Development of a protease inhibitor-based single-tablet complete HIV-1 regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DCFTAF)

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DCFTAF
The first single-tablet regimen containing a boosted PI

- DCFTAF is an HIV-1 regimen in clinical development that combines darunavir (DRV, D, 800mg), with cobicistat (COBI, C, 150mg), emtricitabine (FTC, F, 200mg), and tenofovir alafenamide (TAF, 10mg)[1]
  - Boosted DRV 800mg has demonstrated a high and durable virologic response, with a high genetic barrier to the development of resistance, in various patient populations[2–4]
  - TAF, a novel prodrug of tenofovir (TFV), provides comparable efficacy to tenofovir disoproxil fumarate (TDF) at one-tenth the dose, resulting in a ~90% lower TFV plasma concentration and fewer adverse effects, particularly renal and bone[1,5–7]
- Current treatment guidelines recommend DRV, boosted with ritonavir or COBI, combined with other antiretroviral (ARV) drugs, for HIV-1-infected treatment-naïve patients[8]

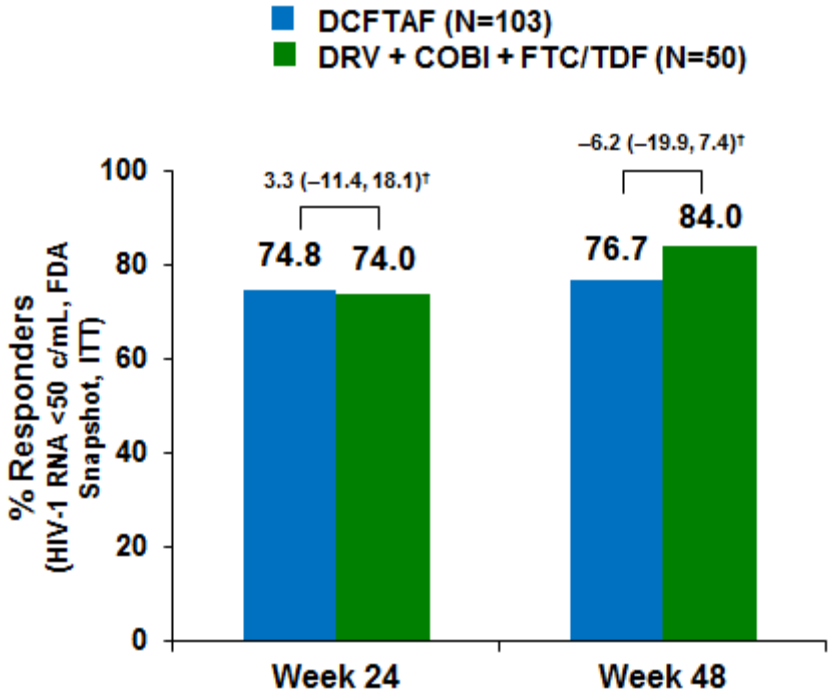
1. Mills A, et al. J Acquir Immune Defic Syndr 2015;69:439–45; 2. Cahn P, et al. AIDS 2011;25:929–39
3. Mills AM, et al. AIDS 2009;23:1679–88; 4. Flynn P, et al. PIDJ 2014;33:940–5
5. Ruane PJ, et al. J Acquir Immune Syndr 2013;63:449–55; 6. Custodio JM, et al. ASCPT 2015. Abstract PI-052
7. De Clercq E. Biochem Pharmacol 2016 pii:S0006-2952(16)30069–7
8. DHHS. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. July 14, 2016

Baugh B, et al. HIV DART & Emerging Viruses 2016. Abst# O_04

Exploratory Phase II study*: efficacy of DCFTAF

ART-naïve, HIV-1-infected adults (N=153) randomized 2:1 to each arm:

DCFTAF vs DRV + COBI + FTC/TDF[1]



- Non-inferior virologic efficacy at Week 24 (FDA snapshot analysis; primary endpoint)
- Difference in virologic response rates at Week 48 was primarily due to a higher rate of discontinuations for reasons other than virologic failure or AEs in the DCFTAF arm 16 (15.5%) vs 3 (6.0%) patients, respectively‡
- No treatment-emergent phenotypic resistance to any of the compounds

*GS-US-299-0102 (NCT01565850)
†Weighted difference in response rates (95% CI)
‡Main reason for these discontinuations was loss to follow-up (10/16 vs 1/3 patients)
ART=antiretroviral treatment; AE=adverse event
ITT=intent-to-treat

1. Mills A, et al. JAIDS 2015;69:439–45

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Exploratory Phase II study: safety of DCFTAF

Incidence, n (%)	DCFTAF N=103	DRV + COBI + FTC/TDF N=50
Any AE	95 (92)	47 (94)
Serious AEs	5 (5)	2 (4)
Grade 3 or 4 AEs	7 (7)	4 (8)
AEs leading to discontinuation	2* (2)	2† (4)
Most common AEs‡		
Diarrhea	22 (21)	13 (26)
Upper respiratory tract infection	16 (16)	7 (14)
Fatigue	14 (14)	9 (18)
Nausea	13 (13)	5 (10)
Rash	12 (12)	4 (8)

*DCFTAF: Rash and substance dependence; †DRV + COBI + FTC/TDF: Worsening of diarrhea and proximal renal tubulopathy; ‡Occurring in ≥10% of patients in DCFTAF group

- **Mean change in serum creatinine at Week 48**
  - DCFTAF: + 0.06 mg/dL
  - DRV + COBI + FTC/TDF: + 0.09 mg/dL (p=0.053)
- **Decreases in hip and spine BMD were smaller in the TAF vs in the TDF group**

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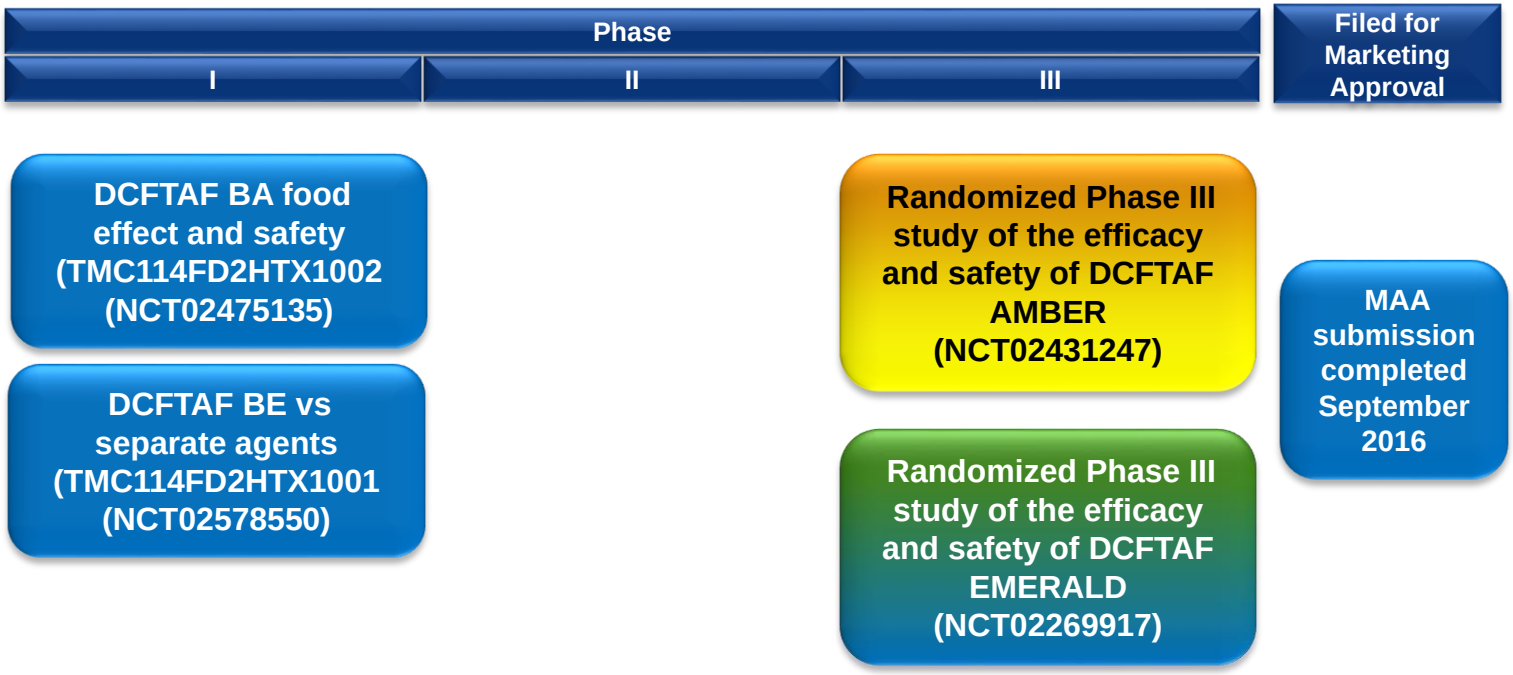
Ongoing DCFTAF clinical development program



An update on the ongoing DCFTAF development program is presented

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DCFTAF BA food effect
Study design* and baseline demographics

- Phase I, open-label, randomized, two-period, single-center, crossover study in 24 HIV-negative, healthy adult participants

	Session 1	At least 7 days washout*	Session 2
Group 1 (N=12)	Single oral dose of DCFTAF under fasted conditions (**test**)	→	Single oral dose of DCFTAF after a standardized high-fat breakfast (**reference**)
Group 2 (N=12)	Single oral dose of DCFTAF after a standardized high-fat breakfast (**reference**)	→	Single oral dose of DCFTAF under fasted conditions (**test**)

* Day 1 of a treatment session is the first day of the washout period

- PK profiles component drugs evaluated over 24 hours; PK parameters determined using non-compartmental analysis
  - Treatment comparison evaluated using GMRs with 90% CIs
- Half of participants were female and all were white of median (range) age 35 (18–54) years and body mass index 23.7 (19.8–29.5) kg/m^2

*TMC114FD2HTX1002 (NCT02475135)
GMR=geometric mean ratio; CI=confidence interval

1. Crauwels H et al. AIDS 2016. Poster THPEB064
2. Crauwels H et al. HIV Drug Therapy, Glasgow 2016. Poster 310

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DCFTAF BA food effect
PK parameters statistical analysis

GMR, % (90% CI)	DRV		COBI	
	Fasted (test)	Fed (high fat) (reference)	Fasted (test)	Fed (high fat) (reference)
n¶	23 vs 24		23 vs 24	
C_{max}	54.99 (46.73–64.71)		76.96 (55.70–106.33)	
AUC_{last}	65.65 (56.76–75.92)		70.90 (51.13–98.30)	
AUC_{inf}	70.25† (59.49–82.95)		84.39‡ (68.52–103.95)	

¶test vs reference; †n=20 for test and reference; ‡n=22 for test; C_{max}=maximum plasma concentration, AUC=area under the plasma concentration-time curve from time of administration up to the last timepoint with a measurable concentration post-dose (AUC_{last}) and extrapolated to infinity (AUC_{inf})

1. Crauwels H et al. AIDS 2016. Poster THPEB064
2. Crauwels H et al. HIV Drug Therapy, Glasgow 2016. Poster 310

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DCFTAF BA food effect

PK parameters statistical analysis, safety and tolerability

GMR, % (90% CI)	FTC		TAF	
	Fasted (test)	Fed (high fat) (reference)	Fasted (test)	Fed (high fat) (reference)
n¶	24 vs 24		24 vs 24	
C_{max}	125.99 (112.85–140.65)		182.29 (140.50–236.50)	
AUC_{last}	100.12 (96.29–104.10)		89.54 (81.20–98.72)	
AUC_{inf}	–		80.38 § (73.04–88.45)	

¶test vs reference; § n=21 for test and n=16 for reference

- Administration of DCFTAF was generally well tolerated under both fed and fasted conditions, and no new safety issues were identified

1. Crauwels H et al. AIDS 2016. Poster THPEB064
2. Crauwels H et al. HIV Drug Therapy, Glasgow 2016. Poster 310

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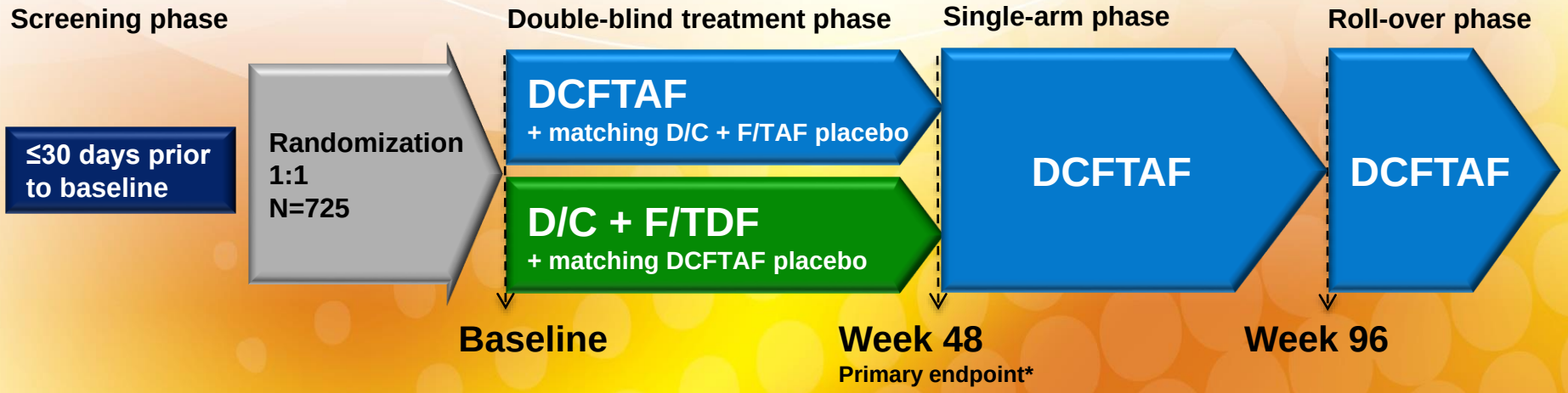
Phase III trial in ART-naïve patients

Double-blind, randomized, multicenter, parallel-group, non-inferiority study

Objective: Evaluate the efficacy and safety of DCFTAF vs D/C + F/TDF in HIV-1-infected, ART-naïve adults

Primary endpoint: Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA Snapshot algorithm for the ITT population

- Non-inferiority margin: -10% NI
- Week 48 data to support NDA/MAA submissions with ongoing observation through Week 96 followed by roll over in extension phase until DCFTAF tablet becomes available



*Will be conducted when all patients have completed Week 48 assessments

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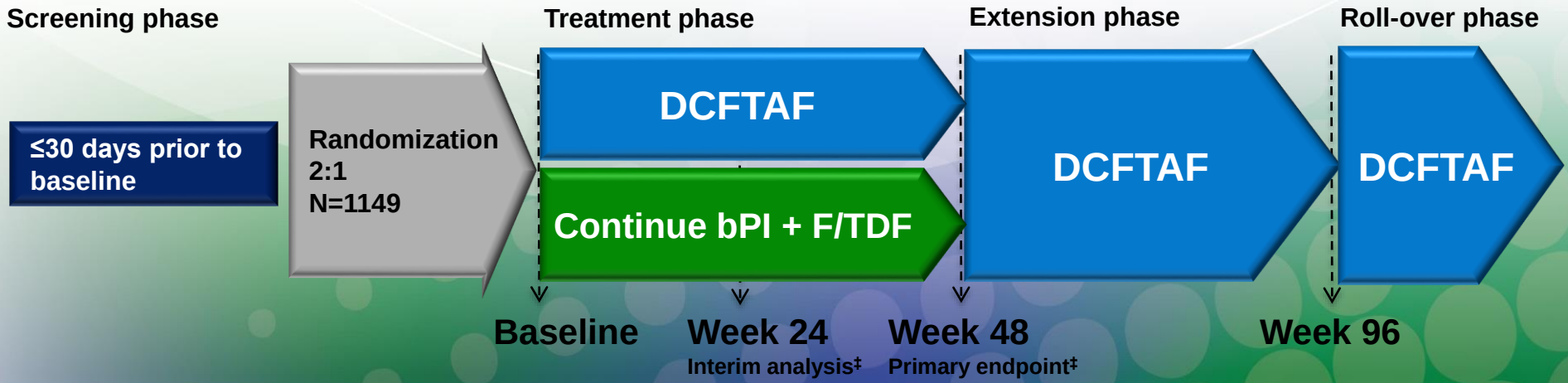
Phase III trial in virologically suppressed patients

Open-label, randomized, multicenter, parallel-group, non-inferiority study

Objective: Evaluate the efficacy and safety of switching to DCFTAF vs continuing the current regimen of a bPI + FTC/TDF in ART-experienced*, virologically-suppressed†, HIV-1-infected adults

Primary endpoint: Proportion of patients with virologic rebound (confirmed HIV-1 RNA ≥50 c/mL or premature discontinuations, with a last single HIV-1 RNA ≥50 c/mL) through Week 48

- Non-inferiority margin: -4% NI
- Week 48 data to support NDA/MAA submissions followed by extension phase with DCFTAF through Week 96 or beyond, until DCFTAF tablet becomes available



*Previous ART virologic failure allowed.
*Absence of history of failure on DRV treatment and absence of DRV RAMs, if historical genotype available
†At least one HIV RNA <50c/mL between 12–2 months before screening visit (HIV RNA <50c/mL) (single viral load blip allowed if re-suppressed)
‡Will be conducted when all patients have completed assessments
bPI=protease inhibitor boosted with low-dose ritonavir or COBI

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Summary

- DCFTAF is a single-tablet regimen containing a boosted PI and TAF in clinical development
- A prior Phase II study with DCFTAF showed good antiviral activity and safety
- DCFTAF is currently in Phase III development
  - Phase III AMBER and EMERALD trials in HIV-1-infected adults are fully recruited and ongoing
  - Treatment-naive HIV-infected adults and switch population
  - 48-week primary endpoint
- Consistent with prescribing recommendations for other DRV formulations,[1] it is recommended that the DCFTAF FDC tablet be taken with food
  - Following administration of DCFTAF in fasted conditions, the DRV exposure (AUC, C_{max}) decreased by 30–45% compared with in fed conditions, consistent with what has been previously reported for DRV/r[2] or DRV/COBI[3]
  - Differences in exposure to COBI, FTC and TAF in fed versus fasted conditions were not considered to be clinically relevant
  - The food effect for DRV was previously shown to be similar for different types of food[1]
  - Administration of DCFTAF was generally well tolerated under both fed and fasted conditions, and no new safety issues were identified

1. PREZISTA® (darunavir). Full Prescribing Information. June 2016
2. Sekar V, et al. J Clin Pharmacol 2007;47:479–84; 3. Kakuda TN, et al. Antivir Ther 2014;19:597–606

Acknowledgements and disclosures

- We would like to thank
  - The study participants and site staff for their participation and support during the Janssen-sponsored studies included in this presentation
  - The Janssen team members from the bioanalysis department, in particular Vera Hillewaert for the DCFTAF BA food effect study; Jiri Letal who was the DCFTAF BA food effect study statistician; and Janssen Research & Development team members, in particular Maria Blanca Hadacek, Katia Boven, Kimberley Brown, Julia Sugumar and Eric Y. Wong for their input into this poster
- All authors are full-time employees of Janssen and potential stockholders of Johnson & Johnson
- Medical writing support was provided by Ian Woolveridge from Zoetic Science, Macclesfield, UK, an Ashfield Company. Support for medical writing assistance was provided by Janssen Pharmaceuticals
- The DCFTAF food effect data have been presented previously:
  - Crauwels et al. 21st IAC 2016. Abstract and poster THPEB064
  - HIV Drug Therapy, Glasgow 2016. Abstract and poster P310