CAB simulation: presenting a clinical study

Graphics, Terminology, Statistics

European AIDS Treatment Group

EATG Training Academy

STEP-UP: Skills Training to Empower Patients

Safety, Efficacy and Durability of Long-Acting CAB and RPV as Two Drug IM Maintenance Therapy for HIV-1 Infection: LATTE-2 Week 160 Results

David A. Margolis,[1] Juan Gonzalez Garcia,[2] Hans-Jürgen Stellbrink,[3] Yazdan Yazdanpanah,[4] Gary Richmond,[5] Graham Smith,[6] Kenneth Sutton,[1] David Dorey,[7] Feifan Zhang,[8] Kimberly Smith,[1] Peter Williams,[9] William Spreen[1]

[1]ViiV Healthcare, Research Triangle Park, NC, USA; [2]Hospital La Paz, Madrid, Spain; [3]ICH Study Center, Hamburg, Germany; [4]Hôpital Bichat Claude Bernard, Paris, France; [5]Gary J. Richmond, MD, PA Fort Lauderdale, FL, USA; [6]Maple Leaf Research, Toronto, ON, Canada; [7]GlaxoSmithKline, Mississauga, ON, Canada; [8]GlaxoSmithKline, Collegeville, PA, USA; [9]Janssen Research and Development, Beerse, Belgium

HIV Drug Therapy Glasgow; October 28-31, 2018; Glasgow, UK

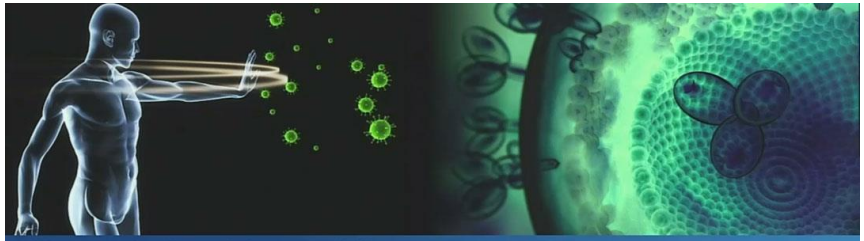
ONCEMRK
HIV Glasgow 2016
Abstract # 3514101

Subgroup Analyses from ONCEMRK, a Phase 3 Study of Raltegravir (RAL) 1200 mg Once Daily vs RAL 400 mg Twice Daily, in Combination with Tenofovir/Emtricitabine, in Treatment-Naïve HIV-1 Infected Subjects

Pedro Cahn[1], Richard Kaplan[2], Paul Sax[3], Kathleen Squires[4], Jean-Michel Molina[5], Anchalee Avihingsanon[6], Winai Ratanasuwan[7], Evelyn Rojas[8], Mohammed Rassool[9], Xia Xu[10], Anthony Rodgers[10], Sandy Rawlins[10], Bach-Yen Nguyen[10], Randi Leavitt[10], and Hedy Teppler[10] for the ONCEMRK Study Group

[1] Fundación Huesped, Buenos Aires, Argentina; [2] Desmond Tutu HIV Foundation, Cape Town, South Africa; [3] Brigham & Women's Hospital, Harvard Medical School, Boston, MA; [4] Thomas Jefferson University, Philadelphia, PA; [5] Hôpital Saint-louis, Paris, France; [6] HIV-NAT Research Collaboration, Bangkok, Thailand; [7] Faculty Of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [8] Cericap Multiclinicas, Guatemala City, Guatemala; [9] University of Witwatersrand, Helen Joseph Hospital, Johannesburg, South Africa; [10] Merck & Co., Inc., Kenilworth NJ, USA

ClinicalTrials.gov NCT02131233



Efficacy and safety of the once-daily, darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) single-tablet regimen in antiretroviral treatment-naïve adults living with HIV-1: AMBER Week 96 results

Chloe Orkin,[1] Joseph J. Eron,[2] Jürgen Rockstroh,[3] Daniel Podzamczer,[4] Stefan Esser,[5] Linos Vandekerckhove,[6] Erika Van Landuyt,[7] Erkki Lathouwers,[7] Veerle Hufkens,[7] John Jezorwski,[8] Magda Opsomer,[7] on behalf of the AMBER study group

[1]Royal London Hospital and Queen Mary University, Barts Health NHS Trust, London, UK; [2]The University of North Carolina School of Medicine, Chapel Hill, NC, USA; [3]Universitätsklinikum Bonn, Bonn, Germany; [4]IDIBELL-Hospital Universitari de Bellvitge, L'Hospitalet, Barcelona, Spain; [5]University Hospital Essen, Essen, Germany; [6]Ghent University and Ghent University Hospital, Ghent, Belgium; [7]Janssen Pharmaceutica NV, Beerse, Belgium; [8]Janssen Research & Development, Pennington, NJ, USA

janssen Infectious Diseases & Vaccines

Orkin C, et al. HIV Glasgow 2018. Abstract O212

Phase III Randomized, Controlled Clinical Trial of Bictegravir Coformulated with FTC/TAF in a Fixed-dose Combination (B/F/TAF) versus Dolutegravir (DTG) + F/TAF in Treatment-naïve HIV-1 Positive Adults: Week 96

Hans Jürgen Stellbrink,[1] Jose Arribas,[2] Jeffrey L. Stephens,[3] Helmut Albrecht,[4] Paul E. Sax,[5] Franco Maggiolo,[6] Catherine Creticos,[7] Claudia T. Martorell,[8] Xuelian Wei,[9] Kirsten White,[9] Sean E. Collins,[9] Andrew Cheng,[9] Hal Martin[9]

[1]ICH Study Center, Hamburg, Germany; [2]Hospital Universitario La Paz, Madrid, Spain; [3]Mercer University School of Medicine, Macon, GA, US; [4]Palmetto Health , Richland, SC, US; [5]Brigham and Women's Hospital, Boston, MA, US; [6]Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; [7]Howard Brown Health Center, Chicago, IL. US; [8]Infectious Diseases and The Research Institute, Springfield, MA, US; [9]Gilead Sciences, Inc., Foster City, CA

HIV Glasgow, Abstract 4185960
28 – 31 October 2018
Glasgow, UK

EATG Training Academy

STEP-UP: Skills Training to Empower Patients

ONCEMRK: Background

- Raltegravir (RAL) 400 mg twice daily (BID) has a well-established safety and efficacy profile
- New RAL formulation: 1200 mg (2 x 600 mg) given once daily (QD)
  - Higher drug loading (QD tablet only slightly larger)
  - Minimal food effect
- In HIV-1-infected treatment-naive subjects receiving tenofovir/emtricitabine (TDF/FTC), RAL 1200 mg QD demonstrated potent and non-inferior efficacy at Week 48 compared to RAL 400 mg BID
- To further characterize the effects of RAL 1200 mg QD, Week 48 results have been summarized across pre-specified subgroups based on baseline demographic and prognostic factors

HIV Glasgow 2016 Abstract # 3514101

ONCEMRK: Multicenter, Double-blind, Randomized Controlled Trial

Primary Hypothesis: RAL 1200 mg QD is non-inferior to RAL 400 mg BID, each in combination with TDF/FTC, as assessed by the proportion of subjects achieving HIV RNA <40 c/mL at Week 48 (non-inferiority margin of 10 percentage points).

Key entry criteria:
ART naïve,
≥18 yrs old,
HIV-1 RNA
≥1000 c/mL

Reformulated RAL 1200 mg QD + TDF/FTC (N ~ 500) → 14 Day Follow-Up

RAL 400 mg BID + TDF/FTC (N ~ 250) → 14 Day Follow-Up

- **Interim Analysis Time Point**
- **Primary Analysis Time Point**
- **Secondary Analysis Time Point**

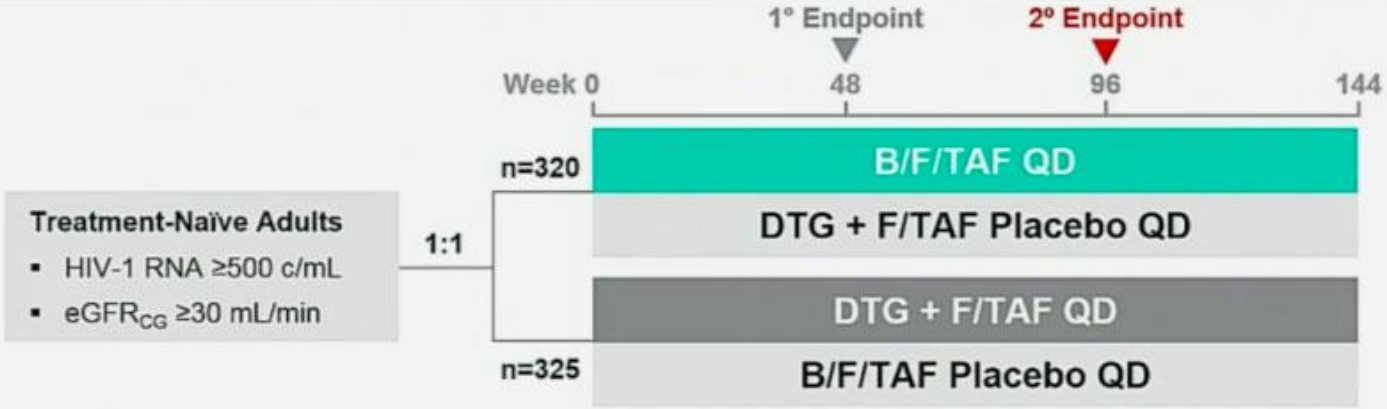
Screening Period was 60 days (~8.5 weeks) prior to randomization.
Subjects randomized in 2:1 ratio (QD:BID), stratified by screening HIV RNA (< / ≥100,000 c/mL) and hepatitis B/C co-infection.
Virologic failure was confirmed with 2 consecutive measurements of HIV RNA at least 1 week apart.

Introduction

- Bictegravir, a novel, potent INSTI with a high barrier to resistance, was coformulated with emtricitabine and tenofovir alafenamide into a single-tablet regimen (B/F/TAF) and is approved in the US, Europe, Australia, and Canada as Biktarvy®
  - Unboosted, once daily dosing without regard to food
- B/F/TAF has shown noninferiority at Week 48 to current standard-of-care comparators, with no treatment-emergent resistance, and was well tolerated across five randomized, phase 3 studies in adults living with HIV-1, including a study of 470 women[1-5]
- A study comparing B/F/TAF to coformulated dolutegravir (DTG), abacavir, and lamivudine, showed noninferior efficacy, changes in bone mineral density and renal markers were comparable between arms, and there were no cases of renal tubulopathy through 96 weeks[6]

1. Sax et al. Lancet 2017;390:2073-82.
2. Gallant et al. Lancet 2017;390:2063-72.
3. Molina et al. Lancet HIV 2018;5:e357-65.
4. Daar et al. Lancet HIV 2018;5:e347-56.
5. Kityo et al. CROI 2018; March 3-7, Boston, abstr #500.
6. Wohl et al. Presented at IDWeek 2018; October 3-7, abstr #74246.

GS-US-380-1490 Study Design



- Phase 3, randomized, double-blind, active-controlled study
  - Stratified by HIV-1 RNA, CD4 cell count, geographic region (USA vs non-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
  - B/F/TAF 89.4% vs DTG + F/TAF 92.9% with HIV-1 RNA <50 c/mL (p=0.12)[1]
- Secondary endpoint: proportion with HIV-1 RNA <50 copies/mL at Week 96
  - Noninferiority margin of 12% based on FDA Snapshot algorithm

ClinicalTrials.gov NCT02607956. c, copies; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation.

1. Sax et al. *Lancet* 2017; 390:2073-82.

Methods: Statistical Analysis

- Primary Analysis Approach
  - HIV RNA: Non-Completer=Failure, FDA snapshot approach
  - CD4 Count: Observed Failure approach
- Subgroup Analysis
  - Pre-specified subgroups based on baseline demographic and prognostic factors
  - Observed Failure approach
    - HIV RNA: discontinuation due to lack of efficacy = failure; subjects discontinued for other reasons are excluded
      - Focus on antiviral effect of treatment
    - CD4 Count: baseline values are carried forward for subjects discontinued due to lack of efficacy

ONCEMRK: Key Baseline Characteristics

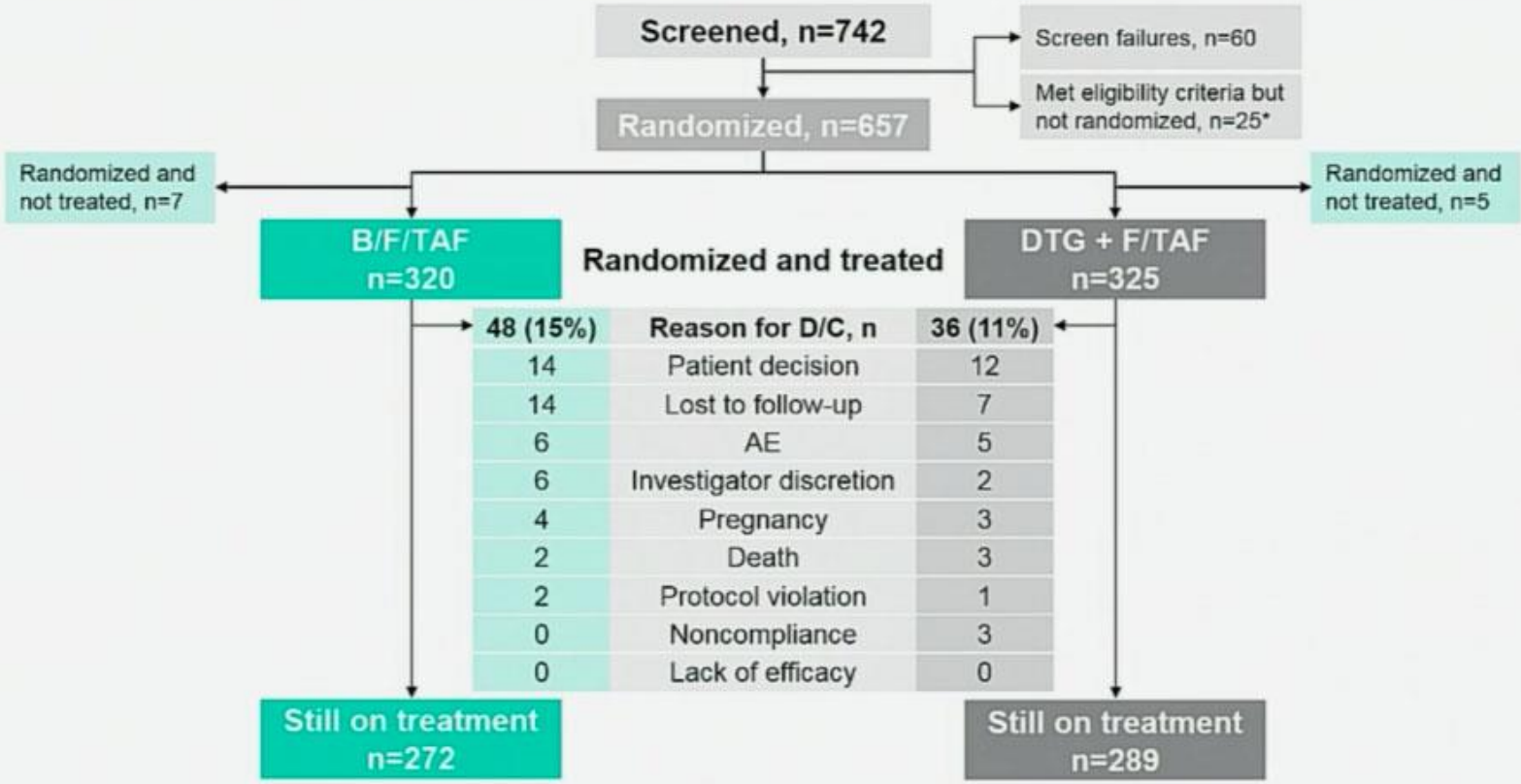
	RAL 1200 mg QD (N=531)	RAL 400 mg BID (N=266)
Male (%)	82.9	88.0
White (%)	56.7	64.7
Age (years), Median (min, max)	34.0 (18, 66)	35.0 (19, 84)
History of AIDS (%)	14.9	10.5
Clade B viral subtype (%)	63.1	69.9
Stratum (%)		
Screening HIV RNA ≤100,000 c/mL	71.9	71.4
Hepatitis B and/or C Positive†	2.8	3.0
Baseline HIV RNA		
Median (IQR), $\log_{10}$ c/mL	4.6 (4.2, 5.1)	4.6 (4.1, 5.1)
> 100,000 c/mL (%)	***28.1***	***28.9***
> 500,000 c/mL (%)	4.7	5.6
Baseline CD4 Count		
Median (IQR), cells/mm^3	380 (264, 512)	416 (275, 557)
< 200 cells/mm^3 (%)	13.0	13.9

† Evidence of hepatitis B surface antigen and/or HCV RNA.
IQR, interquartile range

Worldwide enrollment: Europe 39%, North America 24%, Asia/Pacific 17%, Latin America 13%, Africa 7%

HIV Glasgow 2016 Abstract # 3514101

Participant Disposition From Baseline to Week 96



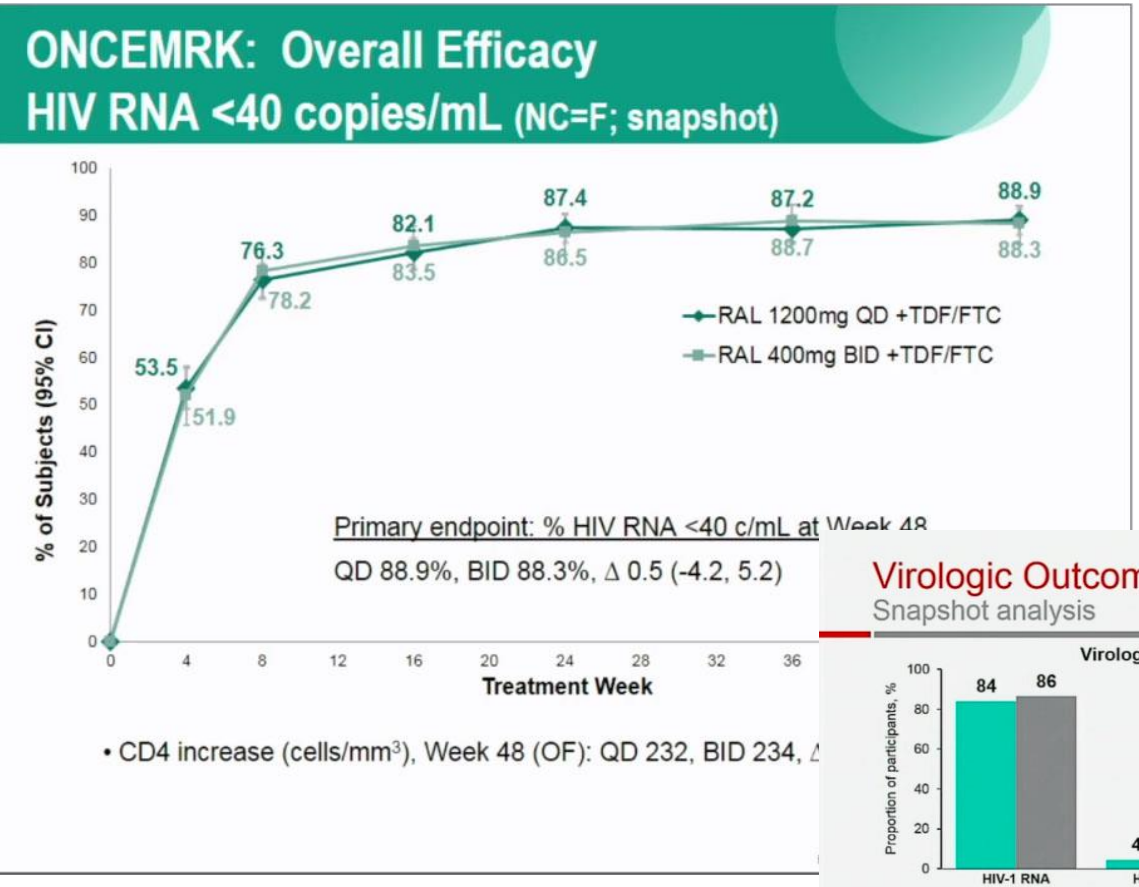
* Lost to follow-up (n=3), withdrew consent (n=14), investigator's discretion (n=2), AE (n=1), outside of visit window (n=2), other (n=3).

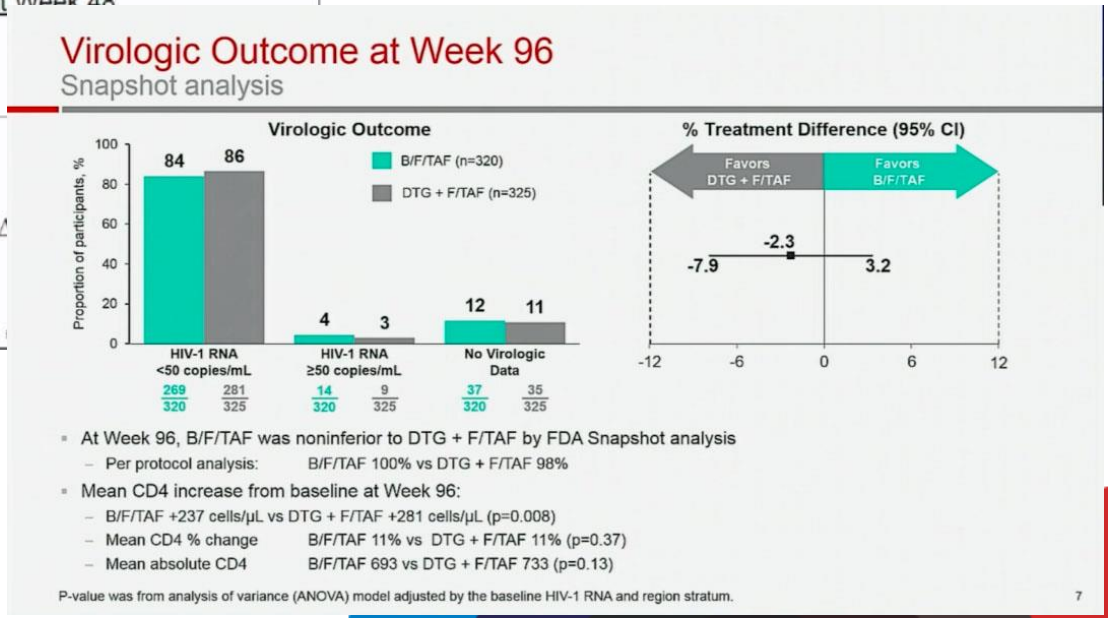
Baseline Characteristics

	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
White	57	60
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 (101, 142)	121 (103, 145)

c, copies; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; IQR, interquartile range.
* Positive HBV surface antigen; isolated positive HBV core antigen, with quantifiable HBV DNA (ie, ≥20 IU/mL) on or prior to 1st dose.
† Positive HCV antibody and quantifiable HCV RNA (ie, ≥15 IU/mL) prior to 1st dose of study drug.

Efficacy data: how to present them





EATG Training Academy
STEP-UP: Skills Training to Empower Patients

Time to loss of virological response (TLOVR)

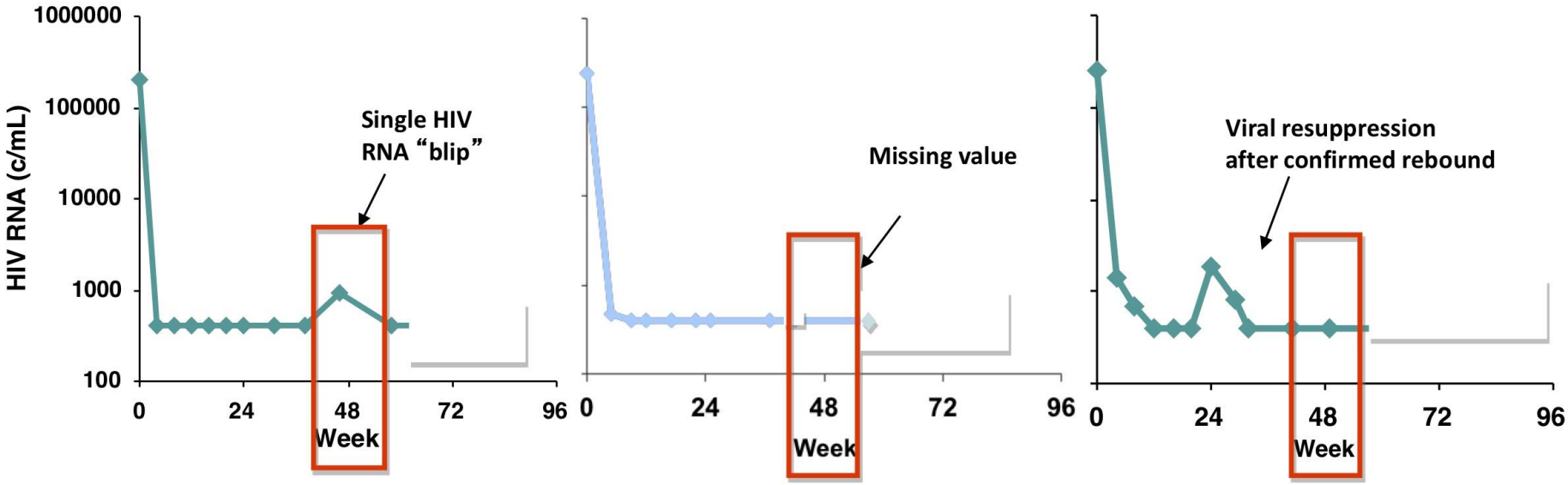
- Composite end point proposed by the FDA in the past years
- Includes
  - Virological failure (2 consecutive measurements above the detection limit)
  - Death=failure
  - Lost to follow up = failure
  - Switch/introduction of drugs (exceptions for OBR)
- Could be added
  - CD4
  - Disease progression
- Lost to follow up
  - Should they be included in a composite endpoint?
  - Censored
  - Failure

Snapshot analysis

- Only used HIV-RNA data at the visit (window period) of interest
- Data should be presented in three groups:
  - Virologic success when HIV RNA <50 cp/ml in window
  - Virological failure when HIV RNA ≥ 50 cp/ml in window
  - No Virologic Data (Discontinued study/study drug due to AE or death, Discontinued study/study drug for Other Reasons, On study but missing data in window)

https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355239.htm

Snapshot Analysis
Differences between TLOVR & SNAPSHOT (simplified explanation)

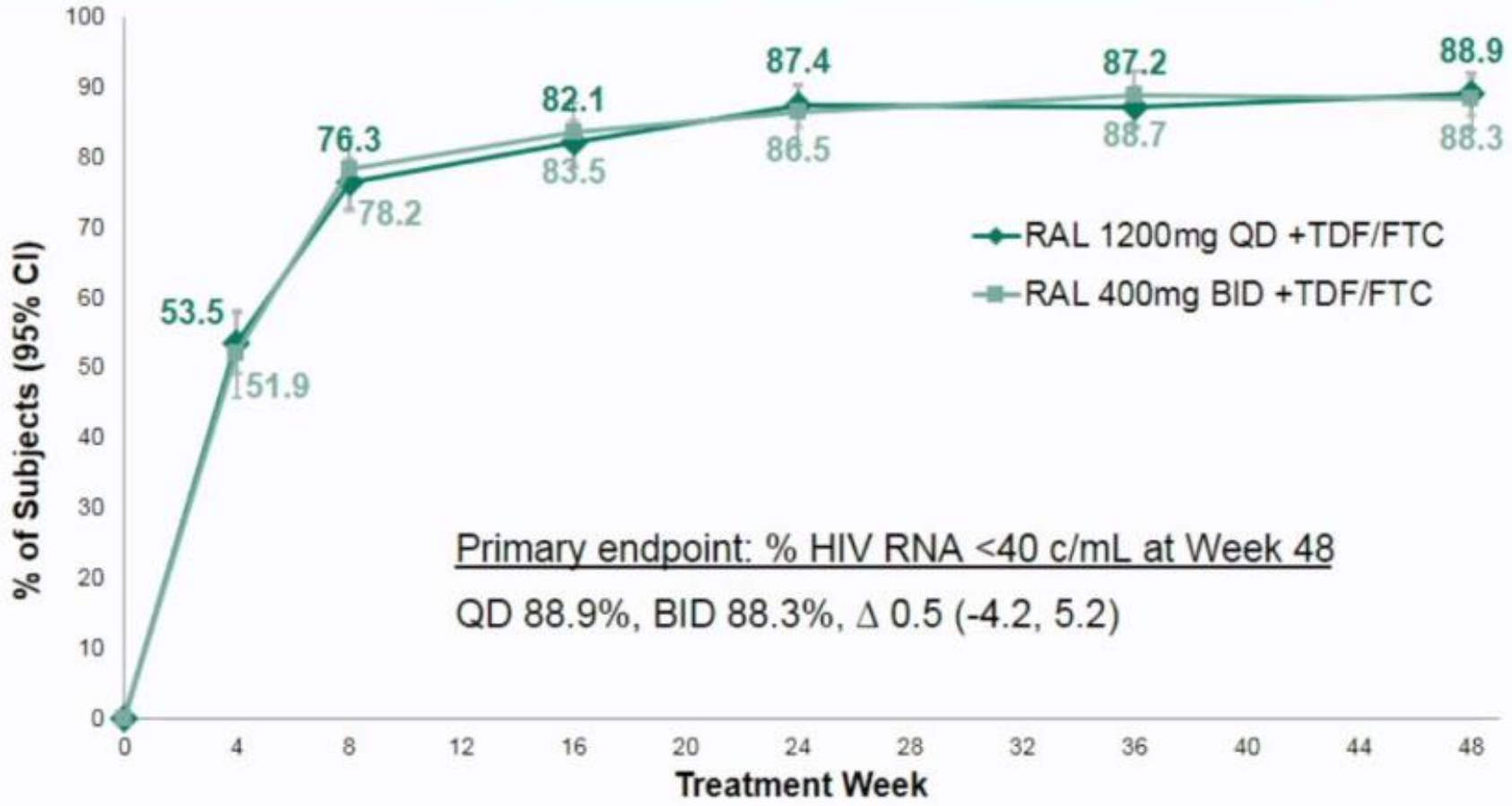


TLOVR	**Success**	**Success**	**Failure**
Snapshot	**Failure**	**No data**	**Success**

SNAPSHOT analysis considers only what is happening during the defined time window

- FAILURE = single blip
- SUCCESS = virologic re-suppression

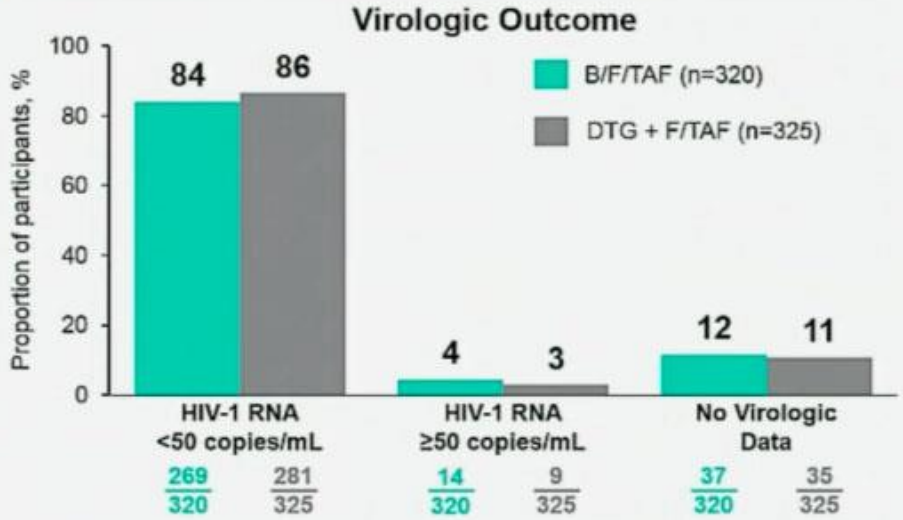
ONCEMRK: Overall Efficacy
HIV RNA <40 copies/mL (NC=F; snapshot)

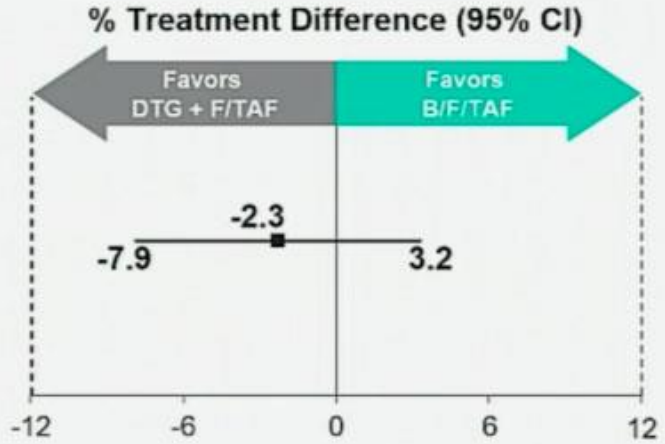


- CD4 increase (cells/mm^3), Week 48 (OF): QD 232, BID 234, Δ -2 (-31, 27)

Virologic Outcome at Week 96

Snapshot analysis



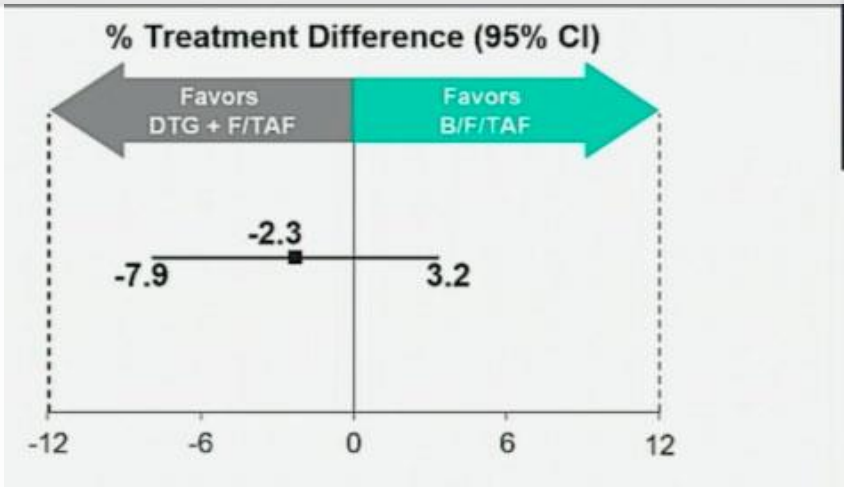


- At Week 96, B/F/TAF was noninferior to DTG + F/TAF by FDA Snapshot analysis
  - Per protocol analysis: B/F/TAF 100% vs DTG + F/TAF 98%
- Mean CD4 increase from baseline at Week 96:
  - B/F/TAF +237 cells/μL vs DTG + F/TAF +281 cells/μL (p=0.008)
  - Mean CD4 % change B/F/TAF 11% vs DTG + F/TAF 11% (p=0.37)
  - Mean absolute CD4 B/F/TAF 693 vs DTG + F/TAF 733 (p=0.13)

P-value was from analysis of variance (ANOVA) model adjusted by the baseline HIV-1 RNA and region stratum.

Confidence Interval

A confidence interval is an estimated range of values in which all data (results) are likely to lie. For a given treatment effect measured in a trial on a sample of a population, the confidence interval can be calculated to give a 'best estimate' range of the treatment effect that will be seen in the whole population. The likelihood that the confidence interval will contain the value is called the confidence level. Traditionally, confidence levels are set at 95% or 99%. This means that researchers are 95% (or 99%) certain that the measured effect lies within the true range. For example, instead of estimating the mean age of a population as 15 years, researchers say that the mean age is between 14 and 16. This confidence interval contains the true value being estimated.



Virologic Outcome at Week 96

Snapshot analysis

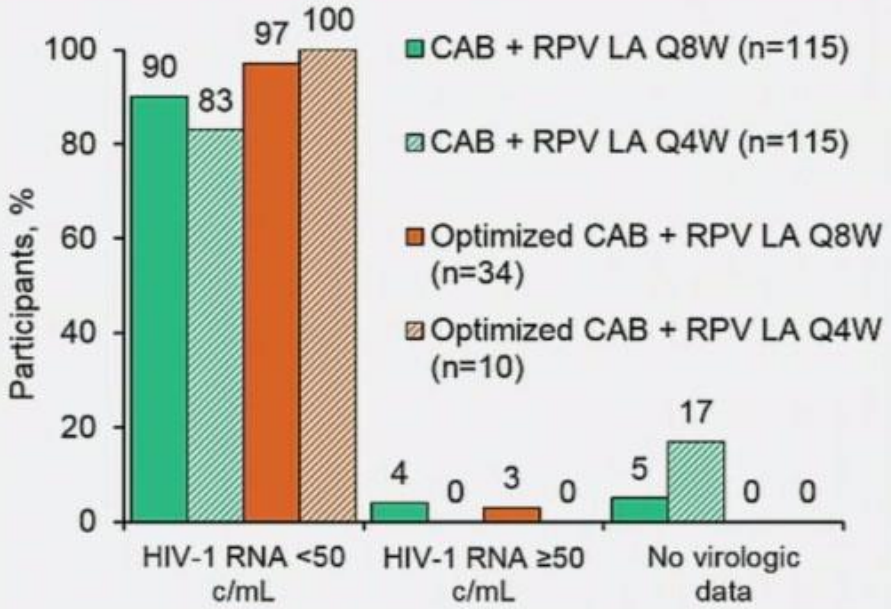
Participants, n (%)	B/F/TAF n=320	DTG + F/TAF n=325
HIV-1 RNA <50 copies/mL	**269 (84)**	**281 (86)**
Difference for <50 copies/mL, % (95% CI)	**-2.3 (-7.9, 3.2; p=0.4)**	
HIV-1 RNA ≥50 copies/mL	**14 (4)**	**9 (3)**
HIV-1 RNA ≥50 copies/mL	0	5 (2)
D/C due to lack of efficacy	0	0
D/C due to other reason* and last VL ≥50 copies/mL	14 (4)	4 (1)
No virologic data in Week 96 window	**37 (12)**	**35 (11)**
D/C due to AE/death	8 (2.5)	8 (2.5)
D/C due to other reason* and last VL <50 copies/mL	26 (8)	23 (7)
On study drug, but missing data in window	3 (1)	4 (1)

VL, viral load.

- Other reasons for discontinuation included: lost to follow-up (7 had no post-baseline visit), investigator's discretion, patient decision, noncompliance with study drug, protocol violation, and pregnancy

Outcomes Randomized and Nonrandomized Switch Arms: Week 160 HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

Virologic outcomes



Snapshot outcomes

Week 160 outcome, n (%)	Q8W IM (n=115)	Q4W IM (n=115)	Optimized Q8W IM (n=34)	Optimized Q4W IM (n=10)
HIV-1 RNA <50 c/mL	**104 (90)**	**95 (83)**	**33 (97)**	**10 (100)**
HIV-1 RNA ≥50 c/mL	**5 (4)**	**0**	**1 (3)**	**0**
Data in window not <50 c/mL	1 (<1)[a]	0		
DC for lack of efficacy	1 (<1)[a]	0	1 (3)[b]	0
DC for other reason while not <50 c/mL	3 (3)	0		
No virologic data in window	**6 (5)**	**20 (17)**	0	0
DC due to AE or death	1 (<1)[c]	12 (10)[c]		
DC for other reasons	5 (4)	8 (7)		

CAB, cabotegravir; DC, discontinuation; IM, intramuscular; ITT-ME, intention-to-treat–maintenance exposed; LA, long-acting; Q4W, every 4 wk; Q8W, every 8 wk; RPV, rilpivirine.
[a]2 PDVF on Q8W at W8 (no emergent resistance) and W48 (emergent K103N, E138G, and K238T [FC RPV = 3.3; etravirine = 1.9]; INI—Q148R [FC CAB = 5.1; dolutegravir = 1.38]). [b]HIV-1 RNA 139 c/mL at withdrawal. [c]Q8W: injection-site reaction/chills/body pain (n=1); Q4W: hepatitis C, rash, depressive reaction, psychotic state, Churg-Strauss vasculitis, epilepsy (death), mesenteric vein thrombosis, QT prolongation/sinus tachycardia, met liver stopping criteria, coronary artery disease, myocardial infarction (death), motor neuron disease (all n=1).

Margolis et al. HIV Glasgow; Glasgow, UK. Poster 118.

Clinical Trial analysis

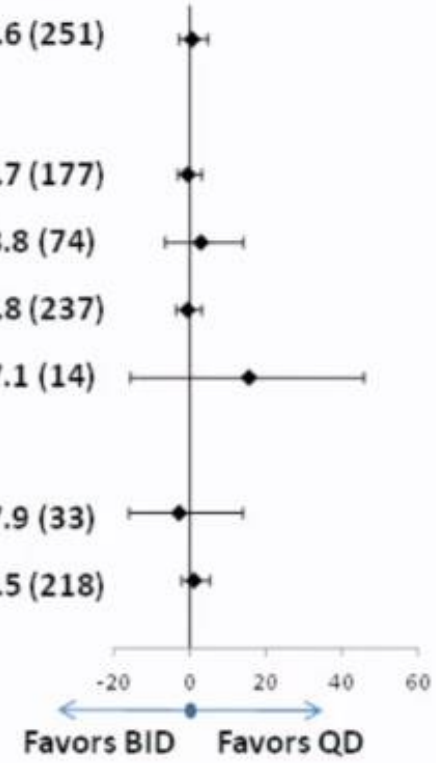
Intention to Treat (ITT)	Intention-to-treat (ITT) is an analysis of the participants taking part in a clinical trial, based on the group to which they were initially assigned, and not on the treatment eventually received. It does not matter if they drop out, whether they fully adhere to the treatment, or even if they switch to an alternative treatment. Intention-to-treat analyses are often used to assess the effectiveness of a new treatment because they are seen to reflect real life: not everyone adheres to the treatment they are given, and doctors often change treatments depending on how their patient's condition changes.
Per Protocol (PP)	An analysis that is restricted to the participants who fulfil the protocol in terms of the eligibility, interventions, and outcome assessment. This analysis restricts the comparison of the treatments outcomes to the participants who adhered perfectly to the clinical trial instructions as stipulated in the protocol, i.e. completed the full treatment. If done alone, this analysis leads to bias because it does not consider participants who did not follow the protocol completely for any reason.

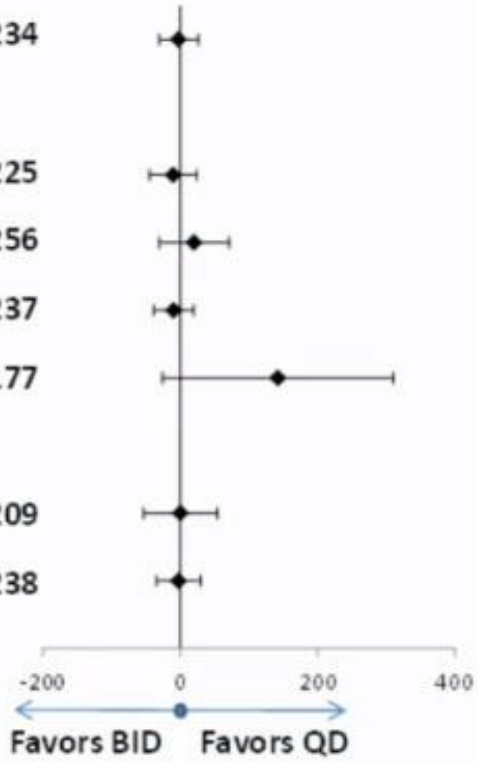
Source: EUPATI Glossary
https://www.eupati.eu/glossary/

ONCEMRK: Efficacy by Prognostic Factors (Observed Failure Approach)

Consistent efficacy across baseline HIV RNA and CD4 subgroups

	HIV RNA <40 copies/mL			CD4 Count (cells/mm^3)		
	% of Subjects (N)		QD – BID	Mean Change from BL		QD – BID
	1200 mg QD	400 mg BID	(95% CI)	1200 mg QD	400 mg BID	(95% CI)
All subjects	94.2 (501)	93.6 (251)		232	234	
Baseline HIV RNA						
≤100,000 c/mL	97.2 (358)	97.7 (177)		214	225	
>100,000 c/mL	86.7 (143)	83.8 (74)		276	256	
≤500,000 c/mL	95.2 (479)	95.8 (237)		228	237	
>500,000 c/mL	72.7 (22)	57.1 (14)		319	177	
Baseline CD4 Count						
≤200 cells/mm^3	85.1 (67)	87.9 (33)		209	209	
>200 cells/mm^3	95.6 (434)	94.5 (218)		235	238	





HIV Glasgow 2016 Abstract # 3514101

Resistance Analysis Population through Week 96

	B/F/TAF n=320	DTG + F/TAF n=325
Resistance analysis population	7	6
Emergent resistance	0	0

- **No participant developed treatment-emergent resistance through Week 96**
- Resistance analysis population includes any participant with virologic rebound at or after Week 8
  - Confirmed virologic failure without resuppression
    - Two consecutive HIV-1 RNA tests ≥ 50 c/mL after achieving < 50 c/ml and HIV-1 RNA ≥ 200 c/mL at the confirmation test

      or
    - ≥1 $\log_{10}$ copies/mL increase in HIV-1 RNA from nadir
  - HIV-1 RNA ≥ 200 c/mL at Week 96 or last visit on study drug (did not require confirmation)
- The second, confirmatory sample was sent for resistance analysis, unless there was no follow-up sample

ONCEMRK: Clinical Adverse Events by Race/Ethnicity

% Subjects with:	White		Black	
	RAL 1200 mg QD (N=301)	RAL 400 mg BID (N=172)	RAL 1200 mg QD (N=98)	RAL 400 mg BID (N=36)
Any Adverse Event (AE)	82.7	86.0	90.8	94.4
Drug-Related‡ (DR) AE	25.9	22.7	27.6	36.1
Serious AE	5.0	9.9	11.2	8.3
Serious & DR AE	0.3	0.6	0.0	2.8
Discontinued§ due to AE	0.3	1.2	1.0	5.6
% Subjects with:	**Asian**		**Hispanic/Latino**	
	RAL 1200 mg QD (N=83)	RAL 400 mg BID (N=40)	RAL 1200 mg QD (N=126)	RAL 400 mg BID (N=52)
Any Adverse Event (AE)	69.9	85.0	88.1	84.6
Drug-Related‡ (DR) AE	15.7	25.0	30.2	19.2
Serious AE	4.8	12.5	1.6	7.7
Serious & DR AE	0.0	0.0	0.0	0.0
Discontinued§ due to AE	0.0	2.5	1.6	1.9

‡ Determined by the investigator to be related to study drug.
§ Study medication withdrawn.

HIV Glasgow 2016 Abstract # 3514101

Adverse Events

Adverse Event (AE)	Any untoward (not favourable) medical occurrence in a patient, or clinical trial participant receiving a medicine, and which does **not** necessarily have a causal relationship with this treatment. Adverse events can therefore be: any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease **temporally associated with the use of a medicine**, whether or not considered related to the medicine.
Adverse Drug Reaction (ADR) *or Drug-Related AE*	A response to a medicinal product which is harmful and unintended. Response in this context means that a causal relationship between the medicinal product and an adverse event is at least a reasonable possibility. Adapted from the Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 3) 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294

EATG Training Academy
STEP-UP: Skills Training to Empower Patients

Source: EUPATI Glossary
https://www.eupati.eu/glossary/

ONCEMRK: Laboratory Abnormalities by Hepatitis B/C Co-Infection

	Hepatitis B/C Negative		Hepatitis B/C Positive	
% Subjects with:	RAL 1200 mg QD (N=515)	RAL 400 mg BID (N=258)	RAL 1200 mg QD (N=15)	RAL 400 mg BID (N=8)
Total Bilirubin (mg/dL)				
Grade 2: 1.6 - 2.5 x ULN	1.2	0.8	6.7	0.0
Grade 3: 2.6 - 5.0 x ULN	0.6	0.0	0.0	0.0
Grade 4: >5.0 x ULN	0.0	0.0	6.7†	0.0
Aspartate Aminotransferase (IU/L)				
Grade 2: 2.6 - 5.0 x ULN	2.9	1.9	6.7	0.0
Grade 3: 5.1 - 10.0 x ULN	1.2	0.4	0.0	0.0
Grade 4: >10.0 x ULN	0.2	0.0	6.7†	0.0
Alanine Aminotransferase (IU/L)				
Grade 2: 2.6 - 5.0 x ULN	1.7	0.4	26.7	12.5
Grade 3: 5.1 - 10.0 x ULN	1.0	0.4	0.0	0.0
Grade 4: >10.0 x ULN	0.2	0.0	6.7†	0.0

Subjects are counted once per test in the highest grade reported.

† Grade 4 ALT/AST/bili all occurred in a single patient: HBV flare (Gr 3 ALT/AST) occurred on Day 1 of study; Day 17: study treatment discontinued (due to worsening HBV); Day 28: Gr 4 ALT/AST/Bili; Day 43: mostly resolved.

HIV Glasgow 2016 Abstract # 3514101

Adverse Events Grading

Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	Severe	Hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living
Grade 4	Life-threatening or disabling	Urgent intervention indicated
Grade 5	Death	

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Adverse Events Leading to Study Drug Discontinuation Through Week 96

B/F/TAF n=320	DTG + F/TAF n=325
6 (1.9%)	**5 (1.6%)**
Atypical chest pain* [Day 31]	Erythema, Pruritis [Day 112]
Sleep disorder/dyspepsia/tension headache /depressed mood/insomnia [Day 65]*	Depression* [Day 420]
Cardiac arrest† [Day 28]	Lipoatrophy* [Day 464]
Paranoia [Day 302]	Depression* [Day 532]
Abdominal distention* [Day 304]	Supraventricular tachycardia [Day 597]
Depression* [Day 337]	

- 3 deaths were reported in the B/F/TAF arm:
  - Cardiac arrest† following appendicitis and septic shock [Day 28]
  - Gastric adenocarcinoma [Day 376]
  - Hypertensive heart disease and congestive cardiac failure [Day 412]

- 3 deaths were reported in the DTG + F/TAF arm:
  - Unknown [Day 174]
  - Pulmonary embolism, with ongoing chronic obstructive pulmonary disease [Day 266]
  - Lymphoma [Day 422]

*Reported as treatment-related.
† Participant was reported both to have discontinued due to AE and have cause of death as cardiac arrest.

Adverse Events Through Week 96

All Grade, %	B/F/TAF n=320	DTG + F/TAF n=325
Any AE	**88**	**89**
AEs occurring with ≥10% frequency		
Diarrhea	18	16
Headache	16	15
Nasopharyngitis	11	16
Upper respiratory tract infection	10	13
Nausea	9	11
Fatigue	8	10
Any drug-related AE	**20**	**28**
AEs occurring with ≥3% frequency		
Nausea	3	5
Diarrhea	3	3
Headache	4	3

p=0.02*

* Fisher Exact Test.

Laboratory Abnormalities Through Week 96

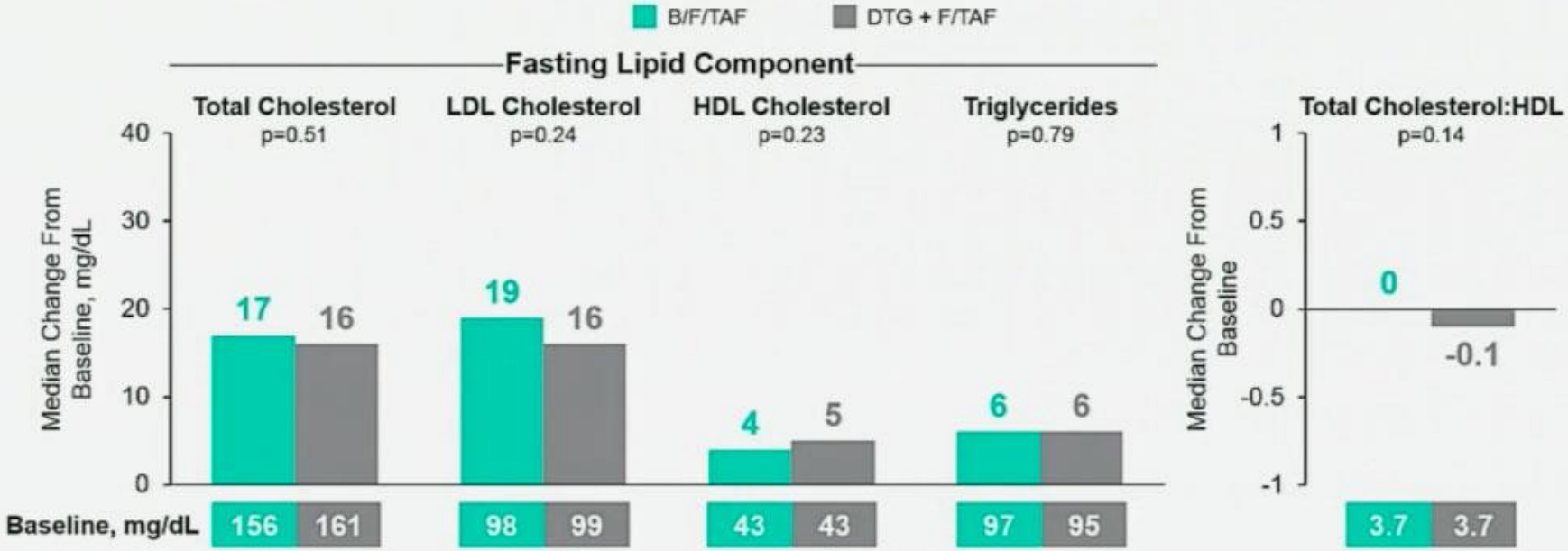
Grade 3 or 4 in ≥ 3% of either group

Grade 3 or 4, %	B/F/TAF n=320	DTG + F/TAF n=325
Creatine kinase elevation	5	3
LDL elevation, fasting	4	4
ALT elevation	3	1
Neutropenia	3	<1
Amylase elevation	2	3
AST elevation	2	3
Hyperglycemia, fasting	1	3
Glycosuria	1	3

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low-density lipoprotein.

* 2-sided Wilcoxon rank sum test.

Fasting Lipid Changes at Week 96



- Similar percentages of participants:
  - Were on lipid-lowering agents at baseline: B/F/TAF 6.6%, DTG + F/TAF 5.5%, p=0.62
  - Initiated lipid-lowering agents during the study: B/F/TAF 3.4%, DTG/ABC/3TC 3.7%, p=1.00

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.

ONCEMRK: Conclusions

- In HIV-1 treatment-naïve subjects, RAL 1200 mg QD demonstrated non-inferior efficacy compared to RAL 400 mg BID (both in combination with TDF/FTC) at Week 48
- Subgroup analyses confirm consistent virologic and immunologic efficacy across baseline demographic and prognostic factors, including vRNA >100,000 and >500,000 copies/mL, CD4 count ≤200 cells/mm^3, HBV/HCV co-infection, gender, viral subtype, and geographic region
- Among all subgroups examined, RAL 1200 mg QD was generally well tolerated with a safety profile similar to RAL 400 mg BID

HIV Glasgow 2016 Abstract # 3514101

Conclusions

- Initial HIV-1 therapy with B/F/TAF was noninferior to DTG + F/TAF at Week 96 by Snapshot algorithm with high rates of virologic suppression (HIV-1 RNA <50 copies/mL)
  - 84% B/F/TAF vs 86% DTG + F/TAF
  - Sensitivity analyses confirmed noninferiority
    - Per-protocol: 100% B/F/TAF vs 98% DTG + F/TAF
- No treatment-emergent resistance
- B/F/TAF was well tolerated
  - Few AEs leading to discontinuation occurred (6 vs 5 in the DTG + F/TAF arm)
  - More treatment-related AEs were reported in the DTG + F/TAF arm (p=0.02)
- There were no discontinuations due to renal AEs and no cases of tubulopathy, including Fanconi syndrome, in either treatment group
- Changes from baseline in lipid parameters were equivalent
- These results provide further evidence of longer-term safety, efficacy, and high barrier to resistance of B/F/TAF in people living with HIV-1

Comparison of Viral Replication Below 50 c/mL for Two-Drug (DTG+RPV) vs Three-Drug Current Antiretroviral Therapy in the SWORD-1 and SWORD-2 Studies

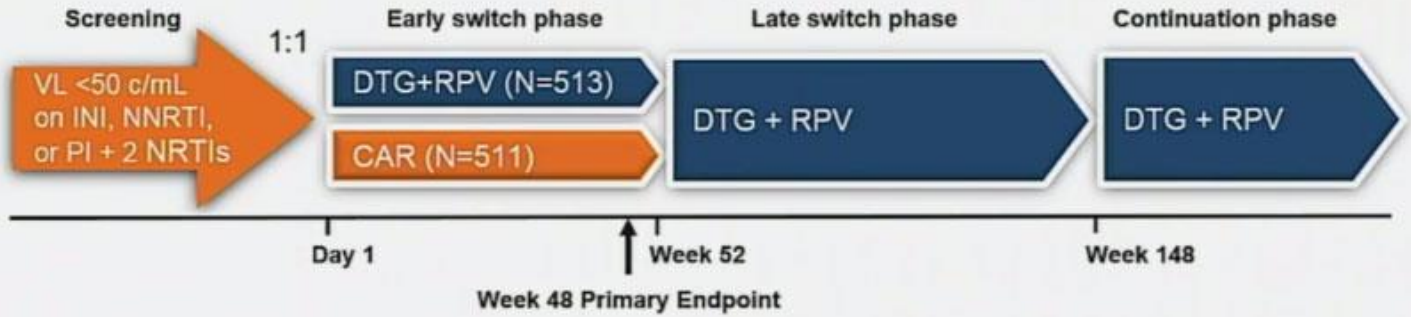
Mark Underwood,[1] Kostas Angelis,[2] Ruolan Wang,[1] Brian Wynne,[1] Veerle Van Eygen,[3] Libby Blair,[1] Lesley Kahl,[2] Tia Vincent,[4] Justin Koteff,[1] Michael Aboud[4]

[1]ViiV Healthcare, Research Triangle Park, NC, USA; [2]GlaxoSmithKline, Stockley Park, UK; [3]Janssen Pharmaceutica, Beerse, BE; [4]ViiV Healthcare, Brentford, UK

HIV Drug Therapy Glasgow; October 28-31, 2018; Glasgow, UK

SWORD-1 and SWORD-2 Phase III Study Design

Identically designed, randomized, multicenter, open-label, parallel-group, non-inferiority studies



- Week 48, 95% of participants in both arms remained suppressed with snapshot VL <50 c/mL in ITT–E population[1]
- Two subjects per arm met confirmed virologic withdrawal criteria (CVW).

CAR, current antiretroviral regimen; DTG, dolutegravir; INI, integrase inhibitor; ITT–E, intention-to-treat–exposed; NNRTI, non-NRTI; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine; VL, viral load.

1. Llibre et al. *Lancet*. 2018;391:839-849.

Underwood et al. HIV Glasgow 2018; Glasgow, UK. Poster P311.

Viral Load Assay

Abbott HIV-1 Realtime Assay

- Generates quantitative HIV-1 RNA viral load (VL) from 40 to 10,000,000 c/mL
- Generates qualitative data for VL<40 c/mL
  - HIV-1 RNA present → **TD** (target detected)
  - HIV-1 RNA not present → **TND** (target not detected)

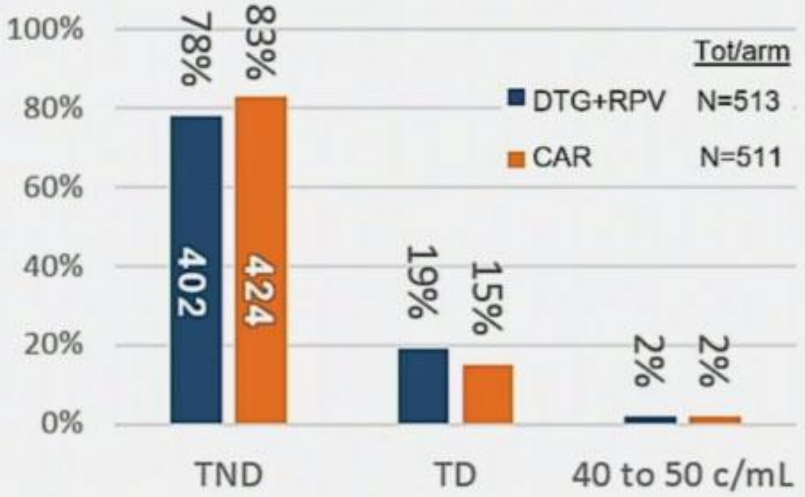
- Goal: Assess differences in low-level viremia for DTG+RPV 2-drug regimen vs CAR 3-drug regimen

CAR, current antiretroviral regimen; DTG, dolutegravir; RPV, rilpivirine; TD, target detected; TND, target not detected; VL, viral load.

Underwood et al. HIV Glasgow 2018; Glasgow, UK. Poster P311.

Proportions of VL Categories at Baseline

- TND and TD data showed variability at Baseline (Day 1) between arms
  - 5% higher TND for CAR arm
  - 4% higher TD for DTG+RPV arm



The Abbott Realtime assay measures quantitative HIV-1 RNA VL from 40 to 10,000,000 c/mL and generates qualitative TD or TND for VL<40 c/mL.
CAR, current antiretroviral regimen; DTG, dolutegravir; RPV, rilpivirine; TD, target detected; TND, target not detected; VL, viral load.

Underwood et al. HIV Glasgow 2018; Glasgow, UK. Poster P311.

Changes in VL Levels by Baseline VL Category Through Week 48

		DTG+RPV (N=513)			CAR (N=511)		
	Baseline	TND	TD	40-50 c/mL	TND	TD	40-50 c/mL
		399 (78%)	98 (19%)	12 (2%)	422 (83%)	76 (15%)	11 (2%)
Post-Baseline	≥50 c/mL[a]	21 (5%)	14 (14%)	4 (33%)	22 (5%)	13 (17%)	2 (18%)
	≥40 to <50 c/mL[a]	12 (3%)	4 (4%)	2 (17%)	5 (1%)	6 (8%)	1 (9%)
	TD[a]	177 (44%)	61 (62%)	4 (33%)	172 (41%)	43 (57%)	7 (64%)
	TND[b]	189 (47%)	19 (19%)	2 (17%)	223 (53%)	14 (18%)	1 (9%)

- By Baseline category, there were similar proportions of TD and TND Post-Baseline between the DTG + RPV and CAR arms
- Post-baseline TD was more common with Baseline TD compared with Baseline TND

Post-baseline categories are mutually exclusive; inclusion of participants into a category is based on highest VL observed (ie, from top to bottom rows). The percentages for post-baseline below the solid line are calculated from the percentages at baseline for categories above the solid line. Number and percentage colors and bolding in table are to increase visibility for DTG+RPV and CAR across arm comparisons. Three participants with TND in DTG+RPV and 2 in CAR had no post-baseline on-treatment VL data and thus are not included here in baseline TND totals. CAR, current antiretroviral regimen; DTG, dolutegravir; RPV, rilpivirine; TD, target detected; TND, target not detected; VL, viral load.

[a]In ≥1 time point after baseline through Week 48. [b]In all time points post-baseline.

Underwood et al. HIV Glasgow 2018; Glasgow, UK. Poster P311.

Similar Proportions of Participants With TND for DTG+RPV and CAR Arms Through Week 48

- Patients with TND at Baseline
- Similar proportions of TND and no changes in TND over time

CAR, current antiretroviral regimen; DTG, dolutegravir; RPV, rilpivirine; TND, target not detected.

Underwood et al. HIV Glasgow 2018; Glasgow, UK. Poster P311.

Snapshot Response by TND Similar Across DTG+RPV and CAR arms at Week 48

Virologic success, n (%)	DTG+RPV N=402	CAR N=424	Crude difference in proportions (95% CI)[a]	Adjusted difference in proportions (95% CI)[b]
VL <40 c/mL and TND	336 (84)	341 (80)	3.2 (−2.1 to 8.4)	3.1 (−2.2 to 8.3)

- Patients with TND at Baseline.
- Week 48 success as defined by TND was similar across the DTG+RPV and CAR arms.

CAR, current antiretroviral regimen; CI, confidence interval; DTG, dolutegravir; INI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine; TND, target not detected; VL, viral load. [a]Difference: Proportion on DTG + RPV − Proportion on CAR. [b]Based on Cochran–Mantel–Haenszel stratified analysis adjusting for stratifications factors: baseline age (< 50 or ≥50 years) and baseline third agent (PI, NNRTI, INI).

Underwood et al. HIV Glasgow 2018; Glasgow, UK. Poster P311.

Summary

- Participants with Baseline TD had more frequent TD occurences Post-Baseline than with Baseline TND.
  - Similar proportions of participants in the Post-Baseline categories of TND and TD were seen across the DTG+RPV and CAR arms.
- Similar proportions of participants with TND were observed at each visit through Week 48 for DTG+RPV and CAR arms.
- Using the more stringent TND as endpoint, no difference by snapshot was observed for the DTG+RPV 2-drug regimen vs the CAR 3-drug regimen at Week 48.

CAR, current antiretroviral regimen; DTG, dolutegravir; RPV, rilpivirine; TD, target detected; TND, target not detected.

Underwood et al. HIV Glasgow 2018; Glasgow, UK. Poster P311.