NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Naloxegol for treating opioid-induced constipation

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The marketing authorisation states that naloxegol is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s). The summary of product characteristics and the company's submission defines a laxative inadequate responder (LIR) as someone who in the 2 weeks prior to first study visit reported concurrent OIC symptoms of at least moderate severity while taking at least 1 laxative class for a minimum of 4 days during the pre-study period. The ERG commented that this definition may not be appropriate given that for some laxatives, the effectiveness may take longer than 4 days to be assessed.
  - What is the Committee's view on the appropriateness of this definition?

  - Is it clinically relevant and usable in clinical practice? To what extent does this definition match with current UK clinical practice?
- Although the KODIAC 4 and 5 studies were international multicentre randomised controlled studies, they were primarily conducted in the United States. In KODIAC 4, 88 out of 98 study sites were based in the US, as were 88 out of 167 sites in KODIAC 5. There were 3 UK sites included in KODIAC 5 and none included in KODIAC 4. In light of this, what is the committee's view on the generalisability of the clinical evidence to the UK population?
- The company's submission includes placebo (supplemented by rescue therapy), methylnaltrexone and naloxone-oxycodone as comparators. However the final scope only lists methylnaltrexone and naloxone-oxycodone as comparators for the relevant population. What does the Committee consider the most appropriate comparator to be in clinical practice?
- Does the Committee consider the 8 trials used in the mixed treatment comparison (MTC) to be comparable?
- Does the Committee consider the results from the MTC reliable considering that data from the LIR subgroup in the KODIAC studies were included for naloxegol while data from the comparator studies included all patients in the intention-to-treat population?
- People with cancer who have OIC were not included in the clinical studies for naloxegol. Does the evidence provided allow the Committee to make any recommendations regarding the use of naloxegol for people with cancer who have OIC?

Cost effectiveness

- Although the ERG considered the company's model structure to be generally acceptable, it considered the non-OIC health state to be too broad. The ERG was concerned that all patients in the non-OIC health state were assumed to have the same quality of life over the same period, irrespective of how many spontaneous bowel movements they experienced (for example, people with 9 SBMs were assumed to have the same quality of life as people with 28 SBMs)
  - What is the Committee's view on the structure of the company's model?

  - Does the Committee consider it clinically plausible to assume similar utility values for all patients in the non-OIC state?
- The company used the comparison of naloxegol to placebo as the base case analysis, since it was deemed an appropriate regimen that reflected the design and endpoints of the KODIAC 4 and 5 trials. The ERG stated that a more appropriate comparison would have been naloxegol plus bisacodyl compared with placebo plus bisacodyl, since the addition of bisacodyl is both clinically relevant and the use of rescue medication with bisacodyl was permitted in all arms of the KODIAC 4 and 5 trials. What does the Committee consider to be the most appropriate comparison?
- The ERG questioned the face validity of the economic model with regards to the time patients stay in the non-OIC (on treatment) health state. After only two years all patients have left this health state, which was expected for the placebo group but was surprising for the naloxegol group. What is the Committee's view on the plausibility that people in the non-OIC (on treatment) health state in the model will all discontinue treatment within 2 years?
- The various sensitivity and scenario analyses performed by the company and ERG revealed that the ICER is relatively robust to changes in most input values. What is the Committee's view on the robustness of the cost effectiveness evidence presented by company?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of naloxegol within its licensed indication for treating opioid-induced constipation.

Table 1 Decision problem (from *CS, pages 43-44*)

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	Adults with opioid-induced constipation	Adults with opioid-induced constipation who have had an inadequate response to laxative(s)	As per licensed indication: the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s)	There is some uncertainty regarding the definition of laxative inadequate response (LIR) it would appear that the definition of LIR used by the company is a broad definition of criteria for LIR.
Intervention	Naloxegol	Same		No comment
Comparator	oral laxative treatment without naloxegol For adults in whom oral laxatives have provided inadequate relief: - peripheral mu-opioid receptor antagonists (methylnaltrexone) - opioid analgesic and opioid receptor antagonist combinations (naloxone-oxycodone) - rectal interventions (e.g. suppositories and enemas)	For adults in whom oral laxative(s) have provided inadequate relief: Oral laxative(s) treatment without naloxegol (i.e. rescue medication is used as a proxy for stimulant laxative used as needed (PRN) Methylnaltrexone Naloxone-oxycodone Rectal interventions	As per licensed indication as above.	The company's submission eligibility criteria used in search strategy for comparators did not clearly include rectal interventions (suppositories or manual evacuation) nor was this included in the clinical effectiveness section although it was included in the scope.
Outcomes	- frequency of spontaneous bowel movements - symptoms of constipation - use of rescue medication or interventions - response rate - upper gastrointestinal symptoms including nausea - effects on analgesic efficacy - adverse effects of treatment - health-related quality of life	As defined by scope	N/A	The outcomes in the company's submission match the outcomes described in the final scope , however, some outcomes were not considered or discussed in the company's submission (for example, effects on analgesic efficacy).

2 The technology and the treatment pathway

2.1 Naloxegol (Moventig, AstraZeneca) is a pegylated form of naloxol, an analogue of the opioid receptor antagonist naloxone that selectively antagonises peripheral opioid receptors to relieve constipation. It is administered orally. It has a marketing authorisation for treating opioid-induced constipation in adult patients who have had an inadequate response to laxative(s). The summary of product characteristics defines an inadequate response to laxatives in relation to the pivotal studies of naloxegol as opioid-induced constipation symptoms of at least moderate severity while taking at least 1 laxative class for a minimum of 4 days during the 2 week pre study period.

2.2 There are currently no clear treatment pathways or guidelines for people with opioid-induced constipation. However, laxatives are typically used as an initial treatment option for opioid-induced constipation in clinical practice. People who have had an inadequate response to more than 1 laxatives and are still experiencing opioid-induced constipation have no alternative treatment options unless they have advanced illness, in which case they would receive methylnaltrexone or are eligible for naloxone-oxycodone combination therapy. People whose opioid-induced constipation has not responded to treatment may require rectal interventions to alleviate their condition (i.e. suppositories, enema, manual evacuation) which are often unpleasant and distressing.

2.3 According to the marketing authorisation, naloxegol could fit into the treatment pathway as:

- an alternative treatment option to existing laxative(s) for people who have had a laxative inadequate response to at least one laxative class
- an alternative treatment option for people who are experiencing inadequate response provided by laxative(s) who would be suitable for methylnaltrexone or naloxone-oxycodone, that is, those who have

advanced illness and are receiving palliative care or are suitable for oxycodone

- an alternative treatment option for patients no longer on active therapy requiring rectal intervention

Table 2 Technology and comparators

	Naloxegol	**Comparators**	
		Methylnaltrexrone	**Naloxone-oxycodone**
Marketing authorisation	Naloxegol has a marketing authorisation for the treatment of OIC in adult patients who have had an inadequate response to laxative.	Methylnaltrexrone is indicated for the treatment of opioid-induced constipation in advanced illness adult patients, aged 18 years and older, who are receiving palliative care when response to usual laxative therapy has not been sufficient	Naloxone-oxycodone is indicated for severe pain requiring opioid analgesia
Administration method	A single oral dose, administered daily.	Methylnaltrexrone is a subcutaneous injection normally administered by a healthcare professional	Orally administered twice daily.
Cost related information	The list price for a 30 tablet pack of 25 mg or 12.5 mg tablets is anticipated to be £55.20 equating to a daily cost of £1.84.	Dose: body-weight under 38 kg, 150 micrograms/kg on alternate days; body-weight 38–62 kg, 8 mg on alternate days; body-weight 62–114 kg, 12 mg on alternate days; body-weight over 114 kg, 150 micrograms/kg on alternate days; may be given less frequently depending on response; 2 consecutive doses may be given 24 hours apart if no response to treatment on the preceding day; Max. duration of treatment 4 months. Price: 20 mg/mL, net price 0.6-mL vial = £21.05, 7-vial pack (with syringes and needles) = £147.35	Dose: People over 18 years not currently treated with opioid analgesics, initially 10 mg/5 mg every 12 hours, increased according to response; patients already receiving opioid analgesics can start with a higher dose of naloxone-oxycodone; max. naloxone-oxycodone 40 mg/20 mg every 12 hours Price: £8.464 per mg. 40 mg/20 mg, f/c, m/r, oxycodone hydrochloride 40 mg, naloxone hydrochloride 20 mg (yellow), net price 56-tab pack = £169.28.

See summary of product characteristics for details on adverse reactions and contraindications.

3 Consultee submissions

3.1 The clinical experts agreed that there is a lack of high quality experimental data to support clinical guideline development. Although some guidelines exist, these rely heavily on expert opinion which has led to a lack of consensus on the treatment of constipation in general. Generally, the guidelines recommendations and current clinical practice comprise of stool softeners and stimulant laxatives. For opioid-induced constipation specifically, the clinical experts indicated that methylnaltrexone is also used, but is administered by injection only. Although there is evidence of efficacy, its high cost and associated adverse effects have limited its uptake by clinicians. The clinical experts stated that methylnaltrexone is the most appropriate comparator for naloxegol. Additionally, changing the opioid used periodically is also common practice for managing opioid induced constipation as well as using a combination of opioids with naloxone.

3.2 The clinical experts stated that historically, opioid-induced constipation has been associated predominantly in patients with cancer; however, they acknowledged that some evidence exists, which suggests that it may be more common in people with non-cancer related pain. One clinical expert stated that patients with hepatic and renal impairment have limited laxative treatment options, and therefore, have poorer prognosis.

3.3 The clinical experts stated that the introduction of naloxegol should reduce the need for rectal interventions for opioid-induced constipation and free up nursing time for other activities. It should also reduce the need for outpatient reviews and inpatient admissions for opioid-induced constipation, thereby freeing up resources for other activities. Given the mechanism of action is similar to methylnaltrexone, the clinical experts expect the use of naloxegol to be more suitable to secondary and tertiary care at least for initial treatment. Depending on the clinical experience, maintenance therapy could be performed in primary care or the

community. The clinical experts did not identify any additional resources required to implement the use of naloxegol

3.4 No equality and diversity issues were identified by the clinical experts. However they stated that although only patients without cancer were enrolled in the KODIAC studies, the results should be applicable to patients with cancer pain as well, given that the problem relates to the opioid use and not the underlying disease causing the pain.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The key clinical evidence came from the pivotal phase III trials, KODIAC 4 (n= 649) and KODIAC 5 (n= 697). These were international, multi-centre, randomised, double-blind, placebo-controlled trials comparing naloxegol with placebo in adults with non-cancer pain who have opioid-induced constipation. Patients included in the trials took 1or more laxative class for 4 or more days in the 2 weeks prior to screening and reported moderate, severe or very severe symptoms in at least 1 of the 4 stool symptom domains (that is, incomplete bowel movement, hard stools, straining or false alarms). The 2 trials excluded patients receiving opioids for cancer-related pain.

4.2 In both trials, patients were randomised in a 1:1:1 ratio to receive either 12.5 mg of naloxegol, 25 mg of naloxegol or placebo once daily for 12 weeks. Patients were allowed to continue their baseline opioid pain control regimen with dose adjustments according to clinical need. They were also allowed to receive bisacodyl rescue laxative if they had not experienced a bowel movement within 72 hours or more. No other laxatives were allowed in the trials. Patients in both trials were required to complete a daily eDiary throughout the double-blind treatment period. The eDiary was used to record bowel movements, stool consistency, straining, complete and incomplete evacuation, pain level, use of rescue medication and use of opioid medication.

4.3 Subgroups were pre-defined in terms of age group, family origin, location and response to laxatives at baseline. Patients were categorised according to their response to laxatives using the baseline laxative response status questionnaire (BLRSQ):

- Laxative inadequate responder (LIR): people who were taking 1 or more laxative class for 4 or more days prior to screening, who reported moderate, severe or very severe symptoms in at least 1 of 4 stool symptom domains. 54.6% of patients in KODIAC 4 and 53.2% of patients in KODIAC 5 were classified as laxative inadequate responders. This is the group covered by the marketing authorisation for naloxegol.
- Laxative adequate responder (LAR): people who responded adequately to prior laxative treatment 4 or more days prior to screening, who reported mild or no symptoms.
- Laxative unknown responder (LUR): people who had not used laxatives over the previous 2 weeks or had taken 1 or more laxatives less than 4 days over the previous 2 weeks.

Due to the small number of people in the LAR group, the company chose to consider the LAR and LUR groups together, described as the non-LIR subgroup (the group not covered by the marketing authorisation).

Table 3 Baseline characteristics for KODIAC 4: ITT and licensed populations (from *CS, tables 9-10, pg 62-65)*

		Intention to treat analysis set			Population covered by the marketing authorisation		
KODIAC 4		**Naloxegol 12.5 mg (n=213)**	**Naloxegol 25 mg (n=214)**	**Placebo (n=214)**	**Naloxegol 12.5 mg (n=115)**	**Naloxegol 25 mg (n=117)**	**Placebo (n=118)**
Characteristic	Age, mean (SD)	51.9 (10.43)	52.2 (10.29)	52.9 (9.99)	52.9 (10.3)	53.3 (10.72)	53.6 (9.96)
	Female, n (%)	135 (63.4)	118 (55.1)	140 (65.4)	72 (62.6)	68 (58.1)	77 (65.3)
Race, n (%)	White	164 (77.0)	173 (80.8)	160 (74.8)	88 (76.5)	101 (86.3)	92 (78.0)
	Black or African American	42 (19.7)	38 (17.8)	44 (20.6)	21 (18.3)	14 (12.0)	20 (16.9)
	Asian	5 (2.3)	1 (0.5)	4 (1.9)	5 (4.3)	1 (0.9)	2 (1.7)
	American Indian or Alaska native	1 (0.5)	0	2 (0.9)	0	0	1 (0.8)
	Other	1 (0.5)	2 (0.9)	4 (1.9)	1 (0.9)	1 (0.9)	3 (2.5)
BMI (kg/m2)	<18.5	1 (0.5)	1 (0.5)	0	0	0	0
	18.5 – <30	98 (46.0)	102 (47.7)	108 (50.5)	51 (44.3)	59 (50.4)	57 (48.3)
	≥30	114 (53.5)	111 (51.9)	106 (49.5)	64 (55.7)	58 (49.6)	61 (51.7)
Primary reason for pain, n (%)	Back pain	131 (65.1)	110 (51.4)	118 (55.1)	70 (60.9)	61 (52.1)	62 (52.5)
	Joint pain	8 (3.8)	7 (3.3)	7 (3.3)	6 (5.2)	3 (2.6)	5 (4.2)
	Fibromyalgia	6 (2.8)	9 (4.2)	15 (7.0)	2 (1.7)	7 (6.0)	9 (7.6)
	Headache/migraine	1 (0.5)	4 (1.9)	3 (1.4)	0	2 (1.7)	2 (1.7)
	Arthritis	20 (9.4)	22 (10.3)	22 (10.3)	10 (8.7)	12 (10.3)	12 (10.2)
	Neuralgia	1 (0.5)	8 (3.7)	4 (1.9)	1 (0.9)	5 (4.3)	3 (2.5)
	Pain syndrome	5 (2.3)	7 (3.3)	5 (2.3)	2 (1.7)	4 (3.4)	2 (1.7)
	Other	41 (19.2)	46 (21.5)	39 (18.2)	24 (20.9)	23 (19.7)	23 (19.5)
Lifetime opioid use (months),median		84.0	72.0	60.0	96.0	72.0	60.0
Duration of current opioid use (months), median		24.0	24.0	24.0	26.0	24.0	24.0

Table 4 Baseline characteristics for KODIAC 5: ITT and licensed populations (from *CS, tables 9-10, pg 62-65)*

		Intention to treat analysis set			Population covered by the marketing authorisation		
KODIAC 5		**Naloxegol 12.5 mg (n=232)**	**Naloxegol 25 mg (n=232)**	**Placebo (n=232)**	**Naloxegol 12.5 mg (n=125)**	**Naloxegol 25 mg (n=124)**	**Placebo (n=121)**
Characteristic	Age, mean (SD)	52.0 (11.02)	51.9 (12.11)	52.3 (11.62)	53.2 (11.02)	53.5 (11.36)	53.0 (11.99)
	Female, n (%)	149 (64.2)	147 (63.4)	145 (62.5)	85 (68.0)	82 (66.1)	74 (61.2)
Race, n (%)	White	187 (80.6)	189 (81.5)	183 (78.9)	102 (81.6)	107 (86.3)	98 (81.0)
	Black or African American	41 (17.7)	40 (17.2)	44 (19.0)	22 (17.6)	16 (12.9)	21 (17.4)
	Asian	1 (0.4)	0	0	0	0	0
	Native Hawaiian or other Pacific Islander	0	1 (0.4)	0	0	0	0
	American Indian or Alaska native	1 (0.4)	1 (0.4)	2 (0.9)	0	0	0
	Other	2 (0.9)	1 (0.4)	3 (1.3)	1 (0.8)	1 (0.8)	2 (1.7)
BMI (kg/m^2)	<18.5	3 (1.3)	2 (0.9)	3 (1.3)	0	1 (0.8)	3 (2.5)
	18.5 – <30	123 (53.0)	112 (48.3)	118 (50.9)	68 (54.4)	65 (52.4)	62 (51.2)
	≥30	106 (45.7)	115 (49.6)	111 (47.8)	57 (45.6)	57 (46.0)	56 (46.3)
Primary reason for pain, n (%)	Back pain	136 (58.6)	130 (56.0)	129 (55.6)	71 (56.8)	74 (59.7)	62 (51.2)
	Joint pain	11 (4.7)	16 (6.9)	10 (4.3)	6 (4.8)	7 (5.6)	4 (3.3)
	Fibromyalgia	16 (6.9)	11 (4.7)	18 (7.8)	10 (8.0)	3 (2.4)	9 (7.4)
	Headache/migraine	1 (0.4)	5 (2.2)	2 (0.9)	0	2 (1.6)	1 (0.8)
	Arthritis	20 (8.6)	27 (11.6)	21 (9.1)	8 (6.4)	14 (11.3)	9 (7.4)
	Neuralgia	6 (2.6)	7 (3.0)	5 (2.2)	5 (4.0)	4 (3.2)	5 (4.1)
	Pain syndrome	0	3 (1.3)	2 (0.9)	0	2 (1.6)	0
	Other	42 (18.1)	33 (14.2)	44 (19.0)	25 (20.0)	18 (14.5)	31 (25.6)
Lifetime opioid use (months), median		81.5	78.0	72.0	78.0	84.0	84.0
Duration of current opioid use (months), median		36	24	24	36.0	24.0	24.0

4.4 An additional subgroup of the LIR population (that is the population covered by the marketing authorisation) was defined for analysis as people whose constipation did not adequately respond to at least 2 classes of laxatives for 4 or more days in the 2 weeks prior to study entry or who reported an unsatisfactory response from 1 or more additional laxative class from the 6 month opioid-induced constipation history prior to screening.

4.5 The company also conducted a post-hoc analysis of a subgroup of people within the LIR population who were receiving step 3 opioids (classified according to the World Health Organisation analgesic ladder). The company stated that this is a clinically valid subgroup of patients with opioid-induced constipation as the more severe forms of opioid-induced constipation are more likely to be related to the use of step 3 opioids.

ERG comments

4.6 The ERG noted that the population criteria in the company's submission concentrates on the subgroup proposed in the scope of 'laxative inadequate responders' and not on the broader criteria of the scope, which is all patients with opioid-induced constipation. It noted that the marketing authorisation was based on this population. Similarly, the outcomes of interest were broader in the scope than in the company's submission.

4.7 The ERG noted that the company did not discuss the underlying disease states that lead to opioid treatment of pain in non-cancer patients. These were identified by the ERG to include back pain, spinal osteoarthritis, and failed back surgery. It is important to note that patients suffering from cancer pain or non-cancer pain can have constipation due to multiple causes (dehydration, poor diet, inactivity, spinal cord injuries, tumour activity) and this can lead to difficulties in correctly estimating the prevalence of OIC.

4.8 The ERG also noted that opioid treatment for pain induces many side effects (nausea, vomiting, sedation, respiratory depression, pupil dilation, euphoria, unease, low blood pressure, urinary retention, and OIC) of which OIC is only 1 and therefore opioid antagonists will alleviate multiple side effects particularly those of the peripheral nervous system (low blood pressure, urinary retention, and OIC).

Clinical trial results

4.9 The primary outcome of the KODIAC 4 and 5 studies was response to treatment, defined as the proportion of patients with 3 or more spontaneous bowel movements (SBM) per week (defined as a bowel movement without the use of laxatives in the previous 24 hours), with improvement from baseline of 1 or more spontaneous bowel movements per week, for 9 weeks or more out of 12 weeks and 3 out of the last 4 weeks in the study. The company stated that spontaneous bowel movement frequency is a clinically meaningful measure commonly employed in clinical research to assess the efficacy of a treatment for chronic constipation.

4.10 The main secondary outcomes included:

- response to treatment (as defined for the primary outcome) in the LIR population only
- Time to first post-dose spontaneous bowel movement without the use of rescue medication in the previous 24 hours
- The mean number of days per week with 1 or more spontaneous bowel movement.

4.11 Naloxegol 25 mg (recommended dose) resulted in significantly higher response rates in the overall population (see table 5) and in the LIR population compared with placebo in both trials (KODIAC 4, 48.7% versus 28.8% patients, respectively; p=0.002: KODIAC 5, 46.8% versus 31.4% patients, respectively; p=0.014) (see table 6). In both studies, naloxegol showed a consistent improvement in a range of secondary endpoints, for example, time to first post-dose SBM (see table 7), total SBMs per week,

number of days per week with at least one SBM, use of rescue medication at least once over the treatment period. The 3 instruments used by the company to measure quality of life (PAC-SYM, PAC-QoL, EQ-5D) also showed advantages of naloxegol compared to placebo.

Table 5: Response rates for Weeks 1–12 in the overall population (the primary efficacy outcome) (from CS table 14, pg 83)

Outcome	KODIAC 4			KODIAC 5		
	Naloxegol 12.5 mg n=213	**Naloxegol 25 mg n=214**	**Placebo n=214**	**Naloxegol 12.5 mg n=232**	**Naloxegol 25 mg n=232**	**Placebo n=232**
n (%) of patients responding	87 (40.8)	95 (44.4)	63 (29.4)	81 (34.9)	92 (39.7)	68 (29.3)
RR (comparison vs placebo)†	1.380	1.509	N/A	1.188	1.348	N/A
95% CI	(1.062, 1.795)	(1.168, 1.949)	N/A	(0.911, 1.548)	(1.045, 1.739)	N/A
p value	0.015	0.001	N/A	0.202	0.021	N/A

CI, confidence interval; N/A, not applicable; RR, relative risk
†Analysed using the Chi-square test.
* Statistically significant under the multiple testing procedure.

Table 6: Response rates for Week 1–12 in the LIR population in KODIAC 4 and 5 (population covered by the marketing authorisation) (from *CS table 15, pg 85)*

Outcome	KODIAC 4			KODIAC 5		
	Naloxegol 12.5 mg n=115	**Naloxegol 25 mg n=117**	**Placebo n=118**	**Naloxegol 12.5 mg n=125**	**Naloxegol 25 mg n=124**	**Placebo n=121**
n (%) of patients responding	49 (42.6)	57 (48.7)	34 (28.8)	53 (42.4)	58 (46.8)	38 (31.4)
RR (comparison vs placebo)†	1.479	1.691	N/A	1.350	1.489	N/A
95% CI	(1.038, 2.107)	(1.205, 2.373)	N/A	(0.967, 1.884)	(1.078, 2.058)	N/A
p value	0.028*	0.002*	N/A	0.074	0.014*	N/A

Abbreviations: CI, confidence interval; RR, relative risk.
†Analysed using the Chi-square test.
* Statistically significant under the multiple testing procedure.

Table 7: Time to first post-dose SBM for the LIR population in KODIAC 4 and KODIAC 5 (population covered by the marketing authorisation) (from *CS table 16, pg 86)*

Outcome	KODIAC 4			KODIAC 5		
	Naloxegol 12.5 mg n=115	**Naloxegol 25 mg n=117**	**Placebo n=118**	**Naloxegol 12.5 mg n=125**	**Naloxegol 25 mg n=124**	**Placebo n=121**
Median time to first SBM, hours, (95% CI)	20.6 (8.1, 23.5)	5.4 (3.9, 10.7)	43.4 (25.2, 48.2)	12.8 (6.4,21.9)	18.1 (6.5,22.8)	38.2 (28.9,57.4)
Patient with SBM by ≤6 hours (%)	38 (33.0)	63 (53.8)	19 (16.1)	46 (36.8)	49 (39.5)	20 (16.5)
Patient with SBM by ≤12 hours (%)	49 (42.6)	71 (60.7)	28 (23.7)	60 (48.0)	59 (47.6)	25 (20.7)
Patient with SBM by ≤24 hours (%)	68 (59.1)	88 (75.2)	43 (36.4)	79 (63.2)	74 (59.7)	44 (36.4)

4.12 In the absence of trial data demonstrating the head-to-head efficacy of naloxegol versus laxatives, the company used trial data from KODIAC 4 and 5 comparing SBMs that occurred without the need for rescue medication in the previous 24 hours with total bowel movements in the placebo plus rescue bisacodyl arm (those bowel movements that occurred as a result of rescue bisacodyl). The company used this comparison as a proxy for stimulant laxative used as required. In KODIAC 4, the mean bisacodyl dose per week over weeks 1–12 was 6.8 mg, 5.6 mg, and 12.5 mg in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. In KODIAC 4, bisacodyl was used at least once over the 12 week treatment period in 65.2%, 56.4%, and 76.3% of patients in the naloxegol 12.5 mg, 25 mg and placebo arms, respectively. In KODIAC 5, the mean bisacodyl dose per week over weeks 1–12 was 6.2 mg, 6.8 mg, and 9.6 mg in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. A single rescue dose of bisacodyl was 10 to 15 mg. In KODIAC 5 60.8% and 62.9% of patients in the naloxegol 12.5 mg and 25 mg arms respectively used bisacodyl at least once compared with 76.9% of patients in the placebo arm.

ERG comments

4.13 The ERG commented that there is lack of direct evidence of trials of naloxegol to any of the relevant comparators.

Mixed treatment comparison

4.14 The company conducted a mixed treatment comparison (MTC) of naloxegol with methylnaltrexone and naloxone-oxycodone using data from the 2 naloxegol trials (KODIAC 4 and 5), 2 methylnaltrexone trials and 4 naloxone-oxycodone trials. All 8 trials compared the active treatments with placebo (see figure1). The company stated that only the naloxegol trials were able to provide data in the specific patient populations of interest, that is, laxative-inadequate responders ([LIR] population covered by the marketing authorisation) and laxative-inadequate responders + step 3 opioids subgroups (population covered by the marketing authorisation + step 3 opioids). As none of the other studies reported data specifically for the LIR and LIR + Step 3 opioids subgroups, the company used the main trial populations in these comparator studies to inform the MTC analyses. The company commented that the trials included in the MTC analyses varied substantially with respect to the definition and severity of opioid-induced constipation, therefore, it did not expect that these subgroups of the KODIAC 4 and 5 trials represented populations substantially different from the included opioid-induced constipation trials, as a whole. Further details on the trials are presented in table 8. Laxatives were not included as a comparator as the systematic review did not identify any laxative studies with outcomes of interest.

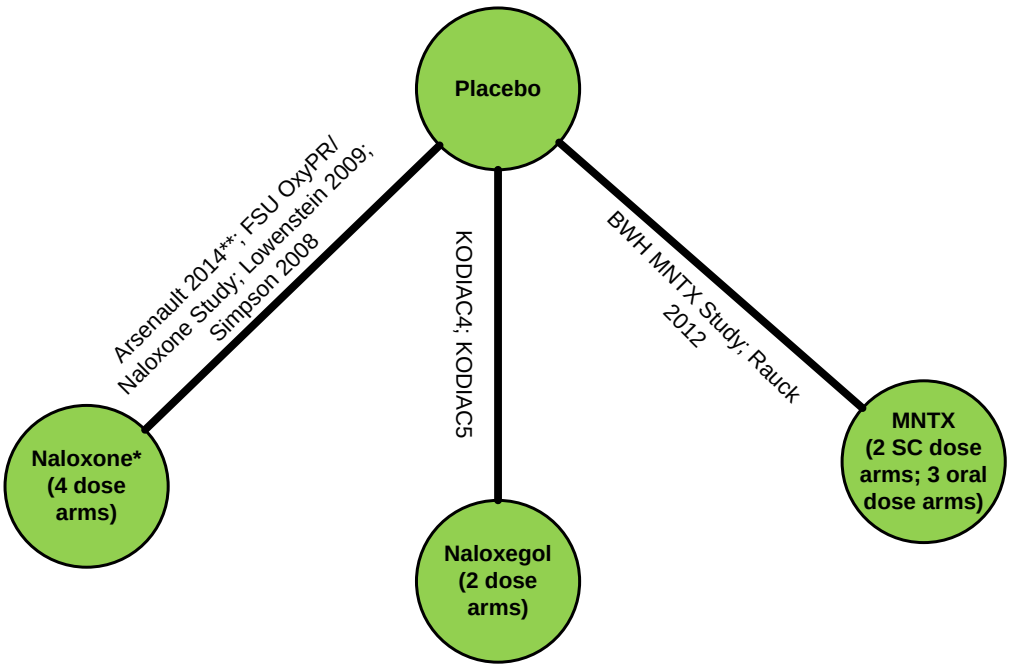

Figure 1 MTC subgroup analysis network diagram (from *CS, figure 11, pg 141*)

Abbreviations: BWH MNTX, Michna et al, 2011; MNTX, methylnaltrexone; SC, subcutaneous.

*The oxycodone PR treatment in this trial was considered to be equivalent to placebo arms. Patients received naloxone/oxycodone or oxycodone alone.

**Arsenault 2014, published as an abstract at the Canadian Digestive Disease Week, was not identified as part of the Systematic review, as this conference was not searched as part of the prospectively designed protocol.

Table 8 Summary of trials used to conduct the mixed treatment comparison (from *CS, table 43, pg 134, table 48, pg 147 and revised table 1 from company's response to ERG report, pg 19)*

Study	Trial design	Dura-tion	Patient population	Treatment/dose	Outcomes used in the MTC
Naloxegol					
KODIAC 4	Phase III, double-blind RCT	12 weeks	OIC patients with non-malignant pain. Only data from the LIR and LIR + 3 step opioid subgroup is included in the MTC	• naloxegol 12.5 mg OD, n=114 • naloxegol 25 mg OD, n=117 • placebo OD, n=118	• mean change from baseline in SBMs/ week • SBM response (%) • CSBM response • DAEs (%) • TEAEs (%)
KODIAC 5	Phase III, double-blind RCT	12 weeks	OIC patients with non-malignant pain. Only data from the LIR and LIR + 3 step opioid subgroup is included in the MTC	• naloxegol 12.5 mg OD, n=122 • naloxegol 25 mg OD, n=121 • placebo OD, n=120	• mean change from baseline in SBMs/ week • SBM response (%) • CSBM response • DAEs (%) • TEAEs (%)

Study	Trial design	Dura-tion	Patient population	Treatment/dose	Outcomes used in the MTC
Methylnaltrexone					
Michna 2011	Phase III, double-blind RCT	4 weeks	OIC patients with non-malignant pain, n=469	• Methylnaltrexone 12 mg OD, n=150 • Methylnaltrexone 12 mg QAD, n=148 • placebo OD, n=162	• mean change from baseline in SBMs/ week* • SBM response (%) • DAEs (%) • TEAEs (%)
Rauck 2012	Phase III, double-blind RCT	12 weeks	OIC patients with non-malignant pain, n=804	• Methylnaltrexone 150 mg OD, n=201 • Methylnaltrexone 300 mg OD, n=201 • Methylnaltrexone OD 450 mg, n=201 • placebo OD, n=201	• mean change from baseline in SBMs/ week
Naloxone-oxycodone					
Meissner et al, 2009	Phase II, double-blind RCT	4 weeks	OIC patients, 2.9% with malignant and 97.1% with non-malignant pain, n=202	• naloxone 10 mg OD, n=51 • naloxone 20 mg OD, n=51 • naloxone 40 mg OD, n=50 • placebo OD, n=50	• DAEs (%)
Lowen-stein 2009	Phase III, double-blind RCT	12 weeks	OIC patients with lower back pain, n=278	• Naloxone-oxycodone OD, n=130 • Placebo OD, n=135	• CSBM response • DAEs (%)
Simpson 2008	Phase III, double-blind RCT	12 weeks	OIC patients with non-malignant pain, n=322	• Naloxone-oxycodone, n=162 • placebo, n=160	• CSBM response • DAEs (%)
Arsenault 2014	Randomised, double-blind, cross-over study	5 weeks	OIC patients with chronic non-malignant pain, n=59	• naloxone-oxycodone • placebo	• CSBM response

*outcome extractable from a graph

Abbreviations: CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse event; NR, not reported; OD, once daily; OIC, opioid-induced constipation; QAD, every other day; RCT, randomised controlled trial; SBM, spontaneous bowel movement; TEAE, treatment emergent adverse event

4.15 The company conducted a Bayesian MTC meta-analysis enabling the incorporation of indirect comparisons from 2 or more trials that have 1 treatment in common. The change in SBMs per week was meta-analysed as a mean difference. The relative proportions of patients with SBM within 4 and 12 hours after the first dose, SBM response (percentage with ≥3

SBM/week) at 4 weeks, CSBM response (percentage with ≥3 CSBM/week) at 4 weeks, treatment-emergent adverse events, and discontinuations due to adverse events were meta-analysed using odds ratios. Log-odds and mean differences were computed using the OpenBUGS software package. Because of the methodological heterogeneity between studies (specifically, differences in the definition of opioid-induced constipation), the company used random effects analyses in the base case, with fixed effects used only if there was a strong rationale for its use. The point estimate results of the MTC were similar for the random and fixed-effects model, but the credible intervals for the random effects analysis were wider. The results of the MTC are shown in tables 9, 10 and 11.

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Table 9 Results from MTC in the LIR population (population covered by the marketing authorisation) – treatment vs placebo (from *CS table 50, pg 155*)

		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	**# of studies**	**4 weeks**	**4-12 weeks**				
Naloxegol (12.5 mg)	2	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]
Naloxegol (25 mg)	2	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]
Methylnaltrexone, SC (12 mg OD)	1	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]
Methylnaltrexone, SC (12 mg QAD)	1	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]
Methylnaltrexone, oral (150 mg OD)	1	0.16 [-1.82, 2.17]	0.17 [-1.77, 2.15]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	1	0.67 [-1.38, 2.75]	0.69 [-1.31, 2.71]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	1	0.68 [-1.34, 2.72]	0.68 [-1.32, 2.67]	--	--	--	--
Naloxone PR (FRC)	CSBM: 3 DAEs: 2	--	--	--	2.78 [1.61, 4.83]*	0.72 [0.26, 2.38]	--
Naloxone (10 mg BD)	1	--	--	--	--	6.86 [0.68, 205.82]	--
Naloxone (20 mg BD)	1	--	--	--	--	8.75 [0.87, 246.41]	--
Naloxone (40 mg BD)	1	--	--	--	--	14.44 [1.56, 407.08]*	--

BD – twice daily, CrI – credible interval, CSBM – complete spontaneous bowel movement, DAE – discontinuations due to adverse effects , FRC - fixed ratio combination , MD – mean difference, OD – once daily, OR – odds ratio, PR – prolonged release, QAD – every other day, SBM – spontaneous bowel movement, SC – subcutaneous, TEAE – treatment emergent adverse effects

* 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

Table 10 Results from MTC in the LIR population (population covered by the marketing authorisation) – naloxegol 25 mg vs comparators (from *CS, table 52, pg 157*)

	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)
Naloxegol 25 mg v. treatment	**4 weeks**	**4-12 weeks**				
Methylnaltrexone, SC (12 mg OD)	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]
Methylnaltrexone, SC (12 mg QAD)	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]
Methylnaltrexone, oral (150 mg OD)	1.68 [-0.87, 4.13]	1.28 [-1.16, 3.77]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	1.17 [-1.37, 3.63]	0.76 [-1.7, 3.27]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	1.17 [-1.36, 3.63]	0.77 [-1.64, 3.22]	--	--	--	--
Naloxone PR (FRC)	--	--	--	0.87 [0.38, 2.11]	2.97 [0.59, 13.14]	--
Naloxone (10 mg BD)	--	--	--	--	0.31 [0.01, 4.07]	--
Naloxone (20 mg BD)	--	--	--	--	0.24 [0.01, 3.25]	--
Naloxone (40 mg BD)	--	--	--	--	0.15 [0, 1.87]	--

BD – twice daily, CrI – credible interval, CSBM – complete spontaneous bowel movement, DAE – discontinuations due to adverse effects , FRC - fixed ratio combination , MD – mean difference, OD – once daily, OR – odds ratio, PR – prolonged release, QAD – every other day, SBM – spontaneous bowel movement, SC – subcutaneous, TEAE – treatment emergent adverse effects

* 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

Table 11 Results from MTC in the LIR + Step 3 opioids subpopulation of the population covered by the marketing authorisation – naloxegol 25 mg vs comparators (from *CS, table 55, pg 160)*

	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)
Naloxegol 25 mg v. treatment	**4 weeks**	**4-12 weeks**				
Methylnaltrexone, SC (12 mg OD)	0.68 [-2.52, 3.89]	0.33 [-2.93, 3.61]	1.16 [0.29, 4.7]	--	1 [0.12, 7.5]	1.37 [0.32, 5.86]
Methylnaltrexone, SC (12 mg QAD)	1.69 [-1.51, 4.91]	1.33 [-2, 4.67]	2 [0.5, 8.11]	--	0.74 [0.09, 5.52]	1.63 [0.38, 6.77]
Methylnaltrexone, oral (150 mg OD)	2.12 [-1.12, 5.29]	1.76 [-1.48, 5.09]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	1.6 [-1.64, 4.77]	1.25 [-2.03, 4.52]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	1.6 [-1.62, 4.75]	1.25 [-1.98, 4.52]	--	--	--	--
Naloxone PR (FRC)	--	--	--	1.39 [0.59, 3.5]	4.17 [0.79, 19.69]	--
Naloxone (10 mg BD)	--	--	--	--	0.4 [0.01, 5.49]	--
Naloxone (20 mg BD)	--	--	--	--	0.32 [0.01, 4.57]	--
Naloxone (40 mg BD)	--	--	--	--	0.19 [0, 2.51]	--

BD – twice daily, CrI – credible interval, CSBM – complete spontaneous bowel movement, DAE – discontinuations due to adverse effects , FRC - fixed ratio combination , MD – mean difference, OD – once daily, OR – odds ratio, PR – prolonged release, QAD – every other day, SBM – spontaneous bowel movement, SC – subcutaneous, TEAE – treatment emergent adverse effects

* 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 with Step 3 opioids 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

ERG comments

4.16 The ERG commented that some potentially relevant studies for the MTC may have been omitted because of how the company defined and adhered to the inclusion and exclusion criteria in its literature search. For example, the difference in the specification of the population between the scope and the company's submission is likely to have reduced the number of included studies by limiting the naloxegol studies to the LIR subgroup in the company's submission.

4.17 The ERG stated that insufficient details were presented for comparator study design, quality and data. It stated that the definition of rescue treatment varied between the trials and there was insufficient information to judge the similarity of the rescue treatments used. It also noted that the company did not present details of the baseline characteristics for the comparator studies, thereby preventing any further assessment of the similarities of the studies included in the MTC. These limitations in the ERG's opinion, prevented further analyses based on baseline characteristics (for pain intensity, opioid dose, duration of opioid use, duration of OIC, previous laxative use).The ERG stated that overall, there is no robust evidence of efficacy and safety between naloxegol and the comparators of interest.

4.18 The ERG noted that that some outcomes included in the final scope, such as, symptoms of constipation, use of rescue medication/interventions, upper gastrointestinal symptoms (including nausea), analgesic efficacy or health-related quality of life were not analysed in the MTC. It noted that 3 of the 5 outcomes analysed showed discrepancies between the available data and the results reported, namely:

- CSBM response (≥3 CSBM/week) at four weeks (percentage) – The definitions for CSBM response differs between KODIAC 4 and 5 (percentage days in week with ≥1 CSBM) and the other trials (patients >3 CSBMs/week) and therefore should not have been combined in the

ERG's opinion. Additionally, the results were extracted from the full data set not the LIR subgroup in KODIAC 4 and 5.

- Discontinuations due to adverse events, 4-12 weeks (percentage): This analysis was feasible according to the ERG, but since the data for the KODIAC trials is from the 12 week time point, it should only be compared to other trials with 12 week time points (Lowenstein 2009, Simpson 2008), using the Bucher method.
- Treatment emergent adverse events, 4 weeks (percentage) – the ERG could not find 4 week results for treatment emergent adverse events for the KODIAC trials and only found data relating to 12 weeks for this outcome. Therefore a Bucher analysis would be possible at 12 weeks when the KODIAC trials are compared with Lowenstein 2009.

4.19 The ERG expressed concern that discrepancies in the company's submission made it unclear whether the company used data for the intention-to-treat population or LIR subgroup in the mixed treatment comparison analyses. However, it was unable to replicate and check the results of the mixed treatment comparison analyses as the datasets used in the analyses were not provided in the company's submission. The ERG commented that the fixed effects model would have been preferable for the MTC rather than the random effects model, based on the deviance information criterion (DIC) presented by the company to compare both models. The ERG stated that the company's conclusion regarding the more suitable model contradicted the reported DIC values, although it noted that the differences were generally very small. However these were only for the comparisons with placebo, and not between treatments. Therefore the ERG was not able to assess how the choice of model affected the results comparing different treatments.

Adverse effects of treatment

4.20 In addition to KODIAC 4 and KODIAC 5, 2 studies were primarily designed to assess the safety and tolerability of naloxegol in people with opioid-induced constipation with non-cancer pain. KODIAC 7 was a

12 week extension study of KODIAC 4 while KODIAC 8 was a 52 week open label study comparing naloxegol 25 mg only with placebo. The majority of adverse events reported were mild or moderate in intensity. The number and percentage of patients who had 1or more adverse event in any category during the treatment and follow-up periods are summarised in table 12. The most common drug-related adverse events in the naloxegol arm of KODIAC 8 were abdominal pain (14.8%), diarrhoea (7.9%), flatulence (5.6%) and nausea (4.7%).

Table 12 Summary of adverse events in KODIAC 7 and 8 (Safety analysis set) (from *CS table 74, pg 191)*

Adverse events	KODIAC 7			KODIAC 8	
	Naloxegol 12.5 mg (n=94)	Naloxegol 25 mg (n=97)	Placebo (n=100)	Naloxegol 25 mg (n=534)	usual care (n=270)
Any adverse event, n (%)	32 (34.0)	40 (41.2)	33 (33.0)	437 (81.8)	195 (72.2)
Any adverse event leading to death, n (%)	1 (1.1)	0	0	1 (0.2)	1 (0.4)
Any serious adverse event (including events leading to death), n (%)	6 (6.4)	6 (6.2)	5 (5.0)	51 (9.6)	30 (11.1)
Discontinuation due to adverse events, n (%)	4 (4.3)	4 (4.1)	3 (3.0)	56 (10.5)	NA†

†Patients in the usual care group were not taking any study drug and thus could not be categorised for this parameter.

4.21 There were no differences in adverse events observed between the ITT and population covered by the marketing authorisation (the laxative-inadequate responders) in KODIAC 4 and 5. The most frequently reported adverse events were gastrointestinal (GI) events (predominantly diarrhoea, abdominal pain, nausea, and flatulence), which was not unexpected given the nature of the disease and the pharmacological mechanism of action of naloxegol. GI-related adverse events occurred at a higher frequency in the naloxegol 25 mg treatment group compared with the naloxegol 12.5 mg and placebo groups. The majority of GI-related adverse events occurred within the first 7 days of treatment and with the

exception of abdominal pain and flatulence, the majority of GI events typically were resolved within 1 week. There were no notable differences in the type or frequency of serious adverse events across treatment groups in the studies. The incidence of discontinuations due to adverse events was dose-related with a higher proportion of patients discontinuing in the naloxegol 25 mg treatment group compared with the naloxegol 12.5 mg and placebo groups. The discontinuation rate observed with the longer-term use of naloxegol (52 weeks) was similar to that seen in the pivotal 12 week RCTs. The most common adverse events resulting in discontinuation were GI events.

4.22 Long-term treatment with naloxegol (52 weeks) was generally well tolerated with an adverse effects profile that was largely consistent with that observed in the confirmatory pivotal 12 week RCTs. Longer exposure to naloxegol (52 weeks) was not associated with clinically relevant differences in opioid withdrawal compared with usual care.

ERG comments

4.23 The ERG did not make any specific comments regarding adverse effects of treatment with naloxegol.

5 Cost-effectiveness evidence

Model structure

5.1 The company constructed a decision-analytic model comparing the cost-effectiveness of naloxegol 25 mg (recommended dose) with several comparators for people with opioid-induced constipation who have had an inadequate response to laxatives (that is, the population covered by the marketing authorisation). The comparator for the base case analysis was placebo as per the pivotal clinical trials, whereas methylnaltrexone was used in a scenario analysis. The company presented a subgroup analysis of patients who have an inadequate response to laxatives and are taking step 3 opioids. The comparators for the subgroup analysis were placebo, methylnaltrexone and naloxone-oxycodone.

5.2 The company also presented 2 additional analyses, which it considered to be the most clinically relevant comparisons given the multifactorial nature of constipation and clinical guidance obtained via an advisory board and company-sponsored research:

- Naloxegol compared with placebo in combination with bisacodyl (where bisacodyl is used as a proxy for stimulant laxative use as required)
- Naloxegol plus bisacodyl compared with placebo plus bisacodyl (to demonstrate the cost-effectiveness of naloxegol when used in combination with a stimulant laxative).

5.3 The model comprised a decision-tree structure for the first 4 weeks of treatment, followed by a Markov structure. All patients begin the model with opioid-induced constipation (OIC) and start taking naloxegol or a selected comparator (figure 2). Response to treatment is assessed after 4 weeks, with patients being classified as responders if they have achieved constipation relief and as non-responders if they have not.

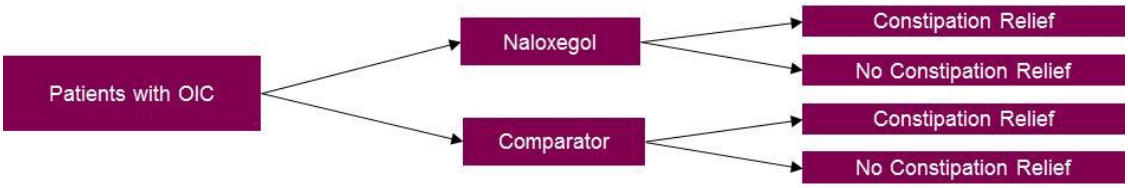


Figure 2 Decision Analytic Schematic (Week 0-4) (based on CS figure 15, pg 231)

5.4 The Markov model consists of 4 health states: OIC; non-OIC (on treatment), non-OIC (untreated) and death, where OIC and non-OIC are defined as:

- OIC: less than 3 spontaneous bowel movements (SBMs) per week in at least 2 out of the last 4 weeks
- Non-OIC: 3 or more SBMs per week in at least 3 out of the last 4 weeks

This change from the clinical definition of effect was chosen by the company because it corresponds with internationally accepted definitions of constipation and simplified the model design for estimating utility and resource use as a function of constipation status, rather than a change in that status. Patients who responded to treatment after 4 weeks entered the Markov phase of the model in the 'non-OIC (on treatment)' health state, whereas patients who did not respond to treatment by week 4 entered in the 'OIC' health state. The company designed the model to take into account the variable nature of opioid-induced constipation. In the model, patients may move between the OIC and non-OIC state, even in the absence of effective treatment. The company stated that clinical expert opinion and trial data suggested that patients in the placebo arm moved between the OIC and non-OIC states.

5.5 The time horizon in the company's base case was 5 years because in the company's opinion, it reflected the upper end of a period of opioid use and because the model suggested that it reaches a steady state within that period. Scenario analyses were conducted on several other time horizons to test the impact on the ICER. The cycle length was 4 weeks and a half-cycle correction was applied. The company applied a discount of 3.5% for costs and benefits and an NHS/PSS perspective was adopted.

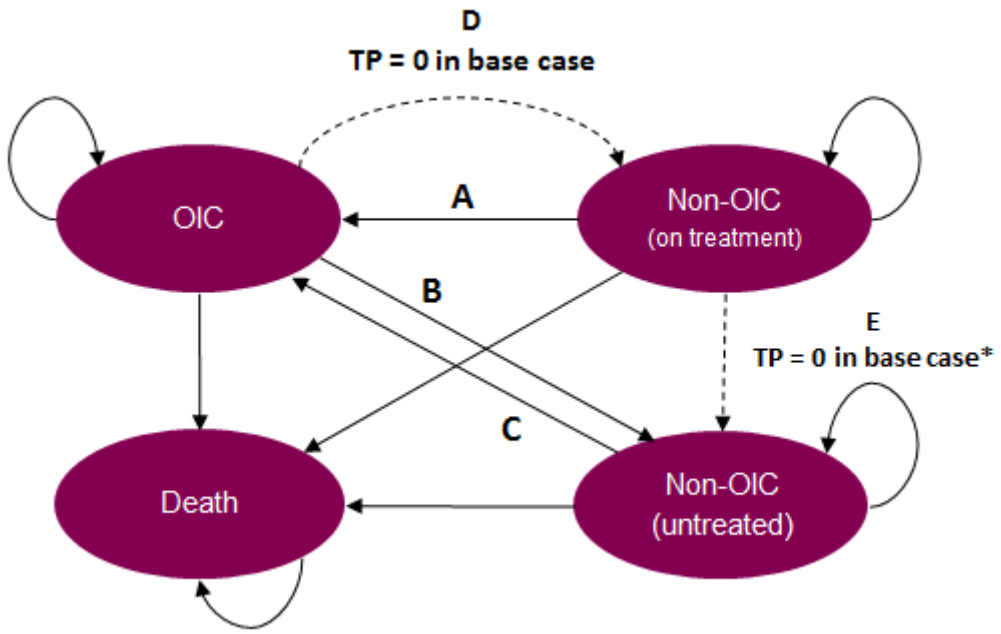


Figure 3 Company's Markov model structure, after week 4 (based on CS figure 16, pg 234)

5.6 The company's base case model included the transitions which occur every 4 weeks in the tables below.

Table 13 Description of transitions in company's economic model (from *CS table 88, pg 236)*

Initial health state	States patients can transition to	Comments
Patients entering the Markov model	Remain constipation-free and stay in the 'non-OIC (on treatment)' health state	Patients on subcutaneous methylnaltrexone can also transition from the 'non-OIC (on treatment)' state to the 'non-OIC (untreated)' state, in accordance to the SPC that subcutaneous methylnaltrexone has not been studied for more than a 16 week duration (as detailed further in section 7.2.3). That is, subcutaneous methylnaltrexone patients are assumed to discontinue treatment if: i) they are non-responders within the first 16 weeks (and so move to the 'OIC' state) or ii) they are still responders at 16 weeks (and move to the 'non-OIC (untreated)' state
	Treatment failure and relapse to the 'OIC' state (transition A)	
	Death	
Patients in the 'OIC' health state	Continue to experience OIC;	In the base case, patients are assumed to not move from the 'OIC' state to the 'non-OIC (on treatment)' state. That is, once patients have stopped responding to treatment and discontinued, they
	'Non-OIC (untreated)' state (transition B)	

Initial health state	States patients can transition to	Comments
	Death	cannot go back onto the treatment.
Patients in the 'non-OIC (untreated)' state	Relapse and move back to 'OIC state' (transition C)	
	Death	
Scenario		
Patients who are in the 'OIC' state	May go back onto treatment and transition to the 'non-OIC (on treatment)' state (transition D).	
Patients in the 'non-OIC (on treatment)' state	Can stop taking treatment with no impact on their OIC status, moving to 'non-OIC (untreated)' (transition E).	

5.7 The proportion of patients in the non-OIC (on treatment) state of the model were estimated based on the response rates derived from the KODIAC 4 and 5 trials for the naloxegol and placebo arms (with or without bisacodyl). For the comparisons with methylnaltrexone and naloxone-oxycodone, the outcomes of the MTC were used. The company used a number of methods to generate estimates for transition A (from the non-OIC [on-treatment] health state to the OIC health state in the model) (see table 14. The Kaplan-Meier curve of the patients in the non-OIC (on treatment) state was derived from the KODIAC 4 and 5 studies for the comparison with placebo. The company conducted parametric survival analyses in order to predict the proportion of patients remaining in the non-OIC (treated) health state over time. The company fitted the following curves to the data: exponential, Weibull, gamma, Gompertz, log-normal and log-logistic. Curves were fitted separately for naloxegol 25 mg and placebo, to allow for the possibility that changes in constipation status followed a different distribution in the two arms. The company selected the same function for both arms. Based on the best fitting distribution, the company chose 4 functions for inclusion in the model – exponential, Weibull, log-logistic and log-normal. The company included these in the model because that estimates of statistical fit and clinical opinion failed to identify an obviously preferred function. Because the exponential was

function the most conservative of the available functions, the company selected it for its base case. For the comparisons with methylnaltrexone and naloxone-oxycodone, the curves were estimated based on the naloxegol curve, assuming proportional hazards and using the hazard ratios estimated from the MTC. In a scenario analysis, the hazard ratio was set to 1.

5.8 In a scenario analysis, the company used discontinuation data from KODIAC 8 rather than KODIAC 4 and 5 to estimate the transition from the non-OIC to the OIC state for the comparison with placebo. For the other comparisons, the company multiplied the transition probability for naloxegol by the inverse of the relative risk of response from the MTC. The company also included a 'worst case' scenario where no extrapolation beyond the trial period was performed. In a third scenario, the company assumed that patients in the non-OIC (on treatment) state at 12 weeks remained in this state for the remainder of the model.

5.9 The company's estimates for transitions B (from the OIC health state to the non-OIC [untreated] health state) and C (from the non-OIC [untreated] health state to the OIC health state) were generated from an analysis of the population of patients covered by the marketing authorisation in the placebo arm of KODIAC 4 and 5. The company analysed the placebo data because the model assumed that patients are not on treatment in the OIC and non-OIC (untreated) health states. This same transition estimates were assumed for all comparisons in the model. For transition B, patients who had entered the 'OIC' state either at Week 4 or via transition A were followed until the time when they next became non-OIC. For transition C, patients in the non-OIC state were followed until time-to-next OIC state. For the transition to death, the company applied the same mortality rate, based on the UK general population to all health states. Mortality was calculated based on UK life table for the years 2008–2010. The company used the exponential function to calculate cycle probability of mortality.

Table 14 Summary of transition probabilities used in company's model (from CS table 87, pg 235)

Transition probability	Definition	Source	Comments
A	Treatment failure rates: non-OIC (on treatment) to OIC for subsequent cycles (after week 4)	KODIAC 4 and 5 trial data	Base case: • exponential functions (base case) Other type of curves used for extrapolation: • proportional hazard model: • exponential functions • Weibull functions • non-proportional hazard model • lognormal, • log logistic The trial data on which these function were fitted (KODIAC 4 and 5) were only available for naloxegol and placebo patients
B	Proportion of patients who move from OIC to non-OIC (untreated) per cycle Patients who had entered the 'OIC' state either at Week 4 or via transition A were followed until the time when they next became non-OIC	Analysis of the population covered by the marketing authorisation (LIR) patients in the placebo arm of the KODIAC 4 and KODIAC 5 datasets	Placebo data was analysed because the model assumes that patients are not on treatment in the 'OIC' and 'non-OIC (untreated)' states. This is why the same transition B and C estimates were used across the treatments included in the model.
C	Proportion of patients who move from non-OIC (untreated) to OIC per cycle Patients in the non-OIC state were followed until time-to-next OIC state		
D	OIC to non-OIC (on treatment)		Set to zero
E	non-OIC (on treatment) to non-OIC (untreated)		Set to zero

ERG comments

5.10 The ERG indicated that the company's model was generally well presented and reported. It noted that the model structure was based on a

revised definition of response compared with the one used in the clinical studies. Thus, the model was able to use absolute health states rather than health states relative to a baseline situation. The ERG considered the 5-year time horizon to be acceptable.

5.11 The ERG noted that the modelled population was based on the marketing authorisation for naloxegol. However, it questioned whether the trial definition of inadequate response to laxatives (that is, concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of 4 days during the 2 weeks prior to the screening period) reflects clinical practice. It argued that while the effectiveness of some types of laxatives can be reasonably assessed after 4 days (for, example bisacodyl), other types would require a slightly longer period of use before the effectiveness can be fully assessed (for example, lactulose). To assess the impact of this, a clarification request was made to the company to present analysis for patients with inadequate response from at least 2 classes of laxatives for 4 or more days in the 2 weeks prior to study entry or reported unsatisfactory laxation from 1 or more additional laxative class from the sixth month of OIC history prior to screening (known as the 2 x LIR population and used in previous NICE appraisals). However, the company did not consider it necessary to provide this analysis given that the KODIAC trials were not powered to detect statistical significance in the 2 x LIR subgroups and also the analysis presented in its submission was in line with the marketing authorisation, among other reasons.

5.12 The ERG stated that the main weakness of the cost-effectiveness analysis is the definition of the intervention and comparator. It noted that the cost-effectiveness analysis compared naloxegol with placebo based on SBM in the base case, and naloxegol plus bisacodyl with placebo plus bisacodyl based on BM in a scenario analysis. However, the ERG considered the base case analysis (that is, naloxegol without bisacodyl) to be neither clinically relevant nor consistent with the KODIAC 4 and 5 trials in which rescue medication was permitted in all arms. The ERG argued

that the use of naloxegol without rescue medication is implausible in clinical practice considering the SBM observed in the trial could not be seen as being independent from the use of rescue medication in the trial. At the same time, for the analysis including bisacodyl, the ERG indicated that SBM should be the basis for the definition of a response rather than BM. For the comparisons with methylnaltrexone and naloxone-oxycodone, the ERG stated that all the issues regarding the MTC (described in sections 4.16 to 4.19) carry over into the cost-effectiveness analysis, although the impact of the uncertainty is expected to be limited.

5.13 The ERG noted that the hazard ratios used to estimate the transition estimates for methylnaltrexone and naloxone-oxycodone were estimated based on the assumption that non-response after four weeks is likely to be related to the response rate at four weeks. While the ERG agreed that a correlation is likely, it was not convinced that this relation is strictly 1 on 1. It tested this assumption in a sensitivity analysis and concluded that while the assumption is not unreasonable in the absence of any other data, it still leads to uncertainty.

Utilities

5.14 Utility estimates in the economic model were derived from an analysis of KODIAC 4 and KODIAC 5 EQ-5D data, collected at 0, 4 and 12 weeks. These data were used with the Dolan algorithm to derive utility scores. To test the hypothesised treatment and time effects, a repeated measures mixed-effects (RMME) model was run for change in utility from baseline. The model used pooled KODIAC 4 and 5 data, and was run separately for the population covered by the marketing authorisation and population covered by the marketing authorisation on Step 3 opioids populations. The following variables were included in the model: time, treatment, baseline utility, OIC status, and an interaction between treatment and time. In the population covered by the marketing authorisation, a significant impact was identified between change in utility and a time-treatment interaction effect. Given this effect, the economic model was run

using time and treatment-specific utility effects in the base case. The company also presented scenario analyses applying treatment-specific utility only (utility differed between treatments in the non OIC state but was constant over time) and health state-specific utility only (utility was not differentiated between treatments for the non-OIC state). The company's model is constructed so that a treatment-specific and time-specific effect only applies to patients on naloxegol treatment and during the time they are non OIC.

5.15 Trial data collected at 4 weeks for patients on naloxegol, who responded to treatment, were used to estimate the utility of patients in the naloxegol arm in the 'non-OIC (on treatment)' of the model in cycles 1 and 2. Data collected at 12 weeks for patients on naloxegol who responded to treatment, were used to estimate the utility of patients in the naloxegol arm in the 'non-OIC (on treatment)' state of the model in cycles 3 onwards. Pooled data for week 4 and 12 for patients receiving placebo and responding to treatment, were used to estimate the utility of patients in the placebo arm in the 'non-OIC (on treatment)' state, and patients in both the naloxegol and placebo arms in the 'non-OIC (untreated)' state, as the model assumed that patients discontinue active treatment in this state. Pooled data for weeks 4 and 12 for patients on placebo who did not respond to treatment, were used to estimate the utility of patients in both the naloxegol and placebo arms in the 'OIC' state, as the model assumed that patients discontinue active treatment in this state.

5.16 As time- and treatment-dependent utility inputs were only available for naloxegol, a health-state only (non-time- and non-treatment-specific) utility input was estimated for the comparison with subcutaneous methylnaltrexone and naloxone-oxycodone. This was also used in a scenario analysis for the comparison of naloxegol with placebo.

Table 15 Summary of utility inputs (non-treatment-specific) (from *CS table 104 and 106, pg 266-268*)

State	Treatment	Source (OIC status, treatment arm, and time point)	Population covered by the marketing authorisation (all)		Population covered by the marketing authorisation + Step 3 opioids	
			Mean	Std Error	Mean	Std Error
Non-OIC (on treatment) cycles 1 and 2	Naloxegol	Non-OIC, naloxegol 25 mg, 4 weeks	0.620	0.025	0.594	0.030
Non-OIC (on treatment) Cycles 3 onwards		Non-OIC, naloxegol 25 mg, 12 weeks	0.665	0.026	0.679	0.030
Non-OIC (on treatment)	Placebo	Non-OIC, placebo, 4 and 12 weeks pooled	0.613	0.021	0.572	0.027
OIC	Naloxegol and Placebo	OIC, placebo, 4 and 12 weeks pooled	0.553	0.022	0.537	0.027
Non-OIC (no treatment)		Non-OIC, placebo, 4 and 12 weeks pooled	0.613	0.021	0.572	0.027
OIC	SC methyl-naltrexone and naloxone-oxycodone	non-time- and non-treatment-specific	0.564	0.017	0.546	0.021
Non-OIC		non-time- and non-treatment-specific	0.630	0.014	0.610	0.017

5.17 No direct estimates of the impact of adverse events on utility were included in the model. The company stated that its clinicians advised that adverse events were unlikely to have a significant impact on the health-related quality of life. However, it stated that the utility impact from adverse events was captured by treatment-specific utility inputs. In a scenario analysis, the company applied alternative utility values estimated using the Wittrup-Jensen tariff rather than the Dolan algorithm used in the base case. It also presented a separate scenario analysis using the utility values from the published study by Penning van Beest et al. 2010.

ERG comments

5.18 EQ-5D data were available from the clinical studies to inform the utilities used in the model, thus providing good quality evidence for the cost-effectiveness analysis. The ERG commented that the health-related quality of life analysis indicates that the health state non-OIC is too broad to be homogeneous with regards to quality of life. In the current definition only 9 SBMs should occur over a 28 day period to be classified as a responder (move to the non-OIC on treatment state). But patients who have 28 SBM in these 28 days are in the same health state and thus are assumed to have the same quality of life as those with only 9 SBM. This appears clinically implausible in the opinion of the ERG.

5.19 The ERG commented that in the company's base-case analysis, the utility value for the OIC health state was derived from patients treated with placebo, because it was assumed that patients in the OIC state did not receive treatment. Therefore, the ERG considers that health-related quality of life in the OIC state is treatment-independent and that this utility should also be used for the health-state specific utilities used in the comparison with methylnaltrexone and naloxone-oxycodone and in the scenario-analysis with health-state specific utilities (rather than the time and treatment independent values used by the company). Nevertheless, the utility estimated in both patients treated with naloxegol and placebo was larger, thus decreasing the utility difference between OIC and non-OIC. This means that the current ICER for naloxegol in comparison with methylnaltrexone and naloxone-oxycodone is conservative.

5.20 The ERG did not consider the company's scenario analysis using the Wittrup-Jensen tarriff to be relevant because it is not valid to correct for severe health conditions of patients when using utilities to calculate health-related quality of life. In addition, comparisons shown in the Wittrup-Jensen paper between the UK tariff and the Danish tariff shows that the latter is higher for all 5 health states that are reported on.

Resource use estimates

5.21 The company's estimates of resource use associated with managing constipation and adverse events were based on a survey of clinicians. Costs were based on the British National Formulary (BNF), NHS reference costs and the Payment by Results tariff. The treatment and administration costs are presented in table 16.

Table 16 Unit costs for technologies in company's in economic model (2014£)

Items	Naloxegol	Naloxegol + bisacodyl	SC MNTX QAD	OXN	Placebo	Placebo + bisacodyl
Technology cost per pill or vial	£ 1.84 25 mg pill	£ 1.84/ 25 mg Naloxegol pill £ 0.04 / 5 mg bisacodyl pill	£ 21.05/ 12 mg vial	£ 1.51/ 25 mg pill	-	£ 0.04 / 5 mg bisacodyl pill
Technology cost per 4 weeks	£51.52	£51.81	£294.70	£ 125.54	-	£ 0.29
Administration unit cost	-	-	£ 22.48	-	-	-
Administration cost per 4 weeks	-	-	£ 314.75	-	-	-
Total cost per 4 weeks	**£51.52**	**£51.81**	**£609.45**	**£ 125.54**	**£ 0**	**£ 0.29**
MNTX, methylnaltrexone, OXN - naloxone-oxycodone, SC - subcutaneous						

5.22 Laxative medications were incorporated into the company's model in 3 ways.

- Non-OIC (on treatment) health state: No laxative use was included in the 'Non-OIC (on treatment)' state unless it was defined as part of the treatment regimen, in which case laxative costs were included in the unit cost of treatment.
- OIC health state: Laxatives were used upon treatment failure and movement to the 'OIC' state.

- Non-OIC (untreated) health state: Laxatives were used after the resolution of constipation as subsequent prophylaxis).

Other costs for managing constipation (including inpatient care, outpatient care, emergency care, GP visit and consultation, nurse visits, rescue therapy and medical tests) were included in the OIC health state only. These costs were based on the GP survey and estimated to be £31.70 and £371.32 in the base case for the LIR and LIR + step 3 opioids groups respectively. In a sensitivity analysis, the company applied an alternative cost of £371.32 and £1709 for the LIR and LIR + step 3 opioids based on a burden of illness survey.

5.23 The opioid costs included in the model for the analysis of the naloxegol arm compared with naloxone-oxycodone are summarised in table 17. In the 'non-OIC (on treatment)' state, patients receiving naloxone-oxycodone do not incur additional opioid costs, since the opioid oxycodone is a component of naloxone-oxycodone The company applied the adverse events costs to cycle 1 only on the basis that this was not a driver in the model and for simplification.

Table 17 Opioid use costs per cycle (2014 £) (from *CS table 115, pg 285)*

Opioid scenario	OIC	Non OIC (on treatment)[‡§]	Non OIC (untreated)
1. Most commonly prescribed Step 3 opioid, morphine (sustained release and instant release) at an average dose of 50mg per day.	£14.86	£14.86[¶]	£14.86
2. Exclusive use of OXY	£37.51	£37.51[¶]	£37.51

ERG comments

5.24 The ERG noted that resource use estimates in the company's submission were based on a GP survey and burden of illness survey rather than a systematic search of the literature. The ERG commented that the large difference between the GP omnibus survey and the burden of illness study lacked explanation, although it noted that using the estimates from the burden of illness survey in the base case would have resulted in more

favourable results for naloxegol. It also commented that the adverse event calculations were not transparent and therefore added further uncertainty to the cost estimations. However, it noted that sensitivity analyses on adverse events costs had little or no impact on the cost effectiveness results. The ERG stated that a literature search could have addressed the shortcomings of resource utilisation assumptions made in the model.

Company's base-case results and sensitivity analyses (naloxegol versus placebo)

5.25 The company compared the clinical results from the economic analysis with the trial data. The company stated that the responses in the economic analysis were similar in the naloxegol and placebo, respectively to the results observed in the clinical trials.

Table 18 Summary of model results compared with clinical data for the population covered by the marketing authorisation (from *CS table 121, pg 293)*

Outcome	Treatment	Clinical trial ('observed')	Economic analysis ('modelled')
Response rate at 4 weeks	Naloxegol	56.8%†	58.51%‡
	Placebo	36.4%†	39.75%‡

†Response during Weeks 1 to 12 is defined as patients with at least 3 SBMs/week and at least a 1 SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks
‡Response is defined as patients with ≥3 SBMs/week (%) over at least 3 out of past 4 weeks

5.26 In the company's base case analysis (the inputs of which are based on the KODIAC 4 & 5 data), the ICER for naloxegol compared with placebo is £10,849 per QALY gained. However, the company stated that the most clinically relevant comparisons are;

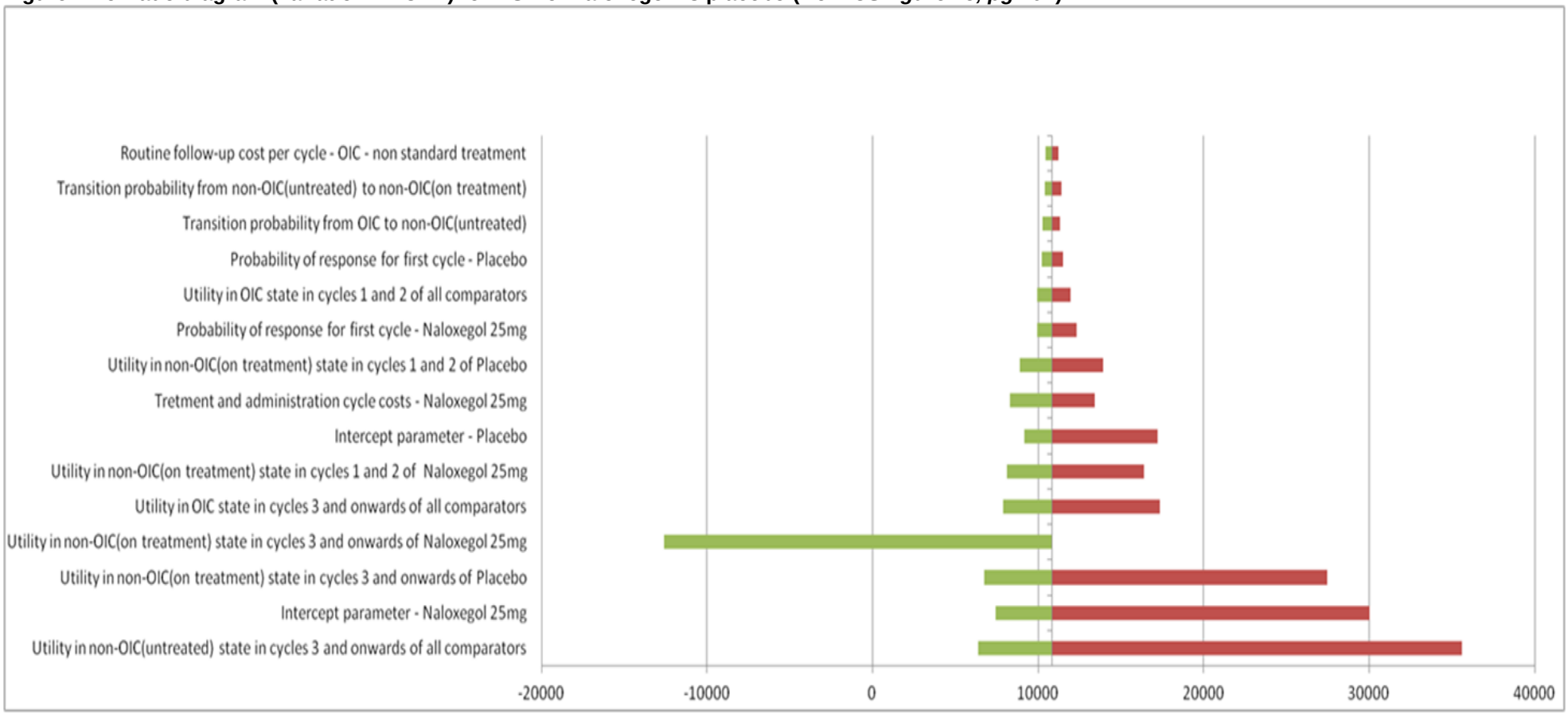
- Naloxegol compared with placebo in combination with bisacodyl (ICER £12,639 per QALY gained)
- Naloxegol plus bisacodyl compared with placebo in combination with bisacodyl (ICER £11,175 per QALY gained)

Table 19 Company's cost effectiveness results (from *CS tables 123-124, 126-127)*

	Naloxegol (+ bisacodyl)	**Placebo (vs Naloxegol) (base case)**	**Placebo + bisacodyl (vs Naloxegol)**	**Placebo + bisacodyl (vs Naloxegol + bisacodyl)**
Total costs	£1,272 (£1,313)	£1,016	£1,000	£1,000
Difference in total costs	N/A	£256	£272	£313
LYG	4.534 (4.534)	4.534	4.534	4.534
LYG difference	N/A	0.000	0.000	0.000
QALYs	2.686 (2.693)	2.663	2.665	2.665
QALY difference	N/A ()	0.024	0.0215	0.028
ICER	N/A ()	**£10,849**	**£12,639**	**£11,175**

5.27 The company conducted a number of one-way sensitivity analyses in order to demonstrate the robustness of the model to changes in the model parameters and assumptions. In nearly all of the sensitivity analyses naloxegol was found to be below £20,000 per QALY gained (see figure 4).

Figure 4 Tornado diagram (variation in ICER) for DSA of naloxegol vs placebo (from *CS figure 25, pg 297*)



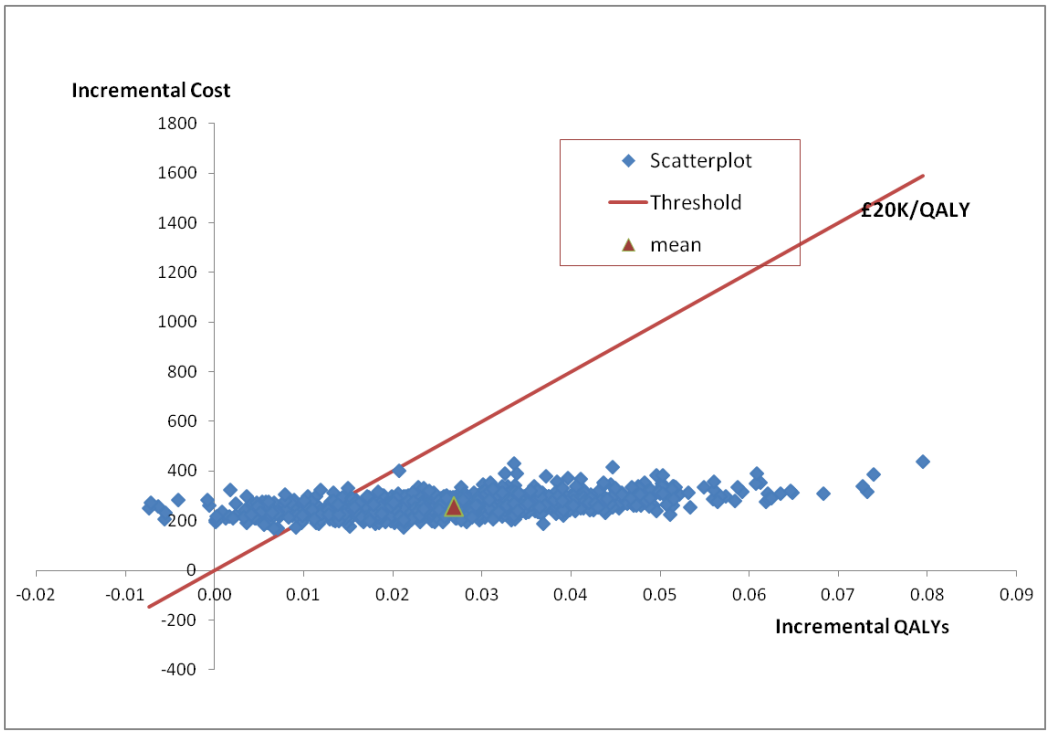


Figure 5 Scatterplot for naloxegol compared with placebo, population covered by the marketing authorisation (10,000 simulations) (*from CS figure 26, pg 298*)

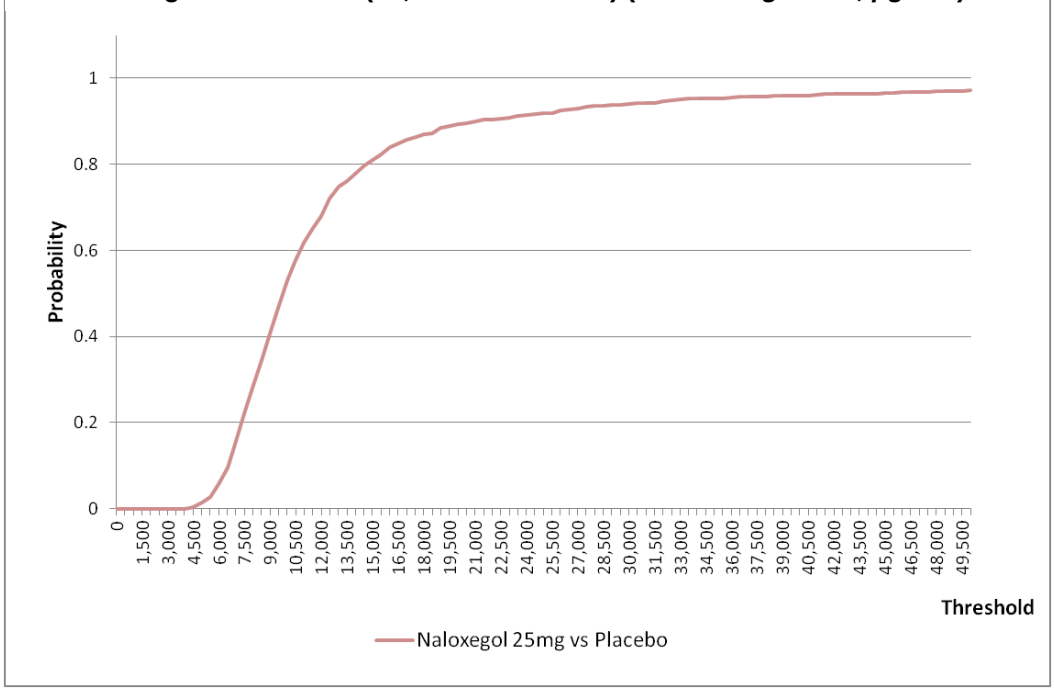


Figure 6 CEAC for naloxegol compared with placebo, population covered by the marketing authorisation (*from CS figure 27, pg 299*)

5.28 The results of the probabilistic sensitivity analysis (PSA) showed that naloxegol has a 91% probability of being cost effective at a maximum

acceptable ICER of £20,000 per QALY gained when compared with placebo. Similarly, the PSA results showed that both naloxegol and naloxegol plus bisacodyl have high probabilities of being cost effective (83% and 87% respectively) at a maximum acceptable ICER of £20, 000 per QALY gained when compared with placebo plus bisacodyl.

5.29 The company assessed structural uncertainty by varying utility input scenarios, the non-laxative costs of managing constipation, using the burden of illness data for resource use costs of managing constipation, and the function used to estimate transition A, D and E. Out of these, 2 scenarios changed the conclusion that the ICER for naloxegol is lower than £20,000 per QALY gained. Using a 12 week time horizon resulted in ICERs of £20,020 for naloxegol compared with placebo and £33,708 for naloxegol compared with placebo plus bisacodyl. When a health-state specific utility input is employed, the ICER for naloxegol increases to £38,921 compared with placebo and £63,423 when compared with placebo plus bisacodyl.

Scenario analyses

Naloxegol versus subcutaneous methylnaltrexone every other day

5.30 Naloxegol generates a greater number of QALYs in this scenario analysis than the base case, as the response data is taken from a different source, the mixed treatment comparison. The results showed that naloxegol dominated methylnaltrexone, that is, naloxegol was more effective and less expensive than methylnaltrexone. The PSA results showed that naloxegol has a 100% probability of being cost effective at a maximum acceptable ICER of £20,000 per QALY gained when compared with methylnaltrexone.

Subgroup analysis

5.31 Subgroup analysis was performed to assess naloxegol for patients who have an inadequate response to laxatives and are taking step 3 opioids.

The proportion of patients in each health state displays a very similar pattern as that observed in the base case population

Table 20 Subgroup results (population covered by the marketing authorisation + Step 3 opioids) (*from CS table 136, pg 319-320)*

Treatment	Comparator	Incremental QALY	Incremental costs (£)	ICER (QALY) (£), treatment vs comparator
Naloxegol	Placebo	0.043	£260	£6,015
Naloxegol	Placebo + rescue bisacodyl	0.042	£280	£6,687
Naloxegol + Rescue laxatives	Placebo + rescue bisacodyl	0.050	£312	£6,219
Naloxegol	SC MNTX QAD	0.006	-£918	Naloxegol Dominant
Naloxegol (morphine)†	OXN	0.0026	-£4,097	Naloxegol Dominant
Naloxegol (OXY) ‡	OXN	0.0026	£78	£30,054

Extrapolation of evidence to patients with cancer and OIC

5.32 The company did not undertake a subgroup analysis on people with cancer who have OIC. However, the company stated that there is no scientific rationale to expect the pharmacodynamic properties of naloxegol to differ in this patient population as the underlying physiology of pain is the same regardless of the underlying cause of that pain. The company stated that pain medications act on the same target receptors regardless of whether the trigger for the pain is cancer or non-cancer. Hence, the extrapolation of the available safety and efficacy data to the treatment of OIC in cancer pain patients is justified (see related consultee comments in section 3.4). The company also stated that people with cancer and OIC would fit within the maximum and minimum ranges for the key model variables which would result in an ICER below £20,000 per QALY gained for naloxegol compared with each comparator.

5.33 The ERG questioned whether the efficacy (as demonstrated in previous studies of methylnaltrexone and naloxone-oxycodone), safety and utility estimates (as they include a time and treatment effect interaction) seen in people with non-cancer pain would be similar for people with cancer pain. The ERG stated that for the subgroup analysis of people with cancer pain, the company maintained the efficacy, adverse effects rates and all transition probabilities (A, B, C, D and E) the same as non-cancer population. As a result, the ERG was unconvinced that the current model is generalisable to cancer patients based on current model inputs & assumptions.

Cost minimisation analysis

5.34 A cost minimisation analysis was conducted to calculate how many months of naloxegol treatment could be given for the cost of one rectal intervention. According to an internal survey by the company, the length of time required to perform a manual evacuation in the community setting is 0.5 hours. Compared with rectal interventions, naloxegol can be provided for 0.68 months for the same cost as a rectal intervention given at the patient's home and for 43.02 months if the rectal intervention is given in an inpatient care hospital setting.

ERG comments

5.35 The ERG commented that the company's cost-effectiveness results were generally robust. The ERG noted that the company's definitions of clinical and safety inputs in the economic model are not fully comparable with the clinical effectiveness section of the submission. In particular, response was defined in the clinical analysis as a measure of absolute constipation status and a minimum change in bowel movements from baseline, whereas the economic analysis focused on absolute constipation status alone. Therefore the response rates from the economic analysis were slightly higher than those observed in the KODIAC trials (see section 5.25). However, the ERG agreed with the changes made for the economic

model, so as to avoid health state definitions that rely on a change from baseline.

5.36 The ERG considered the base case analysis presented by the manufacturer to be limited, and preferred that all comparators be included together to form a full incremental analysis. During clarification, the company was asked to provide a full MTC analysis for the model including placebo, placebo plus bisacodyl and naloxegol plus bisacodyl. The company responded that the MTC analysis requested was not necessary as the KODIAC 4 and 5 trials provide a direct estimate of the comparative efficacy of naloxegol plus bisacodyl versus placebo plus bisacodyl, eliminating a need for this comparator. The ERG commented that by not producing the full MTC analysis, the ICERs presented by the company are incomparable.

5.37 The ERG commented that sensitivity analyses revealed that transition probabilities, costs and adverse events had little effect on the ICER. However, the utility estimates were influential on the cost-effectiveness results. When a health-state specific utility input was used (rather than treatment- and time-dependent utilities), the ICER for naloxegol 25 mg increased to £38,921 per QALY gained compared with placebo and £63,423 per QALY gained when compared with placebo plus bisacodyl. According to the ERG, the most plausible explanation is that the non-OIC (on treatment) state is too broad, thus including a heterogeneous group of patients. However, it is the ERGs view that in the absence of a more refined Markov model, the current approach with treatment specific utilities is a reasonable alternative.

5.38 The ERG commented that the impact of permitted switching between different treatments, which could have an effect on whether naloxegol was placed at a more favourable position in terms of the cost effectiveness analysis in the care pathway, was not addressed in the company's submission. The company indicated that due to lack of comparative efficacy data for conventional laxatives it was impossible for it to confirm

whether or not there are intra-class efficacy differences. But that guidelines on the management of constipation do not recommend within-class switches suggesting that no clearly documented differences exist.

ERG exploratory analyses

5.39 The ERG performed an exploratory base case analysis comparing naloxegol plus bisacodyl with placebo plus bisacodyl. The outcome was spontaneous bowl movement rather than bowel movement used in the company's analysis. The ERG commented that this was the comparison that could be made based on the data from KODIAC 4 and 5. This analysis comparing naloxegol plus bisacodyl with placebo plus bisacodyl increased the ICER to £10,864 per QALY gained.

5.40 The ERG conducted an exploratory sensitivity analysis on response rate as proxy for the 2 x LIR population. The ERG extracted the response rates at 4 weeks from the clinical study reports for KODIAC 4 and 5 for the LIR and 2xLIR populations. Using these data, the ERG calculated a pooled response rate for the 2xLIR population using an adjusted response rate as a proxy for that population. The ERG noted that there was a marked change in the difference in response rate between the LIR and 2xLIR group. The response rate for the LIR group was 20.4% better in the naloxegol arm than the placebo arm, while the response rate in the 2xLIR group was 13.5%. The ERG assumed that all other input parameters would be the same as the company's base case, as there was no 2xLIR data to inform the various transition probabilities in the model. This increased the ICER to £11,406 per QALY gained from £10,849 per QALY gained calculated in the company's base case.

5.41 The ERG conducted threshold analyses on the hazard ratio for the transition from the non-OIC (on treatment) state to the OIC state for methylnaltrexone and naloxone-oxycodone. In the company's model, the hazard ratios for the transition from non-OIC (on treatment) to OIC for methylnaltrexone and naloxone-oxycodone were calculated using the ratio of the 4 week response rate for these 2 comparators relative to the

response rate of naloxegol 25 mg. The ERG found that for any hazard ratios used naloxegol 25 mg dominated methylnaltrexone. For naloxegol plus morphine compared with naloxone-oxycodone, the ERG found that naloxegol dominated naloxone-oxycodone for hazard ratios less than 1.2. For hazard ratios larger than 1.2, naloxone-oxycodone becomes more effective but is also more costly than naloxegol. The ERG compared naloxegol plus oxycodone with naloxone-oxycodone using a hazard ratio of 0.45 which resulted in an ICER of £20,000 per QALY gained, and a hazard ratio of 0.85 resulted in an ICER of £30,000 per QALY gained. The ERG noted that 0.85 was the hazard ratio currently used by the company in its comparison of naloxegol plus oxycodone with naloxone-oxycodone.

5.42 The ERG also undertook an exploratory analysis of structural uncertainty related to curve extrapolation. It changed the parametric form of the time-to-event curve used to estimate the transition probability from non-OIC (on treatment) to OIC, with different combinations of distributions assumed for naloxegol and placebo instead of assuming that the curve for each was the same (as done by the company). The ERG's results showed that various combinations led to ICERs between £8,000 and £13,000 per QALY gained.

5.43 None of the additional economic analysis undertaken by the ERG resulted in central ICERs that varied from the company's results in any meaningful way. Therefore the ERG considered that the company's cost-effectiveness results were generally robust. However, given that the company did not perform a full MTC (see sections 4.16 to 4.19), the ERG stated that the cost-effectiveness results presented are not comparable and that the results of the comparisons with methylnaltrexone and naloxone-oxycodone should be interpreted with care.

Innovation

5.44 The company stated that naloxegol's innovation lies in the combination of its mode of action, as it offers more flexibility in dosing unlike naloxone-oxycodone and it can be used independently of the opioid prescribed.

Further, unlike conventional laxatives, naloxegol requires no up-titration so is therefore simpler to manage for both physicians and patients. The company stated that naloxegol is a step-change to the management of opioid-induced constipation as there is no restriction for its use in specific patient populations, unlike methylnaltrexone and naloxone-oxycodone.

6 Equality issues

6.1 No specific equality and diversity issues were identified in the submissions received. However, 1 clinical expert stated in his submission that although only patients without cancer were enrolled in the KODIAC studies, the results should be applicable to patients with cancer pain as well, given that the problem relates to the opioid use and not the underlying disease requiring the opioid.

7 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002810/WC500179077.pdf