Seven-Year Sustained Efficacy, Safety, and Immunological Improvement With Fostemsavir-Based Regimens in Individuals With HIV and Limited Treatment Options

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**Presenting on behalf of the authors.*

Key Takeaways

- **BRIGHTE is the largest recent study with the longest follow-up to date (7 years) in people with multidrug-resistant (MDR) HIV-1**
- **Fostemsavir-based regimens demonstrated durable virologic efficacy and were generally well tolerated through 7 years**
- **Immune recovery was sustained through 7 years**
- **These long-term results reinforce the value of fostemsavir for people with HIV-1 and limited treatment options**

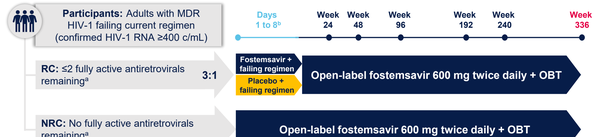
Introduction

- Individuals with MDR HIV-1 are at heightened risk of disease progression, comorbid conditions, and premature mortality, underscoring the urgent need for effective therapies[1,2]
- Effective antiretrovirals with a unique mechanism of action are necessary for treatment success in this population
- Fostemsavir, the prodrug of temsavir, is a first-in-class attachment inhibitor with a distinct mechanism of action targeting viral-bound and soluble gp120[3-6]
- Fostemsavir-based regimens have demonstrated durable viral suppression and sustained immunologic improvements and were well tolerated over ~5 years in the large, registrational, phase 3 BRIGHTE study[4]
- We present the longest follow-up of individuals with MDR HIV-1 to date, through 7 years (Week 336), evaluating efficacy, immunologic changes, and safety with fostemsavir-based regimens

Methods

- BRIGHTE is a large (N=371), ongoing, global, multicenter, phase 3 study conducted across 22 countries evaluating twice-daily fostemsavir + optimized background therapy (OBT) in adults with MDR HIV-1 (Figure 1), as previously described[4]
- Participants with 1 to 2 fully active antiretrovirals were assigned to the Randomized Cohort (RC) and those with none were assigned to the Non-randomized Cohort (NRC)
- Samples for biomarker analysis were collected from the RC
- BRIGHTE was planned to continue beyond Week 96 until participants could access fostemsavir through other means[4]

Figure 1. BRIGHTE Study Design



[a]Fully active based on susceptibility (current or historical resistance) and availability (participant is tolerant of, eligible for, and willing to take [in the case of enfuvirtide only] the antiretroviral). Use of investigational agents in OBT was permitted in the NRC. [b]Participants in the RC were randomly assigned 3:1 to receive fostemsavir 600 mg twice daily or placebo + current failing regimen for 8 days, after which all participants received open-label fostemsavir.

Results

Demographics and Baseline Characteristics

- 272 participants entered the RC and 99 entered the NRC
- Most participants were male (RC, 74%; NRC, 90%), and 22% and 23% identified as Black or African American in the RC and NRC, respectively (Table 1)
- Median baseline age was 48 years in the RC and 51 years in the NRC
- Participants were from North America (RC, 40%; NRC, 57%), South America (RC, 39%; NRC, 14%), and Europe (RC, 19%; NRC, 27%)
- Participants in both cohorts had baseline characteristics consistent with advanced HIV-1, including low CD4+ T-cell counts (median: RC, 99.5 cells/mm^3; NRC, 41.0 cells/mm^3)
- At Week 336, 80 participants were still enrolled in BRIGHTE (RC, n=72; NRC, n=8)

Table 1. Demographics and Baseline Characteristics (Safety Population[a])

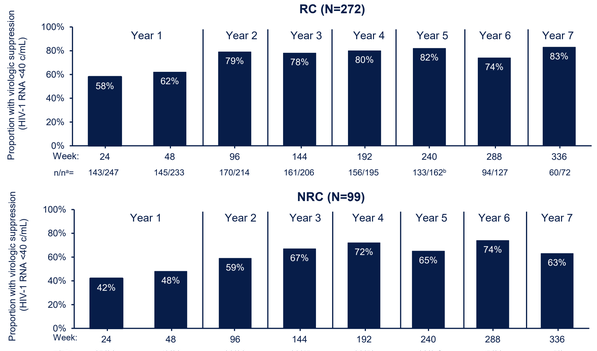
Characteristic	RC (N=272)	NRC (N=99)
Age, n (%), y		
<35	61 (22)	14 (14)
35 to <50	100 (37)	30 (30)
≥50	111 (41)	55 (56)
Sex, n (%)		
Female	71 (26)	10 (10)
Male	201 (74)	89 (90)
Race, n (%)		
Black or African American	60 (22)	23 (23)
White	185 (68)	74 (75)
Other races[b]	27 (10)	2 (2)
Ethnicity		
Hispanic or Latin American	79 (29)	28 (28)
Not Hispanic or Latin American	102 (38)	53 (54)
Missing[c]	91 (33)	18 (18)
HIV-1 RNA, n (%), c/mL		
<400	21 (8)	5 (5)
400 to <1000	10 (4)	4 (4)
≥1000	241 (89)	90 (91)
CD4+ T-cell count, n (%), cells/mm^3		
<350	243 (89)	94 (95)
350 to <500	14 (5)	3 (3)
≥500	15 (6)	2 (2)
No. of fully active ARVs in initial OBT, n (%)		
0	15 (6)[d]	79 (80)
1	142 (52)	20 (20)[e]
2	115 (42)	0

ARV, antiretroviral. [a]All participants who received ≥1 dose of study treatment. [b]Includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, individuals of multiple races, and individuals of other races. [c]Ethnicity was only required to be collected for US participants but was recorded for some but not all non-US participants. [d]Includes participants who discontinued the study during the blinded period and never started OBT, not treated with a fully active ARV in initial OBT despite having a fully active ARV available at screening, and inadvertently assigned to the RC despite having no fully active ARV available at screening. [e]4 participants had 1 fully active and available ARV at screening, and 16 received ibalizumab, which was still investigational at study start.

Virologic Suppression

- Participants in BRIGHTE maintained durable and consistent virologic suppression (observed analysis), with 83% (60/72; RC) and 63% (5/8; NRC) suppressed at Week 336 (Figure 2)

Figure 2. Virologic Suppression Through Week 336 (Observed Analysis; ITT-E Population)

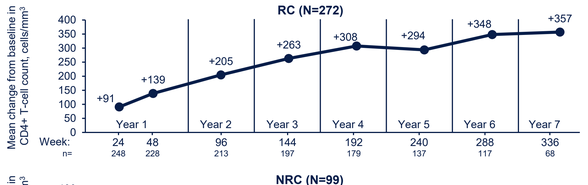


*Number of participants with HIV-1 RNA <40 c/mL over number of participants with available data. [b]Week 240 n's updated based on revised treatment status from new study-end data.

Immunologic Change

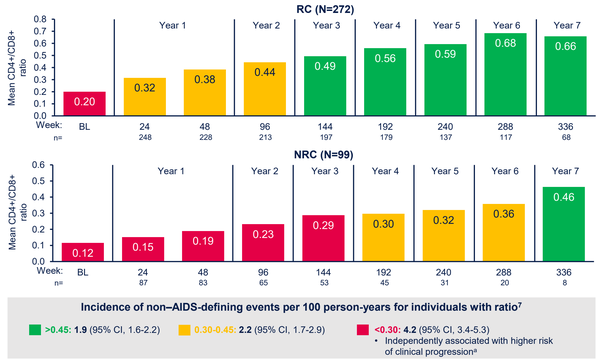
- Durable improvements in CD4+ T-cell count were observed in the RC and NRC through Week 336 (Figure 3)
  - The RC had a mean increase from baseline of 357 cells/mm^3 and the NRC had a mean increase from baseline of 371 cells/mm^3

Figure 3. Mean Change From Baseline in CD4+ T-Cell Count Through Week 336 (Observed Analysis; ITT-E Population)



- Durable and clinically meaningful improvements in CD4+/CD8+ ratio were observed in the RC and NRC through Week 336 (Figure 4)
  - In the RC, mean CD4+/CD8+ ratio increased from 0.20 at baseline to 0.66 at Week 336; in the NRC, mean CD4+/CD8+ ratio increased from 0.12 to 0.46 over the same period
  - Improvements of this magnitude have been associated with a significantly lower rate of non–AIDS-defining events, as shown in the color-coded bars[7]

Figure 4. Mean CD4+/CD8+ Ratio Through Week 336 (Observed Analysis; ITT-E Population)



Incidence of non–AIDS-defining events per 100 person-years for individuals with ratio[7]

- **>0.45: 1.9** (95% CI, 1.6-2.2)
- 0.30-0.45: **2.2** (95% CI, 1.7-2.9)
- **<0.30: 4.2** (95% CI, 3.4-5.3)
  - Independently associated with higher risk of clinical progression[a]

Bars are color-coded to match the CD4+/CD8+ ratio indicated in the legend. [a]CD4+/CD8+ ratio <0.30 was independently associated with higher risk of non–AIDS-defining events or death vs CD4+/CD8+ ratio >0.45 (adjusted risk ratio, 1.51; 95% CI, 1.09-2.09; *P*=0.0137).[7]

Safety

- The safety profile at Week 336 was consistent with that of the overall study population at Week 240[4] (Table 2)
  - Adverse events leading to discontinuation occurred in 7% (19/272) of participants in the RC and 13% (13/99) in the NRC
  - No deaths due to COVID-19 occurred

Table 2. Cumulative Safety Summary Through Week 336 (Safety Population[a])

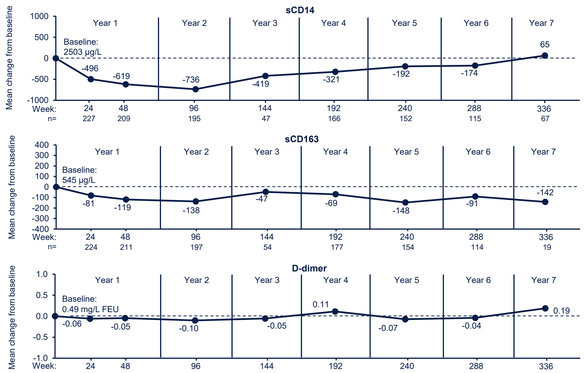
	RC (N=272)			NRC (N=99)		
Safety outcome, n (%)	Week 96	Week 240	Week 336	Week 96	Week 240	Week 336
Any AE	249 (92)	259 (95)	259 (95)	98 (99)	98 (99)	98 (99)
Grade 3-4 AEs	78 (29)	110 (40)	125 (46)	49 (49)	60 (61)	62 (63)
Any serious AE[b]	92 (34)	122 (45)	130 (48)	48 (48)	55 (56)	58 (59)
AEs leading to discontinuation[c]	14 (5)	17 (6)	19 (7)	12 (12)	13 (13)	13 (13)

[a]All participants who received ≥1 dose of study treatment. [b]Through Week 336 in the RC, there were 12 drug-related serious AEs, including 1 fatal drug-related serious AE of immune reconstitution inflammatory syndrome. Through Week 336 in the NRC, there were 4 drug-related serious AEs. [c]Across both cohorts, the most common AEs leading to discontinuation were due to non–COVID-19 infections (RC, 8 [3%]; NRC, 6 [6%]).

Inflammatory Biomarkers

- Biomarkers were generally comparable to baseline levels at Week 336 (Figure 5)

Figure 5. Mean Change From Baseline in Biomarkers of Immune Activation (sCD14 and sCD163) and Residual Coagulopathy (D-dimer) in the RC (Observed Analysis; ITT-E Population)[8-10]



Limitations

- Key limitations are the absence of a comparator group beyond the initial 8-day blinded period, use of individualized OBT, and use of observed analyses for efficacy endpoints
- The study was impacted by COVID-19–related disruptions in care access and follow-up around the Week 192 time point

Conclusions

- Treatment with fostemsavir-based regimens maintained durable and consistent virologic suppression and sustained improvements in CD4+ T-cell count and CD4+/CD8+ ratio through 7 years (Week 336)
- Previous data have shown that fostemsavir-based regimens have a consistent safety profile, with no notable changes in safety or tolerability after Week 96[11]
  - Safety findings should be interpreted in the context of a population that is heavily treatment-experienced with limited treatment options
- In general, biomarkers were consistent with baseline levels at Week 336

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