**Online supplementary materials**

**Supplementary Table 1.** Abdominal symptom responder rates (ITT analysis set)

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| **Responder rate** | **Placebo  (n = 300)** | **Tenapanor 50 mg b.i.d. (n = 293)** |
| **Abdominal discomfort responder rate, 6/12 weeks, n (%)a** | 108 (36.0) | 139 (47.4) |
| Risk difference | – | 11.4 |
| 95% CI | – | 3.6–19.3 |
| Adjusted RR | – | 1.32 |
| 95% CI | – | 1.09–1.60 |
| CMH *P* value | – | 0.005 |
| **Abdominal bloating responder rate, 6/12 weeks, n (%)a** | 103 (34.3) | 126 (43.0) |
| Risk difference | – | 8.7 |
| 95% CI | – | 0.9–16.5 |
| Adjusted RR | – | 1.25 |
| 95% CI | – | 1.02–1.54 |
| CMH *P* value | – | 0.031 |
| **Abdominal cramping responder rate, 6/12 weeks, n (%)a** | 121 (40.3) | 145 (49.5) |
| Risk difference | – | 9.2 |
| 95% CI | – | 1.2–17.1 |
| Adjusted RR | – | 1.23 |
| 95% CI | – | 1.03–1.47 |
| CMH *P* value | – | 0.024 |
| **Abdominal fullness responder rate, 6/12 weeks, n (%)a** | 101 (33.7) | 130 (44.4) |
| Risk difference | – | 10.7 |
| 95% CI | – | 2.9–18.5 |
| Adjusted RR | – | 1.32 |
| 95% CI | – | 1.08–1.62 |
| CMH *P* value | – | 0.007 |
| **Abdominal discomfort responder rate, 9/12 weeks, n (%)b** | 71 (23.7) | 98 (33.4) |
| Risk difference | – | 9.8 |
| 95% CI | – | 2.6–17.0 |
| Adjusted RR | – | 1.42 |
| 95% CI | – | 1.09–1.84 |
| CMH *P* value | – | 0.008 |
| **Abdominal bloating responder rate, 9/12 weeks, n (%)b** | 66 (22.0) | 85 (29.0) |
| Risk difference | – | 7.0 |
| 95% CI | – | 0.0–14.0 |
| Adjusted RR | – | 1.33 |
| 95% CI | – | 1.01–1.76 |
| CMH *P* value | – | 0.044 |
| **Abdominal cramping responder rate, 9/12 weeks, n (%)b** | 79 (26.3) | 104 (35.5) |
| Risk difference | – | 9.2 |
| 95% CI | – | 1.8–16.6 |
| Adjusted RR | – | 1.35 |
| 95% CI | – | 1.06–1.73 |
| CMH *P* value | – | 0.014 |
| **Abdominal fullness responder rate, 9/12 weeks, n (%)b** | 60 (20.0) | 91 (31.1) |
| Risk difference | – | 11.1 |
| 95% CI | – | 4.1–18.0 |
| Adjusted RR | – | 1.56 |
| 95% CI | – | 1.18–2.07 |
| CMH *P* value | – | 0.002 |
| **Abdominal discomfort responder rate, 13/26 weeks, n (%)c** | 118 (39.3) | 141 (48.1) |
| Risk difference | – | 8.8 |
| 95% CI | – | 0.8–16.7 |
| Adjusted RR | – | 1.22 |
| 95% CI | – | 1.02–1.47 |
| CMH *P* value | – | 0.031 |
| **Abdominal bloating responder rate, 13/26 weeks, n (%)c** | 106 (35.3) | 131 (44.7) |
| Risk difference | – | 9.4 |
| 95% CI | – | 1.5–17.2 |
| Adjusted RR | – | 1.26 |
| 95% CI | – | 1.04–1.54 |
| CMH *P* value | – | 0.020 |
| **Abdominal cramping responder rate, 13/26 weeks, n (%)c** | 125 (41.7) | 149 (50.9) |
| Risk difference | – | 9.2 |
| 95% CI | – | 1.2–17.2 |
| Adjusted RR | – | 1.22 |
| 95% CI | – | 1.03–1.46 |
| CMH *P* value | – | 0.025 |
| **Abdominal fullness responder rate, 13/26 weeks, n (%)c** | 107 (35.7) | 129 (44.0) |
| Risk difference | – | 8.4 |
| 95% CI | – | 0.5–16.2 |
| Adjusted RR | – | 1.23 |
| 95% CI | – | 1.01–1.50 |
| CMH *P* value | – | 0.039 |

b.i.d., twice daily; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention-to-treat; RR, relative risk.

a6/12-week responder rates for abdominal symptoms were defined as the proportion of patients with a decrease of ≥ 30.0% from baseline in the average weekly severity score (on a scale of 0–10: 0 = absent, 10 = very severe) for ≥ 6 of the first 12 treatment weeks.

b9/12-week responder rates for abdominal symptoms were defined as the proportion of patients with a decrease of ≥ 30.0% from baseline in the average weekly severity score (on a scale of 0–10: 0 = absent, 10 = very severe) for ≥ 9 of the first 12 treatment weeks.

c13/26-week responder rates for abdominal symptoms were defined as the proportion of patients with a decrease of ≥ 30.0% from baseline in the average weekly severity score (on a scale of 0–10: 0 = absent, 10 = very severe) for ≥ 13 of 26 treatment weeks. Adjusted RR was based on the ratio of responder rates for tenapanor 50 mg b.i.d. versus placebo, stratified by pooled investigator sites using the Mantel–Haenszel method. The CMH *P* value was based on a 1 degree of freedom test for association between treatment (tenapanor 50 mg b.i.d. and placebo), stratified by pooled investigator sites.

**Supplementary Table 2.** Other secondary endpoints (ITT analysis set)

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| **Secondary endpoint** | **Placebo (n = 300)** | **Tenapanor 50 mg b.i.d.  (n = 293)** |
| **Proportion of patients with ≥ 3 CSBMs/week** | | |
| n/N (%) | 51/183 (27.9) | 73/186 (39.2) |
| Risk difference at week 26 | – | 11.4 |
| 95% CI | – | (1.8–20.9) |
| Adjusted RR | – | 1.40 |
| 95% CI | – | (1.05–1.88) |
| CMH *P* value | – | 0.022 |
| **CSBMs/week** | | |
| Change from baseline at week 26, LS mean | 1.6 | 3.3 |
| 95% CI | (1.1–2.1) | (2.8–3.8) |
| Difference treatment vs placebo, LS mean | – | 1.64 |
| 95% CI | – | (0.95–2.33) |
| *P* value | – | < 0.001 |
| **SBMs/week** | | |
| Change from baseline at week 26, LS mean | 2.1 | 4.3 |
| 95% CI | (1.5–2.7) | (3.7–4.9) |
| Difference treatment vs placebo, LS mean | – | 2.21 |
| 95% CI | – | (1.42–3.00) |
| *P* value | – | < 0.001 |
| **Stool consistencya** | | |
| Change from baseline at week 26, LS mean | 1.1 | 2.4 |
| 95% CI | (0.9–1.4) | (2.1–2.6) |
| Difference treatment vs placebo, LS mean | – | 1.22 |
| 95% CI | – | (0.90–1.54) |
| *P* value | – | < 0.001 |
| **Strainingb** | | |
| Change from baseline at week 26, LS mean | 0.3 | 0.3 |
| 95% CI | (0.2–0.4) | (0.2–0.4) |
| Difference treatment vs placebo, LS mean | – | 0.02 |
| 95% CI | – | (−0.15, 0.18) |
| *P* value | – | 0.857 |
| **IBS severityc** | | |
| Change from baseline at week 26, LS mean | −1.2 | −1.4 |
| 95% CI | (−1.4, −1.0) | (−1.6, −1.3) |
| Difference treatment vs placebo, LS mean | – | −0.26 |
| 95% CI | – | (−0.50, −0.03) |
| *P* value | – | 0.030 |
| **Constipation severityc** | | |
| Change from baseline at week 26, LS mean | −1.3 | −1.7 |
| 95% CI | (−1.4, −1.1) | (−1.8, −1.5) |
| Difference treatment vs placebo, LS mean | – | −0.40 |
| 95% CI | – | (−0.63, −0.17) |
| *P* value | – | 0.001 |
| **Degree of relief from IBSd** | | |
| Change from baseline at week 26, LS mean | 2.9 | 2.5 |
| 95% CI | (2.7–3.1) | (2.3–2.7) |
| Difference treatment vs placebo, LS mean | – | −0.40 |
| 95% CI | – | (−0.70, −0.10) |
| *P* value | – | 0.002 |
| **Proportion of patients with adequate relief from IBSe** | | |
| n/N (%) | 71/146 (48.6) | 90/147 (61.2) |
| Risk difference at week 26 | – | 12.6 |
| 95% CI | – | (1.3–23.9) |
| Adjusted RR | – | 1.28 |
| 95% CI | – | (1.03–1.58) |
| CMH *P* value | – | 0.021 |
| **Treatment satisfactionf** | | |
| Change from baseline at week 26, LS mean | 2.9 | 3.6 |
| 95% CI | (2.8–3.1) | (3.4–3.7) |
| Difference treatment vs placebo, LS mean | – | 0.70 |
| 95% CI | – | (0.40–0.90) |
| *P* value | – | < 0.001 |

ANCOVA, analysis of covariance; ANOVA, analysis of variance; b.i.d., twice daily; BSFS, Bristol Stool Form Scale; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CSBM, complete spontaneous bowel movement; IBS, irritable bowel syndrome; ITT, intention-to-treat; LS, least-squares; N, number of patients evaluable at the week; RR, relative risk; SBM, spontaneous bowel movement.

Adjusted RR was based on the ratio of responder rates for tenapanor 50 mg b.i.d. versus placebo, stratified by pooled investigator sites using the Mantel–Haenszel method. The CMH *P* value was based on a 1 degree of freedom test for association between treatment (tenapanor 50 mg b.i.d. and placebo), stratified by pooled investigator sites. LS means, 95% CIs, and *P* values are based on an ANCOVA model with treatment and pooled investigator site as factors and baseline value as a covariate. Baseline is defined as the average of week 1 and week 2 of the screening period. For degree of relief from IBS and treatment satisfaction, LS means, 95% CIs, and *P* values were based on an ANOVA model with treatment and pooled investigator site as terms.

aAssessed using the 7-point BSFS (17). The average weekly score was calculated from scores for all valid SBMs during the week. For the purpose of calculating an average score, days with no stools were assigned a score of 0.

bAssessed for each SBM using a 1–5-point scale: 1 = not at all, 5 = an extreme amount. The average weekly score was calculated from scores for all valid SBMs during the week.

cAssessed weekly using a 1–5-point scale: 1 = none, 5 = very severe.

dAssessed weekly on a 1–7-point scale: 1 = complete relief, 7 = as bad as I can imagine.

eAssessed weekly through a yes/no question.

fAssessed using a 1–5-point scale: 1 = not at all satisfied, 5 = very satisfied.

**Supplementary Table 3.** Rescue medication use over time (ITT analysis set)

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| **Rescue medication usea, n (%)** | **Placebo (n = 300)** | **Tenapanor  50 mg b.i.d. (n = 293)** |
| Overall | 155 (51.7) | 117 (39.9) |
| Week 1 | 49 (16.3) | 26 (8.9) |
| Week 2 | 36 (12.0) | 21 (7.2) |
| Week 3 | 43 (14.3) | 13 (4.4) |
| Week 4 | 40 (13.3) | 16 (5.5) |
| Week 5 | 35 (11.7) | 11 (3.8) |
| Week 6 | 32 (10.7) | 12 (4.1) |
| Week 7 | 23 (7.7) | 9 (3.1) |
| Week 8 | 26 (8.7) | 10 (3.4) |
| Week 9 | 29 (9.7) | 14 (4.8) |
| Week 10 | 31 (10.3) | 11 (3.8) |
| Week 11 | 28 (9.3) | 14 (4.8) |
| Week 12 | 24 (8.0) | 12 (4.1) |
| Week 13 | 22 (7.3) | 7 (2.4) |
| Week 14 | 20 (6.7) | 11 (3.8) |
| Week 15 | 21 (7.0) | 12 (4.1) |
| Week 16 | 23 (7.7) | 9 (3.1) |
| Week 17 | 22 (7.3) | 10 (3.4) |
| Week 18 | 26 (8.7) | 12 (4.1) |
| Week 19 | 20 (6.7) | 16 (5.5) |
| Week 20 | 18 (6.0) | 12 (4.1) |
| Week 21 | 17 (5.7) | 13 (4.4) |
| Week 22 | 24 (8.0) | 10 (3.4) |
| Week 23 | 19 (6.3) | 15 (5.1) |
| Week 24 | 21 (7.0) | 7 (2.4) |
| Week 25 | 18 (6.0) | 11 (3.8) |
| Week 26 | 19 (6.3) | 14 (4.8) |

aAssessed weekly through yes/no questions. b.i.d., twice daily; ITT, intention-to-treat.