ARV Therapies and Therapeutic Strategies

INDEPENDENT REPORTING ON IAS 2017

COMPREHENSIVE EXPERT REVIEW AND DISCUSSION OF KEY PRESENTATIONS

A PHASE 3 RANDOMIZED CONTROLLED CLINICAL TRIAL OF BICTEGRAVIR IN A FIXED DOSE COMBINATION, B/F/TAF, VS ABC/DTG/3TC IN TREATMENT-NAÏVE ADULTS AT WEEK 48

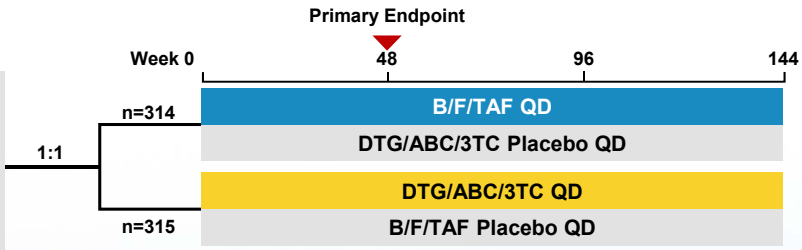
J. Gallant, A. Lazzarin, A. Mills, C. Orkin, D. Podzamczer, P. Tebas, P.-M. Girard, I. Brar, E. Daar, D. Wohl, J. Rockstroh, X. Wei, K. White, H. Martin, E. Quirk, A. Cheng

Abstract MOAB0105LB

GS-1489: STUDY DESIGN

Treatment-Naïve Adults

- HIV-1 RNA ≥ 500 copies/mL
- $eGFR_{CG}$ ≥ 50 mL/min
- HLA B*5701 negative
- Negative for chronic HBV



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GS-1489: 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)

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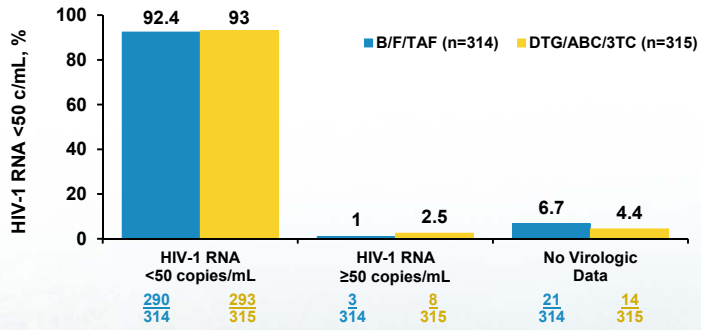
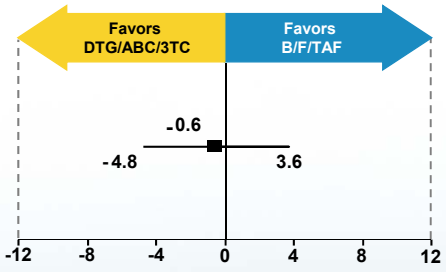
GS-1489 STUDY: RESULTS

Virologic Outcome



% Treatment Difference (95% CI)



- BF-TAF non-inferior to DTG/ABC/3TC
  - No resistance in either study arm
- Lipids not significantly different
- No drug-related renal events
- Significantly less nausea and minor adverse events with BF-TAF

Gallant J, et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. MOAB0105LB.

GS-1489 STUDY: 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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GS-1489 STUDY: 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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GS-1489 STUDY: 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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GS-1489 STUDY: 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

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

No differences between arms

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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GS-1489 STUDY: 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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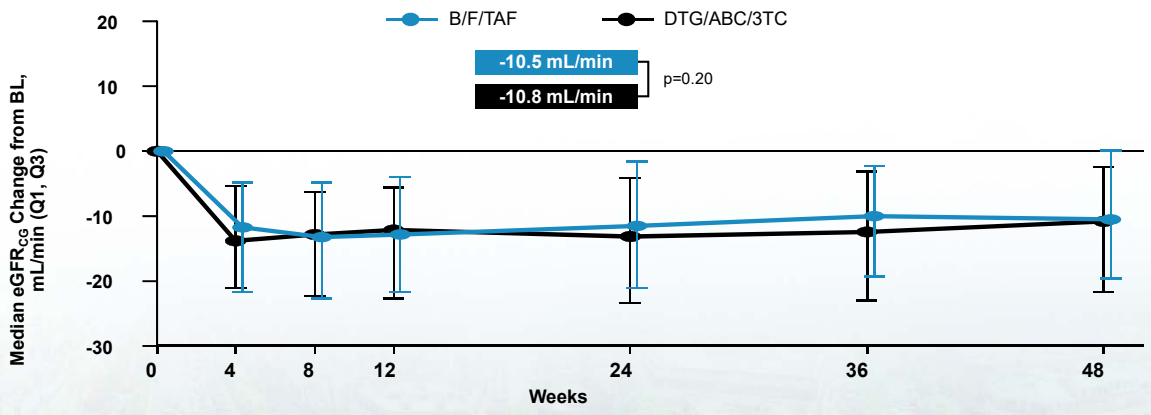
GS-1489 STUDY: CHANGE FROM BASELINE IN ESTIMATED GFR_{CG}



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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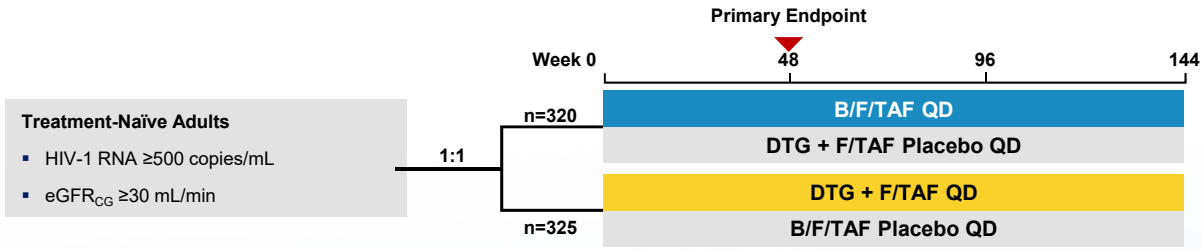
COMPREHENSIVE EXPERT REVIEW AND DISCUSSION OF KEY PRESENTATIONS

PHASE 3 RANDOMIZED, CONTROLLED CLINICAL TRIAL OF BICTEGRAVIR COFORMULATED WITH FTC/TAF IN A FIXED-DOSE COMBINATION (B/F/TAF) VS DOLUTEGRAVIR (DTG) + F/TAF IN TREATMENT-NAÏVE HIV-1 POSITIVE ADULTS: WEEK 48 RESULTS

P.E. Sax, A. Pozniak, J. Arribas, E. Koenig, E. Dejesus, H.-J. Stellbrink, A. Antinori, K. Workowski, J. Slim, J. Reynes, W. Garner, D. Sengupta, H. Martin, E. Quirk, A. Cheng

Abstract TUPDB0201LB

GS-1490: STUDY DESIGN



- Phase 3, randomized, double-blind, active-controlled Study 1490 (ClinicalTrials.gov NCT02607956)
  - Stratified by HIV-1 RNA, CD4 cell count, and geographic region (USA vs ex-USA)
  - North America, Europe, Australia, and Latin America
  - Chronic hepatitis B and/or C virus (HBV/HCV) infection allowed
- Primary endpoint: proportion with HIV-1 RNA <50 copies/mL at Week 48
  - Noninferiority margin of 12% based on US Food and Drug Administration-defined snapshot algorithm

Sax P, et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. TUPDB0201LB.

GS-1490: BASELINE CHARACTERISTICS

	B/F/TAF (n=320)	DTG + F/TAF (n=325)
Median age, y (range)	33 (18–71)	34 (18–77)
Male, %	88	89
Race/ethnicity, %		
Black or African descent	30	31
Hispanic/Latino	26	25
Median HIV-1 RNA, log_{10} copies/mL (Q1, Q3)	4.43 (3.95, 4.90)	4.45 (4.03, 4.84)
HIV-1 RNA >100,000 copies/mL, %	21	17
Median CD4 cell count, cells/µL (Q1, Q3)	440 (289, 591)	441 (297, 597)
CD4 count <200 cells/µL, %	14	10
HBV*/HCV† coinfection, %	3/2	2/2
Median $eGFR_{CG}$, mL/min (Q1, Q3)	120.4 (100.8, 141.8)	120.6 (102.8, 145.1)

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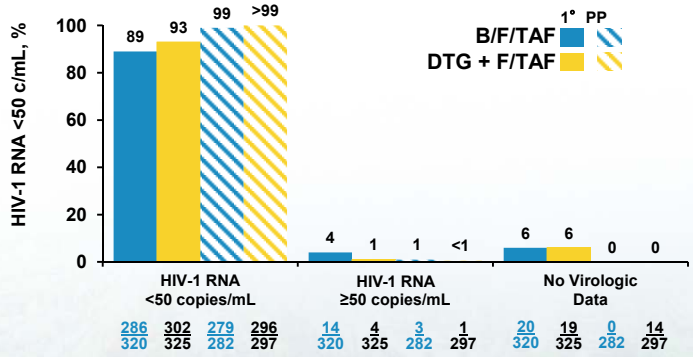
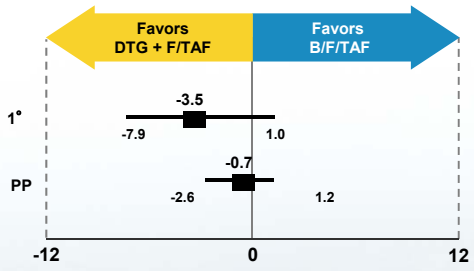
GS-1490 STUDY: RESULTS

Virologic Outcome



% Treatment Difference (95% CI)



- Bictegravir non-inferior to dolutegravir
- Results consistent in sensitivity analyses

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GS-1490 STUDY: PRIMARY ENDPOINT

Patients, n (%)	B/F/TAF n=320	DTG + F/TAF n=325
HIV-1 RNA <50 copies/mL	286 (89.4)	302 (92.9)
Difference for <50 copies/mL, % (95.002% CI)	**-3.5 (-7.9, 1.0; p=0.12)**	
HIV-1 RNA ≥50 copies/mL	14 (4.4)	4 (1.2)
HIV-1 RNA ≥50 copies/mL	3 (0.9)	1 (0.3)
D/C due to lack of efficacy	0	0
D/C due to other reason* and last VL ≥50 copies/mL	11 (3.4)	3 (0.9)
No virologic data in Week 48 window	20 (6.3)	19 (5.8)
D/C due to AE/death	3 (0.9)	3 (0.9)
D/C due to other reason and last VL <50 copies/mL	11 (3.4)	14 (4.3)
On study drug, but missing data in window	6 (1.9)	2 (0.6)

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GS-1490 STUDY: PATIENTS DISCONTINUED FOR REASONS OTHER THAN ADVERSE EVENT/DEATH AND LAST HIV-1 RNA ≥50 COPIES/ML

Group	Patient	Day of Last HIV-1 RNA	Last HIV-1 RNA, Copies/mL	Reason for Discontinuation
B/F/TAF	1	1 (baseline)	438	Patient decision (did not want to participate in study)
	2	1 (baseline)	185,000	Protocol violation (incarcerated)
	3	1 (baseline)	56,500	Lost to follow-up (moved away)
	4	1 (baseline)	71,900	Investigator discretion (inconsistent state of residency)
	5	1 (baseline)	17,300	Patient decision (no reason provided)
	6	1 (baseline)	9600	Patient decision (moved away)
	7	58	317,000	Investigator discretion (erratic behavior)
	8	62	9000	Lost to follow-up (unresponsive to contact attempts)
	9	169	23,400	Patient decision (wanted drug holiday)
	10	176	4440	Investigator discretion (multiple missed appointments)
	11	253	8630	Lost to follow-up (unresponsive to contact attempts)
DTG + F/TAF	12	10	213	Pregnancy
	13	62	22,800	Lost to follow-up (incarcerated)
	14	253	12,000	Noncompliance with study drug

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FUTURE DIRECTIONS FOR B/F/TAF

- A manuscript of these data has been submitted to a peer-reviewed journal
- Results from a naïve study of B/F/TAF vs. DTG + F/TAF will be presented in Poster TUPDB0201LB (Poster Discussion Tuesday 13:00)
- 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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