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

| **Endpoint** | **PBO(n = 66)** | **LIN IR290 μg(n = 66)** | **LIN DR130 μg(n = 67)** | **LIN DR1100 μg(n = 67)** | **LIN DR1300 μg(n = 67)** | **MD-724630 μg(n = 67)** | **MD-7246100 μg(n = 66)** | **MD-7246300 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.