CLINICAL IMPACT OF ANTIRETROVIRAL AGENTS USED IN OPTIMIZED BACKGROUND THERAPY WITH FOSTEMSAVIR IN HEAVILY TREATMENT-EXPERIENCED ADULTS WITH HIV-1: EXPLORATORY ANALYSES OF THE PHASE 3 BRIGHTE STUDY

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Introduction

- Fostemsavir, an oral prodrug of the first-in-class attachment inhibitor temsavir, is approved for the treatment of multidrug-resistant HIV-1 infection in heavily treatment-experienced (HTE) adults who are otherwise unable to form a suppressive antiretroviral (ARV) regimen due to resistance, prior intolerance, or other safety concerns[1-4]
- In the phase 3 BRIGHTE study, in HTE adults with advanced HIV-1 disease and limited treatment options, fostemsavir plus optimized background therapy (OBT) was generally well tolerated and showed a trend of increasing virologic and immunologic response rates through 96 weeks[1-5]
- This post hoc analysis evaluated the most common ARVs included in the initial OBT and their association with Week 96 virologic response

Methods

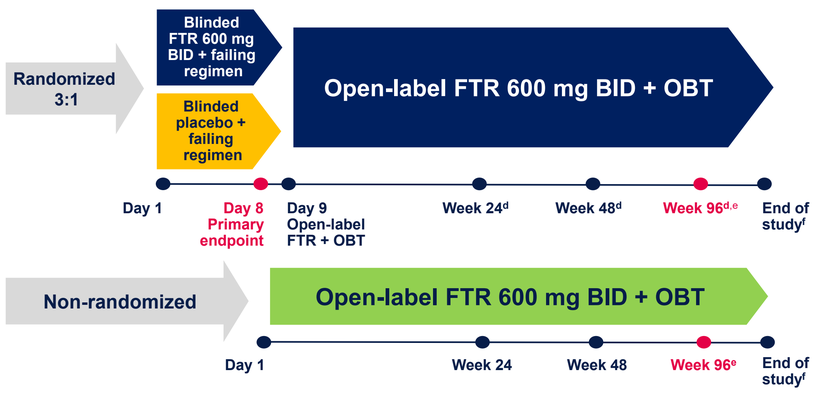
Study Design

- BRIGHTE is an ongoing phase 3 study evaluating twice-daily (BID) fostemsavir 600 mg plus OBT in HTE adults failing ARV therapy with limited treatment options (Figure 1)

Figure 1. BRIGHTE Study Design

Randomized Cohort[a]
HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and
- 1 or 2 ARV classes remaining with ≥1 approved fully active[b] agent per class
- Unable to construct viable regimen from remaining agents

Non-Randomized Cohort[a]
HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and
- 0 ARV classes remaining and no remaining approved fully active[b] agents[c]

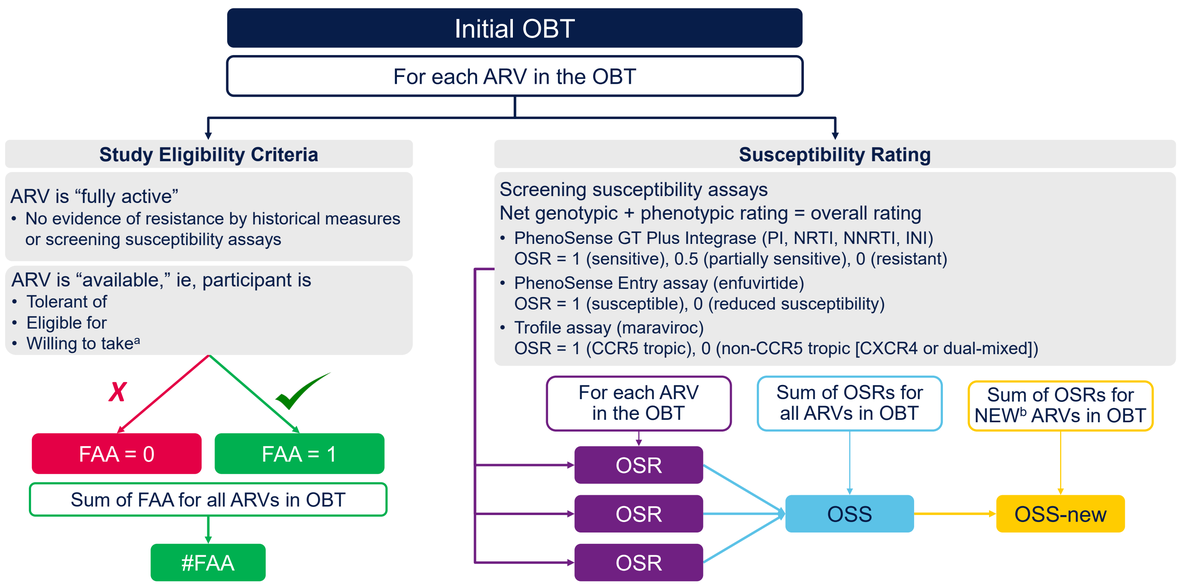


[a]There were no screening temsavir susceptibility criteria. [b]Fully active is based on susceptibility (current or historical resistance measures) and availability (the participant is tolerant of, eligible for, and willing to take [in the case of enfuvirtide only] the antiretroviral). [c]Use of investigational agents as part of OBT was permitted in the Non-randomized Cohort only. [d]Measured from the start of open-label FTR 600 mg BID + OBT. [e]The Week 96 database lock was August 14, 2018 (first participant, first visit: February 23, 2015; last participant, first dose of study treatment: August 11, 2016; last participant, last visit for Week 96: June 22, 2018). [f]The study is expected to be conducted until participants can access FTR through other means (eg, rollover study or marketing approval).

Analysis

- The composition of the OBT was summarized for both study cohorts
- For the Randomized Cohort (RC), virologic response (HIV-1 RNA <40 c/mL, by Snapshot analysis) through Week 96 was analyzed by subgroups based on
  - ARVs in the initial OBT
  - Overall susceptibility scores (OSS, OSS-new) for the initial OBT (Figure 2)
  - Number of fully active and available ARVs (FAA) in the initial OBT

Figure 2. Susceptibility Ratings and Scores



FAA, fully active and available; OSR, overall susceptibility rating; OSS, overall susceptibility score. [a]For enfuvirtide only (twice-daily injectable). [b]New ARVs are those that have never been previously taken by the participant.

Results

Baseline Characteristics

- Most BRIGHTE study participants were male and White (Table 1)
- Compared with the Non-randomized Cohort (NRC), the initial OBT for participants in the RC included fewer ARVs, but more were classified as FAA (Table 1)

Table 1. Baseline Characteristics

Parameter, n (%)[a]	RC (N=272)	NRC (N=99)
Sex, female	72 (26)	10 (10)
Age, ≥50 years	110 (40)	55 (56)
Race		
African American/African heritage	60 (22)	23 (23)
White	185 (68)	74 (75)
History of AIDS	231 (85)	89 (90)
HIV-1 RNA, ≥100,000 c/mL	80 (29)	15 (15)
CD4+ T-cell count		
<200 cells/mm^3	199 (73)	79 (80)
<20 cells/mm^3	72 (26)	40 (40)
Prior ARV therapy		
>15 years	182 (67)	80 (81)
≥5 regimens	226 (83)	90 (91)
Number of ARVs in initial OBT		
Mean (SD)	3.6 (1.4)	4.7 (1.3)
Median (range)	4 ([b]0-8)	5 (1-8)
Susceptibility scores for initial OBT, mean (SD)		
#FAA	1.4 (0.6)	0.2 (0.4)
OSS	2.2 (0.8)	1.6 (1.1)
OSS-new	1.3 (0.8)	0.5 (0.7)

[a]Unless otherwise specified. [b]1 participant discontinued during the blinded phase and never received an OBT.

Composition of the Initial OBT

- Integrase inhibitors (INI), particularly dolutegravir BID, were frequently used in both cohorts (Figure 3)
- Protease inhibitors (PI), particularly darunavir BID, and nucleoside reverse transcriptase inhibitors (NRTI) were more commonly used in the NRC than RC (Figure 3)

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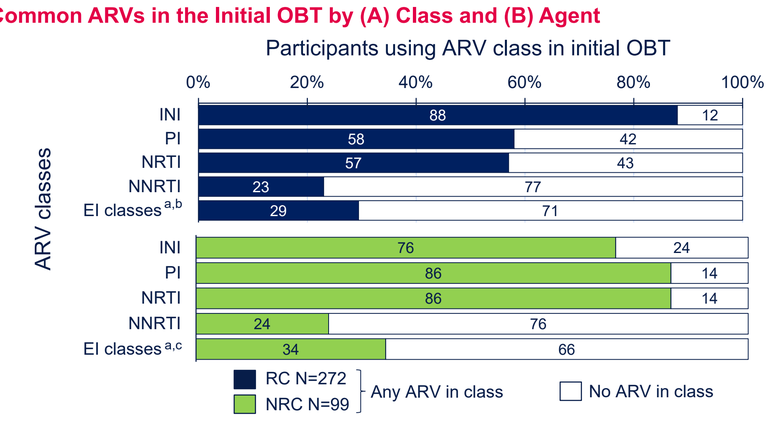
Figure 3. Most Common ARVs in the Initial OBT by (A) Class and (B) Agent

A



B Most Common ARV Agents in the Initial OBT

ARV class	ARV agent, n (%)	RC (N=272)	NRC (N=99)
INI	Dolutegravir QD/BID[d]	58 (21)/171 (63)	6 (6)/68 (69)
PI	Darunavir QD/BID[e]	35 (13)/99 (36)	8 (8)/63 (64)
NRTI	FTC or 3TC	136 (50)	76 (77)
	TDF or TAF[f]	116 (43)	74 (75)
NNRTI	Etravirine	54 (20)	21 (21)
EI classes[a]	Maraviroc	52 (19)	8 (8)
	Ibalizumab[b]	0	15 (15)
	Enfuvirtide	28 (10)	11 (11)
INI + PI	Dolutegravir + darunavir	117 (43)	55 (56)

EI, entry inhibitor. [a]EI classes include the CCR5 inhibitor (maraviroc), post-attachment inhibitor (ibalizumab), and fusion inhibitor (enfuvirtide) classes. [b]No participants in the RC used ibalizumab, which was investigational at the time of study enrollment and was only permitted in the NRC. [c]15 participants in the NRC used ibalizumab. [d]Total dolutegravir use: 229/272 (84%) in the RC and 74/99 (75%) in the NRC. [e]Total darunavir use: 134/272 (49%) in the RC and 71/99 (72%) in the NRC. [f]Mostly TDF (5 participants [2 RC, 3 NRC] used TAF).

Impact of OBT on Virologic and Immunologic Responses in the RC

- In the RC, Week 96 virologic response rates and change from baseline in CD4+ T-cell count were similar regardless of the presence or absence of core ARV agents, except for dolutegravir (Tables 2 and 3)
  - Virologic response rate and mean change from baseline in CD4+ T-cell count were higher among participants who included dolutegravir in the initial OBT than among those without dolutegravir in the initial OBT

Table 2. Week 96 Virologic Response and CD4+ T-cell Count Change From Baseline at Week 96 by ARVs in the Initial OBT (RC)

		HIV-1 RNA <40 c/mL (Snapshot analysis), n/N (%)		Change in CD4+ T-cells/mm^3 (observed analysis), mean (SD) [n]	
ARV class	ARV agent	ARV present	ARV absent	ARV present	ARV absent
INI	Any	152/239 (64)	11/33 (33)	214.8 (187.1) [198]	72.0 (203.5) [15]
	Dolutegravir, any	146/229 (64)	17/43 (40)	216.2 (188.5) [191]	105.0 (190.8) [22]
	Dolutegravir, QD	40/58 (69)		162.8 (136.0) [46]	
	Dolutegravir, BID	106/171 (62)		233.2 (199.7) [145]	
PI	Any	94/158 (59)	69/114 (61)	195.0 (191.8) [130]	220.0 (190.7) [83]
	Darunavir, any	83/134 (62)	80/138 (58)	180.6 (179.8) [110]	230.6 (200.5) [103]
	Darunavir, QD	17/35 (49)		173.8 (129.6) [25]	
	Darunavir, BID	66/99 (67)		182.6 (192.6) [85]	
NNRTI	Any	41/62 (66)	122/210 (58)	196.5 (245.3) [52]	207.4 (171.1) [161]
	Etravirine	35/54 (65)	128/218 (59)	211.7 (227.0) [46]	202.8 (181.0) [167]
EI classes[a]	Maraviroc	25/52 (48)	138/220 (63)	142.8 (215.7) [36]	217.4 (184.1) [177]
	Enfuvirtide	13/28 (46)	150/244 (61)	194.4 (158.7) [20]	Not reported
NRTI	Any	92/154 (60)	71/118 (60)	225.6 (195.5) [118]	178.8 (183.6) [95]
	FTC or 3TC	82/136 (60)	81/136 (60)	205.6 (161.0) [106]	203.9 (218.0) [107]
	TDF or TAF	72/116 (62)	91/156 (58)	237.0 (200.8) [88]	182.0 (181.7) [125]
NRTI + INI	Any	87/134 (65)	76/138 (55)[b]	233.9 (196.5) [111]	173.0 (181.1) [102][b]
NRTI + PI	Any	46/82 (56)	117/190 (62)[b]	200.0 (208.0) [66]	206.9 (184.0) [147][b]
PI + INI	Any	86/141 (61)	77/131 (59)[b]	201.0 (195.6) [119]	209.5 (186.6) [94][b]
	Dolutegravir + darunavir	75/117 (64)	88/155 (57)[b]	188.1 (183.0) [99]	219.2 (198.0) [114][b]

EI, entry inhibitor. [a]EI classes used in the RC include the CCR5 inhibitor (maraviroc) and fusion inhibitor (enfuvirtide) classes. [b]Absence of at least one of the agents in the specified combination.

Table 3. Week 96 Virologic Response Rates by Susceptibility Rating of Core ARVs in the OBT (RC)

	HIV-1 RNA <40 c/mL (Snapshot analysis), n/N (%)			
	OSR		OSR-new	
ARV agent	= 1.0	<1.0	= 1.0	<1.0
Dolutegravir, any	127/190 (67)	13/32 (41)	118/167 (71)	22/55 (40)
Dolutegravir, QD	37/52 (71)		36/48 (75)	
Dolutegravir, BID	90/138 (65)		82/119 (69)	
Darunavir, any	50/79 (63)	32/53 (60)	25/31 (81)	58/103 (56)
Darunavir, QD	15/30 (50)		8/11 (73)	
Darunavir, BID	35/49 (71)		17/20 (85)	
Etravirine	34/48 (71)	1/6 (17)	29/39 (74)	6/15 (40)
Maraviroc	24/49 (49)	0/1 (0)	19/36 (53)	5/14 (36)
Enfuvirtide	13/26 (50)	0/1 (0)	6/13 (46)	7/15 (47)

OSR, overall susceptibility rating.

- Among participants who included dolutegravir in the initial OBT, it represented the only fully active ARV by OSR and OSR-new in 16.2% (37/229) and 34.5% (79/229) of cases, respectively (Table 4)
- When dolutegravir was the only fully active agent in the initial OBT, it was dosed twice daily (BID) in ~75% of cases
- Among participants who had dolutegravir as the only fully active agent in their initial OBT, ~65% achieved virologic suppression at Week 96

Table 4. Week 96 Virologic Response by Susceptibility Rating of Core ARVs and Susceptibility Score of the Initial OBT (RC)

	HIV-1 RNA <40 c/mL (Snapshot analysis), n/N (%)					
	OSS			OSS-new		
Fully active core ARV agent[a]	N[b]	<2	≥2	N[b]	<2	≥2
Dolutegravir, any	188	24/37 (65)	102/151 (68)	165	52/79 (66)	65/86 (76)
Dolutegravir, BID	136	19/29 (66)	70/107 (65)	117	40/59 (68)	41/58 (71)
Darunavir, any	76	2/3 (67)	45/73 (62)	30	1/2 (50)	23/28 (82)
Darunavir, BID	47	1/2 (50)	32/45 (71)	20	0/1 (0)	17/19 (89)
Etravirine	47	0/1 (0)	33/46 (72)	38	2/4 (50)	26/34 (76)
Maraviroc	49	1/3 (33)	23/46 (50)	36	1/5 (20)	18/31 (58)
Enfuvirtide	26	0/5 (0)	13/21 (62)	13	0/5 (0)	6/8 (75)

OSR, overall susceptibility rating; OSS, overall susceptibility score. [a]Fully active based on OSR or OSR-new of 1.0. [b]N=the number of participants with OSR or OSR-new of 1.0 for the indicated core ARV and a valid OSS or OSS-new for the initial OBT.

Conclusions

- In the BRIGHTE study, HTE participants achieved durable rates of virologic response across a wide range of OBT combined with fostemsavir
- Overall, dolutegravir (BID) was the most common ARV included in the OBT
- The inclusion of dolutegravir in the OBT (particularly fully active dolutegravir) appeared to have the greatest impact on efficacy outcomes at Week 96

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