Data on the use of *Rukobia* with Ibalizumab

Summary

- In the phase 3 BRIGHTE study, 15 patients in the non-randomized cohort received ibalizumab (IBA) as part of optimized background therapy (OBT) in addition to *Rukobia* (fostemsavir [FTR]).[1]
    - At Week 48, 8/15 patients who received IBA had a viral load < 40 copies/mL.[1] Virologic response was reduced to 5/15 patients at Week 96 due to 3 deaths after Week 48 that were not treatment-related.[2]
    - The mean increase in CD4+ T-cell count at Week 96 was 18 cells/mm^3 (SD 95) for patients who received IBA compared with 135 cells/mm^3 (SD 210) for patients without IBA.[2]
- At Week 16, one patient (FTR-treated and IBA naïve) who met protocol-defined virologic failure had a treatment emergent mutation (K202E). The Week 16 envelope (with E202) had reduced sensitivity to both temsavir and IBA.[3]
    - HIV-1 gp120 E202 was identified as a substitution that can reduce susceptibility to temsavir, and in a context-dependent format may also result in resistance to IBA.[3]
    - The E202 polymorphism was infrequent in the 2021 release of the Los Alamos National Laboratory database, occurring in 1/8365 (0.01%) isolates, and was not present at screening in any participant in the BRIGHTE study.[3]
- Important safety information can be found in the Prescribing Information link and can also be accessed at Our HIV Medicines.

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BRIGHTE STUDY DESIGN AND PRIMARY ENDPOINT

BRIGHTE is an ongoing, partially-randomized, placebo-controlled, double-blind, phase 3 trial designed to evaluate the efficacy and safety of FTR in heavily treatment-experienced (HTE) patients with multi-drug resistant HIV-1.[4] Patients were failing their current regimen (HIV-1 RNA ≥ 400 copies/mL) and enrolled into 1 of 2 cohorts, according to their remaining treatment options. At baseline, those with ≥ 1 antiretroviral (ARV) drug in at least 1 but no greater than 2 ARV classes were randomized (Day 1 to Day 8) to add either FTR 600 mg twice daily or placebo to their failing regimen (randomized cohort). Patients with no fully active, approved ARV options received open-label FTR and OBT on Day 1 (non-randomized cohort). Patients receiving an investigational anti-HIV-1 agent (other than FTR) and/or an HIV-1 therapeutic vaccine were eligible to participate in the non-randomized cohort.

At Day 8, the mean reduction from baseline in HIV-1 RNA level was 0.79 $\log_{10}$ copies/mL in the FTR group and 0.17 $\log_{10}$ copies/mL in the placebo group (difference −0.63; 95% CI −0.81 to −0.44; P < 0.001).[4]

FTR + IBA EFFICACY

As part of initial OBT, IBA (a CD4-directed post-attachment HIV-1 inhibitor) was permitted in the non-randomized cohort as a protocol-allowed investigational agent.[1,5] For the purposes of assessing the activity

of background regimens, IBA was considered fully-active for all patients, although formal resistance testing for IBA was not available within the BRIGHTE study.[1]

Virologic Response

Within the non-randomized cohort, the presence of IBA appeared to have a positive impact on virologic response through Week 48 and was similar to the level of virologic response at Week 48 in patients from the randomized cohort who had 1 fully-active and available agent (58%).[1] After prior virologic response, 3 patients who received IBA died for reasons unrelated to treatment between Week 48 and Week 96 and were classified as virologic failures at Week 96 by snapshot.[2]

Table 1. Non-Randomized Cohort: Virologic response of Fostemsavir + Ibalizumab[1]

	Week 24	Week 48	Week 96
HIV-1 RNA <40 c/mL (Ibalizumab)	8/15 (53%)	8/15 (53%)	5/15 (33%)
HIV-1 RNA <40 c/mL (No Ibalizumab)	29/84 (35%)	30/84 (36%)	32/84 (38%)

Change in CD4+ T-Cell Count Over Time

The 15 patients with IBA as part of initial OBT had a mean and median baseline CD4 count of 114 cells/mm^3 (SD 121) and 73 cells/mm^3 (IQR 7–230), respectively.[2] The mean increase at Week 96 for patients with IBA in initial OBT was 18 cells/mm^3 (SD 95) compared with 135 cells/mm^3 for patients without IBA. The median increase was 32 cells/mm^3 (IQR -67 to 88) for patients with IBA compared with 90 cells/mm^3 (1–183) for patients without.

RESISTANCE

At Week 16 one patient (FTR-treated and IBA naïve) who met protocol-defined virologic failure (defined as HIV-1 RNA ≥ 400 copies/mL [confirmed or last available] after prior confirmed suppression to < 400 copies/mL or ≥ 1.0 log10 increase in HIV-1 RNA above nadir [≥ 40 copies/mL]) had a treatment emergent mutation (K202E).[3] The Week 16 envelope (with HIV-1 gp120 E202 substitution) had reduced sensitivity to both temsavir and IBA. The E202 polymorphism was infrequent in the 2021 release of the Los Alamos National Laboratory database, occurring in 1/8365 (0.01%) isolates, and was not present at screening in any patient in the BRIGHTE study.[3]

For the patient at Week 16, swapping the V5 region from an IBA-sensitive envelope containing 3 potential N-linked glycosylation sites (PNGSs) restored sensitivity to IBA (indicated by increased maximum percent inhibition), but not temsavir (Table 2).[3] These results indicate that the effect of E202 on IBA resistance appears to be dependent on the sequence context of the V5 region.

Table 2. The Effect of E202 on Sensitivity to Temsavir and IBA Is Dependent on the Sequence Context of the Envelope[3]

Envelope ID	gp120 amino acid at position 202	Temsavir IC_{50}, mean (SD), nM	Ibalizumab IC_{50}, mean (SD), nM	Ibalizumab MPI, %
Swapping the V5 region re-sensitizes envelopes to IBA without affecting sensitivity to TMR				
21-116108	E	>10,000	0.54 (0.04)	72
21-116108_V5 (3 PNGSs)	E	>10,000	0.9 (0.53)	95.5
Patient at Week16	E	1315 (216.4)	3.0 (0.6)	81.8
Patient at Week16_V5 (3 PNGSs)	E	1002.6 (311.1)	0.8 (0.2)	100
The PNGS at gp120 amino acid position 197 can affect sensitivity to TMR and IBA				
21-116108	E	>10,000	0.33 (0.25)	79.42
21-116108N197D	E	28.63 (18.27)	0.19 (0.01)	96.61
21-116108N197D_E202T	T	2.52 (0.26)	0.27 (0.08)	99.86

IC_{50}, half-maximal inhibitory concentration; MPI, maximum percent inhibition; PNGS, potential N-linked glycosylation site; SD, standard deviation.

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This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

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