A Phase 3 Randomized Controlled Clinical Trial of Bictegravir in a Fixed Dose Combination, B/F/TAF, vs DTG/ABC/3TC in Treatment-Naïve Adults at Week 48

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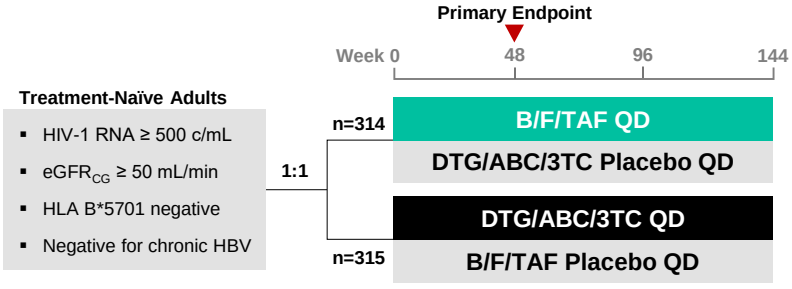
Background

- Integrase strand transfer inhibitors (INSTIs) are recommended by multiple international guidelines as components of first-line antiretroviral therapy in combination with 2 nucleoside reverse transcriptase inhibitors
- Bictegravir (B) is a novel, potent INSTI with a high in vitro barrier to resistance and low potential for drug-drug interactions
- Bictegravir + emtricitabine and tenofovir alafenamide (F/TAF) was studied in a Phase 2 trial vs dolutegravir (DTG) + F/TAF and was safe and effective
  - No participant developed resistance to study medications
- Bictegravir was coformulated into a single tablet regimen with emtricitabine and tenofovir alafenamide (B/F/TAF), for once daily dosing without regard to food

GS-US-380-1489 Study Design*



- Phase 3, randomized, double-blind, active-controlled study
  - Stratified by HIV-1 RNA, CD4 cell count, geographic region
  - North America and Europe
- Primary endpoint: proportion with HIV-1 RNA <50 copies/mL at Week 48
  - Noninferiority margin of 12% based on FDA snapshot algorithm

*ClinicalTrials.gov NCT02607930; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation.

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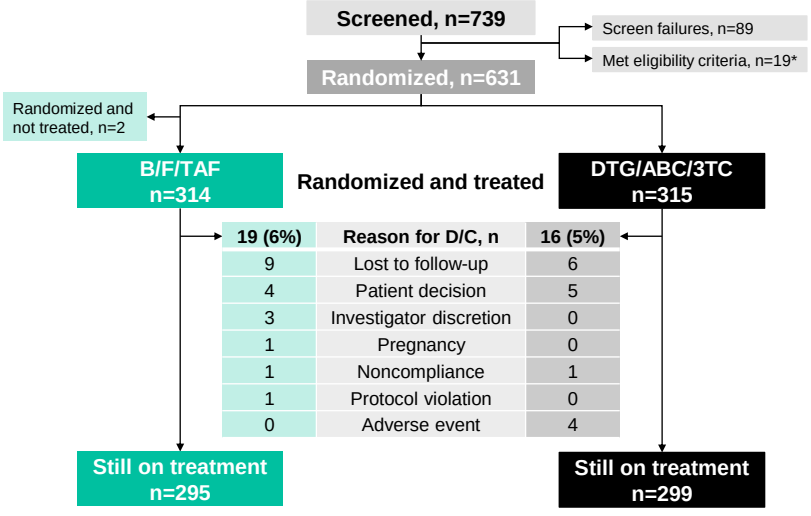
Participant Disposition



*Lost to follow-up (n=8), Withdrew consent (n=6), Investigator's discretion (n=2), Adverse event (n=1), Outside of visit window (n=1), Other (n=1).

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Baseline Characteristics

	B/F/TAF n=314	DTG/ABC/3TC n=315
Age, median years (range)	31 (18–71)	32 (18–68)
Male, %	91	90
Race/ethnicity, %		
Black or African descent	36	36
Hispanic/Latino ethnicity	23	21
HIV-1 RNA, median $\log_{10}$ c/mL (IQR)	4.42 (4.03, 4.87)	4.51 (4.04, 4.87)
HIV-1 RNA >100,000 c/mL, %	17	16
CD4 cell count, median cells/µL (IQR)	443 (299, 590)	450 (324, 608)
CD4 count <200 cells/µL, %	11	10
Asymptomatic HIV infection, %	91	91
$eGFR_{CG}$, median mL/min (IQR)	126 (108, 146)	123 (107, 144)

c/mL, copies/mL; IQR, interquartile range.

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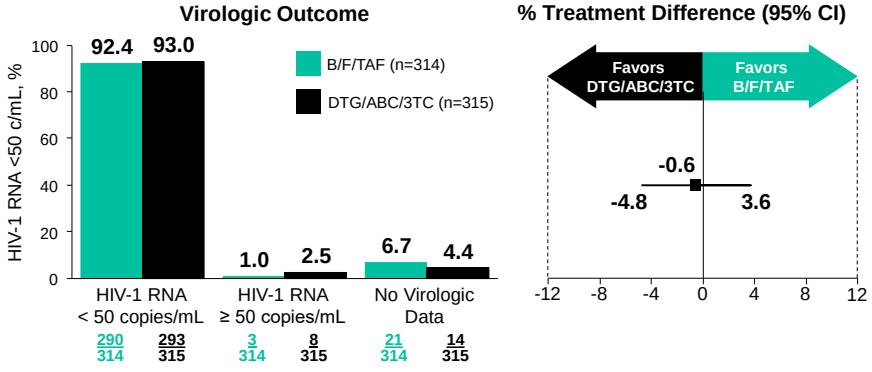
Virologic Outcome at Week 48

HIV-1 RNA < 50 copies/mL



- Non-inferiority confirmed by pre-specified analyses for HIV-1 RNA < 50 copies/mL:
  - Per protocol: B/F/TAF 99.3% vs DTG/ABC/3TC 98.6% (p=0.43)
  - Missing=Failure: B/F/TAF 92.4% vs DTG/ABC/3TC 93.3% (p=0.65)
  - Missing=Excluded: B/F/TAF 99.3% vs DTG/ABC/3TC 97.7% (p=0.10)
- Mean CD4 increase from baseline at Week 48:
  - B/F/TAF +233 cells/µL vs DTG/ABC/3TC +229 cells/µL (p=0.81)

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Virologic Resistance Results

	B/F/TAF n=314	DTG/ABC/3TC n=315
Met criteria for resistance testing	1	4
Assay failure	0	1
NRTI resistance detected	0	0
INSTI resistance detected	0	0

No resistance to any components of the treatment regimens occurred in either treatment group

Resistance testing performed for patients with a confirmed HIV-1 RNA ≥ 200 copies/mL or ≥ 200 copies/mL at last visit.
NRTI, nucleoside reverse-transcriptase inhibitor.

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Adverse Events Leading to Study Drug Discontinuation

B/F/TAF n=314	DTG/ABC/3TC n=315
0	4 (1.3%)
	Nausea, rash [Day 4]
	Thrombocytopenia [Day 50]
	Chronic pancreatitis/steatorrhea [Day 134]
	Depression [Day 248]

No deaths were reported in either treatment arm

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All Grade Adverse Events (≥5%) Through Week 48

All Grade, %	B/F/TAF n=314	DTG/ABC/3TC n=315
Diarrhea	12.7	13.0
Headache	11.5	13.7
Nausea*	10.2	22.9
Nasopharyngitis	7.3	9.2
Cough	6.4	2.5
Upper respiratory tract infection	6.4	10.8
Fatigue	6.1	8.6
Syphilis	3.8	7.9
Insomnia	4.5	6.3
Arthralgia	3.5	6.0
Vomiting	3.8	5.4
Bronchitis	3.2	5.1
Abdominal pain	2.9	5.1

*p<0.001 for difference in nausea between treatment groups, Fisher exact test.

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Patient Reported Outcomes

HIV Symptom Distress Module

Nausea/Vomiting			Loss of appetite			Diarrhea			Bloating		
W4	**W12**	W48	W4	**W12**	**W48**	W4	**W12**	W48	W4	W12	W48
Nervous/Anxious			Sad/Down/Depressed			Fatigue			Dizzy/Lightheaded		
W4	**W12**	**W48**	**W4**	**W12**	**W48**	**W4**	W12	**W48**	**W4**	W12	**W48**
Trouble remembering			Headache			Fevers/Chills			Difficulty sleeping		
W4	W12	**W48**	W4	W12	**W48**	W4	**W12**	**W48**	W4	W12	W48
Pain in hands/feet			Skin problems			Cough			Muscle aches		
W4	W12	W48	W4	W12	W48	W4	W12	W48	W4	W12	W48
Sex problems			Weight gain			Weight loss			Hair loss		
W4	W12	W48	W4	W12	W48	W4	W12	W48	W4	W12	W48

Significantly different favoring B/F/TAF

No differences between arms

Significantly different favoring DTG/ABC/3TC (none)

Pittsburgh Sleep Quality Index:

- Higher “use of sleeping medication” at Week 4 in DTG/ABC/3TC arm
- More “sleep disturbance” at Week 48 in DTG/ABC/3TC

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Laboratory Abnormalities (≥2%) Through Week 48

Grade 3 or 4, %	B/F/TAF n=314	DTG/ABC/3TC n=315
CK elevation	3.5	3.2
LDL elevation	2.3	2.6
Amylase	1.9	2.2
Neutropenia	1.6	3.2

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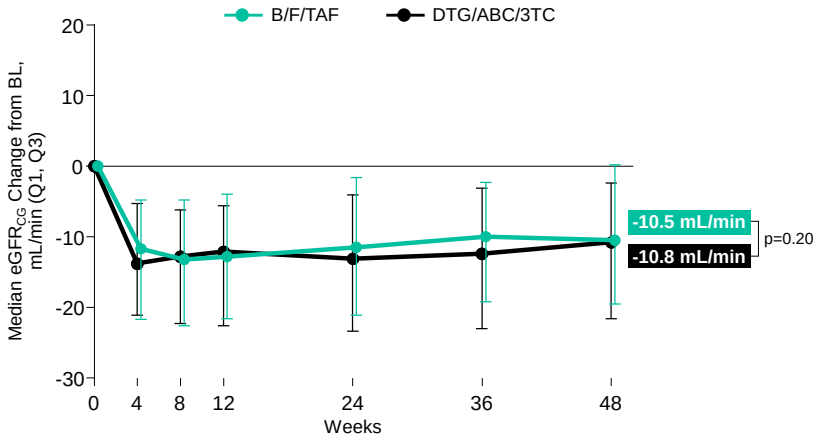
Change from Baseline in Estimated GFR_{CG}



No discontinuations due to renal adverse events and no proximal tubulopathy in either arm

P-value from 2-sided Wilcoxon rank sum test. BL, baseline; Q, quartile.

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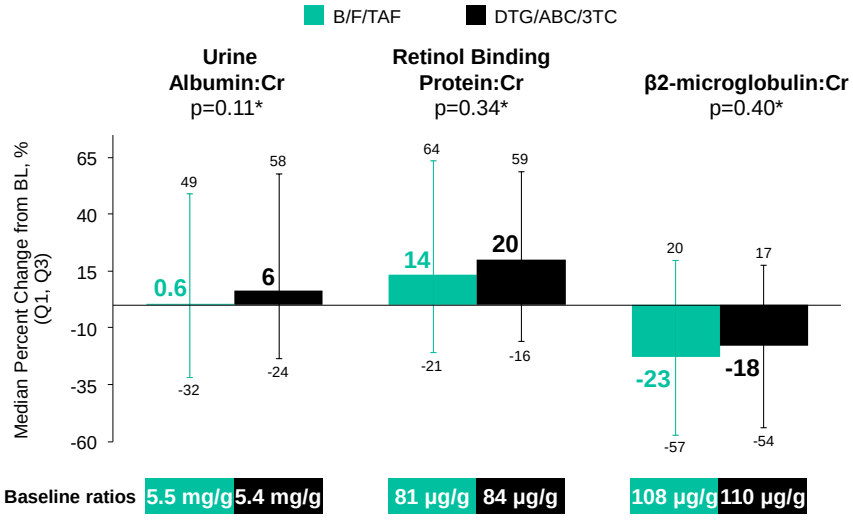
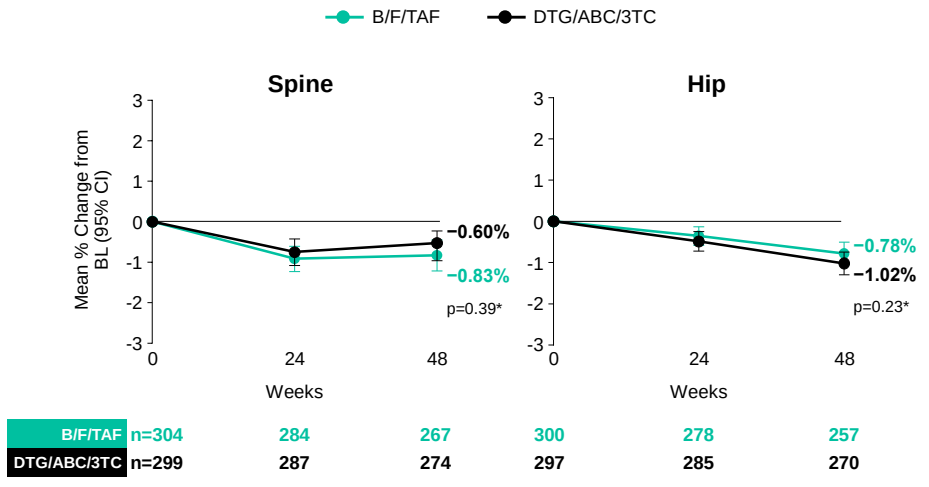
Percent Change from Baseline in Quantitative Proteinuria at Week 48



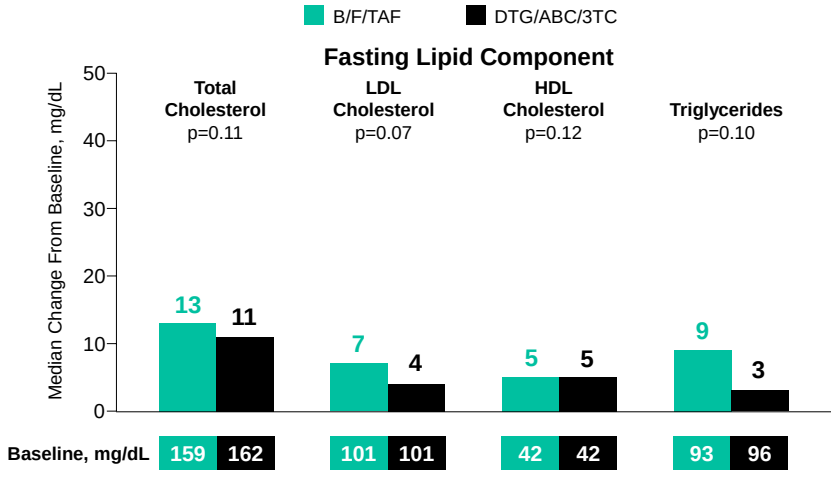
*Difference in percentage change from BL for each marker tested between treatment groups by Wilcoxon rank sum test.

Mean Percentage Changes in Spine and Hip BMD Through Week 48



*Comparison of B/F/TAF vs DTG/ABC/3TC at Week 48 by ANOVA model. CI, confidence interval.

Fasting Lipid Changes at Week 48



Similar percentages of patients:

- were on lipid lowering agents at baseline: B/F/TAF 3.5%, DTG/ABC/3TC 2.2%, p=0.35
- initiated lipid lowering agents during the study: B/F/TAF 2.5%, DTG/ABC/3TC 2.9%, p=1.00

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Conclusions

- Initial HIV-1 therapy with B/F/TAF was noninferior to DTG/ABC/3TC at Week 48 by snapshot algorithm
  - 92.4% of patients on B/F/TAF had HIV-1 RNA <50 copies/mL
  - 93.0% of patients on DTG/ABC/3TC had HIV-1 RNA < 50 copies/mL
  - Sensitivity analyses confirmed noninferiority
- No treatment emergent resistance
- B/F/TAF was well tolerated, with no adverse events leading to discontinuation
- Nausea was reported significantly more frequently in patients treated with DTG/ABC/3TC (p<0.001)
- Gastrointestinal, neuropsychiatric, and sleep-related symptoms were reported more frequently in patients treated with DTG/ABC/3TC
- Changes from baseline in bone mineral density, lipid parameters and renal markers were comparable between treatment arms

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Future Directions for B/F/TAF

- A manuscript of these data has been submitted to a peer-reviewed journal
- Two switch studies in virologically suppressed patients have reached their primary endpoints and will be presented at upcoming conferences
- A fully-enrolled study of 440 women will reach its primary endpoint in early 2018
- A study of B/F/TAF in adolescents and children is ongoing
- Regulatory filings of B/F/TAF have been submitted to the US FDA, the EMA, and other regulatory authorities

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