Amended results for the ITT and LIR populations based on the original and revised results in Table 45

Following the PMB on 10 February 2015, the ERG conducted additional MTCs. Based on table 45 of the original company's submission (CS) as well as the revised version, tables 50 to 52 of the CS were amended in order to compare three set of results:

1. LIR population as reported in the company's submission
2. LIR population calculated by the ERG
3. ITT population using the results from KODIAC 4 and 5 (calculated by the ERG)

Overall, these results are quite similar which means that it is unlikely that there are any major differences between the LIR and ITT populations. However, the committee should still consider whether or not combining these populations in a MTC is clinically justified.

The ERG found some convergence problems when running the random and fixed effect models for DAEs, especially for the results involving naloxone 10 mg, 20 mg, 40 mg and PR which resulted in wide credible intervals. Therefore the results for any comparisons with naloxone may be unreliable. For example the result below for naloxone 40 mg versus placebo was reported to be 14.44 (95% CrI 1.56 to 407.08) when the only head-to-head result for this comparison was an OR of 10.76 (95% CI 1.31 to 88.47). Although the conclusion is the same from both analyses the wide CrI from the Bayesian analysis indicates more uncertainty in this result.

For the outcomes of SBM response and CSBM response the ERG ran the MTC analyses using both the LIR populations from the KODIAC 4 and 5 trials (second row "LIR (ERG)") and the original ITT populations as presented in table 45 of the original submission (third row "ITT (ERG)"). Although there was some variation in the point estimates and credible intervals between the LIR and ITT analyses, none of the conclusions were altered.

Modified Table 1: Results from MTC in the anticipated licensed population – treatment vs placebo†

Treatment	Number of studies	Population	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response‡ (OR [95%CrI])	CSBM Response§ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
			4 weeks	4-12 weeks				
Naloxegol (12.5 mg)	2	LIR (CS)	0.79 [-0.67, 2.23]	0.55 [-0.81, 1.96]	1.98 [0.98, 4.06]	--	0.66 [0.18, 2.21]	1.06 [0.53, 2.13]
		LIR (ERG)			1.99 [0.99, 4.06]		0.65 [0.18, 2.25]	
		ITT (ERG)			1.62 [0.86, 3.06]	1.76 [0.96, 3.24]	0.94 [0.36, 2.48]	
Naloxegol (25 mg)	2	LIR (CS)	**1.85 [0.34, 3.33]***	**1.46 [0.02, 2.93]***	1.88 [0.93, 3.78]	**2.42 [1.25, 4.74]***	2.13 [0.71, 6.57]	1.98 [0.99, 3.99]
		LIR (ERG)			1.85 [0.91, 3.77]	**2.50 [1.29, 4.78]***	2.23 [0.72, 7.06]	
		ITT (ERG)			1.78 [0.93, 3.37]	**1.88 [1.04, 3.42]***	2.33 [0.96, 5.87]	
Methylnaltrexone, SC (12 mg OD)	1	LIR (CS)	1.6 [-0.48, 3.6]	1.6 [-0.41, 3.54]	2.33 [0.91, 5.95]	--	2.93 [0.59, 16.49]	1.56 [0.6, 4.03]
		LIR (ERG)			2.32 [0.90, 5.94]		3.04 [0.59, 17.38]	
		ITT (ERG)			2.32 [0.93, 5.76]		2.96 [0.64, 15.35]	
Methylnaltrexone, SC (12 mg QAD)	1	LIR (CS)	0.59 [-1.43, 2.62]	0.61 [-1.36, 2.58]	1.36 [0.51, 3.46]	--	3.93 [0.84, 21.74]	1.33 [0.52, 3.4]
		LIR (ERG)			1.34 [0.51, 3.46]		4.15 [0.80, 22.94]	
		ITT (ERG)			1.33 [0.54, 3.38]		3.99 [0.90, 20.72]	
Methylnaltrexone, oral (150 mg OD)	1	LIR (CS)	0.16 [-1.82, 2.17]	0.17 [-1.77, 2.15]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	1	LIR (CS)	0.67 [-1.38, 2.75]	0.69 [-1.31, 2.71]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	1	LIR (CS)	0.68 [-1.34, 2.72]	0.68 [-1.32, 2.67]	--	--	--	--

Treatment	Number of studies	Population	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response‡ (OR [95%CrI])	CSBM Response§ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
			4 weeks	4-12 weeks				
Naloxone PR (FRC)	CSBM: 3 DAEs: 2	LIR (CS)	--	--	--	**2.78 [1.61, 4.83]***	0.72 [0.26, 2.38]	--
		LIR (ERG)				**2.82 [1.62, 4.77]***	0.72 [0.25, 2.32]	
		ITT (ERG)				**2.83 [1.61, 4.78]***	0.72 [0.28, 2.12]	
Naloxone (10 mg BD)	1	LIR (CS)	--	--	--	--	6.86 [0.68, 205.82]	--
		LIR (ERG)					6.84 [0.69, 185.2]	
		ITT (ERG)					7.07 [0.69, 325.4]	
Naloxone (20 mg BD)	1	LIR (CS)	--	--	--	--	8.75 [0.87, 246.41]	--
		LIR (ERG)					8.70 [0.92, 231.10]	
		ITT (ERG)					8.81 [0.95, 376.60]	
Naloxone (40 mg BD)	1	LIR (CS)	--	--	--	--	**14.44 [1.56, 407.08]***	--
		LIR (ERG)					**14.62 [1.58, 379.1]***	
		ITT (ERG)					**15.29 [1.65, 658.4]***	

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; SC, subcutaneous; TEAE, treatment-emergent adverse event.

*** Credible interval excludes the null point of 1 (for ORs) or 0 (for MDs)**.

† Populations included in comparisons were main trial populations for methylnaltrexone and naloxone and the LIR population for naloxegol.

‡This is defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.

§ This is defined as the proportion of patients with ≥3 CSBMs/week at four weeks.

Modified able 2: Results from MTC in the anticipated licensed population – naloxegol 12.5 mg vs comparators†

		Mean Change in SBMs per Week (MD [95%CrI])		SBM Response‡ (OR [95%CrI])	CSBM Response§ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
Treatment	**Population**	**4 weeks**	**4-12 weeks**				
Methylnaltrexone, SC (12 mg OD)	LIR (CS)	-0.8 [-3.33, 1.74]	-1.05 [-3.48, 1.39]	0.85 [0.26, 2.84]	--	0.23 [0.03, 1.63]	0.68 [0.21, 2.18]
	LIR (ERG)			0.86 [0.26, 2.85]		0.21[0.02, 1.72]	
	ITT (ERG)			0.70 [0.23, 2.16]		0.32 [0.05, 1.92]	
Methylnaltrexone, SC (12 mg QAD)	LIR (CS)	0.2 [-2.33, 2.7]	-0.05 [-2.48, 2.4]	1.45 [0.45, 4.88]	--	0.17 [0.02, 1.23]	0.79 [0.25, 2.55]
	LIR (ERG)			1.48 [0.45, 4.89]		0.15 [0.02, 1.20]	
	ITT (ERG)			1.22 [0.40, 3.63]		0.23 [0.03, 1.39]	
Methylnaltrexone, oral (150 mg OD)	LIR (CS)	0.63 [-1.9, 3.07]	0.37 [-2.08, 2.8]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	LIR (CS)	0.12 [-2.4, 2.62]	-0.14 [-2.56, 2.25]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	LIR (CS)	0.11 [-2.37, 2.55]	-0.14 [-2.54, 2.26]	--	--	--	--
Naloxone PR (FRC)	LIR (CS)	--	--	--	--	0.9 [0.15, 4.36)	--
	LIR (ERG)					0.90 [0.16, 4.49]	
	ITT (ERG)				0.62 [0.28, 1.42]	1.32 [0.30, 5.08]	
Naloxone (10 mg BD)	LIR (CS)	--	--	--	--	0.09 [0, 1.37]	--
	LIR (ERG)					0.09 [0.001, 1.33]	
	ITT (ERG)					0.13 [0.001, 1.67]	

Treatment	Population	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response‡ (OR [95%CrI])	CSBM Response§ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
		4 weeks	4-12 weeks				
Naloxone (20 mg BD)	LIR (CS)	--	--	--	--	0.07 [0, 1.09]	--
	LIR (ERG)					0.07 [0.001, 0.98]	
	ITT (ERG)					0.10 [0.001, 1.23]	
Naloxone (40 mg BD)	LIR (CS)	--	--	--	--	0.04 [0, 0.62]	--
	LIR (ERG)					0.04 [0.001, 0.58]	
	ITT (ERG)					0.07 [0.001, 0.61]	

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; SC, subcutaneous; TEAE, treatment-emergent adverse event.

*** Credible interval excludes the null point of 1 (for odds ratios) or 0 (for mean differences).**

† Comparator populations were main trial populations, whereas naloxegol populations were LIR populations.

‡ This is defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.

§ This is defined as the proportion of patients with ≥3 CSBMs/week at four weeks.

Modified Table 3: Results from MTC in the anticipated licensed population – naloxegol 25 mg vs comparators†

		Mean Change in SBMs per Week (MD [95%CrI])		SBM Response‡ (OR [95%CrI])	CSBM Response§ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
Treatment	**Population**	**4 weeks**	**4-12 weeks**				
Methylnaltrexone, SC (12 mg OD)	LIR (CS)	0.25 [-2.29, 2.84]	-0.13 [-2.59, 2.29]	0.81 [0.26, 2.63]	--	0.74 [0.09, 5.18]	1.27 [0.4, 4.19]
	LIR (ERG)			0.80 [0.25, 2.62]		0.72 [0.09, 5.83]	
	ITT (ERG)			0.77 [0.25, 2.35]		0.78 [0.12, 4.65]	
Methylnaltrexone, SC (12 mg QAD)	LIR (CS)	1.26 [-1.32, 3.76]	0.85 [-1.61, 3.35]	1.38 [0.43, 4.64]	--	0.54 [0.07, 3.65	1.48 [0.46, 4.82]
	LIR (ERG)			1.38 [0.42, 4.59]		0.53 [0.07, 3.97]	
	ITT (ERG)			1.33 [0.43, 4.01]		0.58 [0.09, 3.40]	
Methylnaltrexone, oral (150 mg OD)	LIR (CS)	1.68 [-0.87, 4.13]	1.28 [-1.16, 3.77]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	LIR (CS)	1.17 [-1.37, 3.63]	0.76 [-1.7, 3.27]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	LIR (CS)	1.17 [-1.36, 3.63]	0.77 [-1.64, 3.22]	--	--	--	--
Naloxone PR (FRC)	LIR (CS)	--	--	--	0.87 [0.38, 2.11]	2.97 [0.59, 13.14]	--
	LIR (ERG)				0.89 [0.39, 2.09]	3.08 [0.62, 14.00]	
	ITT (ERG)				0.66 [0.30, 1.51]	3.27 [0.79, 12.27]	
Naloxone (10 mg BD)	LIR (CS)	--	--	--	--	0.31 [0.01, 4.07]	--

Treatment	Population	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response‡ (OR [95%CrI])	CSBM Response§ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
		4 weeks	4-12 weeks				
	LIR (ERG)					0.32 [0.01, 4.18]	
	ITT (ERG)					0.34 [0.01, 4.11]	
Naloxone (20 mg BD)	LIR (CS)	--	--	--	--	0.24 [0.01, 3.25]	--
	LIR (ERG)					0.25 [0.01, 3.12]	
	ITT (ERG)					0.26 [0.01, 2.93]	
Naloxone (40 mg BD)	LIR (CS)	--	--	--	--	0.15 [0, 1.87]	--
	LIR (ERG)					0.15 [0.01, 1.83]	
	ITT (ERG)					0.15 [0.003, 1.77]	

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; SC, subcutaneous; TEAE, treatment-emergent adverse event.

*** Credible interval excludes the null point of 1 (for odds ratios) or 0 (for mean differences).**

† Comparator populations were main trial populations, whereas naloxegol populations were LIR populations.

‡ This is defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.

§ This is defined as the proportion of patients with ≥3 CSBMs/week at four weeks.