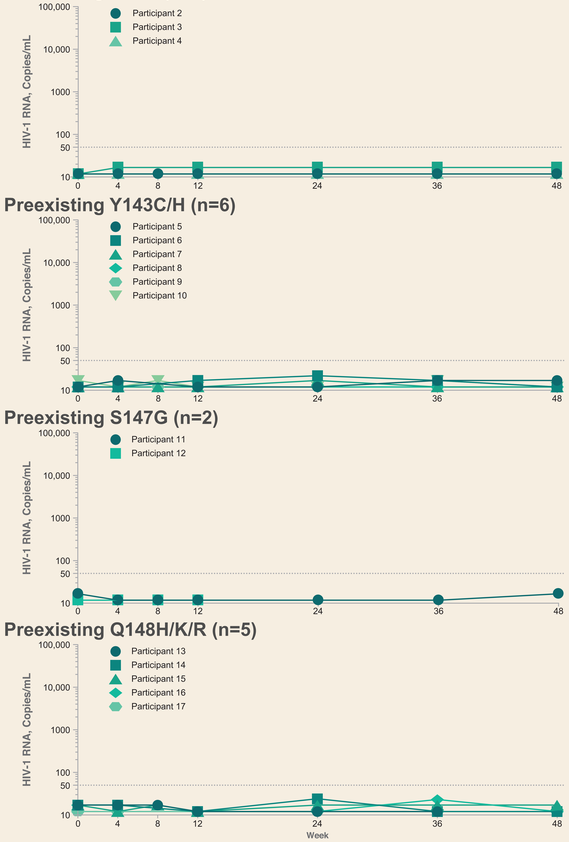
- For the treatment-naïve participant with G140S + Q148H by plasma RNA genotype, baseline viral load was 30,000 copies/mL and the isolate was phenotypically susceptible to BIC (<2.5-fold change)
  - The isolate showed partial susceptibility to DTG

Viral Loads Throughout Study Visits of Treatment-Naïve Participant With Preexisting Q148H + G140S

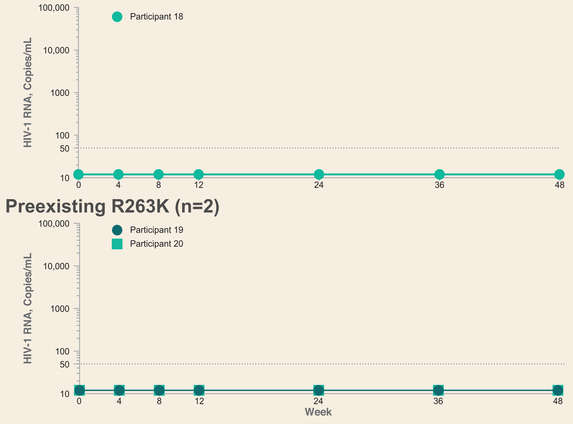


- Treatment-naïve participant (n=1) was suppressed by Week 4 and maintained viral loads <50 copies/mL through Week 48

Viral Loads of Virally Suppressed Participants

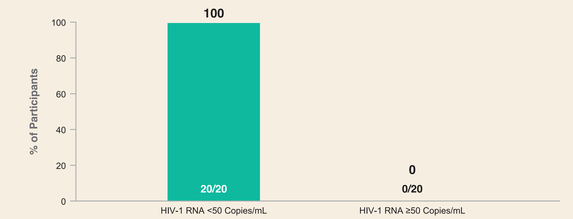


Viral Loads of Virally Suppressed Participants



- Virologically suppressed participants (n=19) maintained HIV-1 RNA <50 copies/mL at all study visits through Week 48 with no blips

Virologic Outcome of Participants With Preexisting INSTI-R



- All study participants achieved virologic success by Week 48 LOCF

Conclusions

- Preexisting primary INSTI-R was detected in 20/1906 B/F/TAF study participants
- Participants with primary INSTI-R substitutions maintained virologic suppression through 48 weeks of B/F/TAF treatment
  - Included 1 treatment-naïve participant with G140S + Q148H who rapidly suppressed after initiating B/F/TAF; the isolate was phenotypically susceptible to BIC, but only partially susceptible to DTG
- Consistent with the potent in vitro activity of BIC against many isolates with INSTI-R mutations, these virologic outcomes in predominantly virologically suppressed individuals support further study of B/F/TAF in participants with preexisting INSTI-R

References: **1.** Margot NA, et al. J Med Virol 2019;91:2188-94; **2.** McClung RP, et al. CROI 2019. abstr 526; **3.** Smith RA, et al. Antimicrob Agents Chemother 2019;63:e00014-19; **4.** Tsiang M, et al. Antimicrob Agents Chemother 2016;60:7086-97; **5.** Andreatta K, et al. J Antimicrob Chemother 2019;74:3555-64; **6.** Wensing AM, et al. Top Antivir Med 2017;24:132-41.

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