**SUPPLEMENT**

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**Supplementary Table 1: Summary of studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study (phase)** | **Therapy** | **Eligibility criteria** | **Dosing protocol** | **Baseline patient characteristics** | **Allowable concurrent use of medications** |
| **Active therapy** | **Placebo** |
| **Female (%)** | **Mean age** | **Mean abd pain+** | **CSBM****/wk** | **SBM****/wk** | **BSS** | **Female (%)** | **Mean age** | **Mean abd pain+** | **CSBM****/wk** | **SBM****/wk** | **BSS** |
| *Chronic idiopathic constipation trials* |
| Lembo 2010(phase IIb) | Linaclotide | Modified Rome II | 75 µg/d; 4 wks | 93% | 46.4 | -- | 0.3 | 2.0 | 2.0 | 88% | 46.1 | -- | 0.5 | 2.3 | 2.5 | Stable doses of fiber & bulk laxatives allowed. |
| Lembo 2010(phase IIb) | Linaclotide | Modified Rome II | 150 µg/d; 4 wks | 96% | 46.4 | -- | 0.4 | 2.3 | 2.4 | 88% | 46.1 | -- | 0.5 | 2.3 | 2.5 | Stable doses of fiber & bulk laxatives allowed. |
| Schoenfeld 2017(phase III) | Linaclotide | Modified Rome III | 72 or 145 µg/d; 12 wks | 76% | 46.3 | 4.2 | 0.2 | 1.7 | 2.0 | 79% | 45.2 | 4.1 | 0.3 | 1.6 | 2.0 | Stable doses of fiber & bulk laxatives allowed. |
| Lembo 2011(two phase III trials) | Linaclotide | \*footnote | 145 µg/d; 12 wks | 90% | 48.0 | -- | 0.3 | 2.0 | 2.4 | 89% | 48.0 | -- | 0.3 | 1.9 | 2.3 | Stable doses of fiber & bulk laxatives allowed. |
| Lacy 2015(phase III) | Linaclotide | Modified Rome II with bloating | 145 µg/d; 12 wks | 90% | 48.3 | -- | 0.2 | 1.7 | 2.4 | 92% | 46.4 | -- | 0.2 | 1.8 | 2.3 | Stable doses of fiber, bulk laxatives, stool softeners allowed. |
| Shailubhai 2011 (phase IIa) | Plecanatide | Modified Rome III | 3mg/d;2 wks | 87% | 48.5 | -- | -- | -- | -- | 90% | 47.7 | -- | -- | -- | -- | Concurrent allowable CIC medications unclear.  |
| Miner 2013(phase IIb) | Plecanatide | Modified Rome III | 3 mg/d; 12 wks | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | Concurrent allowable CIC medications unclear. |
| Miner 2017(phase IIIb) | Plecanatide | Modified Rome III | 3 or 6 mg/d;12 wks | 82% | 45.0 | -- | 0.3 | 1.9 | 2.6 | 79% | 46.4 | -- | 0.4 | 2.2 | 2.6 | Stable doses of fiber allowed. |
| NCT02122471(phase III) | Plecanatide | Modified Rome III | 3 or 6 mg/d;12 wks | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | Stable doses of fiber allowed. |
| *Constipation-predominant irritable bowel syndrome trials* |
| Johnston 2010(phase IIb) | Linaclotide | Rome II | 300 µg/d; 12 wks | 92% | 46.0 | 2.9/5 | 0.2 | 3.2 | 2.4 | 92% | 44.3 | 3.0/5 | 0.3 | 3.1 | 2.3 | Stable doses of fiber & antidepressants allowed. |
| Chey 2012(phase III) | Linaclotide | Modified Rome II | 290 µg/d; 26 wks | 92% | 44.6 | 5.6/10 | 0.2 | 1.7 | 2.4 | 87% | 44.0 | 5.5/10 | 0.2 | 1.7 | 2.3 | Stable doses of antidepressants allowed. |
| Rao 2012(phase III) | Linaclotide | Modified Rome II | 290 µg/d; 12 wks | 91% | 43.3 | 5.7/10 | 0.2 | 1.9 | 2.3 | 90% | 43.7 | 5.6/10 | 0.2 | 1.9 | 2.4 | Stable doses of fiber, bulk laxatives, stool softeners, probiotics allowed. |
| Miner 2014(phase IIb) | Plecanatide | Rome III | 3 mg/d; 12 wks | 81% | -- | -- | 0.3 | 1.8 | -- | 81% | -- | -- | 0.3 | 1.7 | -- | Concurrent allowable CIC medications unclear. |
| NCT02387359(phase III) | Plecanatide | Rome III | 3 or6 mg/d; 12 wks | 72% | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | Concurrent allowable CIC medications unclear. |
| NCT02493452(phase III) | Plecanatide | Rome III | 3 or 6 mg/d; 12 wks | 76% | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | Concurrent allowable CIC medications unclear. |

IBS-C = constipation-predominant irritable bowel syndrome; CSBM = complete spontaneous bowel movement; SBM=spontaneous bowel movement; BSS=Bristol Stool Scale

\*This trial included patients with fewer than 3 SBM/wk and one other criterion during >25% of BM (straining, lumpy/hard stools, or sensation of incomplete evacuation)

+Mean abdominal pain was reported on a five-point scale in the linaclotide phase IIb trial and on a ten-point scale in the linaclotide phase III trials

**Supplementary Table 2: Authors’ risk-of-bias assessment using the Cochrane risk-of-bias tool**

|  |  |
| --- | --- |
| Study | Cochrane risk of bias domain |
| Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding (performance bias and detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) |
| *Chronic idiopathic constipation trials* |
| Lembo 2010(phase IIb) | Low risk; computer-generated schedule using block size of 5 | Low risk; sponsor staff, patients and trial center personnel blinded to allocation | Low risk; double blinded | Low risk; disposition of patients was described | Low risk; all expected outcomes reported |
| Schoenfeld 2017(phase III) | Low risk; computer-generated schedule using block size of 6 | Low risk; sponsor staff, patients and trial center personnel blinded to allocation | Low risk; double blinded | Low risk; disposition of patients was described | Low risk; all expected outcomes reported |
| Lembo 2011(two phase III trials) | Low risk; computer-generated schedule using block size of 6 | Low risk; sponsor staff, patients and trial center personnel blinded to allocation | Low risk; double blinded | Low risk; disposition of patients was described | Low risk; all expected outcomes reported |
| Lacy 2015(phase III) | Low risk; computer-generated schedule using block size of 6 | Low risk; sponsor staff, patients and trial center personnel blinded to allocation | Low risk; double blinded | Low risk; disposition of patients was described | Low risk; all expected outcomes reported |
| Shailubhai 2011 (phase IIa) | Unclear risk | Unclear risk | Low risk; double blinded | Low risk; overall study withdrawal and study withdrawal due to diarrhea were described | Low risk; all expected outcomes reported |
| Miner 2013(phase IIb) | Unclear risk | Unclear risk; interactive voice response system employed | Low risk; double blinded | Low risk; overall study withdrawal and study withdrawal due to diarrhea were described | Low risk; all expected outcomes reported |
| Miner 2017(phase IIIb) | Unclear risk | Unclear risk | Low risk; double blinded | Low risk; overall study withdrawal and study withdrawal due to diarrhea were described | Low risk; all expected outcomes reported |
| NCT02122471(phase III) | Unclear risk | Unclear risk | Low risk; double blinded | Low risk; overall study withdrawal and study withdrawal due to diarrhea were described | Low risk; all expected outcomes reported |
| *Constipation-predominant irritable bowel syndrome trials* |
| Johnston 2010(phase IIb) | Low risk; computer-generated schedule using block size of 5 | Low risk; sponsor staff, patients and trial center personnel blinded to allocation | Low risk; double blinded | Low risk; disposition of patients was described | Low risk; all expected outcomes reported |
| Chey 2012(phase III) | Low risk; computer-generated schedule using block size of 4 | Low risk; sponsor staff, patients, and trial center personnel blinded to allocation | Low risk; double blinded | Low risk; disposition of patients was described | Low risk; all expected outcomes reported |
| Rao 2012(phase III) | Low risk; computer-generated schedule using block size of 4 | Low risk; sponsor staff, patients, and trial center personnel blinded to allocation | Low risk; double blinded | Low risk; disposition of patients was described | Low risk; all expected outcomes reported |
| Miner 2014(phase IIb) | Unclear risk | Unclear risk | Low risk; double blinded | Low risk; disposition of patients was described | Low risk; all expected outcomes reported |
| NCT02387359(phase III) | Unclear risk | Unclear risk | Low risk; double blinded | Low risk; overall study withdrawal and study withdrawal due to diarrhea was described | Low risk; all expected outcomes reported |
| NCT02493452(phase III) | Unclear risk | Unclear risk | Low risk; double blinded | Low risk; overall study withdrawal and study withdrawal due to diarrhea was described | Low risk; all expected outcomes reported |

**Supplementary Table 3: Additional bowel symptom endpoints in CIC trials**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study & treatment arm** | **TherapeuticAgent** | **Studydesign** | **Additional bowel symptom endpoints (improvement over baseline)** |
| **SBM/wk** | **Time to 1st SBM (hr)** | **SBM in 1st 24 hr (%)** | **CSBM/wk** | **Time to 1st CSBM (days)** | **CSBM in 1st 24 hr (%)** | **Weekly SBM w/ BSFS≥3 (%)** | **Weekly SBM w/o significant straining (straining score≤3) (%)** |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Lembo 2010** | linaclotide | phase 2b |  |  |  |  |  |  |  |  |
| Placebo |  |  | 1.5 | 32.6 | 36.8% | 0.5 | 8.3 | 7.4% |  |  |
| 75 µg/d |  |  | 2.6 | 24.0 | 50.8% | 1.5 | 5.9 | 25.4% |  |  |
| 150 µg/d |  |  | 3.3 | 21.9 | 55.4% | 1.6 | 4.6 | 14.3% |  |  |
| 300 µg/d |  |  | 3.6 | 23.1 | 54.8% | 1.8 | 4.0 | 22.6% |  |  |
| 600 µg/d |  |  | 4.3 | 13.0 | 75.8% | 2.3 | 3.0 | 35.5% |  |  |
| **Lembo 2011** | linaclotide | phase 3 |  |  |  |  |  |  |  |  |
| Placebo (Trial 303) |  |  |  |  |  | 0.5 |  |  |  |  |
| 145 µg/d (Trial 303) |  |  |  |  |  | 1.9 |  |  |  |  |
| 290 µg/d (Trial 303) |  |  |  |  |  | 2.0 |  |  |  |  |
| Placebo (Trial 01) |  |  |  |  |  | 0.6 |  |  |  |  |
| 145 µg/d (Trial 01) |  |  |  |  |  | 2.0 |  |  |  |  |
| 290 µg/d (Trial 01) |  |  |  |  |  | 2.7 |  |  |  |  |
| **Schoenfeld 2017** | linaclotide | phase 3 |  |  |  |  |  |  |  |  |
| Placebo |  |  | 1.3 |  |  | 0.9 |  |  |  |  |
| 72 µg/d |  |  | 2.4 |  |  | 1.7 |  |  |  |  |
| 145 µg/d |  |  | 2.6 |  |  | 1.9 |  |  |  |  |
| **Lacy 2015** | linaclotide | phase 3b |  |  |  |  |  |  |  |  |
| Placebo |  |  | 1.6 | 28.1 | 42.1% | 1.0 |  |  |  |  |
| 145 µg/d |  |  | 3.6 | 12.5 | 61.4% | 2.3 |  |  |  |  |
| 290 µg/d |  |  | 3.6 | 19.4 | 59.1% | 2.3 |  |  |  |  |
| **Miner 2013** | plecanatide | phase 2b |  |  |  |  |  |  |  |  |
| Placebo |  |  | 1.4 |  |  | 1.0 |  |  |  |  |
| 0.3 mg/d |  |  | 2.2 |  |  | 1.5 |  |  |  |  |
| 1 mg/d |  |  | 2.4 |  |  | 1.7 |  |  |  |  |
| 3 mg/d |  |  | 3.0 |  |  | 2.0 |  |  |  |  |
| **Miner 2017** |  |  |  |  |  |  |  |  |  |  |
| Placebo |  |  | 1.3 |  | 39.8% | 1.2 |  | 13.3% |  |  |
| 3 mg/d |  |  | 3.2 |  | 59.2% | 2.5 |  | 28.7% |  |  |
| 6 mg/d |  |  | 3.1 |  | 52.6% | 2.2 |  | 25.2% |  |  |

CIC = chronic idiopathic constipation; SBM = spontaneous bowel movement; CSBM = complete spontaneous bowel movement

**Supplementary Table 4: Additional bowel symptom endpoints in IBS-C trials**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study & treatment arm** | **TherapeuticAgent** | **Studydesign** | **Additional bowel symptom endpoints (improvement over baseline)** |
| **SBM/wk** | **Time to 1st SBM (hr)** | **SBM in 1st 24 hr (%)** | **CSBM/wk** | **Time to 1st CSBM (days)** | **CSBM in 1st 24 hr (%)** | **Weekly SBM w/ BSFS≥3 (%)** | **Weekly SBM w/o significant straining (straining score≤3) (%)** |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Johnston 2010** | linaclotide | phase 2b |  |  |  |  |  |  |  |  |
| Placebo |  |  | 1.7 |  | 45.9% | 1.0 |  | 12.9% |  |  |
| 75 µg/d |  |  | 4.6 |  | 74.7% | 2.9 |  | 36.7% |  |  |
| 150 µg/d |  |  | 4.4 |  | 64.6% | 2.5 |  | 28.0% |  |  |
| 300 µg/d |  |  | 5.0 |  | 77.4% | 3.6 |  | 32.1% |  |  |
| 600 µg/d |  |  | 5.6 |  | 71.9% | 2.7 |  | 27.0% |  |  |
| **Chey 2012** | linaclotide | phase 3 |  |  |  |  |  |  |  |  |
| Placebo |  |  | 1.1\* |  | 40.4%+ | 0.7\* |  | 8.4%+ | 62.1%\* | 71.6%\* |
| 290 µg/d |  |  | 3.8\* |  | 65.6%+ | 2.2\* |  | 28.9%+ | 81.0%\* | 83.5%\* |
| **Rao 2012** | linaclotide | phase 3 |  |  |  |  |  |  |  |  |
| Placebo |  |  | 1.1 |  | 43.8% | 0.7 |  | 13.2% | 60.7% | 71.7% |
| 290 µg/d |  |  | 3.9 |  | 67.4% | 2.3 |  | 32.3% | 79.4% | 85.3% |
| **Miner 2014** | plecanatide | phase 2b |  |  |  |  |  |  |  |  |
| Placebo |  |  |  |  |  | 1.3 |  |  |  |  |
| 0.3 mg/d |  |  |  |  |  | 1.3 |  |  |  |  |
| 1 mg/d |  |  |  |  |  | 2.1 |  |  |  |  |
| 3 mg/d |  |  |  |  |  | 2.7 |  |  |  |  |
| 9 mg/d |  |  |  |  |  | 2.4 |  |  |  |  |

IBS-C = irritable bowel syndrome with constipation; SBM = spontaneous bowel movement; CSBM = complete spontaneous bowel movement

\* Calculated using data from weeks 1-26.

+ Calculated using data from weeks 1-12.

**Supplementary Table 5: Additional endpoints on patient-reported outcomes in CIC trials**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study & treatment arm** | **TherapeuticAgent** | **Studydesign** | **Additional endpoints on patient-reported outcomes (improvement over baseline)** |
| **Constipation severity****(1 to 5)** | **Stool consistency (BSS)** | **Straining severity (0 to 4)** | **Straining severity (1 to 5)** | **Straining severity (0 to 10)** | **Abd discomfort (1 to 5)** | **Abd discomfort (0 to 10)** | **Abd pain (0 to 10)** | **Worst abd pain (0 to 10)** | **Abd bloating (1 to 5)** | **Abd bloating (0 to 10)** |
| **Lembo 2010** | linaclotide | phase 2b |  |  |  |  |  |  |  |  |  |  |  |
| Placebo |  |  | 0.2 | 0.5 |  | 0.5 |  | 0.0 |  |  |  | 0.0 |  |
| 75 µg/d |  |  | 0.8 | 1.4 |  | 0.7 |  | 0.3 |  |  |  | 0.4 |  |
| 150 µg/d |  |  | 0.9 | 1.6 |  | 1.0 |  | 0.3 |  |  |  | 0.4 |  |
| 300 µg/d |  |  | 0.9 | 1.7 |  | 1.1 |  | 0.2 |  |  |  | 0.3 |  |
| 600 µg/d |  |  | 1.0 | 2.0 |  | 1.1 |  | 0.3 |  |  |  | 0.3 |  |
| **Lembo 2011** | linaclotide | phase 3 |  |  |  |  |  |  |  |  |  |  |  |
| Placebo (Trial 303) |  |  | 0.3 | 0.6 |  | 0.5 |  |  |  |  | 0.3 | 0.2 |  |
| 145 µg/d (Trial 303) |  |  | 0.9 | 1.9 |  | 1.1 |  |  |  |  | 0.5 | 0.5 |  |
| 290 µg/d (Trial 303) |  |  | 0.8 | 1.8 |  | 1.2 |  |  |  |  | 0.4 | 0.4 |  |
| Placebo (Trial 01) |  |  | 0.3 | 0.6 |  | 0.6 |  |  |  |  | 0.3 | 0.2 |  |
| 145 µg/d (Trial 01) |  |  | 0.9 | 1.8 |  | 1.1 |  |  |  |  | 0.5 | 0.4 |  |
| 290 µg/d (Trial 01) |  |  | 1.0 | 2.0 |  | 1.2 |  |  |  |  | 0.5 | 0.5 |  |
| **Schoenfeld 2017** | linaclotide | phase 3 |  |  |  |  |  |  |  |  |  |  |  |
| Placebo |  |  |  | 1.1 |  | 0.8 |  |  | 1.1 | 1.0 |  |  |  |
| 72 µg/d |  |  |  | 1.7 |  | 1.4 |  |  | 1.3 | 1.2 |  |  |  |
| 145 µg/d |  |  |  | 1.8 |  | 1.5 |  |  | 1.4 | 1.3 |  |  |  |
| **Lacy 2015** | linaclotide | phase 3b |  |  |  |  |  |  |  |  |  |  |  |
| Placebo |  |  | 0.8 | 0.7 |  | 0.8 |  |  |  |  |  |  | 1.6 |
| 145 µg/d |  |  | 1.3 | 1.9 |  | 1.5 |  |  |  |  |  |  | 2.5 |
| 290 µg/d |  |  | 1.4 | 2.3 |  | 1.5 |  |  |  |  |  |  | 2.5 |
| **Miner 2013** | plecanatide | phase 2b |  |  |  |  |  |  |  |  |  |  |  |
| Placebo |  |  |  | 0.8 |  |  | 1.2 |  |  |  |  |  |  |
| 0.3 mg/d |  |  |  | 1.1 |  |  | 1.4 |  |  |  |  |  |  |
| 1 mg/d |  |  |  | 1.6 |  |  | 1.7 |  |  |  |  |  |  |
| 3 mg/d |  |  |  | 2.0 |  |  | 2.1 |  |  |  |  |  |  |
| **Miner 2017** | plecanatide | Phase 3 |  |  |  |  |  |  |  |  |  |  |  |
| Placebo |  |  |  | 0.9 | 0.6 |  |  | 0.4 |  |  |  | 0.4 |  |
| 3 mg/d |  |  |  | 1.5 | 0.9 |  |  | 0.5 |  |  |  | 0.5 |  |
| 6 m/gd |  |  |  | 1.5 | 0.9 |  |  | 0.5 |  |  |  | 0.4 |  |

CIC = chronic idiopathic constipation; BSS = Bristol Stool Form Scale; Abd = abdomen

**Supplementary Table 6: Additional endpoints on patient-reported outcomes in IBS-C trials**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study & treatment arm** | **TherapeuticAgent** | **Studydesign** | **Additional endpoints on patient-reported outcomes (improvement over baseline)** |
| **Constipation severity****(1 to 5)** | **Stool consistency (BSS)** | **Straining severity (1 to 5)** | **Abd fullness (0 to 10)** | **Abd cramping (0 to 10)** | **Abd discomfort (0 to 10)** | **Worst abd pain (0 to 10)** | **Abd pain****(1 to 5)** | **% days with abd pain score≤2** | **Abd bloating (0 to 10)** |
| **Johnston 2010** | linaclotide | phase 2b |  |  |  |  |  |  |  |  |  |  |
| Placebo |  |  | 0.7 | 0.6 |  |  |  |  |  | 0.5 | 22.7% |  |
| 75 µg/d |  |  | 1.2 | 2.0 |  |  |  |  |  | 0.7 | 32.4% |  |
| 150 µg/d |  |  | 1.2 | 1.8 |  |  |  |  |  | 0.7 | 31.1% |  |
| 300 µg/d |  |  | 1.4 | 2.3 |  |  |  |  |  | 0.9 | 38.1% |  |
| 600 µg/d |  |  | 1.4 | 2.2 |  |  |  |  |  | 0.9 | 38.7% |  |
| **Chey 2012** | linaclotide | phase 3 |  |  |  |  |  |  |  |  |  |  |
| Placebo |  |  | 0.6 | 0.6 | 0.7 | 1.2 | 1.2 | 1.3 | 1.2 |  |  | 1.2 |
| 290 µg/d |  |  | 1.2 | 1.9 | 1.3 | 2.3 | 2.0 | 2.2 | 2.1 |  |  | 2.2 |
| **Rao 2012** | linaclotide | phase 3 |  |  |  |  |  |  |  |  |  |  |
| Placebo |  |  | 0.6 | 0.7 | 0.7 | 1.1 | 1.1 | 1.2 | 1.1 |  |  | 1.1 |
| 290 µg/d |  |  | 1.2 | 2.1 | 1.3 | 2.0 | 1.7 | 2.0 | 1.9 |  |  | 1.9 |
| **Miner 2014** | plecanatide | phase 2b |  |  |  |  |  |  |  |  |  |  |
| Placebo |  |  |  |  |  |  |  |  | 1.4 |  |  |  |
| 0.3 mg/d |  |  |  |  |  |  |  |  | 1.5 |  |  |  |
| 1 mg/d |  |  |  |  |  |  |  |  | 1.5 |  |  |  |
| 3 mg/d |  |  |  |  |  |  |  |  | 2.0 |  |  |  |
| 9 mg/d |  |  |  |  |  |  |  |  | 1.8 |  |  |  |

IBS-C = irritable bowel syndrome with constipation; BSS = Bristol Stool Form Scale; Abd = abdomen

**Supplementary Table 7: Additional endpoints evaluating global improvement in CIC and IBS-C trials**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study & treatment arm** | **TherapeuticAgent** | **Studydesign** | **Additional global outcome measures (improvement over baseline)** |
| **IBS severity****(1 to 5)** | **Global relief of constipation****(1 to 7)** | **PAC-QOL** | **IBS-QOL** | **IBS-SSS** |
| *Chronic idiopathic constipation trials* |
| **Lembo 2010** | linaclotide | phase 2b |  |  |  |  |  |
| Placebo |  |  |  | 0.5 |  |  |  |
| 75 µg/d |  |  |  | 1.0 |  |  |  |
| 150 µg/d |  |  |  | 1.1 |  |  |  |
| 300 µg/d |  |  |  | 1.1 |  |  |  |
| 600 µg/d |  |  |  | 1.3 |  |  |  |
| **Schoenfeld 2017** | linaclotide | phase 3 |  |  |  |  |  |
| Placebo |  |  |  |  | 0.7 |  |  |
| 72 µg/d |  |  |  |  | 1.0 |  |  |
| 145 µg/d |  |  |  |  | 1.0 |  |  |
| *Constipation-predominant irritable bowel syndrome trials* |
| **Johnston 2010** | linaclotide | phase 2b |  |  |  |  |  |
| Placebo |  |  | 0.6 |  |  | 14.5 | 81 |
| 75 µg/d |  |  | 1.0 |  |  | 12 | 134 |
| 150 µg/d |  |  | 1.0 |  |  | 14.2 | 113 |
| 300 µg/d |  |  | 1.3 |  |  | 14 | 142 |
| 600 µg/d |  |  | 1.2 |  |  | 14.1 | 154 |
| **Chey 2012** | linaclotide | phase 3 |  |  |  |  |  |
| Placebo |  |  | 0.6 |  |  |  |  |
| 290 µg/d |  |  | 1.0 |  |  |  |  |
| **Rao 2012** | linaclotide | phase 3 |  |  |  |  |  |
| Placebo |  |  | 0.5 |  |  |  |  |
| 290 µg/d |  |  | 1.0 |  |  |  |  |

CIC = chronic idiopathic constipation; IBS-C = irritable bowel syndrome with constipation; IBS-QOL = IBS Quality of Life scale; IBS-SSS = IBS Severity Scoring System

**Supplementary Table 8: Measured outcome assessments for treatment and placebo arms including raw percentages of outcomes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Disease of interest** | **Efficacy (n/N, [%])** | **Diarrhea as an adverse event (n/N, [%])** | **Study withdrawals due to diarrhea (n/N, [%])** |
| **Treatment** | **Placebo** | **Treatment** | **Placebo** | **Treatment** | **Placebo** |
| *Linaclotide trials* |
| Lembo 2010 | CIC | 75 µg: NR150 µg: NR | NR | 75 µg: 3/59 (5.1%)150 µg: 5/56 (8.9%) | 2/69 (2.9%) | 75 µg: 0/59 (0.0%)150 µg: 1/56 (1.8%) | 0/69 (0.0%) |
| Schoenfeld 2017 | CIC | 72 µg: 55/411 (13.4%)145 µg: 51/411 (12.4%) | 19/401 (4.7%) | 72 µg: 79/411 (19.2%)145 µg: 91/411 (22.1%) | 28/401 (7.0%) | 72 µg: 10/411 (2.4%)145 µg: 13/411 (3.2%) | 0/401 (0.0%) |
| Lembo 2011\* | CIC | 80/430 (18.6%) | 20/424 (4.7%) | 69/430 (16.0%) | 20/424 (4.7%) | 20/430 (4.7%) | 2/424 (0.5%) |
| Lacy 2015 | CIC | 24/153 (15.7%) | 13/171 (7.6%) | 9/153 (5.9%) | 4/173 (2.3%) | 2/153 (1.3%) | 1/173 (0.6%) |
| Johnston 2010 | IBS-C | NR | NR | 14/85 (16.5%) | 1/85 (1.2%) | 1/85 (1.2%) | 0/85 (0.0%) |
| Chey 2012 | IBS-C | 135/401 (33.7%) | 56/403 (13.9%) | 79/402 (19.7%) | 10/403 (2.5%) | 18/402 (4.5%) | 1/403 (0.2%) |
| Rao 2012 | IBS-C | 136/405 (33.6%) | 83/395 (21.0%) | 79/406 (19.5%) | 14/396 (3.5%) | 23/406 (5.7%) | 1/396 (0.3%) |
| *Plecanatide trials* |
| Shailubhai 2011 | CIC | NR | NR | 0/15 (0.0%) | 1/20 (5.0%) | 0/15 (0.0%) | 1/20 (5.0%) |
| Miner 2013 (3mg/d)  | CIC | 51/237 (21.5%) | 27/236 (11.4%) | 23/237 (9.7%) | 3/236 (1.3%) | 7/237 (3.0%) | 1/236 (0.4%) |
| Miner 2017 | CIC | 3 mg: 95/453 (21.0%)6 mg: 86/441 (19.5%) | 46/452 (10.2%) | 3 mg: 28/474 (5.9%)6 mg: 26/457 (5.7%) | 6/458 (1.3%) | 3 mg: 13/474 (2.7%)6 mg: 12/457 (2.6%) | 2/458 (0.4%) |
| NCT02122471 | CIC | 3 mg: 89/443 (20.1%) 6 mg: 90/449 (20.0%) | 57/445 (12.8%)  | 3 mg: 14/443 (3.2%)6 mg: 20/449 (4.5%) | 6/445 (1.3%) | 3 mg: 5/443 (1.1%)6 mg: 5/449 (1.1%) | 2/445 (0.4%) |
| Miner 2014 | IBS-C | 36/86 (41.9%) | 21/85 (24.7%) | 8/86 (9.3%) | 0/86 (0.0%) | 5/86 (5.8%) | 0/86 (0.0%) |
| NCT02387359 | IBS-C | 3 mg: 81/377 (21.5%)6 mg: 91/379 (24.0%) | 54/379 (14.2%) | 3 mg: 12/377 (3.2%)6 mg: 14/379 (3.7%) | 5/379 (1.3%) | 3 mg: 3/377 (0.8%)6 mg: 6/379 (1.6%) | 0/379 (0.0%) |
| NCT02493452 | IBS-C | 3 mg: 106/351 (30.2%)6 mg: 103/349 (29.5%) | 63/354 (17.8%) | 3 mg: 19/351 (5.4%)6 mg: 15/349 (4.3%) | 2/354 (0.6%) |  3 mg: 6/351 (1.7%)6 mg: 4/349 (1.2%) | 0/354 (0.0%) |

NR=not reported

\* This study includes pooled results of two phase III trials.