***Supplementary Methods:* Assay interference experiment**

Ten *C. difficile* toxin-positive fecal samples were evaluated. Baseline toxin levels were first determined using EIA (Optical Density value) or CCA (extended titer). Samples then underwent incubation with bezlotoxumab (median *in vivo* fecal concentration of 528.0 ng/mL; 10x median; 100x median; concentrations determined previously in Phase 3 trials) and without bezlotoxumab (control). All samples were thoroughly mixed and incubated for 5 minutes or 4 hours at room temperature to in-part mimic the conditions for stool transport to laboratories for analysis. Following incubation, samples were tested again by toxin EIA or CCA, and toxin levels then compared before and after the addition of bezlotoxumab, and with and without bezlotoxumab.

***Supplementary Table 1:* Type of local laboratory test used for baseline CDI diagnosis according to treatment group (mITT population, MODIFY I and II pooled data)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Bezlotoxumab**  **n=781**  **na (%)** | **Placebo**  **n=773**  **na (%)** | **Overall**  **n=1554**  **na (%)** |
| Toxin EIA | 372 (47.6) | 385 (49.8) | 757 (48.7) |
| Toxin CCA | 10 (1.3) | 6 (0.8) | 16 (1.1) |
| tgPCR | 357 (45.7) | 337 (43.6) | 694 (44.7) |
| Toxigenic culture | 42 (5.4) | 45 (5.8) | 87 (5.6) |

an represents the number of participants in the subgroup analysis population meeting the criteria for the endpoint.

CCA=cell cytotoxicity assay; CDI=*Clostridioides*  *difficile* infection; EIA=enzyme immunoassay; mITT=modified intent-to-treat; tgPCR=toxin gene polymerase chain reaction.

***Supplementary Table 2:* Disposition of participants in each treatment group (mITT population, MODIFY I and II pooled data)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Bezlotoxumab** | | **Placebo** | |
|  | **Toxin EIA + CCA na (%)** | **tgPCR + culture na (%)** | **Toxin EIA + CCA na (%)** | **tgPCR + culture na (%)** |
| Participants in populationb | 382 | 399 | 391 | 382 |
| Completed study | 317 (83.0) | 353 (88.5) | 318 (81.3) | 329 (86.1) |
| Prematurely discontinued study | 65 (17.0) | 46 (11.5) | 73 (18.7) | 53 (13.9) |
| Death | 33 (8.6) | 19 (4.8) | 34 (8.7) | 22 (5.8) |
| Withdrawal by participant | 21 (5.5) | 13 (3.3) | 23 (5.9) | 16 (4.2) |
| Lost to follow-up | 11 (2.9) | 10 (2.5) | 12 (3.1) | 10 (2.6) |
| Other reasons | 0 (0.0) | 4 (1.0) | 4 (1.0) | 5 (1.3) |

an represents the number of participants in the subgroup analysis population meeting the criteria for the endpoint.

bEach participant was counted once.

CCA=cell cytotoxicity assay; EIA=enzyme immunoassay; mITT=modified intent-to-treat; tgPCR=toxin gene polymerase chain reaction.

***Supplementary Table 3:* Proportion of participants with diarrhea recurrence by baseline diagnosis of CDI (Clinical Cure Population; MODIFY I and II pooled data)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Bezlotoxumaba**  **% (n/m)c** | **Placebob**  **% (n/m)c** | **Difference**  **% (95% CI)d** |
| Toxin EIA + CCA | 28.2 (88/312) | 43.8 (142/324) | -15.6 (-22.9, -8.2) |
| tgPCR + culture | 39.9 (125/313) | 49.8 (148/297) | -9.9 (-17.7, -2.0) |
| Toxin EIA + CCA vs. tgPCR + culture, difference % (95% CI)d | -11.7 (-19.0, -4.3) | -6.0 (-13.8, 1.9) |  |

aFor the bezlotoxumab group, 60.6% of the 213 participants who experienced diarrhea recurrence tested positive for toxigenic *C. difficile*. The remaining participants either had a negative test (19.2%) or were not tested (20.2%). Of those who were not tested, the majority (37/43) had diarrhea for only 1 or 2 days.

bFor the placebo group, 71.0% of the 290 participants who experienced diarrhea recurrence tested positive for toxigenic *C. difficile*. The remaining participants either had a negative test (20.0%) or were not tested (9.0%). Of those who were not tested, the majority (17/26) had diarrhea for only 1 or 2 days.

cn represents the number of participants in the subgroup analysis population meeting the criteria for the endpoint; m represents the number of participants included within treatment.

dBased on the Miettinen and Nurminen method.

CCA=cell cytotoxicity assay; CDI=*Clostridioides difficile* infection; CI=confidence interval; EIA=enzyme immunoassay; tgPCR=toxin gene polymerase chain reaction.

***Supplementary Table 4:* Proportion of participants with sustained cure (mITT population; MODIFY I and II pooled data)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Bezlotoxumab**  **% (n/m)a** | **Placebo**  **% (n/m)a** | **Difference**  **% (95% CI)b** |
| Toxin EIA + CCA | 67.3 (257/382) | 55.5 (217/391) | 11.8 (4.9–18.5) |
| tgPCR + culture | 59.9 (239/399) | 51.8 (198/382) | 8.1 (1.1–15.0) |
| Toxin EIA + CCA vs. tgPCR + culture, difference % (95% CI)b | 7.4 (0.6–14.1) | 3.7 (-3.4–10.7) |  |

an represents the number of participants in the subgroup analysis population meeting the criteria for the endpoint; m represents the number of participants included within treatment.

bBased on the Miettinen and Nurminen method.

CCA=cell cytotoxicity assay; CI=confidence interval; EIA=enzyme immunoassay; mITT=modified intent-to-treat; tgPCR=toxin gene polymerase chain reaction.

***Supplementary Table 5:* Summary of changes in diagnostic toxin EIA and CCA results following incubationof *C. difficile* toxin-positive fecal samples with bezlotoxumab**

|  |  |  |
| --- | --- | --- |
| **Samplea,b** | **Diagnostic toxin EIA resultc** | **Diagnostic CCA resultd** |
| 1 | No change | No change |
| 3 | No change | Changed from positive to negative at 10x 528.0 ng/mL and 100x 528.0 ng/mL after 4 hours’ incubation |
| 4 | No change | No change |
| 5 | No change | No change |
| 6 | No change | Changed from positive to negative at 100x 528.0 ng/mL after 5 minutes’ and 4 hours’ incubation |
| 7 | No change | Changed from positive to negative at 100x 528.0 ng/mL after 5 minutes’ and 4 hours’ incubation |
| 8 | No change | Invalid result |
| 9 | No change | No change |
| 10 | No change | No change |

a*C. difficile* toxin-positive samples underwent 5 minutes’ and 4 hours’ incubation with bezlotoxumab (median *in vivo* fecal concentration of 528.0 ng/mL; 10x median; 100x median) and without bezlotoxumab (control).

bResults for Sample 2 are not included as toxin EIA and CCA showed a toxin-negative result at baseline.

cSamples with OD values of ≥0.080 and ≤0.080 were classified as toxin-positive and toxin-negative, respectively.

dSamples with toxin titers of ≥1 and 0 were classified as toxin-positive and toxin-negative, respectively.

CCA=cell cytotoxicity assay; EIA=enzyme immunoassay; OD=optical density.