**Table 2, Supplementary Digital Content 2.** Secondary and additional endpoints (ITT population).

| **Endpoint** | **PBO (n = 66)** | **LIN IR 290 μg (n = 66)** | **LIN DR1 30 μg (n = 67)** | **LIN DR1 100 μg (n = 67)** | **LIN DR1 300 μg (n = 67)** | **MD-7246 30 μg (n = 67)** | **MD-7246 100 μg (n = 66)** | **MD-7246 300 μg (n = 66)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **12-week CFB endpointsa** | | | | | | | | |
| **Percent abdominal pain** | | | | | | | | |
| CFB score (SE)b | –18.917 (4.154) | –29.297 (4.148) | –26.525 (4.035) | –24.796 (4.100) | –32.074 (4.052) | –26.355 (4.091) | –25.907 (4.050) | –23.508 (4.110) |
| Difference vs.  PBO (95% CI)c | - | –10.381  (–21.490, 0.729) | –7.609  (–18.729, 3.511) | –5.880  (–17.042, 5.283) | –13.157  (–24.309,  –2.005) | –7.439  (–18.570, 3.692) | –6.99  (–18.145, 4.164) | –4.591  (–15.744, 6.561) |
| P value | - | 0.07 | 0.18 | 0.30 | 0.02 | 0.19 | 0.22 | 0.42 |
| **Abdominal discomfort** | | | | | | | | |
| CFB score (SE)b | –1.316 (0.240) | –1.911 (0.240) | –1.655 (0.234) | –1.460 (0.237) | –2.048 (0.235) | –1.705 (0.237) | –1.537 (0.234) | –1.500 (0.238) |
| Difference vs.  PBO (95% CI)c | - | –0.595  (–1.238, 0.049) | –0.338  (–0.982, 0.305) | –0.144  (–0.790, 0.503) | –0.731  (–1.377,  –0.086) | –0.389  (–1.033, 0.255) | –0.221  (–0.886, 0.425) | –0.184  (–0.829, 0.461) |
| P value | - | 0.07 | 0.30 | 0.66 | 0.03 | 0.24 | 0.50 | 0.58 |
| **Abdominal bloating** | | | | | | | | |
| CFB score (SE)b | –1.258 (0.247) | –1.932 (0.247) | –1.679 (0.240) | –1.294 (0.244) | –1.781 (0.241) | –1.699 (0.244) | –1.332 (0.241) | –1.399 (0.244) |
| Difference vs.  PBO (95% CI)c | - | –0.675  (–1.334,  –0.015) | –0.421  (–1.081, 0.240) | –0.036  (–0.699, 0.627) | –0.524  (–1.187, 0.139) | –0.441  (–1.104, 0.221) | –0.074  (–0.737, 0.588) | –0.141  (–0.802, 0.521) |
| P value | - | 0.05 | 0.21 | 0.92 | 0.12 | 0.19 | 0.83 | 0.68 |
| **Abdominal scored** | | | | | | | | |
| CFB score (SE)b | –1.289 (0.239) | –1.904 (0.239) | –1.647 (0.233) | –1.417 (0.236) | –1.938 (0.234) | –1.737 (0.236) | –1.487 (0.234) | –1.485 (0.237) |
| Difference vs.  PBO (95% CI)c | - | –0.615  (–1.255, 0.026) | –0.358  (–0.999, 0.283) | –0.128  (–0.771, 0.516) | –0.648  (–1.291,  –0.005) | –0.448  (–1.090, 0.193) | –0.198  (–0.841, 0.445) | –0.196  (–0.838, 0.447) |
| P value | - | 0.06 | 0.27 | 0.70 | 0.05 | 0.17 | 0.55 | 0.55 |
| **SBM frequency** | | | | | | | | |
| CFB no./wk. (SE)b | 1.433  (0.371) | 2.412  (0.371) | 1.709  (0.360) | 2.378  (0.363) | 2.594  (0.359) | 1.432  (0.365) | 1.489  (0.361) | 0.964  (0.366) |
| Difference vs.  PBO (95% CI)c | - | 0.979  (–0.012, 1.970) | 0.276  (–0.716, 1.268) | 0.945  (–0.049, 1.938) | 1.160  (0.168,  2.152) | –0.001  (–0.993, 0.991) | 0.055  (–0.940, 1.051) | –0.469  (–1.463, 0.525) |
| P value | - | 0.05 | 0.59 | 0.06 | 0.02 | 0.99 | 0.91 | 0.35 |
| **Stool consistency (BSFS)** | | | | | | | | |
| CFB score (SE)b | 0.938  (0.148) | 1.774  (0.145) | 1.224  (0.144) | 1.620  (0.151) | 1.825  (0.142) | 0.999  (0.144) | 1.073  (0.148) | 1.152  (0.152) |
| Difference vs.  PBO (95% CI)c | - | 0.836  (0.443,  1.229) | 0.285  (–0.111, 0.681) | 0.682  (0.276,  1.088) | 0.887  (0.490,  1.284) | 0.061  (–0.336, 0.457) | 0.135  (–0.268, 0.538) | 0.214  (–0.194, 0.621) |
| P value | - | <0.001 | 0.16 | 0.001 | <0.001 | 0.76 | 0.51 | 0.30 |
| **Stool consistency (5-point ordinal scale)** | | | | | | | | |
| CFB score (SE)b | 0.617  (0.087) | 1.103  (0.084) | 0.749  (0.084) | 1.018  (0.088) | 1.144  (0.083) | 0.731  (0.084) | 0.716  (0.086) | 0.738  (0.089) |
| Difference vs.  PBO (95% CI)c | - | 0.486  (0.256,  0.715) | 0.132  (–0.098, 0.363) | 0.401  (0.164,  0.637) | 0.527  (0.294,  0.759) | 0.114  (–0.117, 0.345) | 0.099  (–0.136, 0.334) | 0.121  (–0.116, 0.358) |
| P value | - | <0.001 | 0.26 | 0.001 | <0.001 | 0.33 | 0.41 | 0.32 |
| **Straining severity** | | | | | | | | |
| CFB score (SE)b | –0.696 (0.104) | –1.126 (0.101) | –0.870 (0.100) | –0.993 (0.106) | –1.104 (0.099) | –0.861 (0.101) | –0.792 (0.103) | –0.811 (0.107) |
| Difference vs.  PBO (95% CI)c | - | –0.431  (–0.705,  –0.157) | –0.174  (–0.451, 0.102) | –0.298  (–0.581,  –0.014) | –0.408  (–0.686,  –0.131) | –0.166  (–0.442, 0.111) | –0.097  (–0.378, 0.185) | –0.115  (–0.400, 0.170) |
| P value | - | 0.002 | 0.22 | 0.04 | 0.004 | 0.24 | 0.50 | 0.43 |
| **Constipation severity** | | | | | | | | |
| CFB score (SE)b | –0.657 (0.103) | –1.169 (0.103) | –0.853 (0.101) | –0.828 (0.103) | –1.106 (0.101) | –0.805 (0.101) | –0.773 (0.100) | –0.789 (0.101) |
| Difference vs.  PBO (95% CI)c | - | –0.512  (–0.787,  –0.238) | –0.197  (–0.473, 0.080) | –0.171 (–0.450, 0.108) | –0.449  (–0.724,  –0.174) | –0.148  (–0.423, 0.126) | –0.116  (–0.392, 0.160) | –0.132  (–0.407, 0.144) |
| P value | - | <0.001 | 0.16 | 0.23 | 0.001 | 0.29 | 0.41 | 0.35 |
| **IBS symptom severity** | | | | | | | | |
| CFB score (SE)b | –0.593 (0.098) | –0.950 (0.099) | –0.798 (0.096) | –0.704 (0.099) | –0.973 (0.097) | –0.800 (0.097) | –0.750 (0.097) | –0.696 (0.098) |
| Difference vs.  PBO (95% CI)c | - | 0.357  (–0.621,  –0.093) | –0.205 (–0.469, 0.060) | –0.110 (–0.378, 0.158) | –0.379 (–0.644,  –0.115) | –0.207 (–0.471, 0.057) | –0.156 (–0.421, 0.108) | –0.103 (–0.369, 0.163) |
| P value | - | 0.008 | 0.13 | 0.42 | 0.005 | 0.12 | 0.25 | 0.45 |
| **Percentage of days on rescue medication** | | | | | | | | |
| CFB days (SE)b | 0.596  (2.138) | –2.727 (2.137) | 0.745  (2.081) | –3.741 (2.094) | –0.519 (2.080) | –1.487 (2.101) | 0.050  (2.082) | 3.172  (2.111) |
| Difference vs.  PBO (95% CI)c | - | –3.323  (–9.035, 2.389) | 0.148 (–5.590, 5.887) | –4.337  (–10.066, 1.392) | –1.115  (–6.841, 4.611) | –2.083  (–7.805, 3.639) | –0.546  (–6.284, 5.192) | 2.576  (–3.156, 8.307) |
| P value | - | 0.25 | 0.96 | 0.14 | 0.70 | 0.48 | 0.85 | 0.38 |
| **Treatment satisfactione** | | | | | | | | |
| Difference vs.  PBO (95% CI)b | - | –0.236 (–0.711, 0.240) | –0.054 (–0.525, 0.416) | 0.039 (–0.438, 0.516) | –0.305 (–0.778, 0.169) | 0.131 (–0.343, 0.604) | –0.061 (–0.529, 0.406) | –0.099 (–0.570, 0.373) |
| P value | - | 0.33 | 0.82 | 0.87 | 0.20 | 0.59 | 0.80 | 0.68 |
| **Responder endpointsf,g** | | | | | | | | |
| **6/12-week APC+1 responder rateh** | | | | | | | | |
| n (%) | 14 (21.2) | 21 (31.8) | 18 (26.9) | 17 (25.4) | 26 (38.8) | 16 (24.2) | 16 (24.2) | 14 (21.2) |
| OR (95% CI)i | - | 1.71  (0.79, 3.70) | 1.39  (0.61, 3.17) | 1.27  (0.57, 2.85) | 2.39  (1.10, 5.19) | 1.13  (0.49, 2.58) | 1.11  (0.48, 2.58) | 0.89  (0.37, 2.14) |
| P value | - | 0.17 | 0.44 | 0.55 | <0.03 | 0.77 | 0.80 | 0.80 |
| **6/12-week APC+1 sustained responder rateh** | | | | | | | | |
| n (%) | 12 (18.2) | 20 (30.3) | 17 (25.4) | 16 (23.9) | 23 (34.3) | 16 (23.9) | 16 (24.2) | 14 (21.2) |
| OR (95% CI)i | - | 1.95  (0.87, 4.37) | 1.58  (0.67, 3.70) | 1.39  (0.60, 3.23) | 2.50  (1.10, 5.65) | 1.38  (0.59, 3.24) | 1.33  (0.56, 3.18) | 1.07  (0.44, 2.63) |
| P value | - | 0.10 | 0.30 | 0.43 | 0.03 | 0.45 | 0.52 | 0.88 |
| **6/12-week abdominal pain responder ratej** | | | | | | | | |
| n (%) | 24 (36.4) | 23 (34.8) | 30 (44.8) | 22 (32.8) | 35 (52.2) | 24 (35.8) | 24 (36.4) | 27 (40.9) |
| OR (95% CI)i | - | 0.94  (0.46, 1.93) | 1.44  (0.70, 2.98) | 0.85  (0.41, 1.75) | 2.03  (0.99, 4.16) | 0.93  (0.45, 1.93) | 0.96  (0.46, 2.02) | 1.11  (0.54, 2.29) |
| P value | - | 0.87 | 0.33 | 0.66 | 0.05 | 0.86 | 0.92 | 0.78 |
| **6/12-week abdominal pain sustained responder ratej** | | | | | | | | |
| n (%) | 22 (33.3) | 23 (34.8) | 30 (44.8) | 21 (31.3) | 33 (49.3) | 24 (35.8) | 24 (36.4) | 27 (40.9) |
| OR (95% CI)i | - | 1.08  (0.52, 2.24) | 1.65  (0.79, 3.44) | 0.90 (0.43, 1.87) | 2.15  (1.03, 4.48) | 1.08  (0.52, 2.26) | 1.09  (0.51, 2.33) | 1.26  (0.61, 2.62) |
| P value | - | 0.84 | 0.19 | 0.77 | 0.04 | 0.84 | 0.82 | 0.53 |
| **9/12-week abdominal pain responder ratej** | | | | | | | | |
| n (%) | 15 (22.7) | 21 (31.8) | 23 (34.3) | 14 (20.9) | 27 (40.3) | 18 (26.9) | 18 (27.3) | 21 (31.8) |
| OR (95% CI)i | - | 1.62  (0.75, 3.54) | 1.84  (0.83, 4.07) | 0.90  (0.39, 2.07) | 2.49  (1.14, 5.43) | 1.22  (0.54, 2.76) | 1.18  (0.52, 2.69) | 1.45  (0.65, 3.25) |
| P value | - | 0.22 | 0.14 | 0.81 | 0.02 | 0.64 | 0.69 | 0.37 |
| **9/12-week abdominal pain sustained responder ratej** | | | | | | | | |
| n (%) | 15 (22.7) | 21 (31.8) | 23 (34.8) | 14 (20.9) | 26 (38.8) | 18 (26.9) | 18 (27.3) | 21 (31.8) |
| OR (95% CI)i | - | 1.62  (0.75, 3.54) | 1.84  (0.83, 4.07) | 0.90  (0.39, 2.07) | 2.35  (1.08, 5.12) | 1.22  (0.54, 2.76) | 1.18  (0.52, 2.69) | 1.45  (0.65, 3.25) |
| P value | - | 0.22 | 0.14 | 0.81 | 0.03 | 0.64 | 0.69 | 0.37 |
| **6/12-week CSBM+1 responder ratek** | | | | | | | | |
| n (%) | 23 (34.8) | 35 (53.0) | 30 (44.8) | 26 (38.8) | 35 (52.2) | 25 (37.3) | 26 (39.4) | 21 (31.8) |
| OR (95% CI)i | - | 2.07  (1.03, 4.16) | 1.58  (0.76, 3.27) | 1.22  (0.59, 2.54) | 2.15  (1.06, 4.37) | 1.13  (0.54, 2.36) | 1.17  (0.57, 2.39) | 0.81  (0.38, 1.71) |
| P value | - | 0.04 | 0.22 | 0.59 | 0.03 | 0.75 | 0.68 | 0.58 |
| **6/12-week CSBM+1 sustained responder ratek** | | | | | | | | |
| n (%) | 21 (31.8) | 31 (47.0) | 26 (38.8) | 25 (37.3) | 31 (46.3) | 25 (37.3) | 25 (37.9) | 19 (28.8) |
| OR (95% CI)i | - | 1.88  (0.93, 3.79) | 1.41  (0.67, 2.95) | 1.30  (0.62, 2.72) | 2.06  (0.99, 4.26) | 1.31  (0.63, 2.76) | 1.22  (0.59, 2.55) | 0.78  (0.36, 1.70) |
| P value | - | 0.08 | 0.37 | 0.49 | 0.05 | 0.47 | 0.59 | 0.54 |
| **9/12-week CSBM+1 responder ratek** | | | | | | | | |
| n (%) | 16 (24.2) | 24 (36.4) | 10 (14.9) | 20 (29.9) | 24 (35.8) | 13 (19.4) | 13 (19.7) | 11 (16.7) |
| OR (95% CI)i | - | 1.74  (0.83, 3.65) | 0.54  (0.22, 1.34) | 1.26  (0.58, 2.75) | 1.94  (0.90, 4.20) | 0.74  (0.32, 1.71) | 0.71  (0.30, 1.69) | 0.52  (0.21, 1.31) |
| P value | - | 0.13 | 0.18 | 0.56 | 0.09 | 0.47 | 0.45 | 0.16 |
| **9/12-week CSBM+1 sustained responder ratek** | | | | | | | | |
| n (%) | 16 (24.2) | 23 (34.8) | 10 (14.9) | 18 (26.9) | 21 (31.3) | 13 (19.4) | 12 (18.2) | 9 (13.6) |
| OR (95% CI)i | - | 1.64  (0.78, 3.44) | 0.54  (0.22, 1.34) | 1.08  (0.49, 2.38) | 1.58  (0.73, 3.41) | 0.74  (0.32, 1.71) | 0.63  (0.26, 1.52) | 0.41  (0.16, 1.08) |
| P value | - | 0.19 | 0.18 | 0.85 | 0.25 | 0.47 | 0.31 | 0.07 |
| **6/12-week abdominal score responder rated,l** | | | | | | | | |
| n (%) | 24 (36.4) | 25 (37.9) | 30 (44.8) | 22 (32.8) | 34 (50.7) | 28 (41.8) | 21 (31.8) | 26 (39.4) |
| OR (95% CI)i | - | 1.06  (0.52, 2.15) | 1.42  (0.69, 2.91) | 0.90  (0.44, 1.85) | 1.82  (0.89, 3.72) | 1.25  (0.61, 2.56) | 0.73  (0.34, 1.56) | 1.02  (0.49, 2.10) |
| P value | - | 0.88 | 0.35 | 0.77 | 0.10 | 0.55 | 0.41 | 0.96 |
| **9/12-week abdominal score responder rated,l** | | | | | | | | |
| n (%) | 11 (16.7) | 21 (31.8) | 24 (35.8) | 13 (19.4) | 23 (34.3) | 17 (25.4) | 15 (22.7) | 20 (30.3) |
| OR (95% CI)i | - | 2.46  (1.05, 5.75) | 3.06  (1.30, 7.20) | 1.24  (0.50, 3.06) | 2.84  (1.21, 6.66) | 1.81  (0.74, 4.41) | 1.42  (0.57, 3.55) | 2.01  (0.83, 4.89) |
| P value | - | 0.04 | 0.01 | 0.64 | 0.02 | 0.20 | 0.47 | 0.12 |
| **6/12-week adequate relief responder rated,m** | | | | | | | | |
| n (%) | 22 (33.3) | 31 (47.0) | 31 (46.3) | 21 (31.3) | 34 (50.7) | 27 (40.3) | 36 (54.5) | 31 (47.0) |
| OR (95% CI)i | - | 1.83  (0.89, 3.77) | 1.89  (0.91, 3.93) | 1.11  (0.52, 2.38) | 2.38  (1.12, 5.03) | 1.48  (0.71, 3.09) | 2.48  (1.21, 5.08) | 1.91  (0.92, 3.93) |
| P value | - | 0.10 | 0.09 | 0.80 | 0.02 | 0.31 | 0.01 | 0.08 |
| **9/12-week adequate relief responder ratem** | | | | | | | | |
| n (%) | 12 (18.2) | 22 (33.3) | 21 (31.3) | 14 (20.9) | 23 (34.3) | 16 (23.9) | 22 (33.3) | 20 (30.3) |
| OR (95% CI)i | - | 2.37  (1.03, 5.46) | 2.44  (1.03, 5.77) | 1.46  (0.59, 3.62) | 3.24  (1.34, 7.87) | 1.51  (0.63, 3.60) | 2.52  (1.07, 5.96) | 1.85  (0.82, 4.16) |
| P value | - | 0.04 | 0.04 | 0.42 | 0.007 | 0.36 | 0.04 | 0.13 |

a12-week CFB endpoints were calculated over the 12 weeks of the treatment period; bCFB values are the LS means obtained with the use of the ANCOVA model; cDifference values are the LS mean differences between LIN and PBO from the ANCOVA model; dAbdominal score was calculated as the average of the abdominal pain, abdominal bloating, and abdominal discomfort scores; eTreatment satisfaction was measured on a 5-point ordinal scale at each post-dose visit; fFor each endpoint, a 6/12-week responder met the weekly responder criteria for the endpoint for ≥6 of 12 weeks of treatment; a 6/12-week sustained responder met the 6/12-week responder definition and was a weekly responder for ≥2 of the last 4 weeks of treatment; gFor each endpoint, a 9/12-week responder met the weekly responder criteria for the endpoint for ≥9 of 12 weeks of treatment; a 9/12-week sustained responder met the 9/12-week responder definition and was a weekly responder for ≥3 of the last 4 weeks of treatment; hAn APC+1 responder met both the weekly abdominal pain and CSBM+1 responder criteria during the defined time period; iORs refer to a comparison between LIN and PBO; jA weekly abdominal pain responder had a reduction from baseline of ≥30% in the average weekly abdominal pain score; kA weekly CSBM+1 responder had an increase from baseline of ≥1 in the CSBM weekly rate (i.e., CSBMs/week); lA weekly abdominal score responder had a reduction from baseline of ≥30% in the average weekly abdominal score; mAn adequate relief responder reported adequate relief of IBS symptoms during the defined time period.

ANCOVA, analysis of covariance; APC, abdominal pain and constipation; BSFS, Bristol Stool Form Scale; CFB, change from baseline; CI, confidence interval; CSBM, complete spontaneous bowel movement; DR1, delayed-release formulation 1; IBS, irritable bowel syndrome; IR, immediate-release formulation; LIN, linaclotide; LS, least-squares; OR, odds ratio; PBO, placebo; SBM, spontaneous bowel movement; SE, standard error.