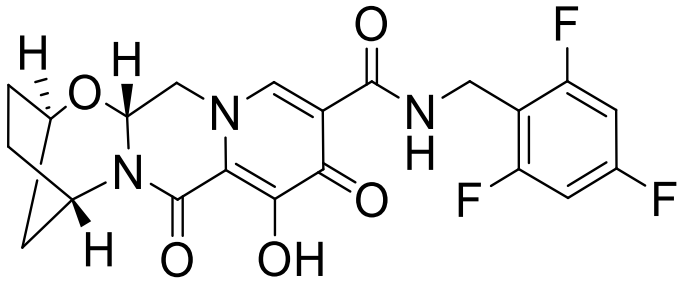
Bictegravir
And The STR B/F/TAF



Thomas Edinger, PhD
Medical Scientist Virology

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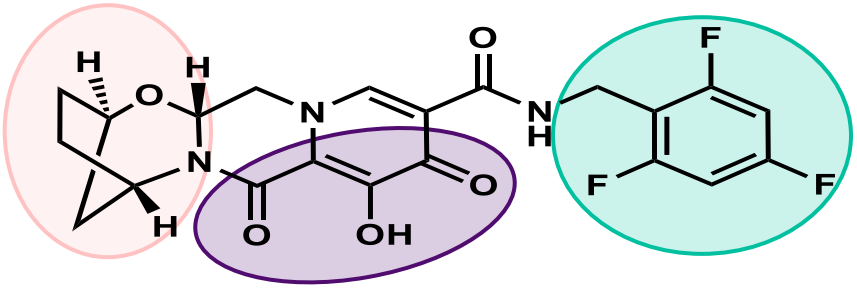
Disclaimer

These non-promotional slides are intended to be used as educational material only in response to an unsolicited question or request.

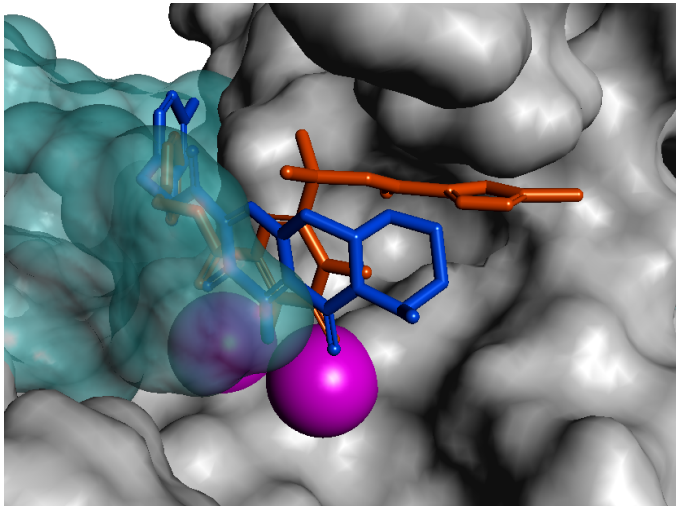
The double-dagger (‡) symbol indicates that these slides may contain information that is not within FDA or EMA approved product labeling and has not otherwise been approved by the FDA or EMA.

Bictegravir: Novel Chemical Structure and PK Profile

Metal-Chelating Core **Halogenated Phenyl Ring** **Side Chain**



BIC



«The better a molecule fits into the Integrase DNA-interface the better it inhibits DNA Integration»

Metal-Chelating Core: Oxygen atoms chelate a pair of Mg^{2+} ions at the integrase catalytic active site

Halogenated Phenyl: Interacts with the integrase pocket that is normally occupied by the terminal 3' base of viral DNA

Side Chain: Bridging bicyclic

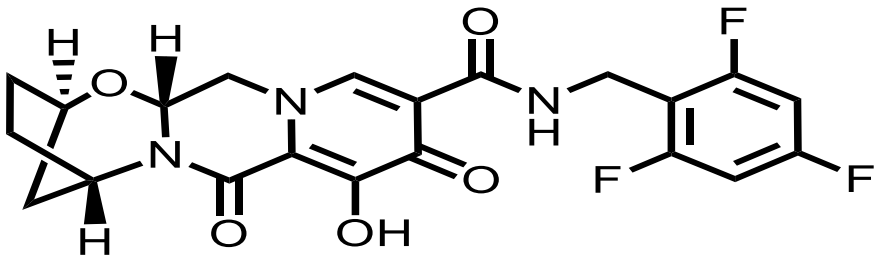
Lazerwith SE, et al. ASM 2016. Boston, MA. Poster #414. 2. Tsiang M, et al. ASM 2016. Boston, MA. Poster #416.

Figure made by the overlay of DTG and RAL bound in the active site of prototype foamy virus (PFV) described in: Hare, S., et al. Mol Pharmacol. 2011, 80, 565-572.
Slide adapted from Lazerwith GS-9883 Discovery ASM 2016 Poster 414

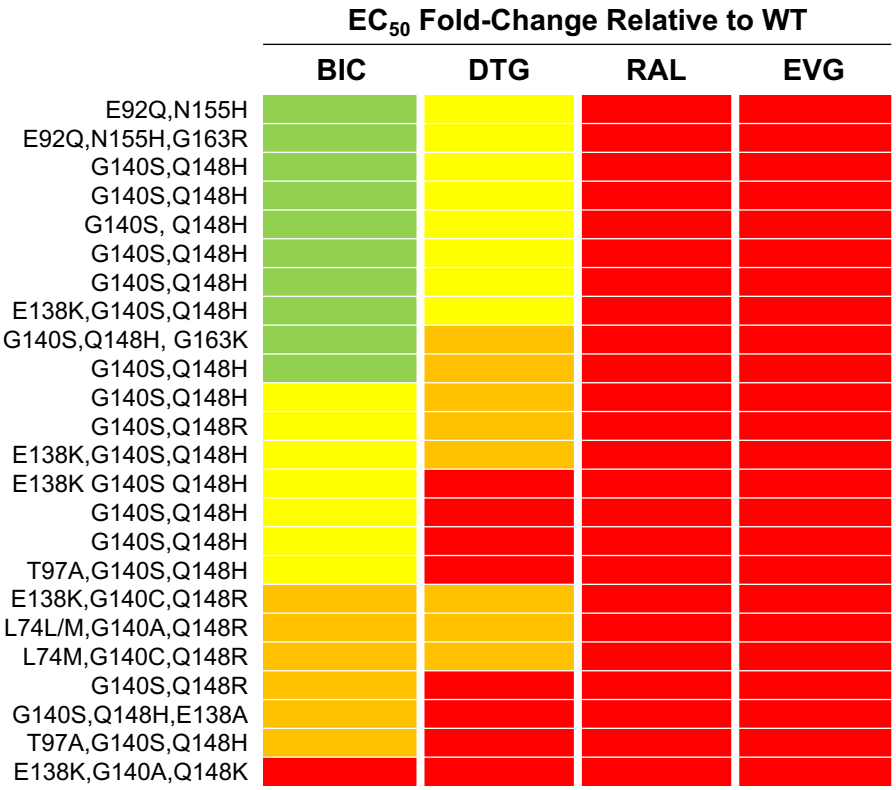
Bictegravir: Novel Chemical Structure and PK Profile

- Unboosted, once-daily integrase inhibitor
- No food restrictions
- Minimal drug interactions
- Not renally metabolized
- Higher barrier to resistance; full activity against RAL/EVG-resistant viruses

Bictegravir (B, BIC)



BIC has a statistically improved resistance profile



Full resistance	>10
High level resistance	>5.0 - ≤10.0
Intermediate resistance	2.5 - 5.0
Sensitive	<2.5

Monogram Biosciences.

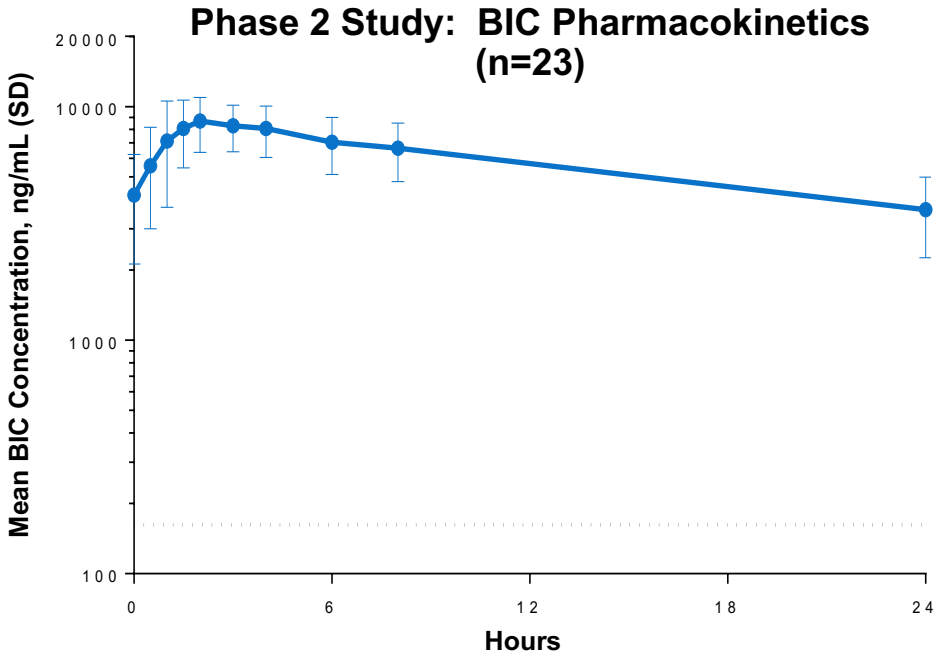
BIC, compared to DTG, displayed more activity against multiple INSTI-resistant isolates

EC_{50}=effective concentration of half maximal response

1. White K, et al., European Workshop HIV & Hep 2016. Rome, Italy. Poster O-01. 2. Tsiang M, et al., AAC 2016;60:7086-7097.

Bictegravir has an improved PK Profile

	RAL	EVG	DTG	BIC
Human Plasma Half-Life	9 hours	8.7 hours	14 hours	18 hours



BIC mean C_{trough}: 3510 ng/mL

IC_{95}: 162 ng/mL

- Dosed once daily (plasma half-life ~18 hours) without regard to food
- No need for a CYP3A4 PK booster - few drug interactions
- Metabolized equally by UGT1A1 and CYP3A4
- Minimal inhibition of renal OCT-2 & MATE-1: no clinically meaningful alteration in metformin levels

- Minimal changes in BIC plasma levels in moderate hepatic impairment
- No renal clearance; minimal change in BIC plasma levels in severe renal impairment

BIC, bictegravir. DTG, dolutegravir. EVG, elvitegravir. OCT, organic cation transporter. MATE, multidrug resistance and toxin extrusion. PK, pharmacokinetic. RAL, raltegravir.

1. Zhang H, et al. CROI 2017. Seattle, WA. Oral#40. 2. Zhang H, et al. IWCPT 2017. Chicago, IL. Poster #50 PK, pharmacokinetic

Drug Interaction Profile: Impact on Concomitant Drug

- BIC is not an inhibitor or inducer of UGT1A1 and CYP3A4

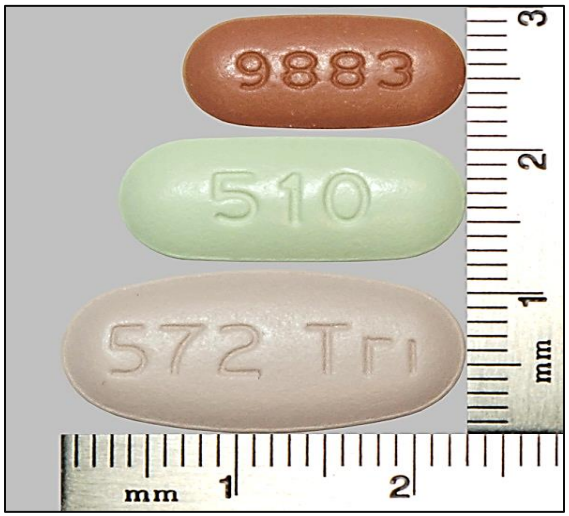
Change in Coadministered Drug Exposure*	
Probe Drug	**[Drug]**
Midazolam	↔
Ledipasvir	↔
Sofosbuvir	↔
Norgestimate	↔
Ethinyl estradiol	↔
Metformin†	↔

* No change in exposures (AUC) defined as > 30% decrease or > 43% increase
† Metformin plasma concentration increases by 39% (due to BIC inhibition of OCT-2)

CYP, cytochrome P450; OCT, organic cation transporter; UGT, UDP-glucuronosyltransferase

1. Zhang H, et al. CROI 2017. Seattle, WA. Oral#40. 2. Zhang H, et al. CROI 2017. Seattle, WA. Abstract Oral#40

BIC co-formulated with FTC and TAF



B/F/TAF (721 mg)

E/C/F/TAF (1082 mg)

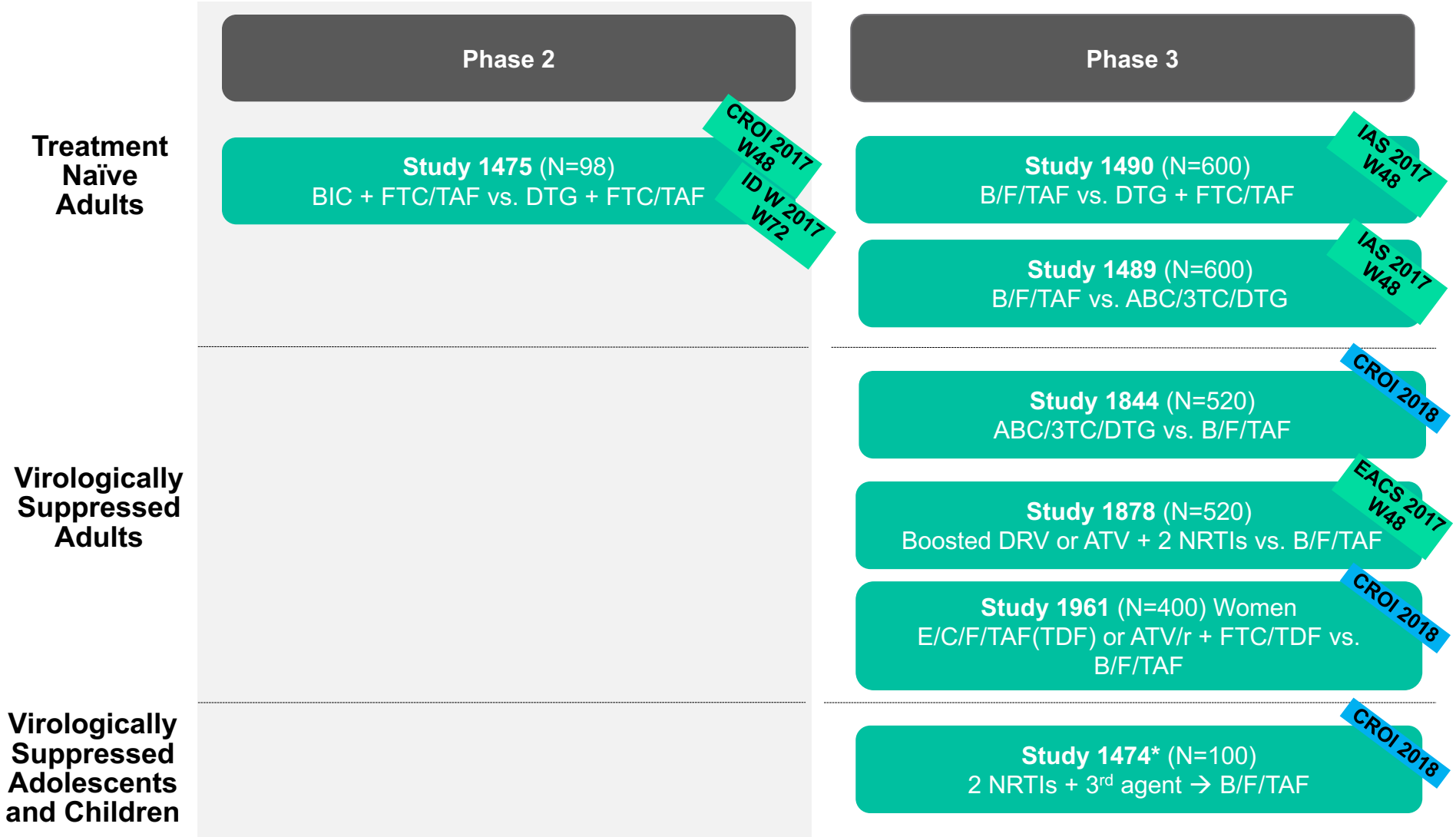
ABC/3TC/DTG (1750 mg)

Number in parenthesis is the total weight in mg of the tablet.
Note: Tablet size is not intended to compare clinical efficacy and safety, indications, dosing regimens, or treatment adherence.

- Investigational B/F/TAF (50/200/25 mg) is a complete single tablet regimen for the treatment of HIV
- Smallest integrase-containing single tablet regimen
- Taken with or without food : *Individuals who find it difficult to swallow tablets and capsules frequently cite the size as the main reason for the difficulty in swallowing**

* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm - June 2015 Data on file, Gilead Sciences, Inc.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide. E/C, elvitegravir/cobicistat. ABC/3TC/DTG, abacavir/lamivudine/dolutegravir

B/F/TAF Clinical Development Program



*All studies are fully enrolled except Study 1474. ClinicalTrials.gov URL: https://clinicaltrials.gov Accessed on Feb. 12, 2017.

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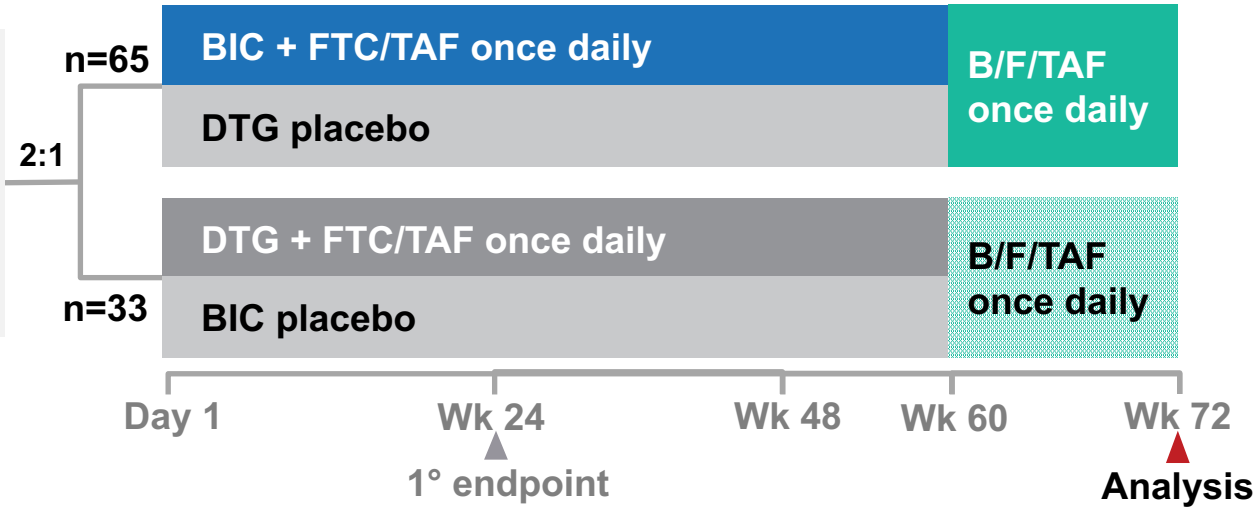
Study Design

Treatment-naïve adults

- HIV-1 RNA ≥ 1000 copies/mL
- HBV and HCV negative
- CD4 cell count ≥ 200/µL



ClinicalTrial.gov: NCT02397694

- Phase 2, randomized, double-blind, active-controlled study
- **Primary endpoint:** proportion with HIV-1 RNA <50 copies/mL at Week 24 by FDA Snapshot
- All participants who completed the double-blind phase were given option to continue on open-label B/F/TAF beginning at Week 60
  - Efficacy and safety were assessed through Week 72 for participants who elected to continue open-label B/F/TAF (n=92)
  - The all B/F/TAF analysis group included participants randomized to BIC + FTC/TAF inclusive of time on blinded and open-label phases, and those switched from DTG + FTC/TAF to B/F/TAF inclusive of time on the open-label phase (n=95)

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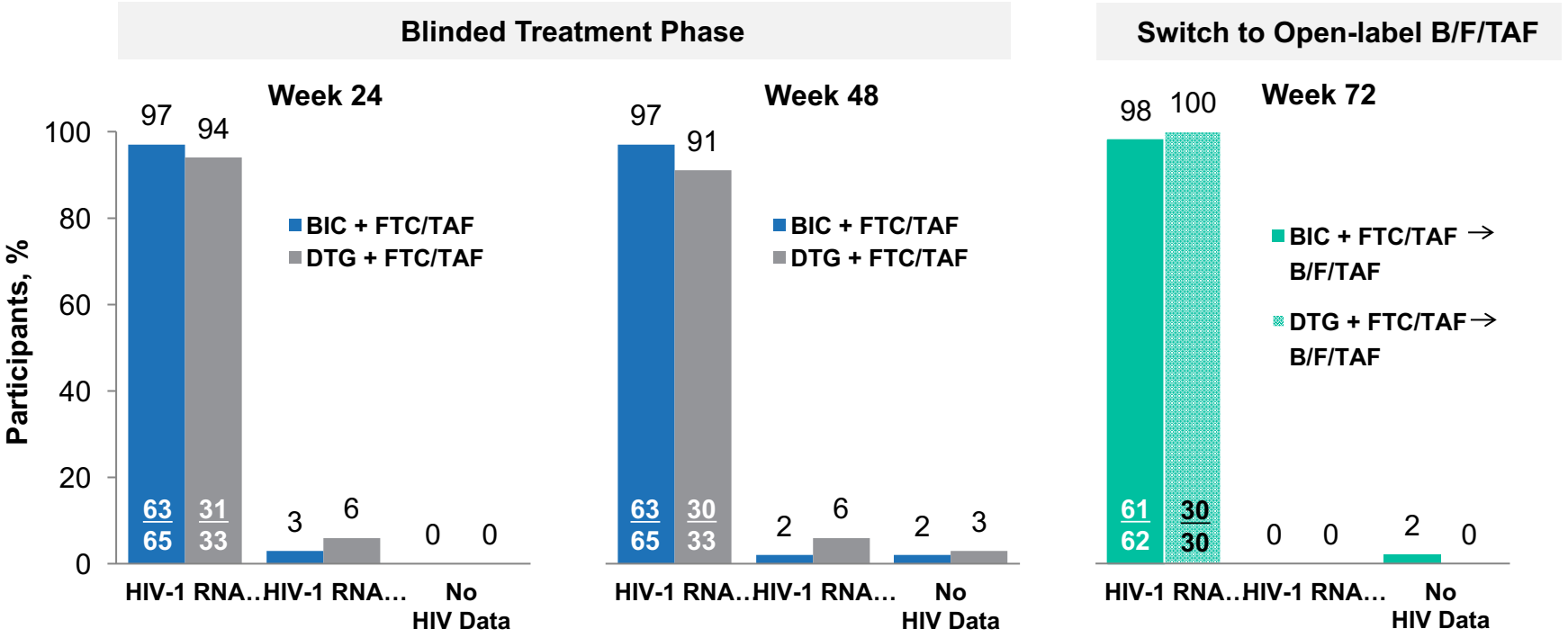
Virologic Outcomes at Weeks 24, 48, and 72



No treatment-emergent resistance was detected in participants treated with B/F/TAF

At Week 72, 98% of participants on B/F/TAF maintained HIV suppression
Switch from DTG + FTC/TAF to B/F/TAF: 100% maintained HIV suppression

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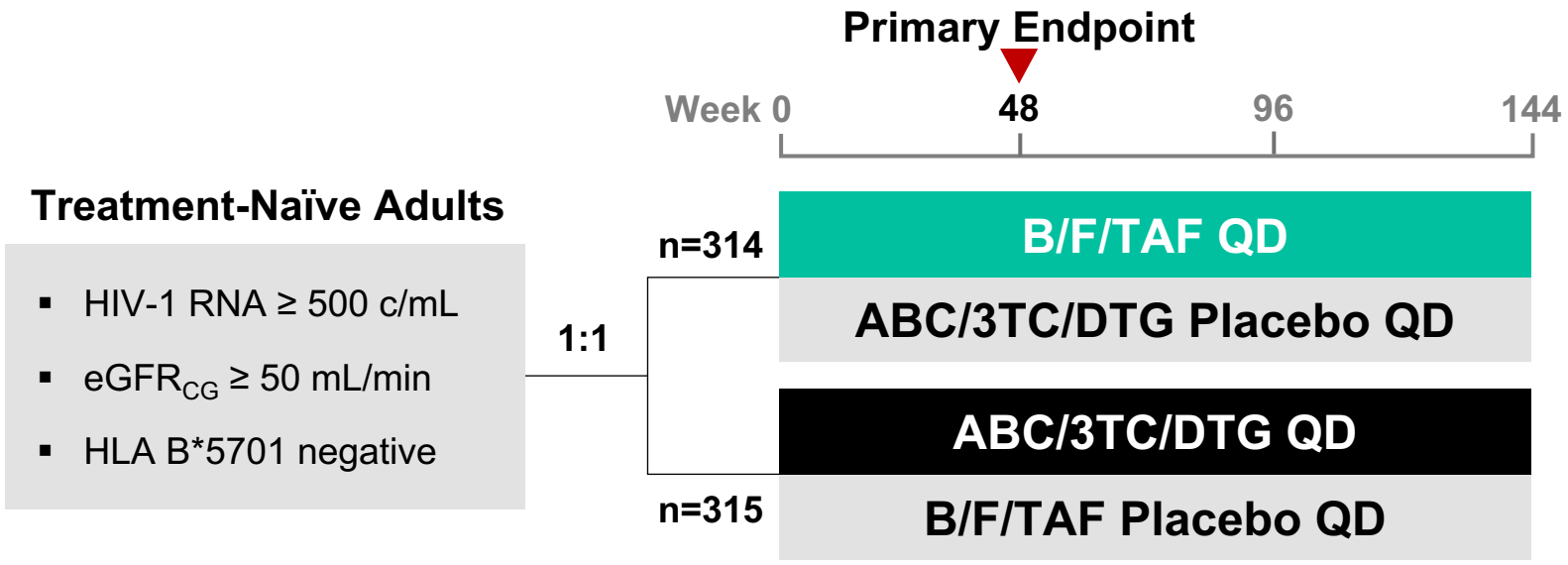
Study Design



- Phase 3, randomized, double-blind, active-controlled study (ClinicalTrial.gov NCT02607930)
  - Stratified by HIV-1 RNA, CD4 cell count, geographic region
  - North America and Europe
  - Chronic hepatitis C virus infection allowed
- Treatment-naïve, HIV-1-infected adults were randomized 1:1 to receive B/F/TAF 50/200/25 mg or ABC/3TC/DTG 600/300/50 mg with matching placebo once daily
- **Primary endpoint**: HIV-1 RNA < 50 copies/mL at Week 48 by FDA Snapshot algorithm (12% NI margin)

Gallant J, et al. IAS 2017. Paris, France. Oral #MOAB0105LB
Gallant J et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32299-7

$eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation. NI, non-inferiority.

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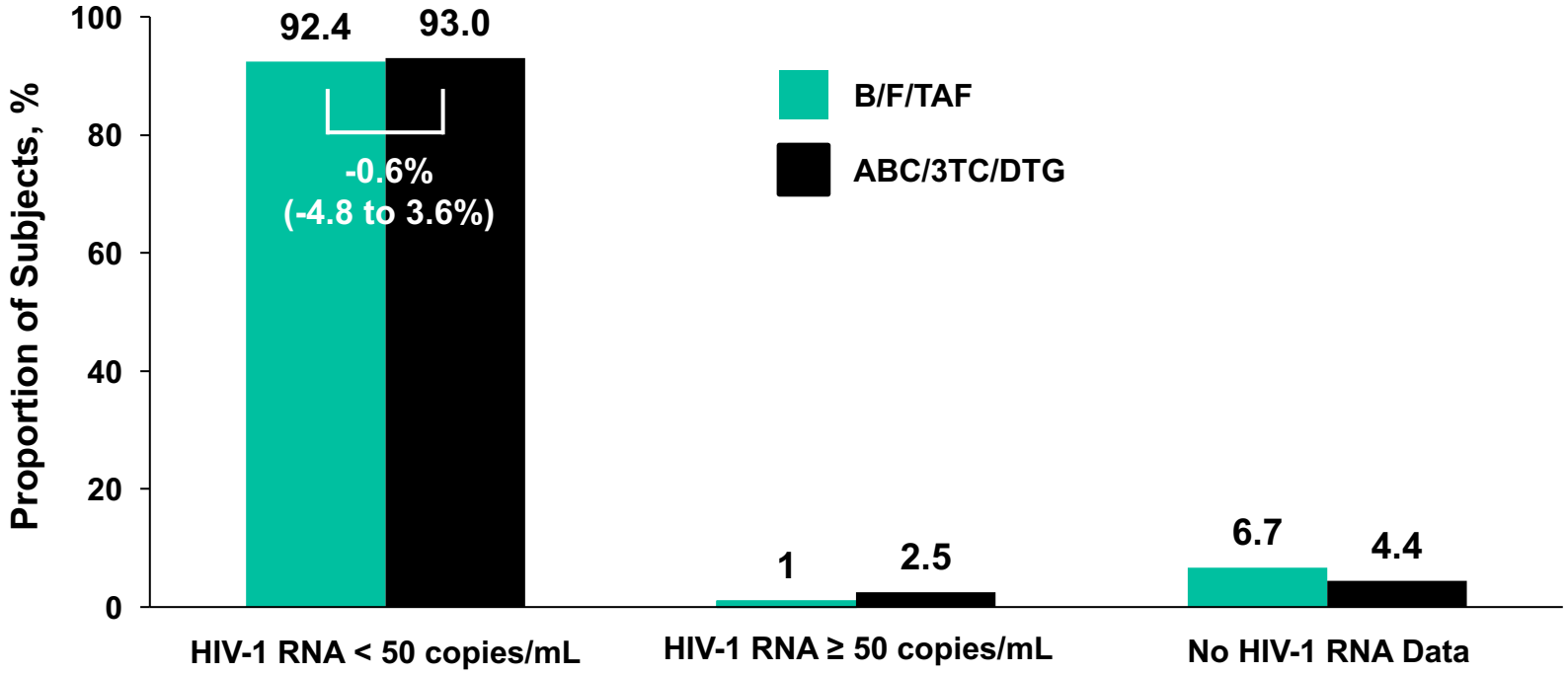
Virologic Outcome at Week 48 by FDA Snapshot Analysis



Mean changes in CD4 cell count (cells/μL) at Week 48: +233 B/F/TAF vs +229 ABC/3TC/DTG (p=0.81)

B/F/TAF vs ABC/3TC/DTG: Non-inferior efficacy at Week 48

Gallant J, et al. IAS 2017. Paris, France. Oral #MOAB0105LB
Gallant J et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32299-7

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Virologic Resistance

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

*Resistance testing performed for subjects with confirmed virologic rebound HIV-1 RNA ≥ 200 copies/mL after Week 8, or with HIV-1 RNA ≥ 200 copies/mL at the last study visit. There was 1 assay failure in the ABC/3TC/DTG arm.

No emergent resistance to any components of either regimen

Gallant J, et al. IAS 2017. Paris, France. Oral #MOAB0105LB
Gallant J et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32299-7

INSTI, integrase strand transfer inhibitor. NRTI, nucleoside reverse transcriptase inhibitor.

‡

Treatment Emergent Adverse Events (AEs) Through Week 48

% Subjects	B/F/TAF n=314	ABC/3TC/DTG n=315
All grade AEs (≥ 5% in either arm)		
Diarrhea	13%	13%
Headache	11%	14%
Nausea*	10%	23%
Nasopharyngitis	7%	9%
Cough	6%	3%
Upper respiratory tract infection	6%	11%
Fatigue	6%	9%
Syphilis	4%	8%
Insomnia	4%	6%
Arthralgia	4%	6%
Vomiting	4%	5%
Bronchitis	3%	5%
Abdominal pain	3%	5%
Drug-related AEs	26%	40%

- **Significantly more subjects on ABC/3TC/DTG experienced treatment emergent nausea***
- **More subjects on ABC/3TC/DTG had drug-related AEs**

*p<0.001 for difference in nausea between treatment arms (Fisher exact test).

Gallant J, et al. IAS 2017. Paris, France. Oral #MOAB0105LB
Gallant J et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32299-7

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Discontinuation Due to Adverse Events

	B/F/TAF n=314	ABC/3TC/DTG n=315
Discontinuations due to adverse events, n	**0**	**4**
Nausea, rash	0	1
Thrombocytopenia	0	1
Chronic pancreatitis, steatorrhea	0	1
Depression	0	1

There were no deaths reported in either treatment arm.

No subject discontinued B/F/TAF due to an adverse event

Gallant J, et al. IAS 2017. Paris, France. Oral #MOAB0105LB
Gallant J et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32299-7

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Patient Reported Outcomes

HIV Symptom Index

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 ($p<0.05$)*

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

No differences between arms

Pittsburgh Sleep Quality Index

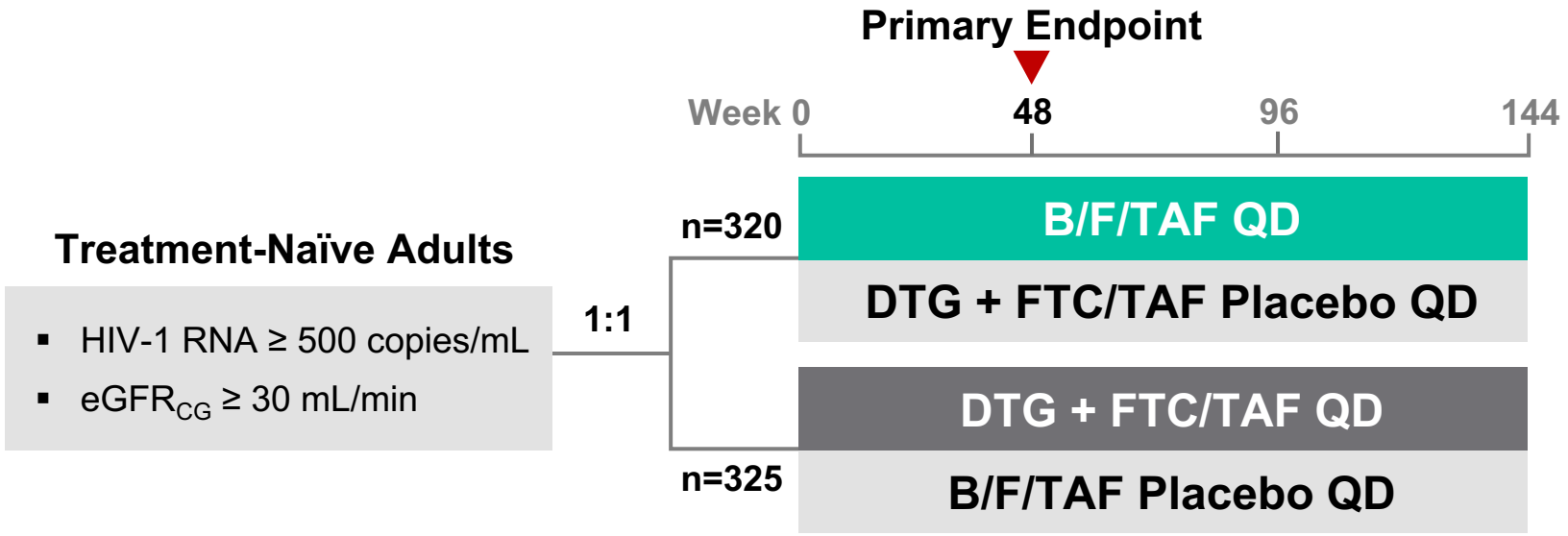
- Significantly higher "use of sleeping medication" at Week 4 in DTG/ABC/3TC arm ($p=0.002$)†
- Significantly more "sleep disturbance" at Week 48 in DTG/ABC/3TC ($p=0.034$)†

* For change from baseline
† From 2-sided Wilcoxon Rank Sum test

Gallant J, et al. IAS 2017. Paris, France. Oral #MOAB0105LB. Gilead Sciences. Data on file

‡

Study Design



- Phase 3, randomized, double-blind, active-controlled study (ClinicalTrials.gov NCT02607956)
  - Stratified by HIV-1 RNA, CD4 cell count, and geographic region
  - North America, Europe, Australia, and Latin America
  - Chronic hepatitis B and/or C virus infection allowed
- Treatment-naïve, HIV-1-infected adults were randomized 1:1 to receive B/F/TAF 50/200/25 mg or DTG 50 mg + FTC/TAF 200/25 mg with matching placebo once daily
- **Primary endpoint:** HIV-1 RNA < 50 copies/mL at Week 48 by FDA Snapshot algorithm (12% NI margin)

$eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation. NI, non-inferiority.

Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
Sax P, et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32340-1

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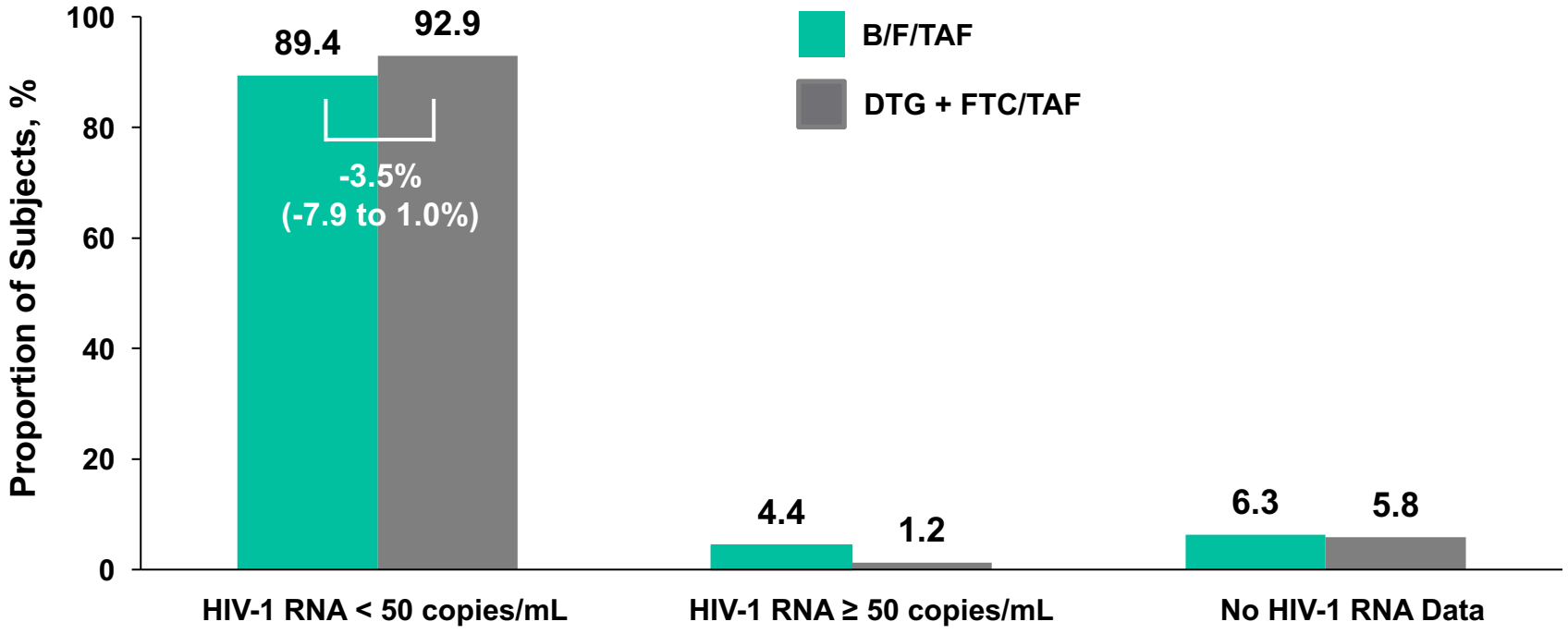
Virologic Outcome at Week 48 by FDA Snapshot Analysis



Mean changes in CD4 cell count (cells/μL) at Week 48: +180 BIC vs +201 DTG (p=0.10)

B/F/TAF vs. DTG + FTC/TAF: Non-inferior efficacy at Week 48

Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
Sax P, et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32340-1

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Virologic Outcome at Week 48 by FDA Snapshot Analysis

	B/F/TAF n=320	DTG + FTC/TAF n=325
HIV-1 RNA < 50 copies/mL	**286 (89.4%)**	**302 (92.9%)**
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 HIV-1 RNA ≥ 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 adverse event or death	3 (0.9%)	3 (0.9%)
D/C due to other reason* and last HIV-1 RNA < 50 copies/mL	11 (3.4%)	14 (4.3%)
On study drug, but missing data in window	6 (1.9%)	2 (0.6%)

*Other reasons include lost to follow up, withdrew consent, noncompliance, protocol violation, pregnancy, and investigator discretion.

D/C, discontinued

Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
Sax P, et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32340-1

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Subjects Discontinued for Reasons Other Than Adverse Event or Death and Last HIV-1 RNA ≥ 50 Copies/mL

	Subject	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 + FTC/TAF	12	10	213	Pregnancy
	13	62	22,800	Lost to follow-up (incarcerated)
	14	253	12,000	Noncompliance with study drug

6 subjects in the B/F/TAF group discontinued prematurely for administrative reasons without post-baseline HIV-1 RNA data

Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB. Sax P, et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32340-1

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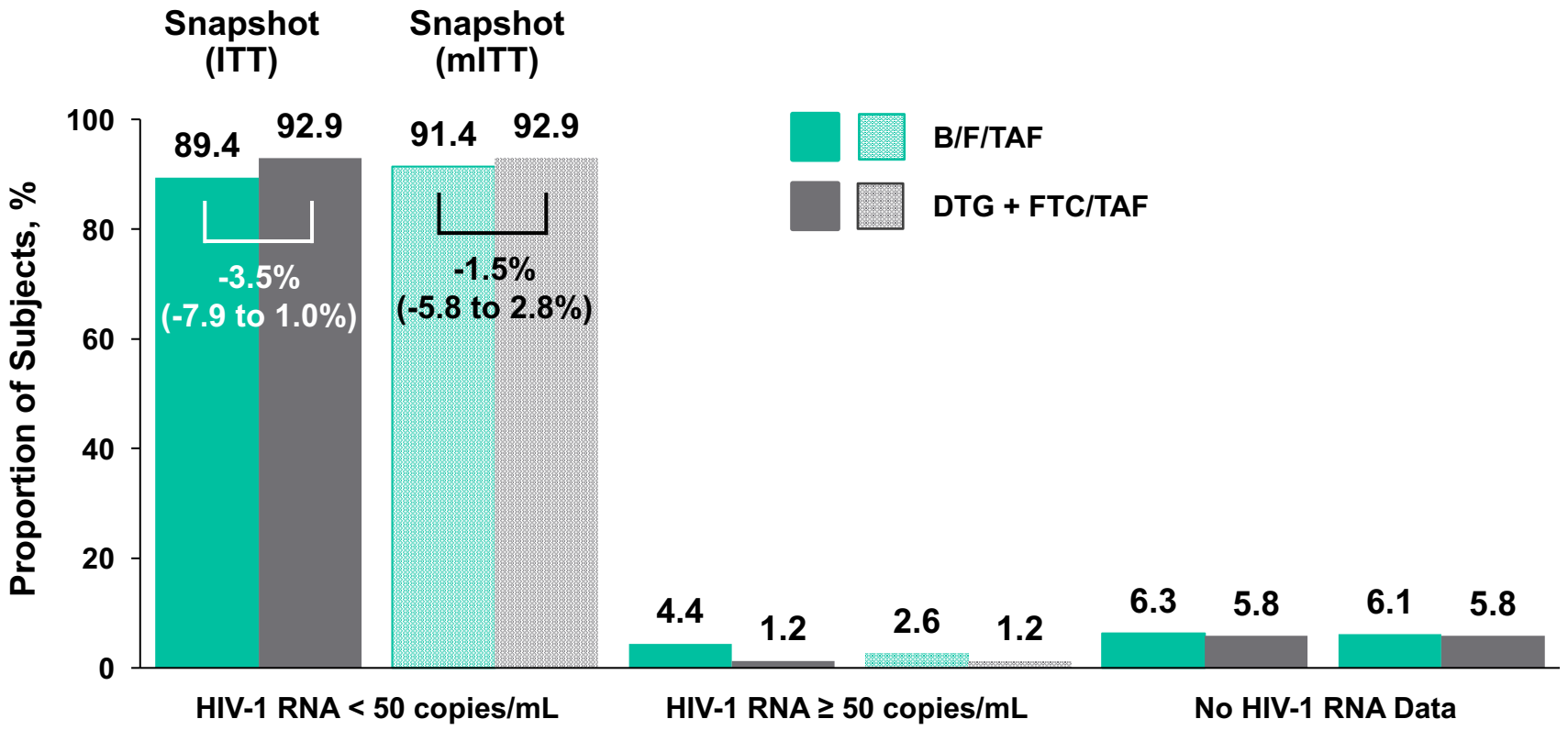
Virologic Outcome at Week 48: Modified ITT (mITT) Population



The mITT population excluded subjects who had no post-baseline HIV-1 RNA data: n=7† B/F/TAF vs n=0 DTG + FTC/TAF

B/F/TAF vs. DTG + FTC/TAF: Non-inferior efficacy at Week 48

Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
Sax P, et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32340-1

†Includes 6 subjects who withdrew prematurely for administrative reasons and 1 subject who died

‡

Virologic Resistance

	B/F/TAF n=320	DTG + FTC/TAF n=325
*Met criteria for resistance testing, n	7	5
NRTI resistance detected	0	0
INSTI resistance detected	0	0

*Resistance testing performed for subjects with confirmed virologic rebound HIV-1 RNA ≥ 200 copies/mL after Week 8, or with HIV-1 RNA ≥ 200 copies/mL at the last study visit. There was no assay failure.

No emergent resistance to any components of either regimen

INSTI, integrase strand transfer inhibitor. NRTI, nucleoside reverse transcriptase inhibitor.

Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
Sax P, et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32340-1

‡

Treatment Emergent Adverse Events (AEs) Through Week 48

% Subjects	B/F/TAF n=320	DTG + FTC/TAF n=325
All grade AEs (≥ 5% in either arm)		
Headache	13%	12%
Diarrhea	12%	12%
Nausea	8%	9%
Nasopharyngitis	7%	10%
Fatigue	6%	8%
Influenza	5%	3%
Lymphadenopathy	5%	6%
Arthralgia	5%	3%
Insomnia	5%	4%
Upper respiratory tract infection	5%	7%
Pyrexia	4%	6%
Back pain	3%	6%
Drug-related AEs*	18%	26%

- **Significantly more subjects on DTG+FTC/TAF vs. B/F/TAF had drug-related AEs***

*p=0.022 for difference in drug-related AEs between treatment arms (Fisher exact test)

Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
Sax P, et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32340-1

‡

Discontinuations Due to Adverse Events

	B/F/TAF n=320	DTG + FTC/TAF n=325
Discontinuations due to adverse events, n	**5**	**1**
Abdominal distention	1	0
Cardiac arrest*	1	0
Chest pain	1	0
Paranoia, crystal methamphetamine use	1	0
Sleep disorder, insomnia, dyspepsia, tension headache, and depressed mood	1	0
Erythema, pruritis	0	1

Discontinuations due to adverse events were low

- Three treatment emergent deaths occurred during the study:
  - *B/F/TAF: n=1 (cardiac arrest in setting of sepsis secondary to appendicitis; same patient who discontinued due to AE of cardiac arrest)
  - DTG + F/TAF: n=2 (n=1 unknown; n=1 possible pulmonary embolism)

Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
Sax P, et al. Lancet. http://dx.doi.org/10.1016/S0140-6736(17)32340-1

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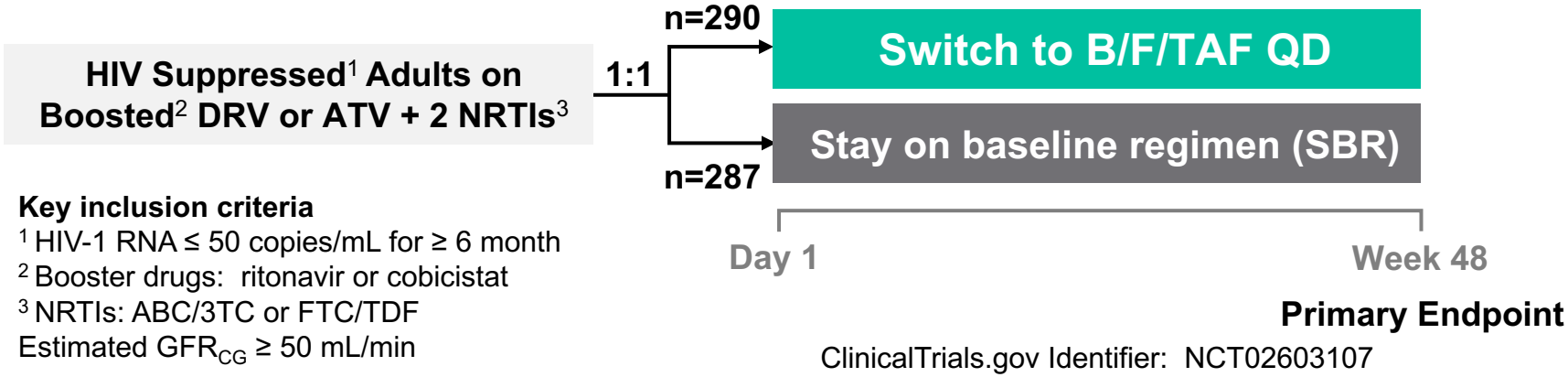
Study Design



Key inclusion criteria

[1] HIV-1 RNA ≤ 50 copies/mL for ≥ 6 month

[2] Booster drugs: ritonavir or cobicistat

[3] NRTIs: ABC/3TC or FTC/TDF

Estimated GFR_{CG} ≥ 50 mL/min

ClinicalTrials.gov Identifier: NCT02603107

- Phase 3, multicenter, randomized, open-label, active-controlled study
  - North America, Europe, and Australia
- **Primary endpoint**
  - Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 based on FDA snapshot algorithm (non-inferiority margin of 4%)

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; COBI, cobicistat; C, copies; DRV, darunavir; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; FTC, emtricitabine; NRTI, nucleoside reverse transcriptase inhibitor; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

Daar E, et al. ID Week 2017. San Diego, CA. Oral LB-4

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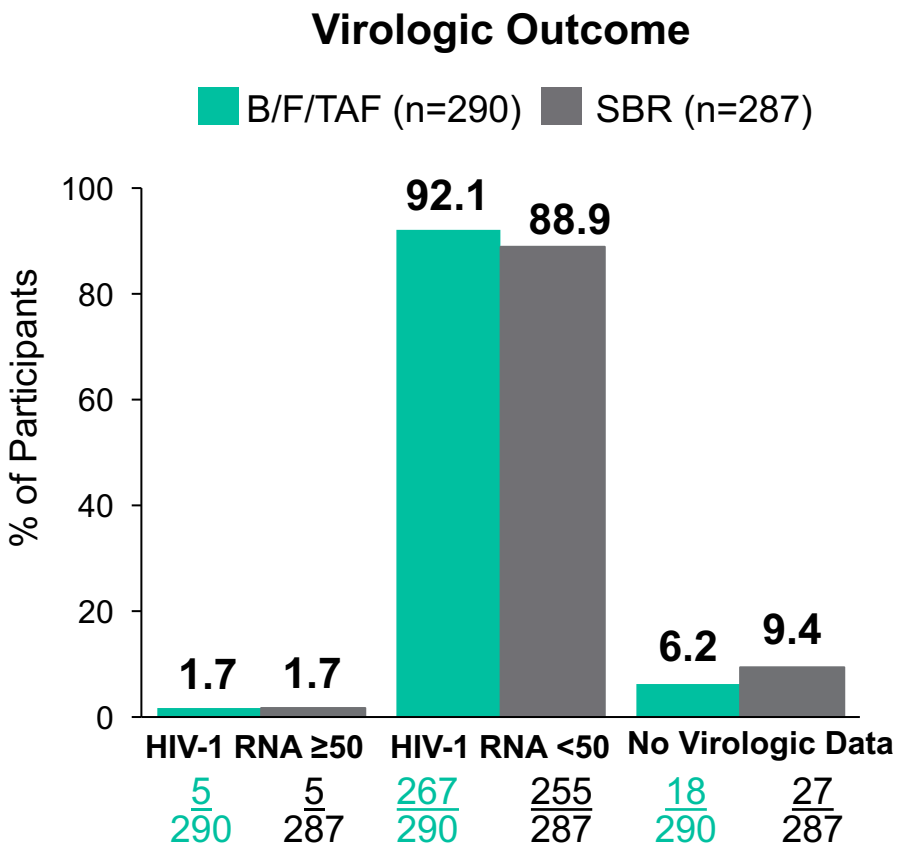
Virologic Outcome at Week 48 by FDA Snapshot Analysis

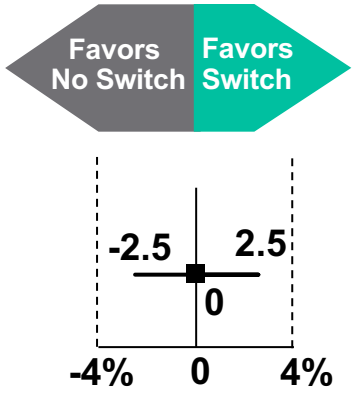


Noninferior efficacy

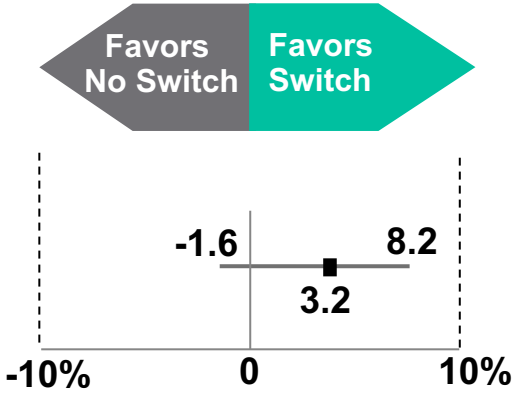
No participants on B/F/TAF developed resistance

**One participant in the SBR group on ABC/3TC + DRV + RTV developed emergent resistance (L74V) in reverse transcriptase*

Primary Endpoint
Difference in HIV-1 RNA ≥50 copies/mL, % (95.002% CI)



Secondary Endpoint
Difference in HIV-1 RNA <50 copies/mL, % (95.002% CI)



Daar E, et al. ID Week 2017. San Diego, CA. Oral LB-4

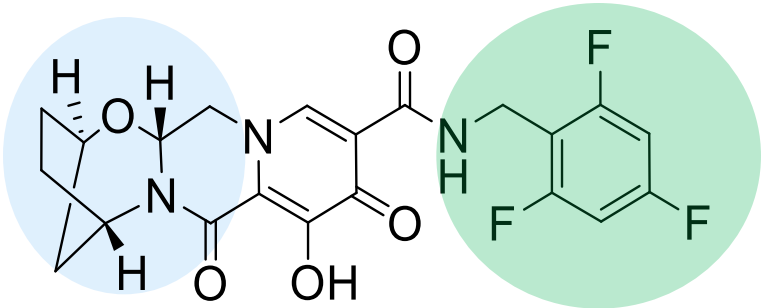
Bictegravir and B/F/TAF

Novel Chemical Structure and PK Profile
(unique structure)

High Potency
(EC_{50}, long dissociation half-life WT & RAMs)

Smallest STR
(in combination with FTC and TAF)

Favorable PRO profile
(compared to DTG)



Bictegravir (GS-9883)
B/F/TAF

Improved Resistance Profile
statistically significant vs EVG, RAL and DTG

No general restrictions:
- *food intake*
- *CD4 count*
- *viral load*
- *HLA-Status*
- *CVD Risk*
- *bone status*
- *eGFR down to 30*
- *hepatic impairment*

Non-inferiority in naïve & switch populations
(shown in large Phase 3 program)

Improved PK Profile
dual metabolism, less drug interactions ,no food restriction

No restriction in terms of HBV/HCV
(TAF active against HBV, no DDIs with SOF etc.)