**SUPPLEMENTARY MATERIAL**

# Week 240 Efficacy and Safety of Fostemsavir Plus Optimized Background Therapy in Heavily Treatment-Experienced Adults With HIV-1

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**Table of Contents**

**Supplementary Methods**

Central laboratory facilities (Laboratory Corporation of America [Indianapolis, IN; Geneva Switzerland; The Synergy, Singapore]) conducted hematology, HIV-1 RNA testing, and other serology. Genotypic and phenotypic analyses were conducted at screening and after protocol-defined virologic failure, and performed by Monogram Biosciences (South San Francisco, CA) using the PhenoSense GT® Plus Integrase, PhenoSense® Entry, and Trofile® Co-receptor Tropism assays. Genotypic susceptibility was evaluated using pre-specified gp160 amino acid substitutions (S375H/I/M/N/T, M426L, M434I/K, M475I) and most relevant substitutions (S375H/I/M/N/Y, M426L, M434K). Phenotypic temsavir susceptibility was evaluated as the fold change in $IC_{50}$ for a test sample vs a laboratory control of HIV-1, with a >3-fold change in $IC_{50}$ considered meaningful.

Week 240 statistical analyses were performed by Parexel (Research Triangle Park, NC) and GSK using SAS® (SAS Institute, Cary, NC) and TIBCO Spotfire® Clinical Graphics (Palo Alto, CA).

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**Table S1.** Demographic and Baseline Disease Characteristics

| Characteristic | Randomized Cohort (N=272)[a] | Non-randomized Cohort (N=99)[a] | Total (N=371) |
|---|---|---|---|
| Age, y, n (%) | | | |
| <35 | 61 (22) | 14 (14) | 75 (20) |
| 35 to 49 | 100 (37) | 30 (30) | 130 (35) |
| ≥50 | 111 (41) | 55 (56) | 166 (45) |
| Sex, n (%) | | | |
| Male | 201 (74) | 89 (90) | 290 (78) |
| Female | 71 (26) | 10 (10) | 81 (22) |
| Race (%) | | | |
| White | 185 (68) | 74 (75) | 259 (70) |
| Black or African American | 60 (22) | 23 (23) | 83 (22) |
| American Indian or Alaska Native | 7 (3) | 1 (1) | 8 (2) |
| Asian | 2 (<1) | 0 | 2 (<1) |
| Native Hawaiian or Other Pacific Islander | 1 (<1) | 0 | 1 (<1) |
| Other races | 17 (6) | 1 (1) | 18 (5) |
| HIV-1 RNA, median (IQR), $log_{10}$ copies/mL | 4.66 (3.87-5.09) | 4.31 (3.64-4.77) | 4.55 (3.85-5.02) |
| Baseline HIV-1 RNA, n (%), copies/mL | | | |
| <1000 | 31 (11) | 9 (9) | 40 (11) |
| 1000 to <10,000 | 44 (16) | 24 (24) | 68 (18) |
| 10,000 to <100,000 | 117 (43) | 51 (52) | 168 (45) |
| ≥100,000 | 80 (29) | 15 (15) | 95 (26) |
| CD4+ T-cell count, median (IQR), cells/$mm^3$ | 99.5 (15-207) | 41.0 (6-161) | 80.0 (11-202) |
| Baseline CD4+ T-cell count, n (%), cells/$mm^3$ | | | |
| <20 | 72 (26) | 40 (40) | 112 (30) |
| 20 to <50 | 25 (9) | 14 (14) | 39 (11) |
| 50 to <100 | 39 (14) | 14 (14) | 53 (14) |
| 100 to <200 | 63 (23) | 11 (11) | 74 (20) |
| ≥200 | 73 (27) | 20 (20) | 93 (25) |
| FAA ARVs in initial OBT, n (%) | | | |
| 0 | 15 (6) | 79 (80) | 94 (25) |
| 1 | 142 (52) | 20 (20)[b] | 162 (44) |
| 2 | 115 (42) | 0 | 115 (31) |

ARV, antiretroviral; FAA, fully active and available; OBT, optimized background therapy.
[a]N=267 and N=92 at Week 240 after 12 participants completed the study. [b]4 participants had 1 fully active and available ARV at screening, and 16 received ibalizumab, which was still investigational at study start.

**Table S2.** Proportion of Participants With Virologic Response (HIV-1 RNA <40 Copies/mL) by Baseline HIV-1 RNA and CD4+ T-Cell Count, Snapshot: ITT-E Population[a]

| | Randomized Cohort (N=272) | | | Non-randomized Cohort (N=99) | | |
|---|---|---|---|---|---|---|
| **Subgroup, n/N (%)** | **Week 144** | **Week 192** | **Week 240[b]** | **Week 144** | **Week 192** | **Week 240[c]** |
| Baseline HIV-1 RNA, copies/mL | | | | | | |
| <1000 | 18/31 (58) | 20/31 (65) | 19/30 (63) | 5/9 (56) | 6/9 (67) | 4/7 (57) |
| 1000 to <10,000 | 28/44 (64) | 28/44 (64) | 23/42 (55) | 11/24 (46) | 8/24 (33) | 4/23 (17) |
| 10,000 to <100,000 | 71/117 (61) | 70/117 (60) | 56/116 (48) | 16/51 (31) | 15/51 (29) | 11/48 (23) |
| ≥100,000 | 31/80 (39) | 27/80 (34) | 22/79 (28) | 3/15 (20) | 3/15 (20) | 1/14 (7) |
| Baseline CD4+ T-cell count, cells/mm$^3$ | | | | | | |
| <20 | 29/72 (40) | 32/72 (44) | 23/70 (33) | 10/40 (25) | 10/40 (25) | 6/37 (16) |
| 20 to <50 | 12/25 (48) | 10/25 (40) | 8/25 (32) | 3/14 (21) | 2/14 (14) | 1/13 (8) |
| 50 to <100 | 21/39 (54) | 17/39 (44) | 15/38 (39) | 8/14 (57) | 6/14 (43) | 2/13 (15) |
| 100 to <200 | 34/63 (54) | 38/63 (60) | 28/62 (45) | 5/11 (45) | 5/11 (45) | 2/10 (20) |
| ≥200 | 52/73 (71) | 48/73 (66) | 46/72 (64) | 9/20 (45) | 9/20 (45) | 9/19 (47) |

ITT-E, intention-to-treat exposed.
[a]Missing and change in optimized background therapy counted as failure. [b]N=267. [c]N=92.

**Table S3.** Incidence of PDVF by Baseline Disease Characteristics Through Week 240

| Category, n/N (%)[a] | Randomized Cohort (N=272) | Non-randomized Cohort (N=99) |
|---|---|---|
| Baseline HIV-1 RNA, copies/mL | | |
| <400 | 4/21 (19) | 2/5 (40) |
| 400 to <1000 | 2/10 (20) | 0/4 (0) |
| 1000 to 10,000 | 8/44 (18) | 12/24 (50) |
| 10,000 to <30,000 | 10/42 (24) | 13/25 (52) |
| 30,000 to <100,000 | 20/75 (27) | 18/26 (69) |
| 100,000 to <500,000 | 23/59 (39) | 7/13 (54) |
| ≥500,000 | 13/21 (62) | 1/2 (50) |
| Baseline CD4+ T-cell count, cells/$mm^3$ | | |
| <20 | 29/72 (40) | 27/40 (68) |
| 20 to <50 | 8/25 (32) | 6/14 (43) |
| 50 to <100 | 12/39 (31) | 6/14 (43) |
| 100 to <200 | 20/63 (32) | 4/11 (36) |
| 200 to <350 | 8/44 (18) | 10/15 (67) |
| 350 to <500 | 1/14 (7) | 0/3 (0) |
| ≥500 | 2/15 (13) | 0/2 (0) |
| History of AIDS | | |
| Yes | 77/231 (33) | 50/89 (56) |
| No | 3/41 (7) | 3/10 (30) |

PDVF, protocol-defined virologic failure.

[a]Percentages are based on participants meeting PDVF out of the total number of participants for the particular row (n/N).

**Table S4.** Quantitative Plasma Viral Loads for Participants Who Included IBA in OBT

| | Study days with IBA in OBT | | Plasma HIV-1 RNA, copies/mL | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Participant** | **First** | **Last** | **Baseline** | **Week 24** | **Week 48** | **Week 96** | **Week 144** | **Week 192** | **Week 240** |
| Non-randomized Cohort | | | | | | | | | |
| 1 | 1 | 1956 | 149,227 | <40 | <40 | <40 | TND | <40/TND | TND |
| 2 | 1 | 1666 | 220 | TND | TND | TND | TND | TND | TND |
| 3 | 1 | 1848 | 22,499 | <40 | TND | TND | TND | TND | Missing[a] |
| 4 | 1 | 1217 | 1806 | TND | <40 | TND | TND | TND | Unavailable[b] |
| 5 | 1 | 1597 | 740 | TND | TND | TND | TND | TND | Completed[c] |
| 6 | 1 | 1573 | 11,447 | 44/<40 | TND | <40 | 2290/1910 | 95,333 | Completed[c] |
| 7 | 1 | 988 | 6427 | 1060 | 51 | 40 | <40 | TND | Completed[c] |
| 8 | 8 | 932 | 1097 | 13,305 | 8401 | 4622/4316 | Last observation: Week 132, 8034 copies/mL | | |
| 9 | 1 | 864 | 169 | 582 | 31,679 | 33,182 | Last observation: Week 120, 5567 copies/mL | | |
| 10 | 1 | 510 | 53,430 | TND | 438/TND | Last observation: Week 72, TND | | | |
| 11 | 1 | 177 | 39,610 | 134,480 | 318,669/343,151 | Last observation: Week 48 | | | |
| 12 | 6 | 510 | 9203 | <40/<40 | <40 | Last observation: Week 72, 672 copies/mL | | | |
| 13 | 6 | 610 | <40 | 8825 | 15,235 | Last observation: Week 84, 3343 copies/mL | | | |
| 14 | 1 | 495 | 112,009 | TND | TND | Last observation: Week 48 | | | |
| 15 | 1 | 28 | 1356 | Last observation: Week 4, 82 copies/mL | | | | | |
| 16 | 8 | 142 | 25,660 | Last observation: Week 16, 83 copies/mL | | | | | |
| 17[d] | 13 | 155 | 16,234 | 33,543 | 34,884 | 32,981 | 15,864 | 8022 | 6937 |
| 18[d] | 292 | 1814 | 22,074 | 9424/22,337 | <40 | <40 | TND | TND | <40 |
| 19[d] | 415 | 1437 | 24,608 | 63,595 | 199,246 | 117,142 | 100,289 | 160,174 | Unavailable[e] |
| 20[d] | 841 | 925 | 40,815 | 37,176 | 19,738 | 50,706 | Last observation: Week 120, 21,402 copies/mL | | |
| 21[d] | 413 | 484 | 42,894 | 85,379 | 85,810 | Last observation: Week 72, 58,467 copies/mL | | | |
| 22[d] | 208 | 585 | 21,252 | 28,703 | 13,760 | Last observation: Week 48 | | | |
| Randomized Cohort | | | | | | | | | |
| 23[d] | 1217 | 1791 | 61,093 | 236 | 54 | <40/<40 | 933 | <40 | 3300/6778 |
| 24[d] | 1133 | 1990 | 52,610 | <40 | <40 | TND | TND | TND | TND |
| 25[d] | 1073 | 1912 | 38,019 | 755 | 1540/889/325 | <40 | TND | TND | TND |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 26[d] | 1101 | 1907 | 245,036 | 112 | <40 | <40 | 15,415 | <40 | <40 |
| 27[d] | 991 | 1998 | 911,694 | 630 | 133 | 52/516 | 142,841/443 | 80,776/16,168 | 546 |
| 28[d] | 1517 | 1769 | 91,433 | 314 | 121 | 43 | TND | TND | TND |

IBA, ibalizumab; OBT, optimized background therapy; TND, target not detected.
[a]Week 240 data missing but later observations recorded. [b]Last observation Week 204, TND. [c]Completed the study at Week 228. [d]Did not include IBA in initial OBT. [e]Last observation at follow-up visit, 119,202 c/mL.

**Table S5.** Summary of Emergent Viral Genotypic Substitutions of Interest in gp160: Protocol-Defined Virologic Failure Population Through Week 240[a]

| n (%) | Randomized Cohort (N=80) | Non-randomized Cohort (N=53) | Total (N=133) |
|---|---|---|---|
| Sequenced | 71 (89) | 51 (96) | 122 (92) |
| Pre-specified substitutions[b,c] | 30 (42) | 33 (65) | 63 (52) |
| Most relevant substitutions[b,d] | 24 (34) | 32 (63) | 56 (46) |
| S375 | 17 (24) | 21 (41) | 38 (31) |
| S375H | 0 | 1 (2) | 1 (<1) |
| S375H/N | 1 (1) | 1 (2) | 2 (2) |
| S375M | 0 | 3 (6) | 3 (2) |
| S375N | 8 (11) | 8 (16) | 16 (13) |
| S375N/T | 1 (1) | 2 (4) | 3 (2) |
| S375S/H | 1 (1) | 0 | 1 (<1) |
| S375S/I | 0 | 1 (2) | 1 (<1) |
| S375S/M/T | 1 (1) | 0 | 1 (<1) |
| S375S/N | 4 (6) | 5 (10) | 9 (7) |
| S375S/T | 1 (1) | 0 | 1 (<1) |
| M426 | 16 (23) | 20 (39) | 36 (30) |
| M426L | 10 (14) | 13 (25) | 23 (19) |
| M426M/L | 6 (8) | 7 (14) | 13 (11) |
| M434 | 6 (8) | 4 (8) | 10 (8) |
| M434I | 1 (1) | 1 (2) | 2 (2) |
| M434K | 1 (1) | 0 | 1 (<1) |
| M434M/I | 3 (4) | 3 (6) | 6 (5) |
| M434M/I/T | 1 (1) | 0 | 1 (<1) |
| M475 | 8 (11) | 6 (12) | 14 (11) |
| M475I | 4 (6) | 2 (4) | 6 (5) |
| M475M/I | 4 (6) | 4 (8) | 8 (7) |

[a]Sequencing results at additional on-treatment time points around the time of protocol-defined virologic failure are included where available (not limited to only the protocol-defined virologic failure time point).
[b]Denominator for proportions with substitutions is the number sequenced for each cohort and overall.
[c]S375H/I/M/N/T, M426L, M434I/K, M475I. [d]S375H/I/M/N/Y, M426L, M434K.

**Table S6.** Baseline and Last Available CD4+ T-Cell Count for Participants Who Died

| Participant | Baseline CD4+ T-cell count, cells/mm$^3$ | Last available CD4+ T-cell count, cells/mm$^3$ | Day of last available CD4+ T-cell count | Day of study withdrawal | Day of death | Primary cause of death |
|---|---|---|---|---|---|---|
| 1 | 98 | 160 | 1387 | 1632 | Unknown | Rectal cancer |
| 2 | 92 | 171 | 1776 | 1821 | 1821 | Pneumonia |
| 3 | 80 | 2 | 1764 | 1772 | 1772 | Progression of AIDS disease |
| 4 | 5 | 0 | 1189 | 1266 | 1266 | Pulmonary septic shock |
| 5 | 1 | 4 | 1008 | 1112 | 1112 | HIV wasting syndrome |
| 6 | 28 | 148 | 1021 | 1094 | 1094 | Hodgkin's disease |
| 7 | 4 | 1 | 1010 | 1089 | 1089 | Respiratory insufficiency possibly due to AIDS-defining illness |
| 8 | 22 | 189 | 840 | 879 | 879 | Cerebrovascular accident (left middle cerebral artery stroke) |
| 9 | 349 | 494 | 847 | 875 | 875 | Cholangiocarcinoma |
| 10 | 249 | 257 | 508 | 736 | 765 | Anal squamous cell carcinoma |
| 11 | 1 | 3 | 577 | 661 | 661 | Disseminated cytomegaloviral infection |
| 12 | 0 | 5 | 588 | 660 | 660 | Hodgkin's disease |
| 13 | 160 | 172 | 511 | 603 | 603 | Pseudomonal sepsis |
| 14 | 35 | 18 | 504 | 580 | 580 | Sepsis |
| 15 | 1 | 2 | 515 | 537 | 537 | Hepatic failure (due to hepatitis B) |
| 16 | 27 | 30 | 486 | 486 | 535 | Squamous cell carcinoma |
| 17 | 6 | 34 | 498 | 530 | 530 | Cardiovascular disorder |
| 18 | 173 | 7 | 510 | 510 | 515 | Tonsil cancer |
| 19 | 1 | 3 | 425 | 511 | 511 | Clostridium difficile colitis |

| | | | | | | |
|---|---|---|---|---|---|---|
| 20 | 7 | 37 | 347 | 504 | 504 | Sepsis |
| 21 | 166 | 176 | 424 | 466 | 466 | Staphylococcal sepsis |
| 22 | 42 | 234 | 335 | 392 | 392 | Pulmonary/Cutaneous sepsis |
| 23 | 3 | 1 | 259 | 277 | 354 | Cytomegalovirus colitis |
| 24 | 1 | 4 | 253 | 350 | 350 | Acute kidney injury (advanced AIDS) |
| 25 | 12 | 37 | 264 | 334 | 334 | Septic shock |
| 26 | 55 | 55 | 262 | 287 | 287 | Progressive multifocal leukoencephalopathy |
| 27 | 1 | 1 | 179 | 179 | 228 | Pneumonia |
| 28 | 1 | 1 | 121 | 199 | 199 | Pneumonia |
| 29 | 2 | 10 | 127 | 160 | 160 | Kaposi’s sarcoma |
| 30 | 4 | 6 | 142 | 158 | 158 | Encephalitis cytomegalovirus |
| 31 | 1 | 2 | 119 | 142 | 142 | Hepatic failure |
| 32 | 11 | 8 | 83 | 101 | 101 | Meningoencephalitis viral |
| 33 | 42 | 24 | 15 | 33 | 33 | Lymphoma |
| 34 | 1 | 5 | 8 | 32 | 32 | Immune reconstitution inflammatory syndrome |
| 35 | 14 | 14 | 1 | 11 | 11 | Acute respiratory failure (community-acquired pneumonia) |

**Figure S1.** Participant disposition through the Week 240 database lock. ARV, antiretroviral. [a]The 2 most common reasons for not meeting study criteria were >2 ARV classes remaining at screening and/or not failing current ARV regimen with a confirmed plasma HIV-1 RNA ≥400 copies/mL. [b]80 participants completed the study by the time of the Week 240 database lock, though only 12 did so before their Week 240 observations. [c]Primary reasons listed. Each participant may have only 1 primary reason. [d]A total of 35 participants died. Death was recorded as the reason for withdrawal in 28/35 cases. [e]Other reasons for discontinuation were investigator decision, HIV resistance, investigator discretion due to the rapid progression of participant's malignancy, and participant developed transportation obstacles preventing ongoing participation.

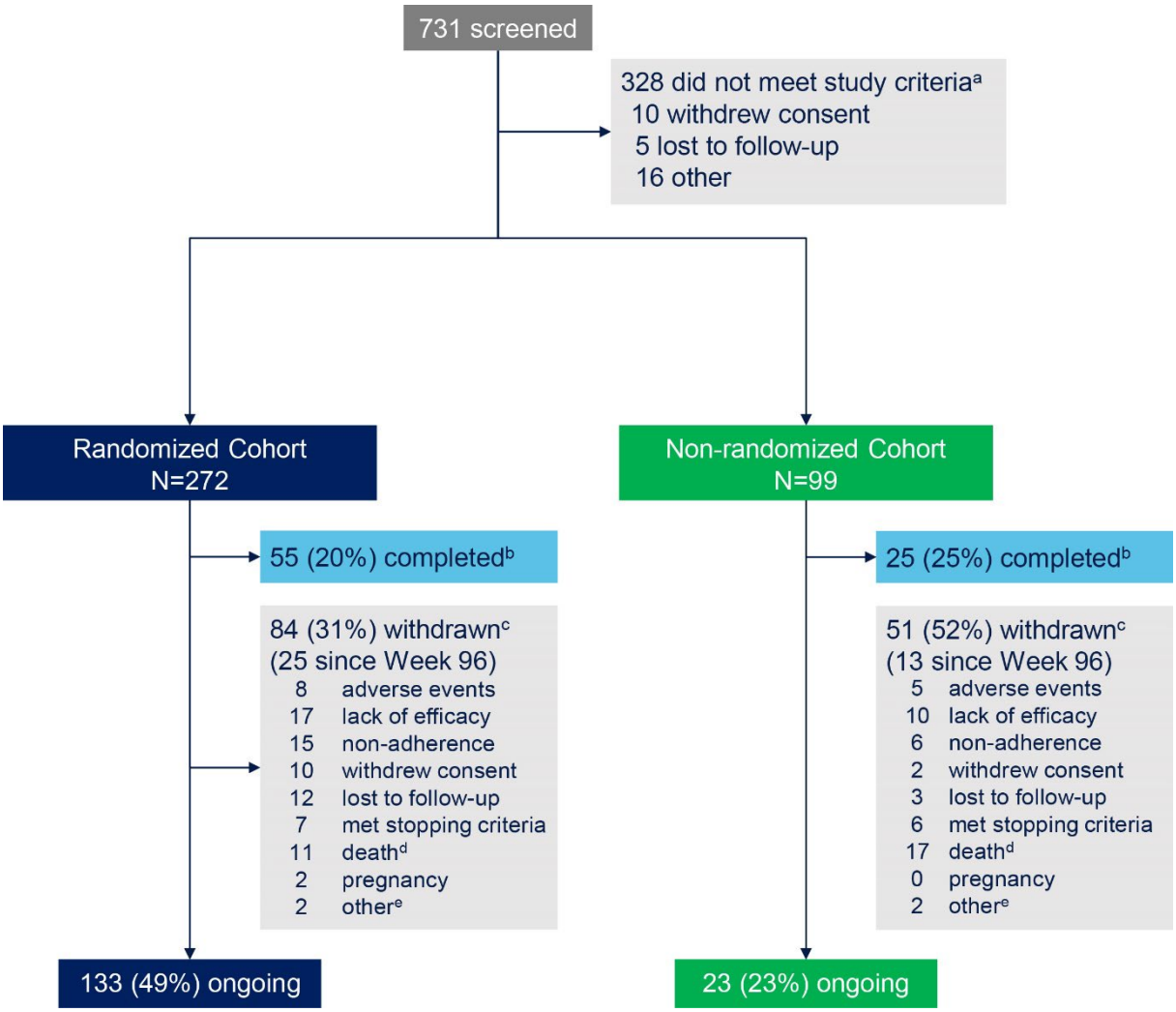

731 screened
328 did not meet study criteria[a]
10 withdrew consent
5 lost to follow-up
16 other
Randomized Cohort
N=272
Non-randomized Cohort
N=99
55 (20%) completed[b]
25 (25%) completed[b]
84 (31%) withdrawn[c]
(25 since Week 96)
8 adverse events
17 lack of efficacy
15 non-adherence
10 withdrew consent
12 lost to follow-up
7 met stopping criteria
11 death[d]
2 pregnancy
2 other[e]
51 (52%) withdrawn[c]
(13 since Week 96)
5 adverse events
10 lack of efficacy
6 non-adherence
2 withdrew consent
3 lost to follow-up
6 met stopping criteria
17 death[d]
0 pregnancy
2 other[e]
133 (49%) ongoing
23 (23%) ongoing

**Figure S2.** Proportion of participants with virologic response (HIV-1 RNA <40 copies/mL) at Weeks 192 and 240 by initial OBT, intention-to-treat–exposed population (Snapshot analysis). The 12 participants who completed before the Week 240 analysis were excluded. IBA, ibalizumab; INSTI, integrase strand transfer inhibitor; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OBT, optimized background therapy; PI, protease inhibitor; T20, enfuvirtide. [a]IBA was an investigational agent at the beginning of BRIGHTE and was not available to the Randomized Cohort as part of their initial OBT. After regulatory approval of IBA, 6 participants in the Randomized Cohort added IBA to their OBT.

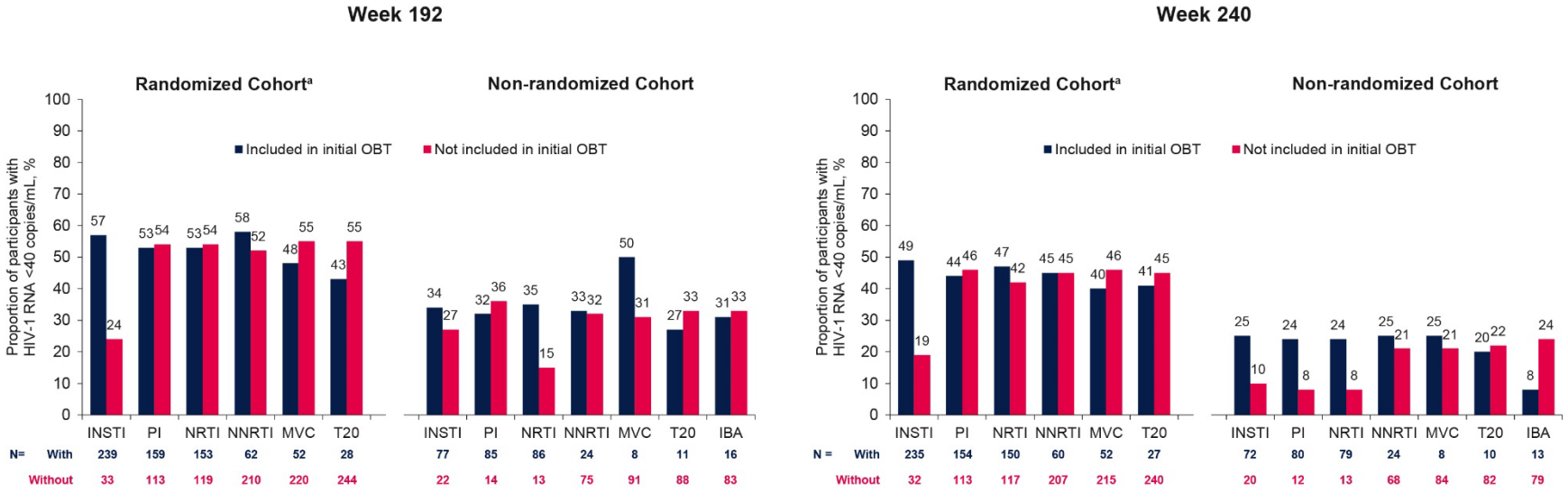
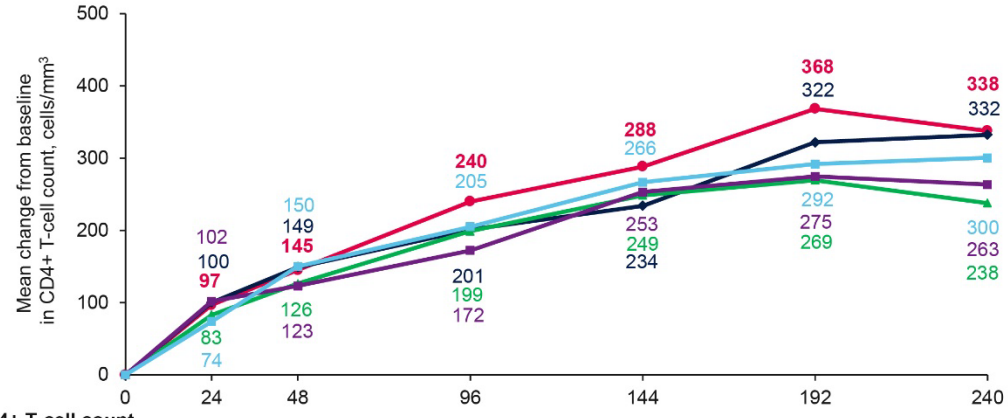


**Figure S3.** Change in CD4+ T-cell count from baseline to Week 240 by **(a)** baseline CD4+ T-cell count, **(b)** baseline viral load, and **(c)** virologic response at the same time point (Randomized Cohort, observed analysis). Mean baseline CD4+ T-cell count by baseline viral load subgroup was <1000 copies/mL: 388.7 cells/$mm^3$; 1000 to <10,000 copies/mL: 200.4 cells/$mm^3$; 10,000 to <100,000 copies/mL: 135.3 cells/$mm^3$; ≥100,000 copies/mL: 59.9 cells/$mm^3$.

**a**

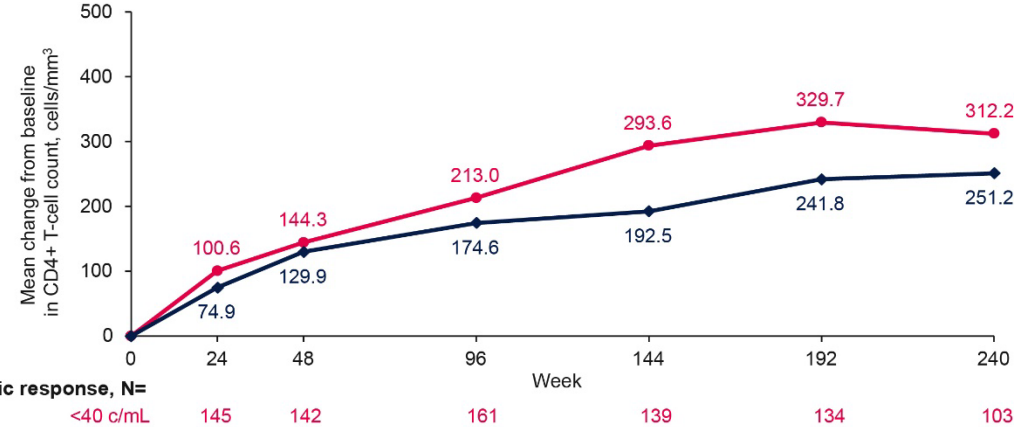



| Baseline CD4+ T-cell count, N= | | | | | | | |
|---|---|---|---|---|---|---|---|
| <20 | 72 | 64 | 58 | 54 | 49 | 47 | 33 |
| 20 to <50 | 25 | 24 | 20 | 17 | 18 | 15 | 13 |
| 50 to <100 | 39 | 34 | 30 | 26 | 26 | 24 | 16 |
| 100 to <200 | 63 | 59 | 57 | 52 | 47 | 40 | 32 |
| ≥200 | 73 | 67 | 63 | 64 | 57 | 53 | 45 |

**b**


| Baseline viral load, N= | | | | | | | |
|---|---|---|---|---|---|---|---|
| <1000 | 31 | 28 | 27 | 25 | 21 | 20 | 18 |
| 1000 to <10,000 | 44 | 38 | 38 | 38 | 37 | 31 | 24 |
| 10,000 to <100,000 | 117 | 108 | 96 | 91 | 85 | 78 | 61 |
| ≥100,000 | 80 | 74 | 67 | 59 | 54 | 50 | 36 |

**c**




| Virologic response, N= | | | | | | |
|---|---|---|---|---|---|---|
| <40 c/mL | 145 | 142 | 161 | 139 | 134 | 103 |
| ≥40 c/mL | 102 | 86 | 50 | 56 | 45 | 36 |