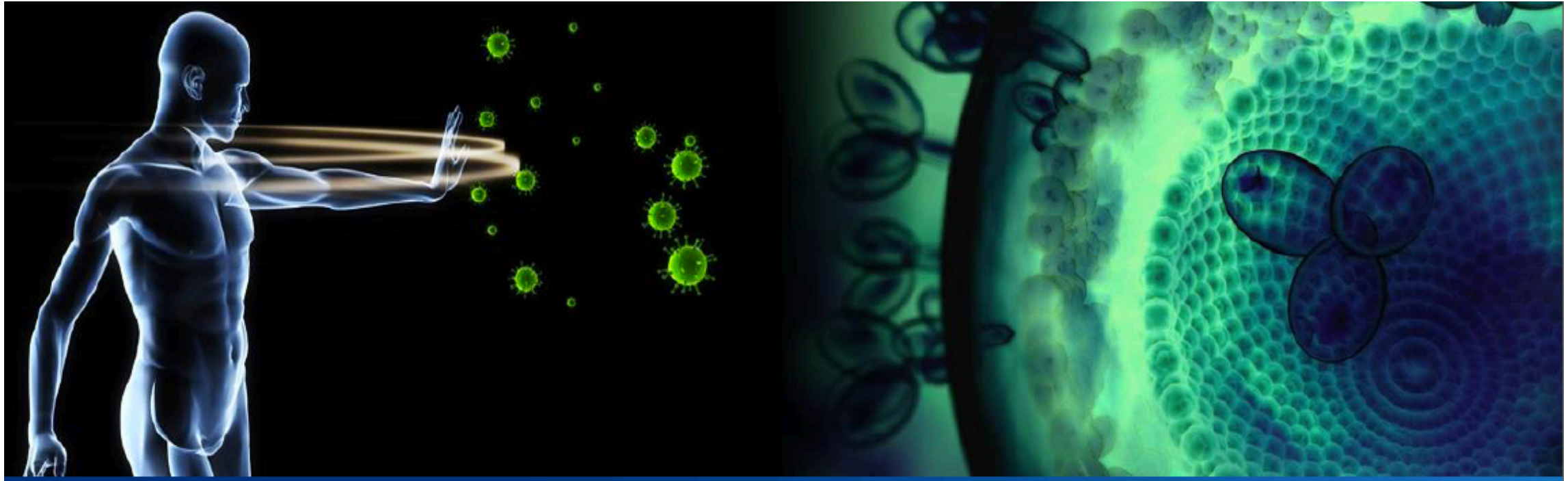
REUNIÃO DO OUTONO

17 de novembro de 2018

Highlights from Glasgow

1. Amber: week 96 results
2. GS-US-380-1490 Study

3. BRIGHTE Study: week 48 safety and efficacy results
4. LATTE-2 Week 160 Results
5. Safety and efficacy of Doravirine/Lamivudine/TDF
6. Efficacy of MK-8591



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

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PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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

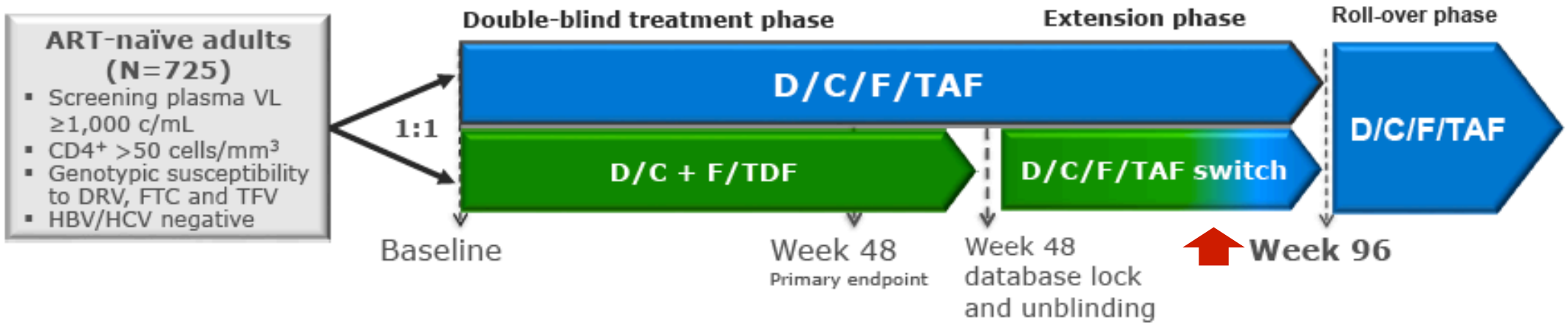
D/C/F/TAF: The First Once-Daily STR Containing Darunavir

- D/C/F/TAF:
  - Darunavir (DRV, D, 800mg), cobicistat (C, 150mg), emtricitabine (FTC, F, 200mg) and TAF, 10mg
  - Is being evaluated in two ongoing, pivotal phase 3 studies
    - AMBER: in ART-naïve adults, D/C/F/TAF was non-inferior to D/C + F/TDF (91% vs 88%; VL <50 c/mL at Week 48 by FDA Snapshot)[1]
    - EMERALD: in virologically suppressed adults, D/C/F/TAF was non-inferior to bPI + F/TDF (2.5% vs 2.1%; PDVR cumulative through Week 48[2]; 3.1% through Week 96 in D/C/F/TAF arm[3])
    - Better outcomes for D/C/F/TAF bone and renal parameters in both studies
  - D/C/F/TAF is a recommended combination in the EACS 2018 guidelines[4]

AMBER (NCT02431247) and EMERALD (NCT02269917)
STR, single-tablet regimen; TAF, tenofovir alafenamide; ART, antiretroviral therapy; VL, viral load; bPI, boosted protease inhibitor; PDVR, Protocol–defined virologic rebound (confirmed VL ≥50 c/mL)

1. Eron J, et al. *AIDS* 2018;32:1431–42
2. Orkin C, et al. *Lancet HIV* 2018;5:e23–e34
3. Eron J, et al. IDWeek 2018. Abstract 1768
4. EACS Guidelines, Version 9.1. October 2018

AMBER: Phase 3, Randomised, Double-blind, Multicentre Trial

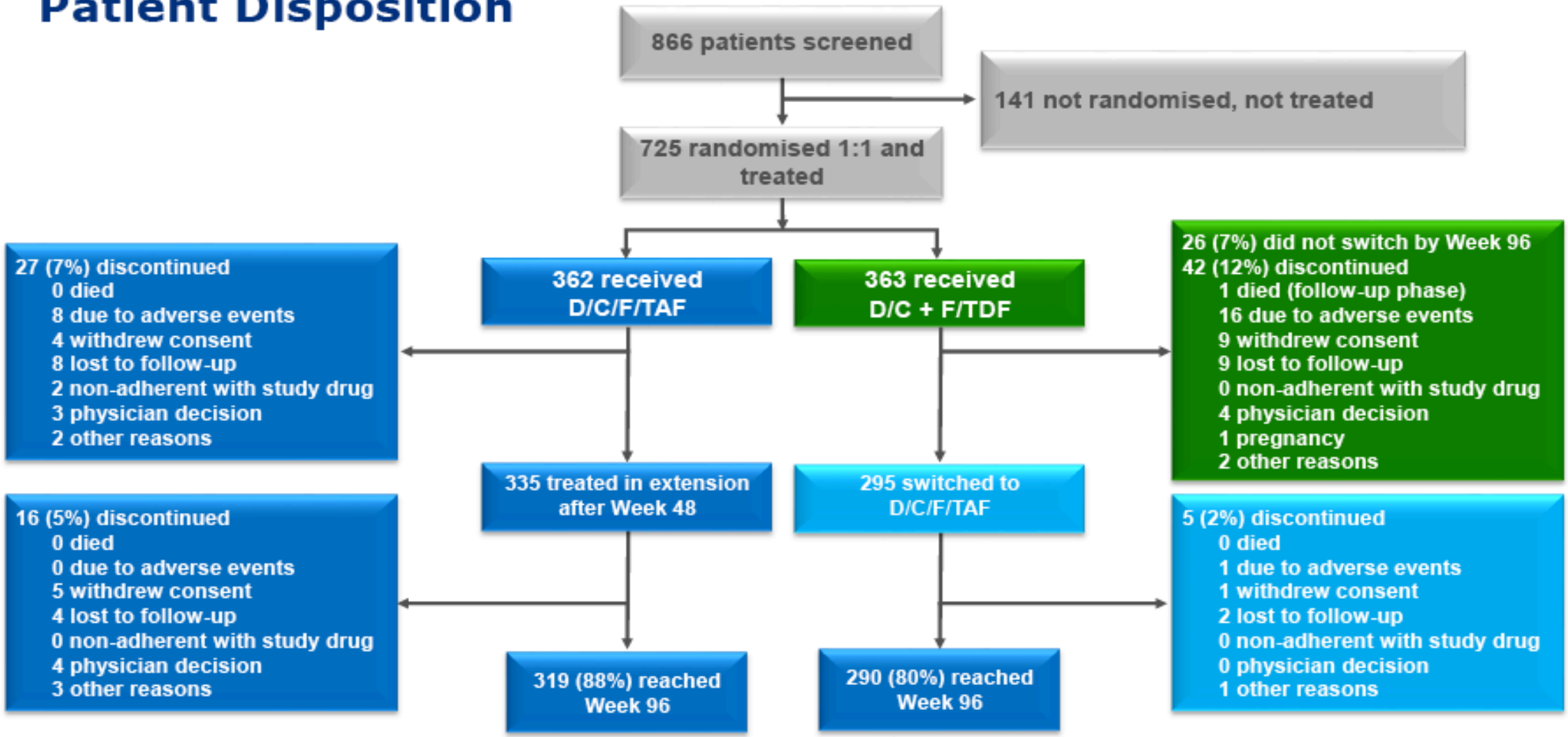


	D/C/F/TAF arm N=362	Control arm N=363	
		D/C+F/TDF N=363	D/C/F/TAF switch N=295
Patient-years of exposure[a]	626	512	109
Median (IQR) exposure, weeks[b]	96.1 (95.6; 97.0)	73.1 (72.0; 84.3)	22.3 (12.1; 24.3)

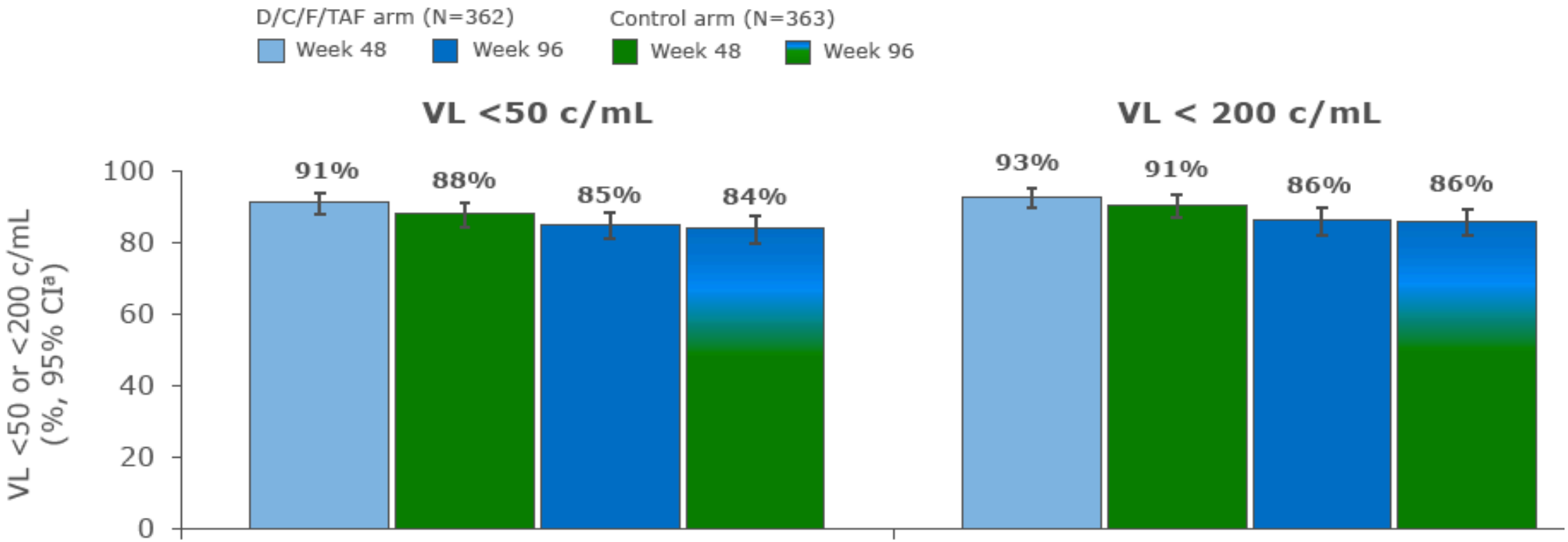
This presentation will focus primarily on the D/C/F/TAF group

ART, antiretroviral therapy; VL, viral load; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, inter-quartile range
[a]Patient-years of exposure = sum of treatment duration (weeks) x 7 /365.25;
[b]Treatment duration, weeks = (end of treatment phase – start of treatment phase + 1) /7

Patient Disposition



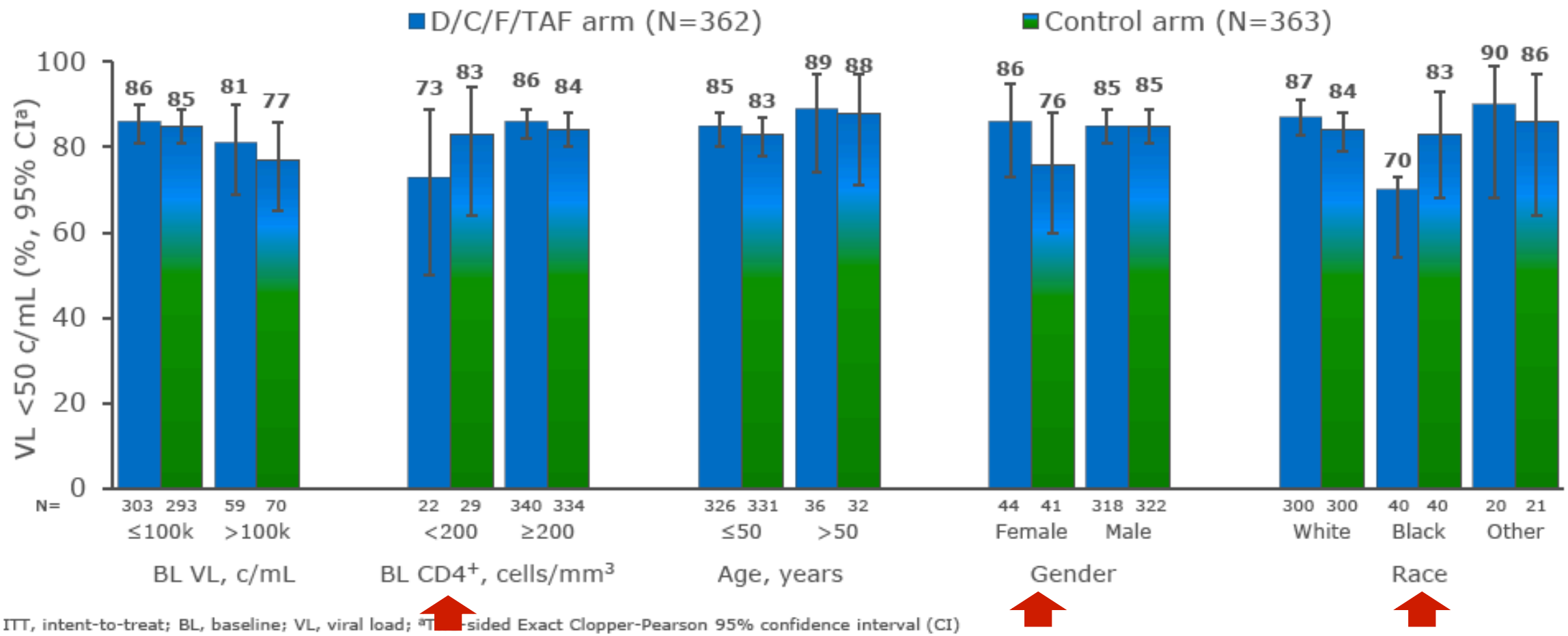
FDA Snapshot at Weeks 48 and 96 (ITT)



VL <50 c/mL	331 (91%)	321 (88%)	308 (85%)	304 (84%)	<200 c/mL	336 (93%)	329 (91%)	312 (86%)	312 (86%)
VL ≥50 c/mL	16 (4%)	12 (3%)	20 (6%)	16 (4%)	≥200 c/mL	10 (3%)	4 (1%)	15 (4%)	6 (2%)
No virologic data	15 (4%)	30 (8%)	34 (9%)	43 (12%)	NVD	16 (4%)	30 (8%)	35 (10%)	45 (12%)

ITT, intent-to-treat; VL, viral load; NVD, no virologic data [a]Two-sided Exact Clopper-Pearson 95% confidence interval (CI)

Snapshot VL <50 c/mL at Week 96 by Subgroups (ITT)



ITT, intent-to-treat; BL, baseline; VL, viral load; [a]Two-sided Exact Clopper-Pearson 95% confidence interval (CI)

Resistance Analysis Through Week 96

- Post-baseline genotyping/phenotyping (PhenoSenseGT) performed in PDVFs (virologic non-response, virologic rebound and/or viraemic at final timepoint) with VL ≥400 c/mL at failure or at later time points
- Available genotype/phenotype data in:
  - 9/15 PDVFs (D/C/F/TAF from baseline through Week 96)
    - M184I/V RAM detected at Week 36 in one patient[a,1]
  - 8/19 PDVFs (Control arm from baseline through Week 96)
    - M184V RAM detected at Week 84 (post-switch visit) in one patient[b]
  - **No DRV, primary PI or TFV RAMs observed post-baseline**

PDVF, protocol-defined virologic failure; VL, viral load; RAMs, resistance-associated mutations;
[a]FTC and 3TC resistance; patient had transmitted NNRTI resistance at screening and M184V was detected pre-treatment as minority variant (9%); Adherence based on pill count: 102%; discontinued due to non-compliance (DRV PK levels low);
[b]FTC and 3TC resistance; Adherence based on pill count: 90%-switch-80%; no PK data

1. Lathouwers E, et al. HIV Glasgow 2018. Abstract P294

Most frequent (≥5%) Grade 3 or 4 Laboratory Abnormalities

Incidence, n/N (%)	D/C/F/TAF arm	
	Baseline–Week 48 N=362	Baseline–Week 96 N=362
Patient-years exposure[a]	**323**	**626**
Fasting LDL-cholesterol (≥4·90 mmol/L; ≥190 mg/dL), n (%)	17/345 (**5**)	30/346 (**9**)

AMBER Week 96 Analysis: Conclusions

- Through Week 96 in treatment-naïve patients, D/C/F/TAF resulted in:
  - High response rates (85% VL <50 c/mL in D/C/F/TAF arm; FDA Snapshot)
    - Consistent results across patient subgroups
  - Low VF rates (6% VL ≥50 c/mL; FDA Snapshot)
  - No development of DRV, primary PI or TFV RAMs
    - M184I and/or V detected in one patient in each arm
- D/C/F/TAF bone, renal and lipid safety consistent with known TAF and cobicistat profiles

AMBER results through 96 weeks confirm the efficacy, high genetic barrier to resistance and bone/renal safety benefits of D/C/F/TAF for treatment-naïve patients

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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]

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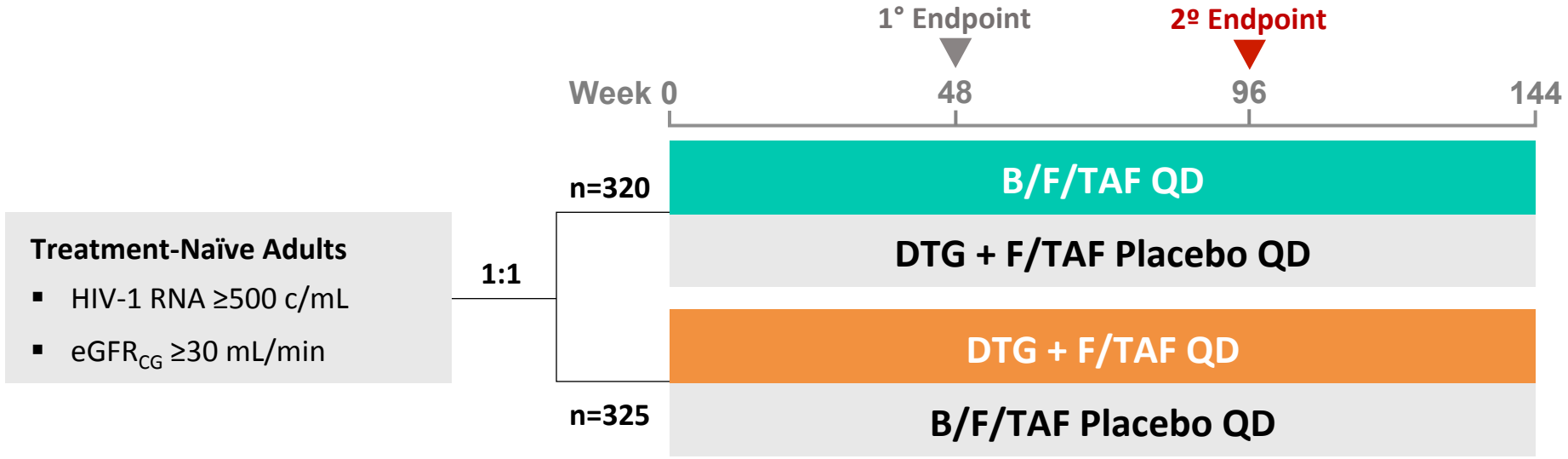
HIV Glasgow, Abstract 4185960
28 – 31 October 2018
Glasgow, UK

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.

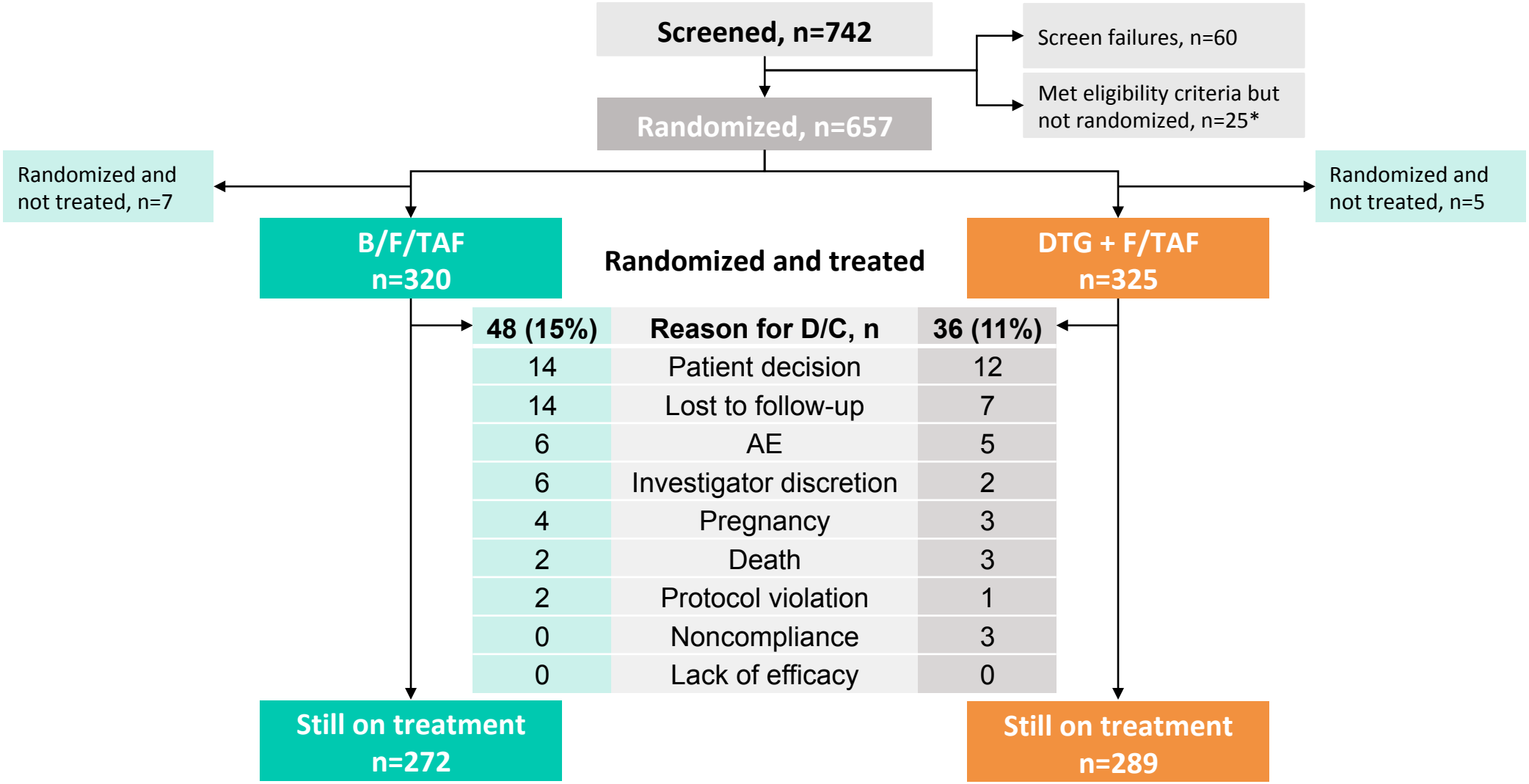
GS-US-380-1490 Study Design



- 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.

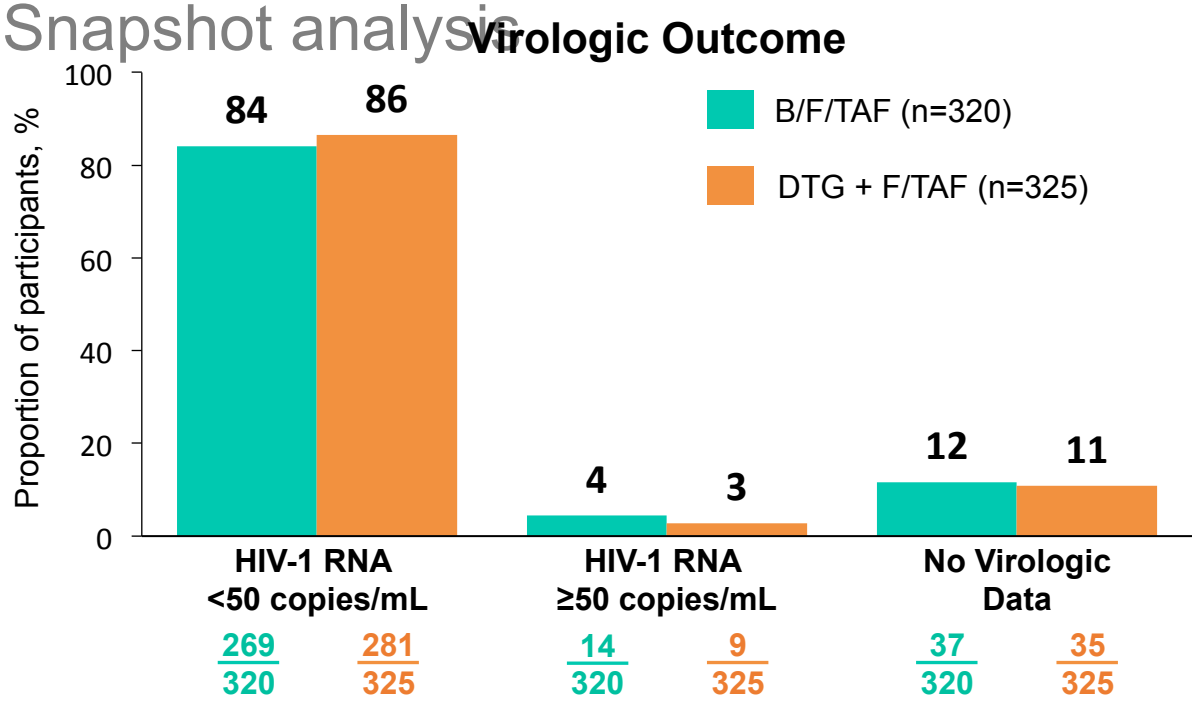
Participant Disposition From Baseline to Week 96

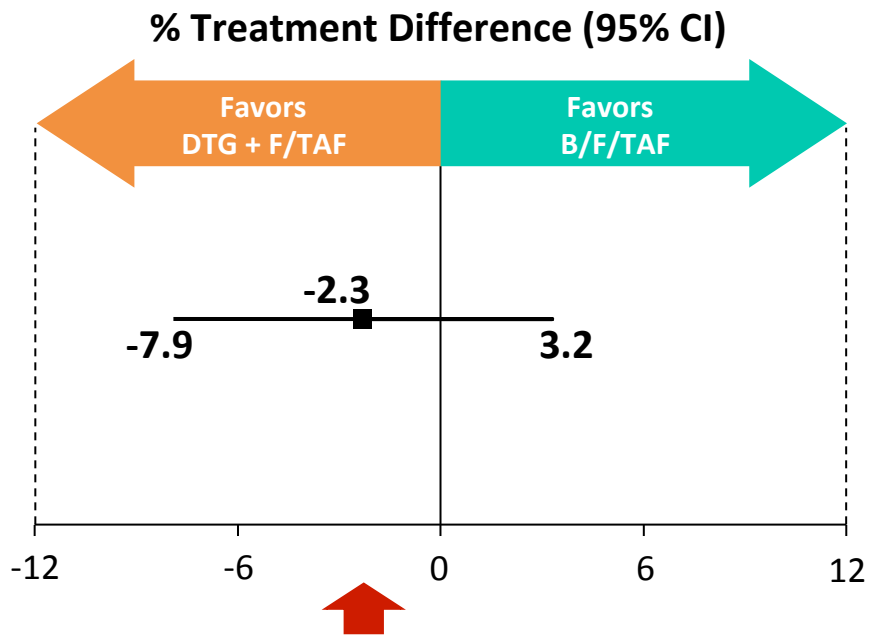


* Lost to follow-up (n=3), withdrew consent (n=14), investigator's discretion (n=2), AE (n=1), outside of visit window (n=2), other (n=3).

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.

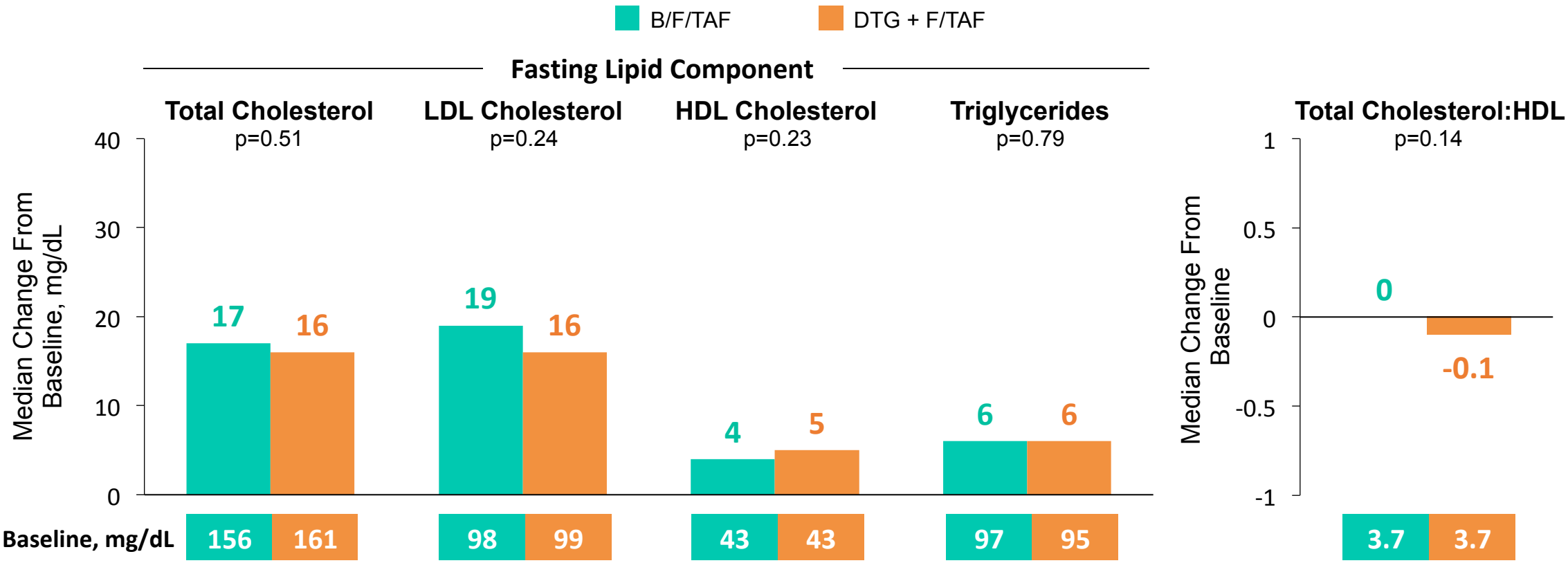
Resistance Analysis Population through Week 96

	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

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.

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

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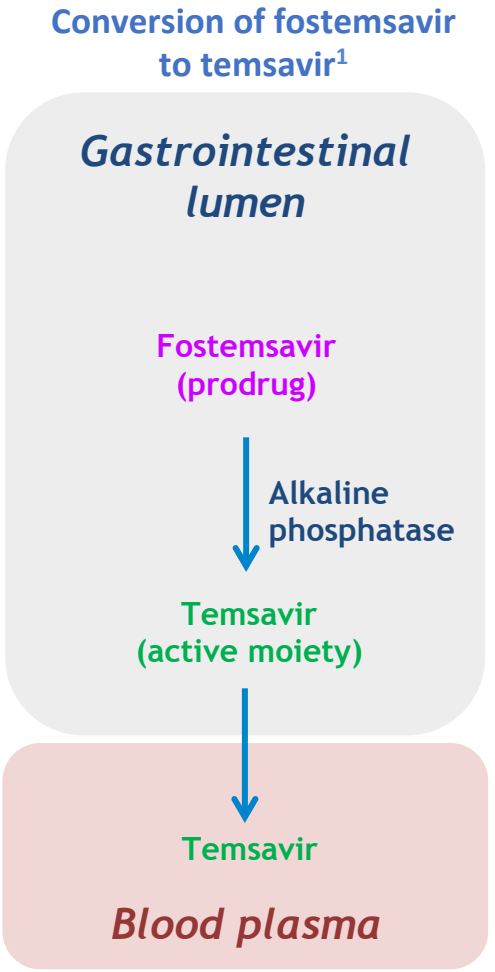
Week 48 Safety and Efficacy of the HIV-1 Attachment Inhibitor Prodrug Fostemsavir in Heavily Treatment-Experienced Participants (BRIGHTE Study)

J Aberg,[1] J-M Molina,[2] M Kozal,[3] P Cahn,[4] J Lalezari,[5] M Thompson,[6] R Diaz,[7] A Castagna,[8] G Pialoux,[9] M Gummel,[10] A Pierce,[11] P Ackerman,[12] C Llamoso,[12] M Lataillade[12]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Hôpital Saint-Louis, APHP and University of Paris Diderot Paris, Infectious Diseases, Paris, France; [3]Yale University School of Medicine, New Haven, CT, USA; [4]Fundación Huesped, Buenos Aires, Argentina; [5]Quest Clinical Research, San Francisco, CA, USA; [6]AIDS Research Consortium of Atlanta, GA, USA; [7]The Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil; [8]Clinic of Infectious Diseases, Vita-Salute San Raffaele University, Milan, Italy; [9]Hôpital Tenon, Paris, France; [10]GlaxoSmithKline, Upper Providence, Philadelphia, PA, USA; [11]ViiV Healthcare, Research Triangle Park, NC, USA; [12]ViiV Healthcare, Branford, CT, USA

Overview of Fostemsavir

- **Fostemsavir (FTR) is a first-in-class attachment inhibitor prodrug[1]** that is being specifically developed for HIV-1-infected, heavily treatment-experienced (HTE) patients
- **FTR has a unique resistance profile with no *in vitro* cross-resistance to other classes of ARVs[2,3]**
- At the Week 24 interim analysis for the ongoing Phase 3 BRIGHTE study, FTR demonstrated[4]
  - Superior efficacy relative to placebo (0.8 $\log_{10}$ c/mL decrease for FTR vs 0.2 $\log_{10}$ c/mL for placebo; treatment difference = 0.625, *P*<0.0001) after 8 days of functional monotherapy (primary endpoint)
  - A median decrease in HIV-1 RNA of 1 $\log_{10}$ c/mL in participants with baseline HIV-1 RNA >1,000 c/mL in the Randomised Cohort at Day 8
  - Virologic suppression (HIV-1 RNA <40 c/mL) in 53% of participants in the Randomised Cohort and 37% in the Non-randomised Cohort (81% of whom had FTR as the only fully active ARV) at Week 24
  - A mean increase in CD4+ T cell count by 90 cells/µL from baseline at Week 24 in the Randomized Cohort
  - A generally well-tolerated safety profile with few AEs leading to discontinuation
- **Here we present Week 48 efficacy and safety results from the ongoing BRIGHTE study** (formerly 205888/AI438-047)



AE, adverse event; ARV, antiretroviral.

1. Brown et al. *J Pharm Sci.* 2013;102:1742-1751. **2.** Nowicka-Sans et al. *Antimicrob Agents Chemother.* 2012;56:3498-3507.
3. Li et al. *Antimicrob Agents Chemother.* 2013;57:4172-4180. **4.** Kozal et al. Presented at: EACS 2017. Oral PS8/5.

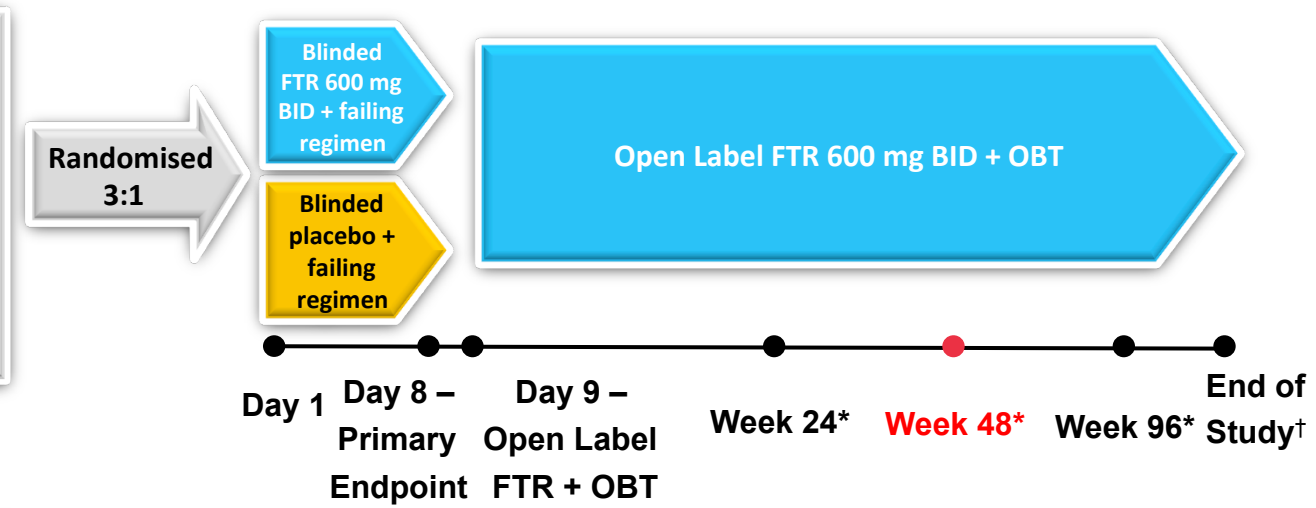
Aberg et al. HIV Glasgow 2018; Glasgow, UK. Oral 334A.

Study Design

BRIGHTE is an ongoing Phase 3 randomised, placebo-controlled, double blind trial

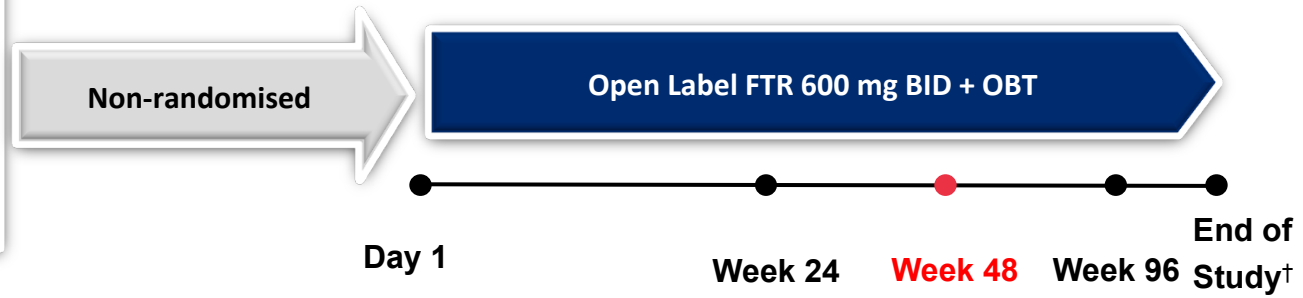
Randomised Cohort §:
HTE participants failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:

- 1 or 2 ARV classes remaining & ≥1 fully active & available agent per class
- Unable to construct viable regimen from remaining agents



Non-randomised Cohort §:
HTE participants, failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:

- 0 ARV classes remaining and no remaining fully active approved agents‡



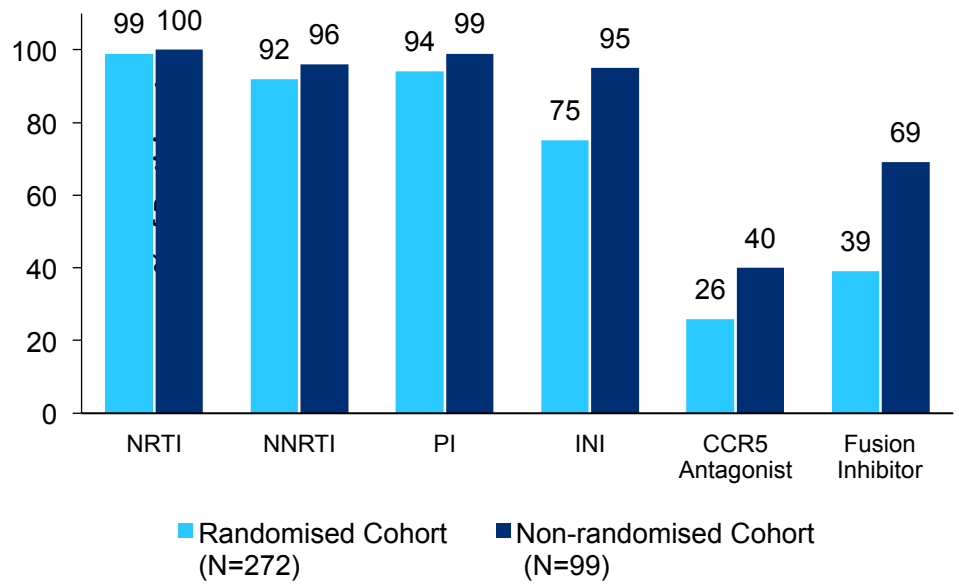
*Measured from the start of open label FTR 600 mg BID + OBT; †The study is expected to be conducted until an additional option, rollover study or marketing approval, is in place; ‡Use of investigational agents as part of OBT was permitted; §There was no screening TMR IC_{50} criteria.

BID, twice-daily; IC_{50}, half maximal inhibitory concentration; OBT, optimised background therapy.

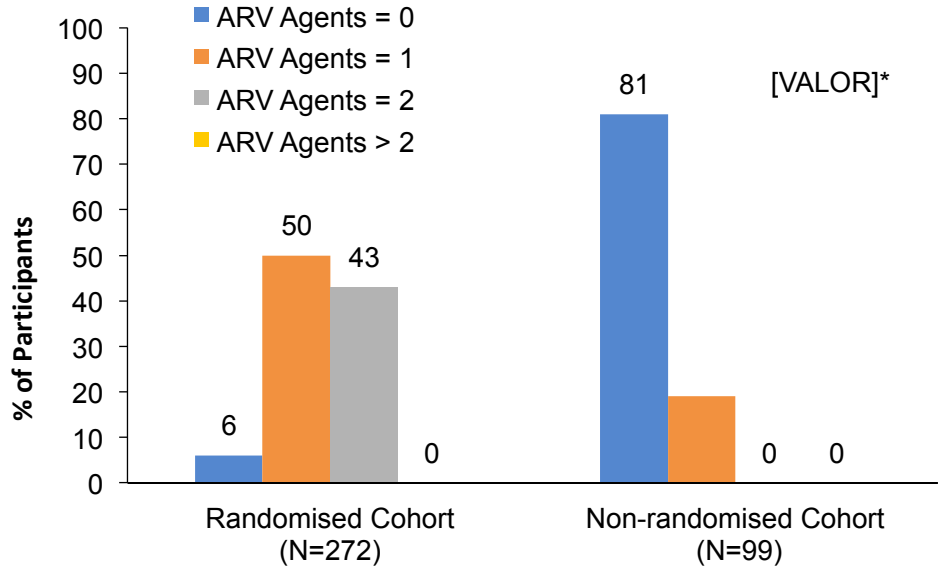
Aberg et al. HIV Glasgow 2018; Glasgow, UK. Oral 334A.

Prior ARV Exposure and Initial OBT

Prior Exposure to ARVs



Fully Active and Available ARV Agents in Initial OBT

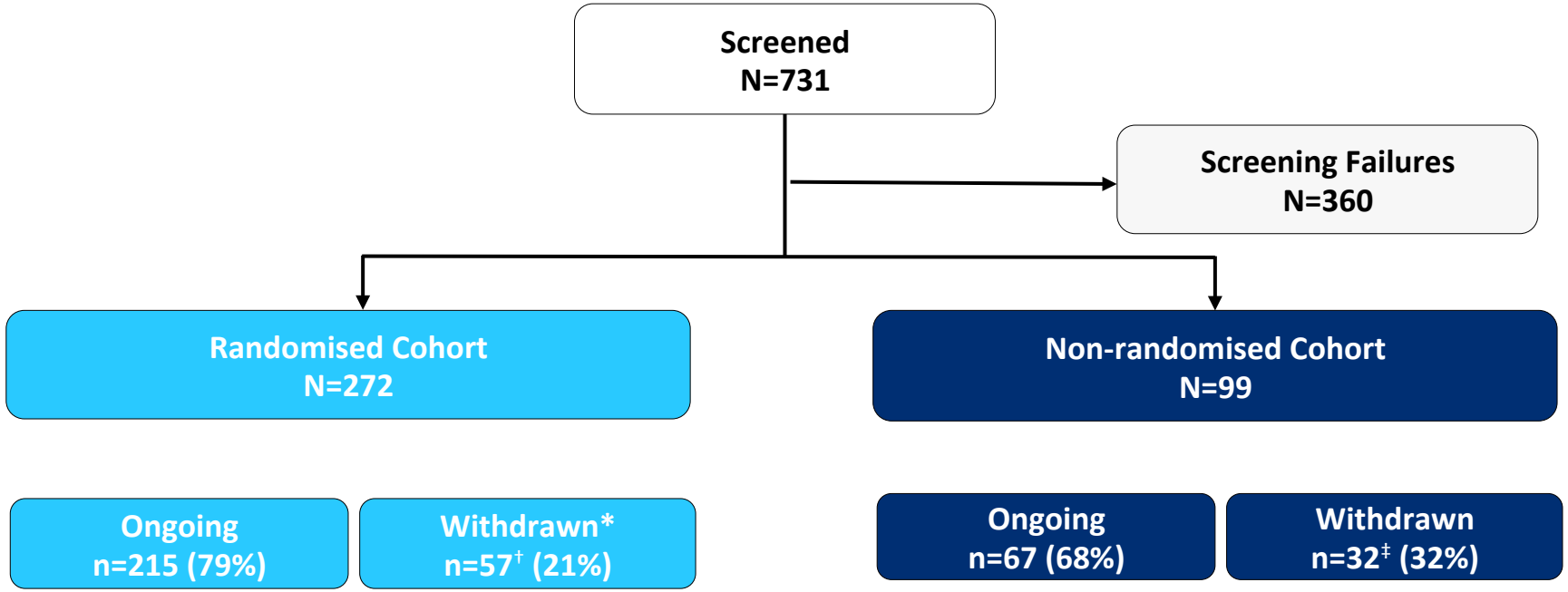


- Overall, 71% (262/371) of participants were treated for HIV-1 infection for>15 years, 85% (316/371) had prior experience with ≥5 ARV regimens (80% and 96% were INSTI and PI experienced, respectively), and 86% (320/371) had a history of AIDS
- In the Randomised Cohort, 50% (137/272) and 43% had 1 or 2 FAAs in their initial OBT, respectively
  - Of the 99 Non-randomized participants, 81 had no approved FAAs or investigational ARVs in their initial OBT and 15 had investigational ibalizumab in their initial OBT

*15/19 received investigational ARV Ibalizumab.
INI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-NRTI; PI, protease inhibitor.

Aberg et al. HIV Glasgow 2018; Glasgow, UK. Oral 334A.

Study Disposition Through Week 48



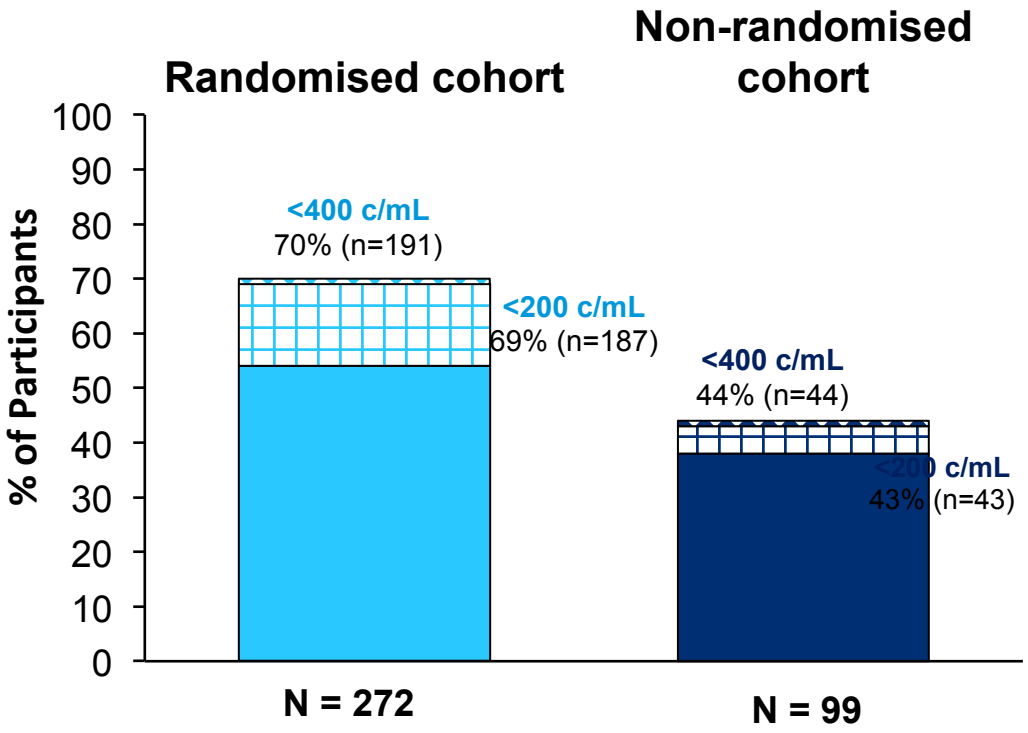
- Through Week 48, 57/272 (21%, Randomised) and 32/99 (32%, Non-randomised) participants discontinued early; six participants (FTR n=5; placebo n=1) discontinued during the double-blind period.

*6 participants (FTR n=5; placebo n=1) discontinued during the double-blind period of the study. †Withdrawal reasons (n, %): AEs (9, 3%), lack of efficacy (12, 4%), non-adherence (11, 4%), withdrawn consent (5, 2%), lost to follow-up (7, 3%), no longer met study criteria (3, 1%), death (8, 3%), pregnancy (1, <1%) and other (1, <1%). §Withdrawal reasons (n, %): AEs (5, 5%), lack of efficacy (6, 6%), non-adherence (5, 5%), withdrawn consent (1, 1%), lost to follow-up (1, 1%), no longer met study criteria (2, 2%) and death (12, 12%).

Aberg et al. HIV Glasgow 2018; Glasgow, UK. Oral 334A.

Virologic Response at Week 48 (Snapshot Analysis)*

Outcome	Randomised Cohort (N=272)	Non-randomised Cohort (N=99)
Virologic Success (<40 c/mL), n (%)	146 (54)	38 (38)
Virologic Failure, (≥40 c/mL), n (%)	104 (38)	52 (53)
Data in window not below threshold	72 (26)	33 (33)
D/C for lack of efficacy	6 (2)	2 (2)
D/C for other reason while not below threshold	9 (3)	3 (3)
Change in OBT*	17 (6)	14 (14)
No Virologic Data	22 (8)	9 (9)
D/C study due to AE or Death	15 (6)	8 (8)
D/C study for Other Reasons	5 (2)	1 (1)
Missing data during window but on study	2 (<1)	0



At Week 24, **53%** of Randomised participants and **37%** of Non-randomised participants had an HIV-1 RNA <40 c/mL

*Change in OBT for efficacy reasons were considered virologic failures in this analysis.

ART, antiretroviral therapy; D/C, discontinued.

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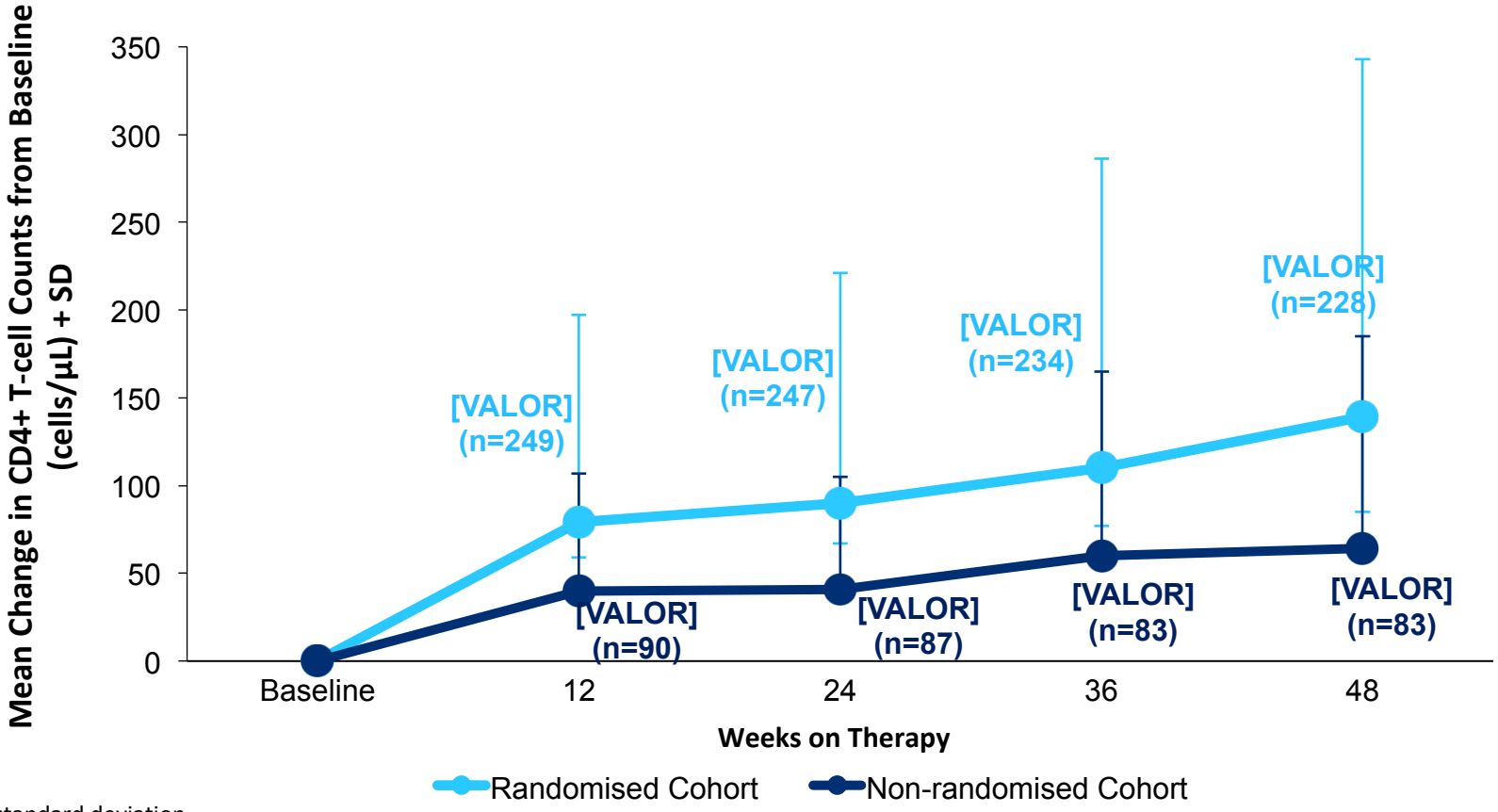
Mean Change in CD4+ T-cell Counts from Baseline through Week 48: Observed Analysis

Mean CD4+ T-cell count at baseline was 153 cells/μL (SD=182) for the Randomised Cohort and 99 cells/μL (SD=131) for the Non-randomised Cohort



SD, standard deviation.

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Week 48 Safety Summary *

Parameter, n (%)	Randomised Cohort (N=272)	Non-randomised Cohort (N=99)	Total Treated Participants (N=371)
Any Event	**247 (91)**	**96 (97)**	**343 (92)**
Grade 2-4 related Aes	55 (20)	22 (22)	77 (21)
Grade 3-4 AEs	70 (26)	47 (47)	117 (32)
AEs leading to Discontinuation	14 (5)	13 (13)	27 (7)
SAEs†	85 (31)	44 (44)	129 (35)
Related SAEs	7 (3)	3 (3)	10 (3)
Deaths‡	11 (4)	14 (14)	25 (7)

- FTR was well tolerated through Week 48 with few discontinuations due to AEs
- 92% (343/371) of participants had ≥1 AEs; most were Grade 1 to 2 in intensity and resolved without interruption of study drug
- 35% of participants had ≥1 serious AE (SAE); most were related to infections
- Compared with the Randomised Cohort, the Non-randomized Cohort experienced higher rates of SAEs (31% vs 44%), Grade 3 to 4 AEs (26% vs 47%) and deaths (4% vs 14%)

*All safety data reflect cumulative results collected through the data cutoff date of 4 March 2018. All treated participants had the opportunity to complete the Week 72 study assessment prior to the current data lock; †**The majority (15%) of SAEs were from the infections/infestations system organ class; ‡17/25 deaths were due to AIDS-related events, IRIS, or acute infection**; estimated median CD4 T-cell count among participants who died was 7 cells/μL IRIS, immune reconstitution inflammatory syndrome; SAE, serious adverse event.

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Grade 2 to 4 Treatment-Related AEs*

Parameter, n (%)	Randomised Cohort (N=272)	Non-randomised Cohort (N=99)	Total Treated Participants (N= 371)
Any Event	**55 (20)**	**22 (22)**	**77 (21)**
Nausea	10 (4)	5 (5)	15 (4)
Diarrhea	7 (3)	3 (3)	10 (3)
Headache	7 (3)	1 (1)	8 (2)
Immune reconstitution inflammatory syndrome	5 (2)	1 (1)	6 (2)
Vomiting	4 (1)	2 (2)	6 (2)
Fatigue	3 (1)	2 (2)	5 (1)
Asthenia	2 (<1)	2 (2)	4 (1)

- Consistent with the results from Week 24, the most common Grade 2 to 4 treatment-related AEs were nausea (4%), diarrhea (3%) and headache (2%)

*Grade 2–4 related AEs occurring in ≥2% of participants in either arm.

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Conclusions

- **Rates of virologic suppression were maintained from Week 24 through Week 48**, despite continued attrition in this active trial
- **There were continued, clinically meaningful, improvements in CD4+ T-cell count through Week 48**, including among those who were most immune-compromised at baseline
- FTR-containing regimens were well tolerated through Week 48 with **few discontinuations due to AEs**
- Majority of significant safety events (Grade 3-4 AEs/SAEs/deaths) were related to infections or progression of AIDS and occurred in participants in the Non-randomised Cohort, who had lower baseline CD4 counts and no approved FAAs to pair with FTR at study start
- **Week 48 results from the ongoing BRIGHTE study support further development of FTR as a therapeutic option for HIV-1-infected HTE participants with multi-drug resistance and few remaining active therapies**

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REUNIÃO DO OUTONO

17 de novembro de 2018

Highlights from Glasgow

1. Amber: week 96 results
2. GS-US-380-1490 Study

3. BRIGHTE Study: week 48 safety and efficacy results
4. **LATTE-2 Week 160 Results**
5. Safety and efficacy of Doravirine/Lamivudine/TDF
6. Efficacy of MK-8591

Safety, Efficacy and Durability of Long-Acting Cabotegravir (CAB) and Rilpivirine (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]

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[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

Introduction

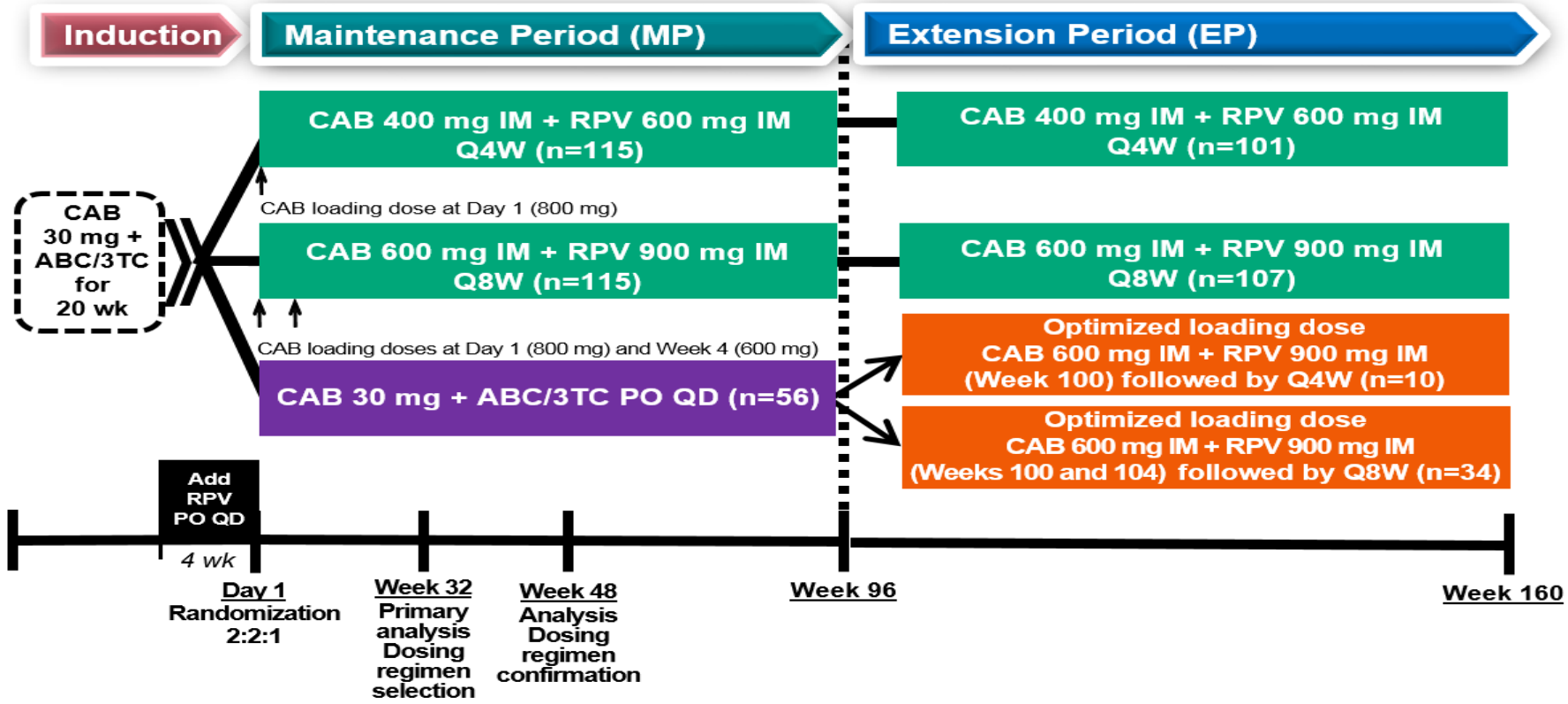
- LA injectable suspensions of CAB and RPV are in phase III development
- LATTE-2 Week 48/96 data supported the decision to evaluate the Q4W and Q8W CAB LA + RPV LA IM regimen in ongoing phase III studies[1]
- **The Week 160 analysis evaluated the long-term efficacy, safety, and tolerability of both IM dosing regimens**

CAB, cabotegravir; IM, intramuscular; LA, long acting; Q4W, every 4 wk; Q8W, every 8 wk; RPV, rilpivirine.

1. Margolis et al. *Lancet.* 2017;390:1499-1510.

LATTE-2 Study Design

- Phase IIb, multicenter, parallel-group, open-label study in ART-naive HIV-infected adults



ART, antiretroviral therapy; CAB, cabotegravir; EP, extension period; IM, intramuscular; LA, long acting; MP, maintenance period; PO, oral; QD, once daily; Q4W, every 4 wk; Q8W, every 8 wk; RPV, rilpivirine.

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Snapshot Outcomes at Week 160

- 309 patients were enrolled (ITT-exposed): 91% male, 20% non-white, and 19% >100,000 c/mL HIV-1 RNA. 286 patients were randomized into the MP; 258 completed MP with 252 entering EP

Outcome at W160[a]	Q8W IM n (%)	Q4W IM n (%)	Optimized Q8W IM n (%)	Optimized Q4W IM n (%)
Snapshot (ITT-ME)	N=115	N=115	N=34	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)[b]	0	0	0
DC for lack of efficacy	1 (<1)	0	1 (3)	0
DC for other reason while not <50 c/mL	3 (3)[c]	0	0	0
No virologic data in window	**6 (5)**	**20 (17)**	**0**	**0**
W/D due to AE or death	1 (<1)	12 (10)[d]	0	0
W/D due to other reasons	5 (4)[e]	8 (7)[f]	0	0

[a]Data presented for the randomized Q8W/Q4W IM arms are inclusive of MP and EP. Data presented for the optimized Q8W/Q4W IM arms are inclusive of on-treatment events occurring from the first date of first injection in the EP, W100.
[b]77 c/mL. [c]>50 c/mL at W96 and did not qualify for EP. [d]Added in EP: CAD; MI (death); motor neuron disease. [e]Relocation; entered LTFU; burden of travel; lost to FU. [f]Added in EP: PD; lost to FU; WD by patient.

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Protocol-Defined Virologic Failure

- Through 160 weeks, there were 2 PDVFs, both Q8W
  - No additional PDVFs occurred after Week 48 in any arm
  - Resistance data were previously reported[1]

PDVF, protocol-defined virologic failure; Q8W, every 8 wk.

1. Margolis et al. *Lancet.* 2017;390:1499-1510.

Margolis et al. HIV Glasgow; Glasgow, UK. Poster P118.

Adverse Events Through Week 160

Week 160 Safety[a]	Q8W IM N=115 n (%)	Q4W IM N=115 n (%)	Optimized Q8W IM N=34 n (%)	Optimized Q4W IM N=10 n (%)
Grade 3/4 AEs, excluding ISRs	24 (21)	29 (25)	0	1 (10)
Drug-related grade 3/4 AEs, excluding ISRs	2 (2)	6 (5)	0	0
Serious AEs	17 (15)	21 (18)	2 (6)	0
Drug-related SAEs	0	1 (<1)[b]	0	0
Fatal SAEs	0	2 (2)[b]	0	0
AEs leading to withdrawal[c]	3 (3)	12 (10)	0	1 (10)
Grade 3/4 hematology labs	4 (3)	2 (2)	0	0
Grade 3/4 chemistry labs	28 (24)	38 (33)	3 (9)	1 (10)
Select grade 3-4 laboratory abnormalities				
Creatine kinase (CK)	11 (10)	13 (11)	1 (3)	0
Alanine aminotransferase (ALT)	6 (5)	5 (4)	0	0
Lipase	8 (7)	7 (6)	1 (3)	1 (10)
Total neutrophils	3 (3)	2 (2)	0	0

[a]Data presented for the randomized Q8W/Q4W IM arms are inclusive of MP and EP. Data presented for the optimized Q8W/Q4W IM arms are inclusive of on-treatment events occurring from the first date of first injection in the EP, W100. [b]MI (possibly drug-related, fatal), epilepsy (fatal). [c]Added in EP: Q8W: Hep C; Q4W: CAD, MI, motor neuron disease, hypoesthesia/muscular weakness/ fatigue; Optimized Q4W: injection site pain.

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Adverse Events Through Week 160 (cont)

- In the randomized Q8W/Q4W IM arms, 99% of ISR events were mild (85%) or moderate (14%), and 87% resolved within 7 days
  - 2/230 (<1%) had an ISR that led to discontinuation (both Q8W subjects) through Week 160
  - No randomized IM patient had an ISR that led to discontinuation after Week 48
- In the optimized Q8W/Q4W IM arms, 98% of ISR events were mild (81%) or moderate (17%), and 91% resolved within 7 days
  - 1/44 (2%) had an ISR that led to discontinuation (Q4W)

IM, intramuscular; ISR, injection-site reaction; LA, long acting; Q4W, every 4 wk; Q8W, every 8 wk; RPV, rilpivirine.

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Conclusions

- **CAB LA + RPV LA, dosed Q8W or Q4W, successfully maintained HIV-1 viral load <50 c/mL**
  - The Week 160 data demonstrate long-term durability and tolerability of both dosing options
- **2 patients on LA dosing met PDVF criteria**, no subjects after Week 48 across all arms
- **Good injection tolerability was demonstrated over time**
  - Majority of ISRs were grade 1/2 pain with a median duration of 3 days
  - ~1% of patients had an ISR that led to discontinuation through 3 years of dosing
- **Q8W and Q4W dosing are both under evaluation in ongoing phase III studies**

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Safety and Efficacy of Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate in Treatment-Naïve HIV-1 Infected Adults With Transmitted Non-Nucleoside Reverse Transcriptase Inhibitor Resistance Mutations

Alexander Wong[1]; Deborah Goldstein[2]; Josep Mallolas[3]; Edwin DeJesus[4]; Margaret Johnson[5]; Jean-Michel Molina[6]; Anton Pozniak[7]; Anthony Rodgers[8]; Valerie Teal[8]; Deborah Hepler[8]; Sushma Kumar[8]; Peter Sklar[8]; George J Hanna[8]; Carey Hwang[8]; Cyrus Badshah[8]; Hedy Teppler[8]

[1]Department of Medicine, University of Saskatchewan, Regina, Canada; [2]Whitman-Walker Institute, Department of Clinical Research, Washington, DC, USA; [3]University of Barcelona, Hospital Clinic-IDIBAPS, Barcelona, Spain; [4]Orlando Immunology Center, Department of Clinical Research, Orlando, FL, USA; [5]Royal Free London NHS Foundation Trust, Department of HIV Medicine, London, UK; [6]University of Paris Diderot, Hôpital Saint-Louis, Paris, France; [7]Chelsea and Westminster Hospital, NHS Foundation Trust, London, UK; [8]Merck & Co., Inc., Kenilworth, NJ, USA

BACKGROUND

- HIV-1 with mutations conferring resistance to antiretroviral drugs can be transmitted from infected individuals to uninfected individuals, increasing the risk for subsequent treatment failure
  - Transmitted mutations associated with resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) have an estimated prevalence ranging from 3% to 10% in treatment-naïve patients[1,2]
  - The most common transmitted NNRTI-resistance mutation is the reverse transcriptase (RT) amino acid substitution K103N, followed by mutations at position Y181 and G190[3]
- Doravirine (DOR) is a novel NNRTI recently approved in the US for the treatment of HIV-1
  - In the DRIVE-FORWARD trial, DOR 100 mg demonstrated non-inferior efficacy to ritonavir-boosted darunavir and a more favorable lipid profile[4]
  - In the DRIVE-AHEAD trial, co-formulated DOR 100 mg, lamivudine 300 mg, and tenofovir disoproxil fumarate 300 mg (DOR/3TC/TDF) demonstrated non-inferior efficacy to co-formulated efavirenz 600 mg, emtricitabine 200 mg, and TDF 300 mg (EFV/FTC/TDF) and a superior CNS safety profile[5]
- DOR is active in vitro against both wild-type HIV-1 and the most common NNRTI-resistant variants at concentrations achieved with 100 mg once-daily dosing[6]
- DOR has an in vitro resistance profile that is unique among NNRTIs[7]
- This study examined the efficacy and safety of DOR in treatment-naïve adults with HIV-1 and transmitted NNRTI resistance mutations

METHODS

Study Design

- Phase 2, multicenter, open-label, single-arm trial in HIV-1 infected adults (≥18 years of age) who were naïve to antiretroviral therapy and had:
  - Plasma HIV-1 RNA ≥1000 copies/mL and $CD4^+$ T-cell count ≥100 cells/mm^3 within 45 days prior to initiation of study treatment
  - A single NNRTI mutation consisting of RT K103N, Y181C, or G190A
  - Calculated creatinine clearance (CrCL) ≥50 mL/min, alkaline phosphatase ≤3.0x upper normal limit, AST (SGOT) and ALT (SGPT) ≤5.0x upper normal limit, and hemoglobin ≥9.0 g/dL for females or ≥10.0 g/dL for males

CONCLUSIONS

- Although the targeted enrollment was not reached, antiretroviral and immunologic efficacy of DOR/3TC/TDF was observed at Week 48 in participants with transmitted NNRTI resistance mutations (K103N in 7, and G190A in 1)
- No participant developed additional drug resistance mutations during the trial
- DOR/3TC/TDF was generally well tolerated in this population with no reported deaths or drug-related serious adverse events and no discontinuations due to an adverse event
- Although further study is needed, these clinical results support the activity of DOR against selected HIV-1 NNRTI resistance mutations, K103N and possibly G190A

Efficacy of MK-8591 Against Diverse HIV-1 Subtypes and NRTI-Resistant Clinical Isolates

J.A. Grobler; Q. Huang; D.J. Hazuda; M.-T. Lai

Merck & Co., Inc., Kenilworth, NJ, USA

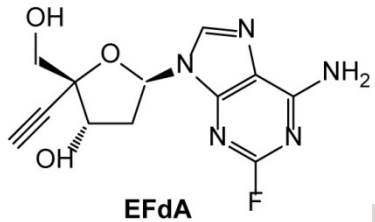
BACKGROUND

MK-8591: A Novel Nucleoside With a Unique Mechanism of Action

MK-8591 (4'-ethynyl-2-fluoro-2'-deoxyadenosine; EFdA), licensed from Yamasa

First-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI)

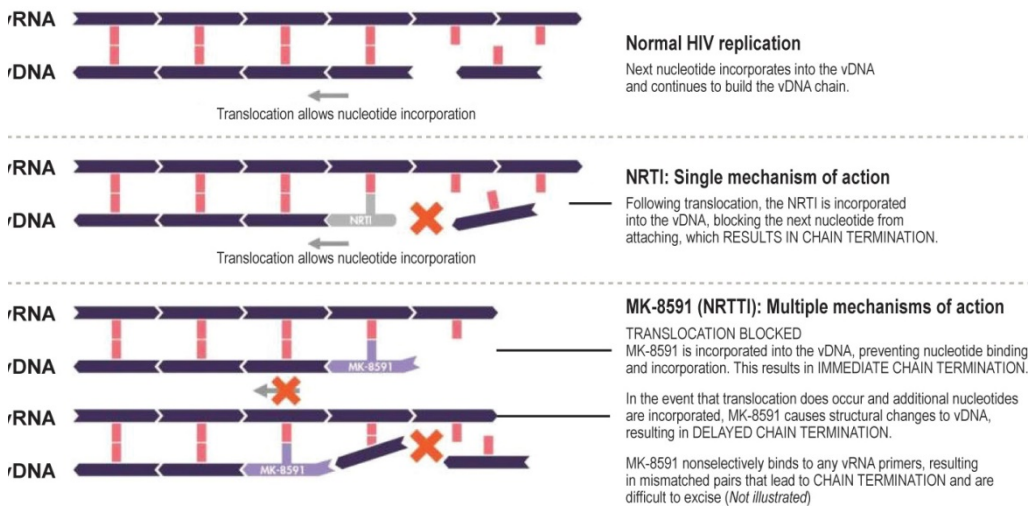
- Inhibits HIV replication through multiple mechanisms
- Potent antiviral activity (PBMC IC_{50} = 0.2 nM) with broad subtype and mutant coverage (HIV-1, HIV-2, MDR strains)
- Additive with respect to antiviral potency with 15 FDA-approved antiviral agents including lamivudine, emtricitabine, and tenofovir
- No/weak inhibition of human DNA polymerases α, β, and γ
- In a Phase 2 clinical trial (NCT03272347) for the treatment of HIV-1 infection with once daily (QD) administration of 0.25 mg, 0.75 mg, or 2.25 mg in combination with doravirine



EFdA

MK-8591: The First NRTTI (nucleoside reverse transcriptase translocation inhibitor)

A new class that disrupts multiple key steps in normal HIV replication



Methods: Antiviral activity of MK-8591, tenofovir alafenamide (TAF), zidovudine (AZT), and lamivudine (3TC) were evaluated in human PBMCs with WT HIV-1. The Monogram PhenoSense assay was employed to evaluate the susceptibility of 50 WT isolates from 11 HIV-1 subtypes and 94 NRTI-resistant clinical isolates to MK-8591, tenofovir (TFV), AZT, and 3TC. Susceptibilities were determined using IC_{50}s of WT HIV-1 in PBMCs and fold-shifts in potencies compared to WT virus.

SUMMARY AND CONCLUSIONS

- MK-8591 displayed similar activity agai (11) HIV-1 subtype viruses tested
- Against WT HIV-1 ($HIV_{NL4-3-GFP}$) in hum PBMCs, MK-8591 (IC_{50} = 0.2 nM) was or more potent as compared to TAF, AZ and 3TC (IC_{50}s of 2.8 nM, 2.6 nM, and 112.3 nM, respectively)
- The NRTI mutations K65R, L74V, and Q rendered viruses hyper-susceptible to in by MK-8591
- Other NRTI resistance mutations mode decreased susceptibility to MK-8591:
  - M184I and M184V, reduced susceptib to MK8591 by 3.9 fold- and 5.0-fold a respectively.
  - Thymidine analog mutations and RT insertion mutations decreased susce less than 4-fold and 10-fold, respecti The susceptibility of these mutants w further reduced 2-fold with M184I/V
- MK-8591 was more potent against all o resistant isolates than TAF was against WT HIV-1 and more potent against com NRTI-resistant HIV-1 isolates than any approved NRTI is against WT HIV-1
- MK-8591 should provide broad mutant subtype coverage as a component of a for HIV-1 treatment or prophylaxis