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PWE-027 MEDIATION ANALYSIS SUPPORTS A DIRECT EFFECT OF LINACLOTIDE (LIN) ON ABDOMINAL PAIN (AP) RELIEF INDEPENDENT OF CONSTIPATION IMPROVEMENT

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Introduction LIN, a 14-amino-acid, minimally-absorbed guanylate cyclase C agonist (GCCA), significantly improved AP and complete spontaneous bowel movements (CSBMs) vs placebo (PBO) in 2 Phase 3 IBS-C trials. Recurrent AP in IBS-C may arise from increased visceral hypersensitivity exacerbated by constipation. Relative direct and mediated (increasing CSBMs) LIN effects on AP improvement are unknown. We estimated the direct effect of LIN on improving AP by controlling for a concurrent increase in CSBMs.

Methods Patients (pts) with IBS-C (Rome II criteria) were randomised to LIN 290 µg po or PBO for 26 wks in a Phase 3 trial. Pts reported abdominal and bowel symptoms, and rescue medication use daily. Percent improvement from baseline in AP scores was analysed via multilevel mediation analysis to estimate the proportion of the LIN treatment effect attributable to increased CSBMs. CSBMs occurring on the reported AP score day and the previous 6 days were mediation variables. Analysis was performed for Wks 13–26, when LIN and PBO effects on AP were generally constant. An additional analysis summarised AP improvement on a particular day (2-way CSBM stratification: days since last CSBM [0, 1, 2, ≥3 days] and CSBMs in previous 3 days [0, 1, 2, ≥3 CSBMs]).

Results Mediation analysis showed the 20% treatment effect of LIN (48%) on AP above PBO effect (28%) resulted from a combined direct effect (18%) on AP and indirect effect (2%) mediated by increasing CSBMs. SBMs without a sense of complete evacuation and BMs with rescue medication use did not increase the mediated LIN pain effect. The 2-way CSBM stratification analysis showed improved AP was influenced by time since last CSBM and no. of recent CSBMs (Table). Consistent with a predominant direct LIN effect on AP (per mediation analysis), in each table cell, LIN-treated pts had more AP relief than PBO pts when controlling for CSBM factors.

Percent Improvement in AP Stratified by No. of Recent CSBMs and Time Since Last CSBM by Treatment Group (LIN/PBO [LIN-PBO difference]).

Abstract PWE-027 Table

CSBMs in prior 3 days, n	Days since last CSBM, n			
	0 (CSBM that day)	1	2	3+
0				45/25 [20]
1	58/43 [16]	61/37 [24]	60/40 [20]	51/38 [14]
2	74/56 [19]	72/54 [17]	65/56 [9]	57/39 [18]
3+	76/67 [9]	76/60 [16]	76/68 [8]	74/48 [25]

ITT Popⁿ, Wks 13–26, median values (includes pts with multiple values in a particular cell)

Conclusion This analysis supports the hypothesis that LIN has direct effects on AP (over PBO), and that AP effects are mediated to a lesser extent by increasing CSBM frequency. Support: Ironwood

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PWE-028 SIGNIFICANTLY IMPROVED ABDOMINAL PAIN (AP) WITH LINACLOTIDE (LIN) VS PLACEBO (PBO) IN PATIENTS (PTS) WITH IRRITABLE BOWEL SYNDROME (IBS) REGARDLESS OF BASELINE PAIN SEVERITY IN 2 PHASE 3 TRIALS

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Introduction LIN, a 14-amino-acid, minimally absorbed, guanylate cyclase C agonist (GCCA), significantly improved abdominal and bowel symptoms in 2 Phase 3 IBS with constipation (IBS-C) trials. Previous IBS trials of other therapies showed inconsistent effects of baseline AP severity on efficacy. This post-hoc analysis determined the LIN effect on AP stratified by pt-reported baseline AP severity.

Methods Pts with IBS-C (Rome II criteria) were randomised to LIN 290 µg od po or PBO. Pts rated daily AP at its worst during the previous 24h (11-point scale; 0 = none, 10 = very severe) during Baseline and Treatment Periods. Using pooled 12-wk ITT data from 2 Phase 3 trials, pts were stratified by mean baseline AP score (< 5, ≥5- < 7, ≥7). At each post-randomisation visit pts rated their relief of AP over the past wk vs baseline (7-point balanced scale; 1 = completely relieved, 7 = as bad as I can imagine). The Least Squares (LS) mean change from 2-wk Baseline to 12-wk Treatment Period, % improvement, difference estimates and p-values were calculated (ANCOVA; factors = treatment group, geographic region and study. Covariate = baseline AP).

Results Overall, LIN significantly improved 12-wk AP vs PBO. LIN also led to significant benefit in all 3 baseline stratified AP subgroups, with pain score decreases of 29–36% vs 18–20% for PBO (p < 0.0001; Table); improvement was numerically less in pts with milder (< 5) baseline severity. Baseline AP scores significantly correlated with absolute magnitude of change from baseline improvement in AP (r = 0.26; p < 0.0001) but not with % improvement (r = 0.00; p = 0.9184). Pt-rated relief of AP was significantly improved with LIN vs PBO overall (LS mean 2.9 vs 3.5; p < 0.0001); relief of AP was also seen for all 3 baseline AP subgroups (baseline AP < 5: 2.8 vs 3.4; ≥5- < 7: 2.9 vs 3.5; ≥7: 3.0 vs 3.6; p < 0.0001 for all).

Abstract PWE-028 Table 1

Baseline AP group	Baseline score	Absolute change (LS mean)				% Change			
		LIN	PBO	Δ	p	LIN	PBO	Δ	p
Overall (n = 1602)	5.6	1.8	1.1	0.8	< 0.0001	32.2	18.9	13.3	< 0.0001
< 5 (n = 649)	3.9	1.1	0.7	0.4	< 0.0001	29.0	18.2	10.8	< 0.0001
≥5- < 7 (n = 577)	5.9	2.1	1.2	1.0	< 0.0001	35.7	19.6	16.1	< 0.0001
≥7 (n = 376)	8.0	2.6	1.5	1.0	< 0.0001	32.1	18.7	13.3	< 0.0001