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12th December 2014

Dear Lori,

Thank you for the opportunity to respond to the clarification questions posed by the Evidence Review Group, Kleijnen Systematic Reviews Ltd, regarding the AstraZeneca submission for Moventig (naloxegol) [ID674]. Please find below responses to the clarification questions which I hope will be helpful. In summary AstraZeneca has provided a response to all 82 questions posed however AstraZeneca would like to highlight the following:

- The definition used in previous technology appraisals for inadequate response to laxatives is neither applicable nor clinically relevant to naloxegol and OIC
- The KODIAC ITT data set should not be used to appraise naloxegol as this represents patients outside of the licensed indication and NICE can only make recommendations on the use of the technology for the population in line with the marketing authorisation
- The 2xLIR data is neither warranted nor necessary for this appraisal as a robust clinical and cost effectiveness case has been put forward within the licensed population and a clinically relevant sub population (LIR and Step 3 Opioids) within the naloxegol STA submission
- The MTC is utilised within the naloxegol STA appraisal to allow comparisons to methylnaltrexone and naloxone/oxycodone. However neither are considered appropriate comparators due to the differences in their respective indications, and thus decision problems and limited use in clinical practice

I am also delighted to confirm that the European Commission adopted the decision to grant a marketing authorisation for Moventig on 8th December 2014.

If you require any further information please let me know,

Best regards,

Stuart Mudunkotuwe
AstraZeneca UK Ltd
UK Market Access Manager

Abbreviations

BLRSQ	Baseline Laxative Response Status Questionnaire
BM	Bowel movement
BMI	Body mass index
BNF	British National Formulary
BOI	Burden of illness
CEAC	Cost-effectiveness acceptability curves
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CSBM	Complete spontaneous bowel movement
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Cardiovascular
DAE	Discontinuation due to adverse event
DDW	Digestive Disease Week
DSA	Deterministic sensitivity analysis
DIC	Deviance information criterion
EMA	European Medicines Agency
EQ-5D	EuroQol 5 Dimension
ERG	Evidence Review Group
GI	Gastrointestinal
GP	General practitioner
HCRU	Healthcare resource use
HES	Hospital episodes statistics
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat
LAR	Laxative adequate responder
LIR	Laxative inadequate responder
LUR	Laxative unknown responder
LYG	Life years gained
MACE	Major adverse cardiovascular events
MED	Morphine equivalent dose
MEU	Morphine equivalent dose units
mHS	Modified Himmelsbach scale

MNTX	Methylnaltrexone
MTC	Mixed treatment comparison
N/A	Not applicable
NHS	National Health Service
NKTR-118	Naloxegol
OD	Once daily
OIC	Opioid-induced constipation
OR	Odds ratio
OTC	Over the counter
OXN	Oxycodone plus naloxone
OXY	Oxycodone
PAC-QoL	Patient Assessment of Constipation Quality of Life
PAC-SYM	Patient Assessment of Constipation Symptoms questionnaire
PAMORA	Peripherally acting mu-opioid receptor antagonist
PBAC	Pharmaceutical Benefits Advisory Committee
PK	Pharmacokinetics
PNS	Peripheral nervous system
PP	Per-protocol
PR	Prolonged release
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
QAD	Every other day
QALY(s)	Quality adjusted life year(s)
RCT	Randomised controlled trial
RR	Relative Risk
SAE	Serious adverse event
SBM	Spontaneous bowel movement
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SOC	Standard of care
SmPC	Summary of product characteristics
STA	Single technology appraisal
TEAE	Treatment emergent adverse event

Section A: Clarification on effectiveness data

1. **Please provide an overview of all KODIAC trials, including the study design, details on the PICO and the follow-up period as well as reasons for exclusion from the submission, if applicable.**

The designation of KODIAC to naloxegol studies has been used to simplify the referencing of the studies. It is applicable to all studies conducted following the licensing of naloxegol by AstraZeneca from Nektar Therapeutics. Studies with the internal AstraZeneca study code D3820C000xx can be considered as KODIAC studies with the xx expressed in numbers giving the KODIAC study reference number.

The naloxegol clinical program consisted of:

Phase 1 studies: 14 Phase I studies investigated the biopharmaceutics and clinical pharmacology of naloxegol in 438 volunteers, including 24 subjects with varying degrees of hepatic impairment and 16 subjects with varying degrees of renal impairment. A brief summary of these 14 studies is shown below in Figure 1 and further information is available in the redacted CHMP assessment report. Two of these Phase I studies were included in the NICE submission for naloxegol (D3820C00009: KODIAC 9 and D3820C00010: KODIAC 10) as they contained additional safety data in patients with renal and hepatic impairment respectively. PICO information for these two studies is included in Table 1. The remaining 12 Phase I studies were excluded from the NICE submission as they did not contain efficacy outcomes or relevant safety data to the submission.

Figure 1. Summary of the naloxegol Phase I studies

Clinical Biopharmaceutic and Pharmacology studies	
Relative BA/BE, and food interaction	3 studies (08-PNL-04, D3820C00025* and D3820C00018)
Pharmacokinetic, proof of mechanism and initial tolerability	3 studies (05-IN-0X001**, 07-IN-NX-002 and D3820C00020)
ADME	1 study (D3820C00001)
Pharmacokinetic – intrinsic factors	2 studies (D3820C00009 and D3820C00010)
Pharmacokinetic – extrinsic factors (drug/drug interaction)	4 studies (D3820C00011***, D3820C00012, D3820C00015, and D3820C00032)
Pharmacodynamic (TQT)	1 study (D3820C00014)

Phase II study: a single phase II study was conducted and is included in Table 1 below.

Phase III studies: two pivotal Phase III studies (KODIAC 4 & 5) were conducted as well as two Phase III longer term safety studies (KODIAC 7 & 8). A further Phase III study (KODIAC 6) was initiated but closed prematurely due to recruitment difficulties. Further details on the Phase III studies are outlined in Table 1 below. The recruitment difficulties that led to the closure of KODIAC 6 are discussed in the response to question 5 of this document.

Table 1. KODIAC Trials PICO Summary

KODIAC trial number	Study design	Patient population	Interventions	Comparator(s)	Outcomes
Not assigned a KODIAC number (NCT00600119)	A Phase 2, Double-Blind, Multiple-Dose Escalation Study to Evaluate naloxegol in Patients With Opioid-Induced Constipation (OIC)	Chronic adult pain patients receiving opioid medication for at least 4 weeks and on a stable dose.	Dose escalation of naloxegol, 5 mg, 25 mg, 50 mg and 100 mg	Placebo	Increase in number of spontaneous bowel movements from baseline Dose-response, safety, tolerability, pharmacokinetics, other symptoms of Opioid induced Bowel Dysfunction assessed using the Patient Assessment of Constipation Symptoms (PAC-SYM), QOL, measurements, and maintenance of opioid analgesic effect
KODIAC 4 (identical to study 5 but no overlapping study sites) & KODIAC 5 (identical to study 4 but no overlapping study sites)	Placebo-controlled, double-blind, 12-week efficacy and safety studies of naloxegol 12.5 mg and 25 mg	Chronic adult pain patients receiving opioid medication for at least 4 weeks and on a stable dose.	Naloxegol 12.5 mg and naloxegol 25 mg given orally once a day. Bisacodyl available as rescue medication if no SBM in the previous 72 hours.	Placebo arm. Bisacodyl available as rescue medication if no SBM in the previous 72 hours.	Primary objective: To compare the efficacy of naloxegol 12.5 and 25 mg with placebo in the treatment of patients who have opioid-induced constipation (OIC). Secondary objectives: To compare naloxegol 12.5 and 25 mg with placebo on the daily signs and symptoms associated with OIC (straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and quality of life. Safety objectives: To assess the safety and tolerability of naloxegol 12.5 and 25 mg, when used for the treatment of OIC.
KODIAC 6 (NCT01384292)	A 4 week randomised, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of naloxegol in Relieving Opioid-Induced Constipation (OIC) in Patients With Cancer-Related Pain (part A) There was a 12 week active treatment extension phase (part B)	Adult patients with a histologically or cytologically confirmed neoplasm and with a life expectancy of >3 months who are receiving a stable maintenance opioid regimen for a minimum of 4 weeks prior to screening for cancer-related pain with no anticipated change in opioid dose requirement as a result of disease progression over the	Naloxegol 12.5 mg and naloxegol 25 mg given orally once a day.	Placebo	Primary objective: To compare the efficacy of naloxegol 12.5 mg and 25 mg with placebo in the treatment of opioid-induced constipation (OIC) in pain related to malignancy in a 4-week double-blind study (Part A). Secondary objectives: To compare naloxegol 12.5 mg and 25 mg with placebo on the daily signs and symptoms associated with OIC (degree of straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and overall quality of life over a 4-week double-blind study (Part A) To characterise the maintenance of effect of naloxegol over a 12-week extension (Part B). Safety objectives: To assess the safety and tolerability of naloxegol 12.5 mg and 25 mg, when used for the treatment of OIC.

KODIAC trial number	Study design	Patient population	Interventions	Comparator(s)	Outcomes
		proposed 4-week study period will be eligible to be randomised. The target population must report a history of <3 rescue-free bowel movements/week and at least 1 OIC associated symptom at screening and have a confirmed diagnosis of OIC.			
KODIAC 7	12-week, placebo-controlled, double-blind, rollover safety extension study following Study KODIAC 4	Chronic adult pain patients receiving opioid medication for at least 4 weeks and on a stable dose	Naloxegol 12.5 mg and naloxegol 25 mg given orally once a day. Bisacodyl available as rescue medication if no SBM in the previous 72 hours.	Placebo arm. Bisacodyl available as rescue medication if no SBM in the previous 72 hours.	Primary objective: To compare naloxegol 12.5 and 25 mg with placebo regarding long-term safety and tolerability in the treatment of opioid-induced constipation (OIC) using descriptive statistics. Secondary objectives: To assess the impact of naloxegol 12.5 and 25 mg on symptoms of constipation and quality of life.
KODIAC 8	Randomised, 52-week, open-label, parallel-group, long-term safety study of naloxegol 25 mg with a Usual Care control arm	Chronic adult pain patients receiving opioid medication for at least 4 weeks and on a stable dose 10% of patients rolled over from KODIAC 5 and 7. 90% of patients were enrolled directly into KODIAC 8.	Naloxegol 25 mg given orally once a day	Usual care laxative regimen - for the Usual Care arm, investigators were permitted to choose laxative based constipation treatment according to their best clinical judgment	Primary objective: To assess the safety and tolerability of naloxegol 25 mg. Secondary objectives: To evaluate the long-term safety and tolerability of naloxegol 25 mg compared with Usual Care using descriptive statistics.
KODIAC 9 (NCT01372826)	An Open-Label, Parallel-Group, Phase I Study to Compare the Pharmacokinetics of naloxegol following a Single Dose of naloxegol 25 mg in Subjects With Renal Impairment and	Healthy adult volunteers in four groups according to renal impairment: Groups: 1 (normal) 2 (moderate)	Naloxegol 25 mg	None	Primary Outcome Measures: To assess the pharmacokinetics of a single dose of naloxegol 25 mg by assessment of area under the curve over time (AUC) and assessment of the maximum concentration (Cmax) over 72 hours. Secondary Outcome Measures: To assess the safety and tolerability of naloxegol in subjects with renal impairment and normal

KODIAC trial number	Study design	Patient population	Interventions	Comparator(s)	Outcomes
	Subjects With Normal Renal Function	3 (severe) 4 (End-stage renal disease requiring hemodialysis) Total number of subjects = 32			renal function by assessing adverse events To assess the safety and tolerability of naloxegol in subjects with renal impairment and normal renal function by assessing vital signs To assess the safety and tolerability of naloxegol in subjects with renal impairment and normal renal function by assessing safety blood samples
KODIAC 10 (NCT01392807)	An Open-label, Single-centre Study to Assess the Pharmacokinetics of naloxegol in Patients With Impaired Hepatic Function and Subjects With Normal Hepatic Function Following Administration of a Single Dose of naloxegol 25 mg The follow up period was 15 to 18 days.	Healthy adult volunteers in four groups according to hepatic impairment: Groups: 1 (normal) 2 (mild) 3 (moderate) Total number of subjects = 24	Naloxegol 25 mg	None	Primary Outcome Measures: To assess the pharmacokinetics of a single dose of naloxegol 25 mg by assessment of area under the curve over time (AUC) and maximum concentration (Cmax) Secondary Outcome Measures: To examine the safety and tolerability of a single oral dose of 25 mg naloxegol in patients with impaired hepatic function and in subjects with normal hepatic function by collecting adverse events. To examine the safety and tolerability of a single oral dose of 25 mg naloxegol in patients with impaired hepatic function and in subjects with normal hepatic function by collecting vital signs To examine the safety and tolerability of a single oral dose of 25 mg naloxegol in patients with impaired hepatic function by collecting safety blood samples

2. **Priority request: Please provide additional details on KODIAC 4 and 5.**
   a) **How many patients in each arm of the KODIAC 4 and 5 studies were from the UK and the US?**

   These data are presented in Table 11.2.1.5 of the Clinical Study Report for the respective study and summarised below for the full ITT patient group.

Table 2. Patients recruited into KODIAC 4

Country	Number of patients in study arm (ITT group)		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
United States	208	210	208
United Kingdom	0	0	0
Rest of World*	6	3	6

*Rest of world included: Belgium, Croatia, Czech Republic, Germany, Hungary, Slovakia, Sweden, Spain and Australia.

Table 3. Patients recruited into KODIAC 5

Country	Number of patients in study arm (ITT group)		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
United States	210	211	215
United Kingdom	2	1	1
Rest of World*	20	20	16

*Rest of world included: Belgium, Czech Republic, Spain, Croatia, Hungary and Sweden

   b) **Please specify which laxatives patients have failed previously. Do these include dietary fibre and lubricant agents (mineral oil)?**

   AstraZeneca would like to clarify that the information presented is based on an inadequate response to laxative(s) not “have failed previously.”

   Information on the laxative classes that patients took during the 2 week period prior to the OIC confirmatory period are included in Table 11.1.6.2 (LIR group) of the Clinical Study Report for both KODIAC 4 and 5. These data are summarised below in Tables 4 & 5.

   These data were collected using the Baseline Laxative Response Status Questionnaire (BLRSQ). This was an investigator administered questionnaire and asked questions about use of a medicine within a range of laxative classes, as shown in Tables 4 & 5 below, giving examples of possible drugs and brands within each class. Data was not collected on what specific product(s) was used within any laxative class. Mineral oil was a specific example verbalised to patients under the lubricant laxatives section and is therefore included under this laxative class. Dietary fibre was not provided as an option on the BLRSQ.

Table 4. Laxative classes taken by patients during the 2 week period prior to the OIC confirmatory period in KODIAC 4 – LIR group

Laxative class	Number (%) of patients			
	Placebo	12.5 mg naloxegol	25 mg naloxegol	Total
Stimulants	79 (66.9)	71 (61.7)	67 (57.3)	217 (62.0)
Lubricants	16 (13.6)	10 (8.7)	8 (4.8)	34 (9.7)
Osmotics	0	3 (2.6)	3 (2.6)	6 (1.7
Saline laxatives	15 (12.7)	18 (15.7)	14 (12.0)	47 (13.4)
Stool softeners	32 (27.1)	40 (34.8)	42 (35.9)	114 (32.6)
Polyethylene glycol (PEG)	15 (12.7)	18 (15.7)	29 (24.8)	62 (17.7)
Bulk laxatives	10 (8.5)	9 (7.8)	9 (7.7)	28 (8.0)
Prescription constipation products	1 (0.8)	0	5 (4.3)	6 (1.7)
Prescription OIC products	1 (0.8)	1 (0.9)	2 (1.7)	4 (1.1)

Table 5. Laxative classes taken by patients during the 2 week period prior to the OIC confirmatory period in KODIAC 5 – LIR group

Laxative class	Number (%) of patients			
	Placebo	12.5 mg naloxegol	25 mg naloxegol	Total
Stimulants	60 (49.6)	68 (54.4)	62 (50.0)	190 (51.4)
Lubricants	11 (9.1)	8 (6.4)	11 (8.9)	30 (8.1)
Osmotics	6 (5.0)	8 (6.4)	9 (7.3)	23 (6.2)
Saline laxatives	15 (12.4)	17 (13.6)	15 12.1)	47 (12.7)
Stool softeners	52 (43.0)	39 (31.2)	43 (34.7)	134 (36.2)
Polyethylene glycol (PEG)	17 (14.0)	23 (18.4)	23 (18.5)	63 (17.0)
Bulk laxatives	14 (11.6)	12 (9.6)	11 (8.9)	37 (10.0)
Prescription constipation products	2 (1.7)	5 (4.0)	1 (0.8)	8 (2.2)
Prescription OIC products	2 (1.7)	0	0	2 (0.5)

[redacted]

AstraZeneca would like to clarify that the information presented is based on an inadequate response to laxative(s) not “previously failed.”

For the two week period prior to the OIC confirmation, as discussed in response to part b) of this question, data on drugs within each laxative class was not explicitly collected, only on the use of a drug in a laxative class. Consequently, it is not possible to provide the more granular data requested.

d) Please provide the number of bowel movements (BMs) for each arm in KODIAC-4 and 5, with and without rescue remedy, for the intention-to-treat (ITT), laxative inadequate response (LIR) and inadequate response to 2 laxatives (2xLIR) populations.

The ITT population lies outside of the EC approved indication for naloxegol "*for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s)"* and therefore is not relevant to this appraisal on the grounds that the NICE Committee can only make recommendations on the use of the technology for the population in line with the marketing authorisation.

As outlined in the response to Question 25 contained within this document, AstraZeneca do not believe it is necessary to provide data for 2xLIR patients.

Spontaneous bowel movements

The data for spontaneous bowel movements, bowel movements without rescue medication, are presented in table 11.2.4.2 for the LIR group of the CSR and presented in summary below for baseline, and Weeks 4 and 12.

Table 6. KODIAC 4: mean number of spontaneous bowel movements – LIR group

Treatment arm	Placebo		12.5 mg naloxegol		25 mg naloxegol	
Time point	Mean number of BM's (±SD)	Mean change from baseline (±SD)	Mean number of BM's (±SD))	Mean change from baseline (±SD)	Mean number of BM's (±SD)	Mean change from baseline (±SD)
Baseline	1.3 (0.91)		1.3 (0.88)		1.2 (1.03)	
4 weeks	3.1 (2.60)	1.8 (2.56)	4.0 (2.66)	2.7 (2.75)	4.4 (2.54)	3.2 (2.52)
12 weeks	3.7 (2.95)	2.4 (2.71)	4.2 (2.56)	2.8 (2.65)	4.5 (2.87)	3.3 (2.73)

Table 7. KODIAC 5: mean number of spontaneous bowel movements – LIR group

Treatment arm	Placebo		12.5 mg naloxegol		25 mg naloxegol	
Time point	Mean number of BM's (±SD)	Mean change from baseline (±SD)	Mean number of BM's (±SD))	Mean change from baseline (±SD)	Mean number of BM's (±SD)	Mean change from baseline (±SD)
Baseline	1.4 (0.81)		1.6 (1.23)		1.2 (0.85)	
4 weeks	3.3 (2.74)	1.9 (2.67)	4.1 (2.71)	2.5 (2.75)	4.9 (3.97)	3.7 (4.09)
12 weeks	3.6 (2.49)	2.2 (2.50)	4.3 (2.73)	2.7 (2.95)	5.2 (3.31)	4.0 (3.41)

All bowel movements (including use of rescue medication)

The data for all bowel movements, including those bowel movements experienced within 24 hours of taking rescue medication, are presented below for the LIR patient group.

Table 8. KODIAC 4: mean number of all bowel movements – LIR group

Treatment arm	Placebo		12.5 mg naloxegol		25 mg naloxegol	
Time point	**Mean number of BM's (±SD)**	**Mean change from baseline (±SD)**	**Mean number of BM's (±SD))**	**Mean change from baseline (±SD)**	**Mean number of BM's (±SD)**	**Mean change from baseline (±SD)**
Baseline	2.6 (1.3)		2.4 (0.95)		2.4 (1.13)	
4 weeks	3.8 (2.29)	1.2 (2.34)	4.5 (2.59)	2.1 (2.42)	4.8 (2.24)	2.4 (2.26)
12 weeks	4.3 (2.60)	1.7 (2.51)	4.5 (2.45)	2.1 (2.32)	4.9 (2.42)	2.5 (2.48)

Table 9. KODIAC 5: mean number of all bowel movements – LIR group

Treatment arm	Placebo		12.5 mg naloxegol		25 mg naloxegol	
Time point	**Mean number of BM's (±SD)**	**Mean change from baseline (±SD)**	**Mean number of BM's (±SD))**	**Mean change from baseline (±SD)**	**Mean number of BM's (±SD)**	**Mean change from baseline (±SD)**
Baseline	2.5 (1.07)		2.9 (1.52)		2.5 (1.12)	
4 weeks	4.0 (2.39)	1.5 (2.54)	4.6 (2.48)	1.7 (2.28)	5.3 (3.61)	2.9 (3.53)
12 weeks	4.0 (2.25)	1.5 (2.34)	4.7 (2.38)	1.8 (2.54)	5.4 (3.04)	3.0 (2.96)

e) Please specify how many patients received the maximum dose of bisacodyl in KODIAC 4 and 5 for the ITT, LIR and 2xLIR populations, by treatment arm.

The ITT population lies outside of the EC approved indication for naloxegol "*for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s)"* and therefore is not relevant to this appraisal on the grounds that the NICE Committee can only make recommendations on the use of the technology for the population in line with the marketing authorisation.

As outlined in the response to Question 25 contained within this document, AstraZeneca do not believe it is necessary to provide data for 2xLIR patients.

Per the KODIAC trial protocol bisacodyl 5 mg tablets were provided to all patients to use as rescue medication. If after a minimum of 72 hours, the patient had not experienced a BM, he/she was permitted to take bisacodyl rescue therapy (10 to 15 mg dose, i.e. 2 to 3 bisacodyl tablets at a time). If the patient remained constipated, bisacodyl rescue therapy could be repeated up to 2 additional times, as necessary, each 10 to 15 mg dose separated by 12-hour intervals. Data is presented for the LIR patient group on the number (and %) of

patients who took greater or equal to 15 mg and 30 mg bisacodyl on any given day.

Table 10. KODIAC 4: Number of patients who used ≥15 mg and ≥30 mg doses of bisacodyl - LIR group

Study period	Bisacodyl dose on any given day	Number (%) of patients		
		Placebo	12.5 mg naloxegol	25 mg naloxegol
OIC confirmation period (2 weeks)	≥ 15 mg	60 (50.8)	57 (49.6)	55 (47.0)
	≥ 30 mg	12 (10.2)	7 (6.1)	6 (5.1)
Weeks 1 to 4	≥ 15 mg	53 (44.9)	28 (24.3)	32 (27.4)
	≥ 30 mg	11 (9.3)	9 (7.8)	2 (1.7)
Weeks 1 to 12	≥ 15 mg	62 (52.5)	39 (33.9)	43 (36.8)
	≥ 30 mg	15 (12.7)	11 (9.6)	8 (6.8)

Table 11. KODIAC 5: Number of patients who used ≥15 mg and ≥30 mg of bisacodyl - LIR group

Study period	Bisacodyl dose on any given day	Number (%) of patients		
		Placebo	12.5 mg naloxegol	25 mg naloxegol
OIC confirmation period (2 weeks)	≥ 15 mg	51 (42.1)	60 (48.0)	50 (40.3)
	≥ 30 mg	7 (5.8)	7 (5.6)	6 (4.8)
Weeks 1 to 4	≥ 15 mg	40 (33.1)	38 (30.4)	26 (21.0)
	≥ 30 mg	7 (5.8)	1 (0.8)	2 (1.6)
Weeks 1 to 12	≥ 15 mg	52 (43.0)	44 (35.2)	32 (25.8)
	≥ 30 mg	12 (9.9)	4 (3.2)	3 (2.4)

3. **Please confirm that all references have been correctly referenced. We noticed that references 2 and 3 are missing, i.e. the first reference is (1) followed by (4). Please clarify for example, if this is caused by deleting these references without updating the reference list accordingly?**

   References 2 and 3 appear in section 7.2.2, page 231 of the naloxegol STA submission. The references throughout the naloxegol STA submission have been checked and are all correct.

4. **The following reference was not in the reference pack and should be provided:**
   - **Coyne K, Margolis MK, Wilson H, Thompson C, Chen J. Final report for longitudinal study of patients with opioid-induced constipation (12AST11894/A-12292.333). 2014**

   The reference cited was supplied in the reference pack as Coyne_BOI-report; however AstraZeneca have attached the reference to this document as Coyne_BOI-report.

5. **On page 27, it is described that another study (KODIAC 6) had to be terminated due to "severe recruitment difficulties". Please describe these difficulties in more detail.**

   Outlined below is AstraZeneca's rationale for the recruitment challenges associated with KODIAC 6 resulting in a significantly lower number of patients randomised than originally anticipated (14 patients randomised over 10 months; i.e. <5% of the planned 336 patients).

   • Complex and overly stringent patient entry criteria: specific obstacles included the fact that patients were required to be receiving a stable opioid regimen, have active symptoms of OIC confirmed over a 2-week period prior to enrolment (as defined for the chronic non-cancer pain patient population), and have a performance status of 0, 1, or 2 with a life expectancy of >3 months. In combination with the exclusion criteria (in particular, restrictions on the types of eligible cancers and concomitant chemotherapy), investigators provided feedback that the stringent entry criteria significantly reduced the pool of eligible patients.

   • Limited investigator interest: sites based in the United States reported that:
   - there was either insufficient time and/or staff to conduct the trial due to complexity of the procedures and visits required by the study protocol, or
   - they prioritised therapeutic research protocols over supportive care research protocols, or
   - they were not interested in participating in constipation studies

   • Challenges for participating patients: patient feedback indicated that the required study time, visit schedule, and other study requirements were burdensome, especially for patients with progressive disease or those for whom mobility was limited. Older and frailer patients also reported that the daily eDiary entries were challenging, particularly because the protocol did not allow caregivers to enter data for the patient in the 4-week double-blind phase of the study.

   Additionally, the protocol-mandated OIC confirmation period of 2 weeks required the discontinuation of all laxatives used on an as-needed basis during the 2-week confirmation period, although any ongoing maintenance regimens were allowed to be continued. The complexity of the concomitant laxation guidelines created confusion at sites.

   Lastly, for many patients with cancer who still had other anti-cancer therapeutic options, constipation was seen as a secondary concern. The KODIAC 6 protocol did not allow a change in the patient's chemotherapy or simultaneous participation in another investigational study, and it is unlikely that patients with cancer would choose to participate in an OIC trial that prohibited them from receiving a new or experimental treatment for their cancer over the several months' duration of the

trial including the 2-week OIC confirmation period, 4-week double-blind period, and 12-week extension phase.

6. **Page 28 describes that *"Naloxegol will only be contraindicated in the following patients with cancer pain:***
   - ***Patients with underlying cancer who are at a heightened risk of gastrointestinal (GI) perforation, such as those with;***
     - ***underlying malignancies of the GI tract or peritoneum***
     - ***recurrent or advanced ovarian cancer***
     - ***vascular endothelial growth factor inhibitor treatment"***

   Please provide the evidence for this statement or a draft EPAR if it includes the requisite information.

   Please find attached the redacted CHMP Draft Assessment Report which includes the requisite information.

7. **On page 31 of the submission, the company states "Naloxegol should be prescribed with caution in patients with clinically important disruptions to the blood brain barrier (e.g. advanced Alzheimer's, active multiple sclerosis, CNS metastases, primary brain malignancies etc.)." Can you provide references for this statement? Are data on these groupings captured?**

   Please find attached the redacted CHMP Draft Assessment Report which includes the requisite information.

8. **Priority request: Rectal intervention is included in the scope as a comparator, but has not been included as a comparator in the submission. Please clarify the rationale for the decision not to include this as a comparator.**

   As per page 19 of the original submission "*once all treatment options have been exhausted, patients with OIC may require rectal interventions to alleviate their condition (i.e. suppositories, enema, manual evacuation) which are often unpleasant and distressing*[1]*".* Given this**,** as naloxegol is not intended for use in an acute rescue setting, but rather as a chronic, mechanistic, treatment of OIC, rectal interventions are not considered a relevant comparator - AstraZeneca positions, per the licence indication, naloxegol before rectal interventions considering these an option after naloxegol treatment.

   However, owing to rectal interventions being listed as a comparator in the final scope for this appraisal AstraZeneca has, regardless of this stance, made a comparison. In the absence of robust RCT data enabling an indirect comparison with rectal interventions, a cost minimisation analysis was conducted.

   This analysis calculated how many months of naloxegol treatment could be given for the cost of one rectal intervention. The results of this analysis demonstrated that compared with rectal interventions, naloxegol can be provided for 0.68 months for the same cost as a single rectal intervention given at the patient's home and for 43.02

months if the rectal intervention is given in an inpatient setting. See page 327 of the naloxegol STA submission for further details.

9. **Priority request: Please explain why the definition of 'inadequate response to laxatives' in the submission differs from the definition of 'inadequate response to laxatives' in previous NICE technology appraisals: "Treatment with at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months has failed to provide adequate relief."**

In summary, AstraZeneca for reasons outlined below, believe that the definition used in previous technology appraisals is neither applicable nor relevant to naloxegol and OIC. AstraZeneca believe that this definition should neither be considered nor be applied to the naloxegol STA.

AstraZeneca provide the following rationale for the differences in laxative inadequate response definition used for the purpose of the naloxegol appraisal and that observed in previously published HTAs:

- The final scope for the naloxegol appraisal does not explicitly state the definition cited by the ERG in question 9 as a clinically appropriate population for naloxegol. In addition, the definition quoted is from previous appraisals for lubiprostone [TA318] and prucalopride [TA211] which are not listed in the final scope for the naloxegol appraisal as "Related NICE recommendations and NICE pathways"; indeed the lubiprostone STA cited is only for its appraisal within OIC. As a result, it is AstraZeneca's belief that NICE themselves neither mandated, nor recommended, the use of any past precedent for defining laxative inadequate response for the naloxegol STA.

- The lubiprostone and prucalopride technology appraisals cited are for the treatment of chronic idiopathic constipation (CIC) and chronic constipation, respectively, and not for opioid-induced constipation (OIC). Through scoping for this appraisal, NICE deemed these conditions sufficiently clinically distinct from each other for Single Technology Appraisals to be necessary (e.g. lubiprostone STAs for CIC [TA318] and OIC [ID646]). Therefore, AstraZeneca do not believe these CIC definitions are clinically relevant to the naloxegol appraisal as the medication is licensed exclusively for OIC, which as described in page 33 of the naloxegol STA submission is a unique form of constipation.

  Furthermore, the full recommendations published within the cited appraisals have a two part laxative inadequate response definition which AstraZeneca believes further reduces the clinical relevance to this appraisal;

  - The recommendation for prucalopride [TA211] is *"Treatment with at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months has failed to provide adequate relief"* **and "***when invasive treatment is being considered." (formatting retained from published TAG)*

    And

  - The recommendation for lubiprostone [TA318] is: *Lubiprostone is recommended as a possible treatment for people with chronic idiopathic constipation:*

- *who have previously been treated with 2 different types of laxatives at the highest possible recommended dose, for at least 6 months, but these haven't worked well enough, and*
- *when invasive treatment is being considered*

AstraZeneca believe the use of "2 different types of laxatives" and "haven't worked well enough" would also cause potential for confusion and possibly off label usage if this definition were applied to naloxegol owing to the EC licensed indication. In addition the language differences between TA211 and TA318 eg. *has failed to provide adequate relief and these haven't worked well enough)* demonstrate that there is no consistent definition.

AstraZeneca sponsored market research (see 29 clinican survey and 3 KOLs responses outlined in question 42 (a) indicates that invasive treatment as defined in the lubiprostone STA to include the following: *"outpatient appointment, colonoscopy, stoma surgery, sacral neuromodulation and biofeedback"* would not be treatment options for OIC as, unlike CIC, inherently the cause of the constipation has been diagnosed.

The implication of this two part recommendation is to position lubiprostone and prucalopride as interventions before the use of secondary care resources and, more pertinently, in patients refractory to laxatives. Such a definition is not in line with naloxegol as a chronic treatment to directly target the cause of OIC in the GI tract (see response to question 8 in this document) and more critically not in-line with EC approved indication which enables patients to use naloxegol following an inadequate response to at least one class of laxatives

- In addition, a recommendation stating "for at least 6 months treatment" would pose clear inequality implications for end-of-life patients, of which cancer patients represent a sizeable number, suffering from OIC due to their impacted mortality. This is reinforced by:
  - The British Pain Society who stated during the scoping phase for this appraisal that for any studies in this population a "*suitable study duration should be agreed. It would need to be 3-6 months for cancer pain but longer if chronic benign pain is studied separately*" – See NICE Appendix D for this appraisal.

  [redacted]

  Given this, it is AstraZeneca's belief that in order to prevent any inequality issues, and more critically ensure end of life patients suffering from OIC, where their prognosis is less than six months, are not denied access to a medication that has the potential to improve their quality of life, that the definition cited by the ERG be considered irrelevant to the naloxegol STA

- Further justification is owing to the fact AstraZeneca used the definition of inadequate response to laxatives that formed the EC approved indication for naloxegol and defined in Section 5.1 of the SmPC and cited below:

  - *Definition of laxative inadequate responder: To qualify as LIR, in the two weeks prior to first study visit, patients had to have reported concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the pre study period.*

Owing to this wording within the SmPC and NICE's remit that appraisals "can only make recommendations on the use of the technology for the population in line with the marketing authorisation" AstraZeneca believe it would be inappropriate to use the LIR definitions from the previous appraisals for lubiprostone and prucalopride which do not have the LIR population defined in their respective SmPC's [2]. AstraZeneca believe that unlike TA211 and TA318 where no definition exists within lubisprostone's and prucalopride's SmPC justifying the definition created by NICE of inadequate response to laxatives, this is not the case for the naloxegol STA owing to their being a specific definition in Section 5.1 of the naloxegol SmPC as cited above.

AstraZeneca acknowledge that during the scoping workshop for this appraisal, "It was agreed at the scoping workshop that the definitions of an inadequate response to laxatives from the KODIAC trials do not necessarily follow the criteria for response seen and used in clinical practice; therefore they should not be used to define any subgroups in the scope." However owing to the naloxegol license indication, AstraZeneca believe that it is compulsory to use this LIR definition.

As a result for the rational provided, AstraZeneca used a definition of "inadequate response to laxatives" that differs from previous technology appraisals and strongly believe that the definition cited by the ERG should be considered inappropriate for, and ultimately irrelevant to, the naloxegol STA.

10. On page 47 of the submission, it states that [redacted]". However, the referenced document states that 10 clinicians out of 34 agreed. Please provide an explanation for the statement on page 47.

The statement cited should be amended to the following: *"the largest single proportion of responders (10 of 29, 34%) in a market research survey including 34 participants (5 declined to provide a response to the question) felt that the definition of LIR was a reasonable working definition for this population".*

A full summary of the research findings is included in the original submission if further information is required (see reference pack document titled "Consolidated definition of Laxative Inadequate Response")

11. On page 39 of the submission it states that "For patients who experience severe/persistent/worsening GI adverse events, consideration may be given to reducing the dose of naloxegol to 12.5 mg".

- **What proportion of patients experienced these adverse events in the KODIAC trials, and how many patients had dose reductions because of this or because of other reasons?**

The protocols for KODIAC 4 and 5 did not allow for dose reduction from the 25 mg naloxegol dose to the lower 12.5 mg dose. The only option available for any patient receiving the higher dose that experienced severe/ persistent/ worsening GI adverse events that may have been severe enough to consider

or warrant dose reduction was withdrawal from the studies. The advice regarding dose reduction was included in the naloxegol SmPC during the regulatory review process at the request of the regulators. Details of all adverse events including GI adverse events for the LIR patient group are presented in Table 11.3.2.2.4 of the respective KODIAC 4 & 5 CSRs for patients who had at least 1 AE by System Organ Class and Preferred Term for the treatment period only.

- **Please explain whether this was taken into account in the model and, if not, provide a rationale for this (both in terms of costs and in reduced effectiveness of naloxegol in these patients).**

  The health economic model submitted, per the recommended dose in the naloxegol SmPC, only models naloxegol 25mg. As a result down titration to naloxegol 12.5mg is not accounted for. However as patient discontinuation due to adverse events is accounted for, AstraZeneca do not believe there is a need to model for this scenario including adjusting any costs or naloxegol effectiveness.

12. Please confirm that the LIR population refers to all patients randomised with these characteristics (i.e. inadequate-laxative-response within ITT population).

AstraZeneca confirm that the LIR population refers to all patients randomised with these characteristics.

To qualify as LIR, in the two weeks prior to first study visit patients had to have reported concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the pre study period.

13. Please clarify how long patients need to have been continuously on opioids to be eligible for treatment with laxatives?

In the KODIAC studies patients had to have been on opioids for 4 weeks. This was to ensure stable and efficacious doses had been achieved in the management of the patients underlying pain condition as one of the secondary endpoints was the investigation as to whether or not naloxegol had any impact on analgaesia.
The opioid usage from KODIAC 4 and 5 is presented in Table 10 of the CSR and is summarised in Table 12 below for the ITT group.

Table 12. Continuous Opioid usage from KODIAC 4 and 5

Study	Duration of continuous opioid usage prior to study entry (months)		
	Range	Median	Mean (± SD)
KODIAC 4	1 to 276	24.0	42.8 (44.98)
KODIAC 5	1 to 432	27.0	44.1 (47.43)

Data was not collected in KODIAC 4 and 5 regarding when patients first received laxative therapy (either on prescription or as an OTC purchase). These data would have relied on accurate patient recall, which given the median duration of opioid therapy, may not have been sufficiently reliable to draw any conclusions.

14. Is rectal intervention permitted within the care profile of those defined as laxative intolerant and hence eligible for naloxegol or does the period on treatment start again after rescue medication has been implemented?

AstraZeneca would like to clarify that the definition of LIR does not equate to laxative intolerance, which is a clinically distinct condition. Laxative intolerance was not a term used within the KODIAC Phase III studies. Intolerance is suggestive of the patient experiencing adverse events related to a laxative severe enough to require discontinuation of that laxative regardless of its efficacy. Instead the KODIAC Phase III studies investigated patient sub-group termed laxative inadequate responders, which was defined as patient whom in the two weeks prior to first study visit had reported concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the pre study period.

Rectal intervention was permitted within the care profile of those defined as LIR.

15. Please clarify whether switching within class of laxatives is permitted prior to designation of laxative intolerance. Is it possible that one laxative in the same class as another can be more effective?

AstraZeneca would like to clarify that the definition of LIR does not equate to laxative intolerance, which is a clinically distinct condition. Laxative intolerance was not a term used within the KODIAC Phase III studies. Intolerance is suggestive of the patient experiencing adverse events related to a laxative severe enough to require discontinuation of that laxative regardless of its efficacy. Instead the KODIAC Phase III studies investigated patient sub-group termed laxative inadequate responders which was defined as patient whom in the two weeks prior to first study visit had reported concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the pre study period.

Based on the definition given above, the LIR patients in KODIAC 4 and 5 only needed to have been on one laxative class. It is possible that patients may have been on more than one medicine within the same class however this would not be captured in the information presented in response to question 2 (b) & (c).

Many of the conventional laxatives currently used in clinical practice today were originally licensed in the 1950's and 1960's when the requirement for robust RCT efficacy data did not exist. Consequently for these older laxatives, including senna and bisacodyl, there is very little efficacy data either against placebo or against other laxative drugs. It is therefore not possible to confirm whether or not there are intra-class efficacy differences between differing drugs in the same laxative class. However the guidelines that exist (e.g. NICE Clinical Knowledge Summary on Constipation) on the management of constipation regardless of cause do not recommend within-class switches suggesting that no clearly documented differences exist.

16. **Priority request: On page 37 of the submission, it states: *"…In the absence of RCT data demonstrating the head-to-head efficacy of naloxegol versus laxatives, trial data from KODIAC 4 and 5 comparing spontaneous bowel movements (SBMs) – those BMs that occurred without the need for rescue medication (bisacodyl) in the last 24 hours – with total BMs in the placebo plus rescue bisacodyl arm – those BMs that occurred as a result of rescue bisacodyl – will be used as a proxy for stimulant laxative used PRN. An additional analysis comparing total BMs in the naloxegol plus rescue bisacodyl arm with total BMs in the placebo plus bisacodyl arm will demonstrate the effectiveness of naloxegol when used in combination with stimulant laxative used PRN."* Please clarify the following:**
    a) **Is response according to any bowel movement (BM) used as an outcome for any treatment/treatment arm/comparator?**
    b) **If it is then:**
        - **which treatments/treatment arm/comparator is it used for**
        - **which analyses i.e. for clinical effectiveness, cost effectiveness or both?**
    c) **Is the effectiveness of naloxegol plus bisacodyl estimated using spontaneous bowel movement or BM in the definition of response?**

    Please find below in Table 13 an updated version of Table 86 of the naloxegol STA submission which outlines the cost effectiveness analyses conducted and the outcomes ("End-Point"), including any BM data, used per comparator. AstraZeneca have identified that the original definition of response for OXN provided in Table 86 of the naloxegol STA submission was incorrect. The correct definition is in Table 13 below:

Table 13. Comparators used in the health economic model

Treatment	Comparator	Comments	Source	End-Point	Definition of response
Naloxegol 25 mg	Placebo	Patients not on active therapy	Trial	SBM	≥3 SBMs/ week in 3 of the last 4 weeks
	Placebo + rescue bisacodyl	PRN stimulant used as 2nd line therapy	Trial	SBM for naloxegol, BM for placebo + rescue bisacodyl	≥3 SBMs/ week in 3 of the last 4 weeks (naloxegol 25 mg), ≥3 BMs/ week in 3 of the last 4 weeks (placebo + rescue bisacodyl)
	SC MNTX 12mg QAD	As per scope	MTC	SBM	≥3 SBMs/ week in each of the last 4 weeks
	OXN 59.3mg/29.7mg	As per scope	MTC	CSBM	≥3 CSBMs at week 4
	Rectal Interventions	As per scope	Assumptions	NA	NA
Naloxegol 25 mg + rescue bisacodyl	Placebo + rescue bisacodyl	Comparison using common end-point of BMs	Trial	BM	≥3 BMs/ week in 3 of the last 4 weeks

Abbreviations: BMs, Total Bowel Movements = Defined as all bowel movements, CSBMs, Complete Spontaneous Bowel Movements = Defined as spontaneous bowel movements with completeness of evacuation;

OXN, naloxone-oxycodone; SBMs, Spontaneous Bowel Movements. Defined as a BM without the use of rescue medication administered in the last 24 hours; SC MNTX, subcutaneous methylnaltrexone.

d) Can the company confirm that there is no data on the response to any laxative other than bisacodyl e.g. senna, either in the form of a trial vs. placebo or vs. bisacodyl in a similar population?

Owing to KODIAC 4 & 5 trial protocol, AstraZeneca confirm that in relation to these trials there is no data on the response of laxatives other than bisacodyl as used per protocol.

Please see the responses to Question 17 & 18 for discussion of literature relevant to laxative data.

17. According to page 218, "Senna is the most commonly used stimulant laxative in the UK".

a) Are there any studies comparing the effectiveness of bisacodyl compared with senna?

AstraZeneca is not aware of any studies directly comparing the effectiveness of bisacodyl and senna.

A literature search specifically looking for clinical studies of bisacodyl and senna failed to identify any studies in the treatment of constipation. One clinical study was identified:

Ziegenhagen et al. Senna vs. Bisacodyl in addition to Golytely lavage for colonoscopy preparation - A prospective randomized trial Zeitschrift fur Gastroenterologie 1992; 30:(1):17-19).

This randomised prospective trial was designed to evaluate the effects of different laxatives in a combined preparation regimen for colonoscopy preparation. This study demonstrated that there was no significant difference between bisacodyl and senna.

b) If so, please describe and explain why these studies were not considered relevant by the company?

The only identified study was not in constipation but in colonoscopy preparation and thus was not considered applicable to the naloxegol STA.

18. Priority request: Bisacodyl is used as a proxy for laxatives; therefore, please provide clinical trial data for bisacodyl:

The only relevant literature AstraZeneca was able to locate is the following:

Kienzle-Horn S et al. Efficacy and safety of bisacodyl in the acute treatment of constipation: a double-blind, randomized, placebo-controlled study. Aliment Pharmacol Ther 2006; 23: 1479–1488

a) **What is the relative effectiveness of bisacodyl compared with other laxatives?**

A laxative-specific systematic literature search was run in October 2013 specifically to identify relevant studies assessing laxatives and was conducted and no studies investigating the relative effectiveness of bisacodyl compared to other laxatives in the management of constipation were identified. Please see the response to question 73 for further information regarding this literature search.

b) **Please confirm whether any systematic searches were conducted to identify other trials which could have contributed to indirect and/or mixed treatment comparison (page 214), e.g. laxatives vs. placebo? If none were conducted, please provide a rationale for this approach?**

A systematic search was conducted and included terms for laxatives and placebo. No trials were indentified which could have contributed to the indirect and/or mixed treatment comparison. Please see the response to question 73 for further information regarding this literature search.

19. **Please explain why a "wash-out period" was not reported for the trials? A wash out period and is used in trials to ensure that no latent effect of earlier treatment contaminates the results in a trial situation[3] Please explain if a wash out period was considered to be unfeasible or unwarranted.**

KODIAC 4 and 5 included a 2 week OIC confirmation period during which patients were permitted only to take rescue bisacodyl/enema if they did not experience laxation for 72 hours. This would be considered a washout period for their usual care. Rescue medication was permitted for ethical reasons.

20. **How was "usual care" defined in KODIAC 8 (page 46)?**

Patients randomised to the Usual Care treatment arm followed a laxative treatment regimen for OIC determined by the investigator according to his/her best clinical judgment. For patients randomised to the Usual Care arm, the investigator was advised to treat the patient's OIC as they would usually do, following his/her clinical experience, and using laxative agents that were available for treatment of constipation or OIC in their respective country. The investigator could choose from a broad range of laxatives, including milk of magnesia or magnesium citrate, non-absorbable phosphate, Cascara, Senna, castor oil/mineral oil, Epsom salt, Lactulose, Polyethylene glycol, Docusate, enemas, tegaserod, lubiprostone, prucalopride, prune juice, herbal constipation remedies, and bulk laxatives. However, peripheral mu-opioid antagonists, such as methylnaltrexone and naloxone containing products, were not allowed. The investigator could choose to re-start the laxative that the patient was taking prior to the start of the study if that agent had been effective. The investigator was free to modify the treatment regimen as they saw fit throughout the 52 week duration of the trial. No specific rescue laxative protocol was determined for patients randomised to receive Usual Care.

21. **Priority request: Please provide a list of the 26 studies excluded for section 6.1 (according to figure 2).**

    Please see Appendix 1 of this document.

22. **On page 72, a subpopulation of patients is described as having "an inadequate response from at least 2 classes of laxatives for ≥4 days in the 2 weeks prior to study entry or reported unsatisfactory laxation from ≥1 additional laxative class from the 6 month OIC history prior to screening".**
    a) **Please provide details on length of the period of opioid use for the included trials?**

       The data for the LIR groups for the period of opioid use in KODIAC 4 & 5 are presented in question 13 of this document.

    b) **Explain whether there is a minimal period of opioid use for the eligible population in the trials .If there isn't, please state the reasons.**

       For KODIAC 4, 5 and 8, study patients had to have been on a stable opioid dose between 30 mg and 1,000 mg morphine equivalents for four weeks prior to the 2 week OIC confirmatory period. For KODIAC 7, which was a follow on extension study from KODIAC 4, the prior periods of opioid use was in line with KODIAC 4 with the addition of the time period spent in that study.

    c) **Provide frequency distributions of opioid usage for the trials.**

       In the respective CSR's for KODIAC 4 and 5, the maintenance opioid medications at baseline are presented in Table 11.1.12.2.

       Additional data not presented in the CSR is presented in answer to this question. Opioids have been grouped according to the preferred grouping term for each of the opioids used on study entry and this grouping is shown in Table 14 below.

Table 14. Opioid Grouping Terms in the KODIAC baseline characteristics

Opioid class	Preferred Grouping Term
Codeine	'Codeine' 'codeine + paracetamol' 'dihydrocodeine' 'dihydrocodeine bitartrate'
Oxymorphone	'Oxymorphone' 'oxymorphone hydrochloride'
Methadone	'Methadone' 'methadone hydrochloride'
Oxycodone	'Percodan' 'oxycodone' 'oxycodone hydrochloride' 'oxycodone + paracetamol' 'naloxone + oxycodone'
Hydrocodone	'Hydrocodone' 'hydrocodone + paracetamol'
Morphine	'Morphine' 'morphine sulfate'
Tramadol	'Paracetamol + tramadol' 'tramadol' 'tramadol hydrochloride'
Fentanyl	'Fentanyl' 'fentanyl citrate'
Hydromorphone	'Hydromorphone' 'hydromorphone hydrochloride'

Across KODIAC 4 and 5 there was a total of 9 (1.2%) patients who were receiving either tapentadol (7), pethidine (1) or buprenorphine (1) at baseline and additional data for these patients has not been presented as part of this response owing to the limited n numbers.

Table 15 below presents data for the combined LIR patient population from KODIAC 4 & 5 for each of the preferred grouping terms in relation to the mean dose and range of doses (expressed as morphine equivalent doses [meu]).

Table 15. Opioid mean dose and range of doses for the combined LIR patient population from KODIAC 4 & 5

Preferred grouping term	Placebo			12.5 mg naloxegol			25 mg naloxegol		
	Patient number	Mean dose (± SD) as meu	Range (as meu)	Patient number	Mean dose (± SD) as meu	Range (as meu)	Patient number	Mean dose (± SD) as meu	Range (as meu)
Codeine	4	49 (24)	33 to 83	6	68 (46)	9 to 126	1	36 (0)	36
Oxymorphone	5	298 (215)	109 to 615	9	258 (97)	135 to 375	8	199 (95)	45 to 360
Methadone	19	202 (109)	42 to 420	10	251 (199)	64 to 660	18	261 (140)	52 to 630
Oxycodone	81	167 (138)	15 to 615	77	214 (187)	15 to 989	90	167 (148)	15 to 630
Hydrocodone	77	108 (113)	28 to 480	70	93 (95)	17 to 430	62	106 (106)	23 to 480
Morphine	66	201 (162)	30 to 968	57	176 (206)	30 to 1280	57	182 (135)	30 to 600
Tramadol	37	92 (105)	33 to 607	34	68 (54)	17 to 297	36	78 (54)	17 to 247
Fentanyl	21	314 (147)	90 to 607	24	320 (249)	88 to 1280	19	320 (241)	90 to 1080
Hydromorphone	2	75 (21)	60 to 90	10	91 (76)	1 to 225	9	231 (161)	71 to 510

23. Table 5 lists the *"Naloxegol Phase II"* trial which included *"Adult OIC patients with non-cancer or cancer-related pain"*. However, according to section 10.10.6 *"treatment with opioids for cancer-related pain"* was excluded. In addition, figure 2 lists 5 studies that were excluded due to "malignant pain".

a) Please explain these discrepancies.

b) If cancer-related pain was included, please provide results for this subgroup.

AstraZeneca excluded only those studies that exclusively enrolled malignant pain patients. While the Naloxegol Phase II study enrolled a mixed population, this study ultimately did not contribute to analysis as LIR subgroup data for naloxegol was not available.

24. Table 6 lists one *"relevant non-RCT"*. Please justify the inclusion as the population is outside the scope.

Although KODIAC 16 was the only study identified in the non-RCT systematic review, as noted in section 6.8.1, p.174, it was not considered relevant to the naloxegol STA submission due to being conducted in a paediatric population only which is outside of the EC licensed indication.

25. Priority request: Page 73 lists an additional subgroup (2xLIR). The 2xLIR population is closer to NICE's definition of inadequate responders. Given this, please provide further clarification for why you did not provide the same data for the 2xLIR population as for the LIR population, and the same analyses (meta-analyses, and network MA) and economic model in the submission?

In summary, AstraZeneca believe that NICE's previous definition of inadequate responders is specific to CIC and therefore not clinically appropriate to naloxegol's OIC appraisal, and per the rationale detailed below did not believe the provision of 2xLIR data was warranted or necessary.

AstraZeneca's rationale for not providing 2xLIR data is as follows:

- AstraZeneca deemed the "All LIR" population rather than the 2xLIR patient cohort to be the most clinically relevant to the population listed in the scope as: *"For adults in whom oral laxatives have provided inadequate relief"*. In addition, AstraZeneca has demonstrated that for the "All LIR" population naloxegol is cost-effective at a willingness to pay threshold of <£20,000 in the base case and nearly all sensitivity analyses. Owing to this, it was not considered necessary to provide 2xLIR data when cost & clinical effectiveness has been demonstrated in the broader "All LIR" patient cohort.

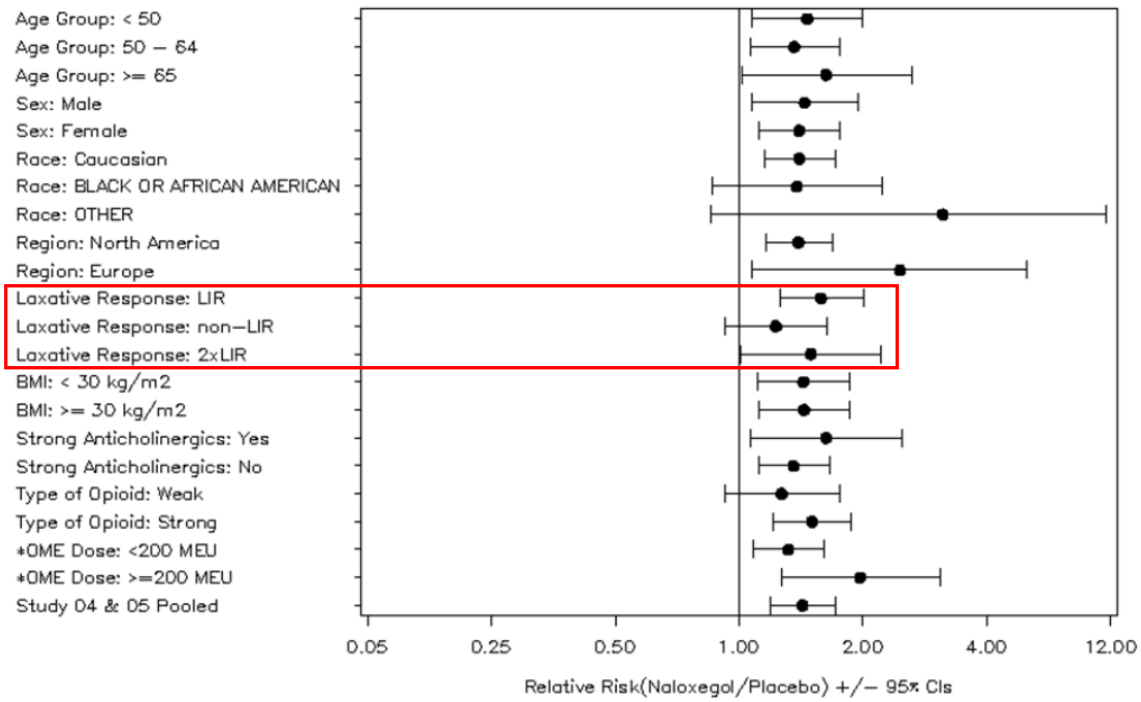
- AstraZeneca proposed 2xLIR as a potential patient population during the scoping workshop for the naloxegol STA in 2013. However, it was agreed during this workshop that *"the population in the scope should remain broad and should not be restricted to people in whom previous treatment with laxatives has failed to provide adequate relief. It was noted that naloxegol may be an appropriate first-line treatment option for some patients (such as those with severe opioid-*

induced constipation) if first line use is permitted in the marketing authorisation". AstraZeneca followed this guidance from NICE, and so focussed on presenting the most robust case possible for clinical and cost-effectiveness within the licensed population for naloxegol

- Furthermore, with regards to robustness of both the clinical and cost-effectiveness data, though 2xLIR was pre-specified in the Phase III KODIAC trials these studies were not powered to detect statistical significance in the 2xLIR sub-group. In KODIAC 4 & 5 there were 99 patients meeting the criteria to qualify as 2xLIR population which equated to 41% of the LIR population in KODIAC 4 & 5. Owing to this, AstraZeneca believes it is more appropriate to focus the submission on the population where greater certainty and confidence in data exists – "All LIR". This can be further reinforced by Figure 2 of the Redacted Draft Assessment Report, provided below, which demonstrates based on the confidence intervals highlighted that it is more appropriate to use the "All LIR" population than the 2xLIR sub-group to make robust clinical & cost-effectiveness arguments as the n number of the 2xLIR dataset would increase the level of uncertainty within the health economic model vs. the all LIR dataset

- Moreover, the comparators listed in the scope do not have data in the 2xLIR population which would make any potential NMA or indirect comparison significantly less robust. *AstraZeneca appreciate this critique can also apply to the LIR population, however this had to be used in the NMA, indirect comparison and health economic model submitted due to the EC approved indication*

Figure 2. Response (naloxegol 25 mg vs placebo) to study drug during Weeks 1 to 12 in subgroups of interest – pooled data, Studies 04 and 05 (ITT)



- Within the naloxegol submission, AstraZeneca proposed the more clinically relevant sub-group of Step 3 opioid patients (see page 44 of the naloxegol STA submission) which in the KODIAC 4 & 5 trials, although a post-hoc analysis,

comprises a larger dataset (n=176, 73% of the LIR population) vs. the 2xLIR cohort (n=99, 41% of the LIR population).

- As per the response to clarification Question 9, AstraZeneca does not believe the NICE definition of inadequate responders applied to lubiprostone and prucalopride was relevant to the naloxegol appraisal; as such its perceived "closeness" to the KODIAC trials 2xLIR sub-population by the ERG is not considered relevant and so further justifying not providing 2xLIR data in the naloxegol submission.

As a result of the rationale provided AstraZeneca did not and does not believe it necessary to provide clinical and cost effectiveness data for the 2xLIR population, as a robust clinical and cost effectiveness case has been put forward within the licensed population and a clinically relevant sub population within the naloxegol STA submission.

26. On page 77, there is a discrepancy between the second bullet point ("5.3%, 9.2%, and 2.5% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively") and the following text ("Discontinuations as a result of adverse events occurred in 5 (4.3%), 11 (9.2%), and 3 (2.5%) patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively."). Please clarify which statement is correct?

The second statement is correct. The second bullet is an error and should read 4.3% not 5.3% for the naloxegol 12.5 mg group.

27. Please provide further details, e.g. frequency count, on the days *"patients had taken more than one laxative class for at least 4 days in the two weeks prior to baseline..."* (Page 78).

Per the response in question 25 of this document, AstraZeneca interpret this question as pertaining to 2xLIR and hence do not believe it is relevant to provide the data requested.

28. Table 39 lists *"History of chronic constipation"* as a key exclusion criterion for the BOI study. Can you please explain why this was done and why this study is still relevant?

The inclusion and exclusion criteria of the BOI study were defined to identify, as robustly as possible, the patients suffering from OIC specifically, and not to identify patients whose constipation was caused by other factors (e.g. CIC). As a result, this study is clinically relevant as it provides data for patients with OIC per the EC licensed indication for naloxegol.

29. Table 189 is entitled *"Profile of Opioid Use for Naloxegol 25mg"* but has *"exclusive use of morphine"* at 100% and exclusive use of oxycodone at 100%. Please provide an explanation for the inclusion of this table and its reported values.

Naloxegol 25 mg was combined with Step 3 opioids when compared with OXN, as OXN's formulation (including a Step 3 opioid, oxycodone) meant that this was the appropriate comparison.

Two opioids were combined with naloxegol 25mg to form this comparison. To provide a like-for-like comparison with OXN, oxycodone was used. To reflect UK prescribing practice, the most commonly prescribed Step 3 opioid – morphine – was used.

The fact that both opioids have exclusive use of 100% is explained by the fact that these numbers describe scenarios run within the model – in the first scenario all opioid use is morphine, in the second all opioid use is oxycodone.

30. EMA states that *"On 25 September 2014 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Moventig, 12.5 mg and 25 mg, film-coated tablet intended for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s)".* Did EMA provide a definition of what was meant by *"an inadequate response to laxative(s)"*? Please provide the definition if possible.

The EC approved indication for naloxegol is:

For the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s)**.** The following definition is included in Section 5.1 of the SmPC:

Definition of laxative inadequate responder:To qualify as LIR, in the two weeks prior to first study visit patients had to have reported concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the pre study period.

Section B: Clarification on Meta-analysis and Mixed Treatment Comparison

31. **Page 127 states that *"Direct meta-analysis of the two included RCTs evaluating methylnaltrexone compared with placebo was not undertaken due to dosing differences (one study of subcutaneous methylnaltrexone and one study of oral methylnaltrexone)".* Please explain why these 2 studies could be combined in the MTC analyses section 6.7.2.**

    Oral and subcutaneous methylnaltrexone were not combined in any of the MTC analyses for AstraZeneca felt it was not clinically appropriate. A more detailed network diagram below has been provided to clarify the specific treatments included in the network.

Figure 3. Network Diagram

*The oxycodone PR treatment in these trials were 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.

32. According to page 127, 2 of the naloxone trials were also excluded due to reporting of results at different timepoints. These studies were evaluated separately. Please explain why these two 4/5-week studies were combined in the MTC analyses in section 6.7.2 and compared with 12-week studies for naloxegol.

Direct meta-analyses were provided in all cases where there were two or more trials available for a treatment comparison in the MTC network for all outcomes with data available. Most of the arms in the MTC network have only one trial (see the more detailed network diagram presented in Q31 above), and so direct meta-analyses could not be conducted for these treatment comparisons. The only treatment comparisons with more than one trial were naloxegol 12.5 mg versus placebo, naloxegol 25 mg versus placebo, and naloxone + oxycodone versus placebo.

On page 127 of the naloxegol STA submission, there is an omission. Arsenault 2014 should be added to the list of naloxone-oxycodone trials contributing to the direct meta-analysis.

33. Priority request: Given the limited number of trials included in the direct comparison meta-analysis (page 128), please provide a rationale for the random effects empirical based methods and present forest plots for all meta-analyses.

Use of a random-effects model was the *a priori* default employed, as the assumption of fixed-effects is a very strong one; the fixed-effects vs random-effects choice is not a matter of choosing Assumption #1 vs Assumption #2, but rather choosing to make an assumption vs not choosing to make one. Except in the case of evidence of small studies having different effect sizes than large studies, or looking for signals for safety issues with rare events, AstraZeneca consider the use of a random-effects model is best as it is more conservative – as the Cochrane guidance states, "The choice between a fixed-effect and a random-effects meta-analysis should never be made on the basis of a statistical test for heterogeneity (Section 9.5.4)." (http://handbook.cochrane.org/)

The forest plots have been modified to show the meta-analysis and Bucher results, each on the same plot with the MTC results. AstraZeneca have provided forest plots for both fixed- and random- effects results. Where no statistical heterogeneity was observed, fixed- and random-effects results are identical for the direct meta-analyses. For the few direct meta-analyses where differences are observed, typically the effect estimates are highly similar, but the credible intervals are narrower with fixed effects; therefore the random effects results are the more conservative estimates. Forest plots can be found attached to this document.

34. Priority request: Table 56 presents *"DIC values for random vs fixed effects models"*. *"Based on the results of the DIC analysis, a random effects model was chosen over a fixed effects model".* Please provide a rationale for choosing the random effects model considering table 56 indicates smaller (i.e. better) DIC values for the fixed effects model.

As above, DIC alone should not determine the choice of the model. AstraZeneca have observed some heterogeneity in certain outcomes. In order to incorporate the heterogeneity assumption in our analyses, AstraZeneca chose a random effects model. The choice of the prior was tested in sensitivity analyses to ensure that it does not impact posterior results.

The results for both the random and fixed effects are presented for completeness. A summary of the Bayesian MTC results for the random and fixed-effects model analysis in the anticipated licensed population and the anticipated licensed population + Step 3 opioids is presented in Table 57 and Table 58 in the naloxegol STA submission**Error! Reference source not found.**. For both the anticipated licensed population and the anticipated licensed population + Step 3 opioids, point estimates for all outcomes assessed were similar for the random and fixed-effects models. However, the credible intervals were slightly wider for the random-effects model compared with the fixed effects model. Given that there were no differences in the results for the random and fixed effects models, a random effects model was deemed to be appropriate in this case.

35. For section 6.7:

a) Did the non-naloxegol studies include the relevant population (anticipated license)? Please define these populations if possible.

The non-naloxegol studies did not include specific sub-groups of the anticipated licensed population, although the non-naloxegol studies may have included LIR patients within the overall OIC populations included. This is explained in section 6.7.4, page 146 of the naloxegol STA submission as follows:

"The review found that only the naloxegol trials were able to provide data in the specific patient populations of interest (i.e. LIR and LIR + Step 3 opioids subgroups). This was possible via custom analysis of the KODIAC 4 and KODIAC 5 Phase III trials, which were designed to provide data for each of the outcomes of interest for the LIR and LIR + Step 3 opioids subgroups. As none of the other trials reported data specifically for the LIR and LIR + Step 3 opioids subgroups, the MTC analysis uses the main enrolled trial populations to inform the analysis as per the pre-specified protocol."

b) **Please provide complete study characteristics for all included studies (by treatment arm) in the MTC: Methodology, see Table 7; Eligibility criteria, see Table 8; Characteristics of patients, see Table 9 and 10; Outcomes, see Table 11; Analyses, see Table 12; Participant flow, see Fig 4 and 5.**

AstraZeneca believe that the tables presented in section 6.7 contain all of the data that would typically be provided to NICE i.e. trial design, population, interventions and severity of OIC (Table 43), study outcomes (Table 45), and study characteristics (Table 47). In addition, NICE were provided with the relevant publications for each of the individual studies included in the MTC analysis.

36. **Section 7.3.1, tables 90 and 92 (MS page 245) show the response rates for naloxegol based on the trial and the MTC. This shows a clear difference. Please confirm that response for the MTC analysis is the same as the model definition of response (as opposed to the clinical effectiveness definition of response)?**

The MTC used common outcomes, between individual comparators. These common outcomes do not exactly correspond to the model definition used for direct trial based comparison or the definition used the clinical effectiveness trails. Please see Table 13 in question 16 of this document for further information.

37. **Priority request: Please provide a full MTC analysis for the model including placebo, placebo plus bisacodyl and naloxegol plus bisacodyl, i.e. please expand the current MTC to include all comparators.**

AstraZeneca do not believe it is required to provide the MTC analysis requested as the KODIAC trials provide a direct estimate of the comparative efficacy of naloxegol plus bisacodyl versus placebo plus bisacodyl, eliminating a need for this comparator.

.

Section C: Clarification on cost-effectiveness data

Please note that any reference to naloxegol in Section C refers to naloxegol 25 mg only as the model only considers this dose.

38. **The economic analysis is based on the premise that the eligible population has failed on a single laxative. This means that switching of treatments (other than to defined comparators or the intervention) is not an issue. [redacted] (as evidenced by comments from clinical experts quoted in the "Consolidated definition of Laxative Inadequate Response (LIR)" document[4]). It would be useful if the company could consider the impact of permitted switching between different treatments which would also help place naloxegol at the most cost-effective position in the care pathway.**

    AstraZeneca would like to clarify that the premise of the economic analysis is based on an inadequate response to laxative(s) not "failed on a single laxative."

    The health economic model submitted is intended for the sole purpose of conforming to the decision problem, the licensed population of naloxegol, and demonstrating cost-effectiveness based on the scope defined by NICE. Based on this objective, modeling permitted switching and most optimum position of naloxegol in the care pathway is not considered necessary, nor the remit of the HTA process of the evaluation of naloxegol within it EC licensed indication. In addition this was not highlighted as a concern in the Decision Problem meeting for this STA.

    Furthermore, another driver for not considering the impact of permitted switching is AstraZeneca's belief (see response to question 18 of this document) that there is insufficient RCT data available for laxatives to develop a robust model with it included.

    As the health economic model is defined by health state rather than laxative status considering the impact of permitted switching is not considered necessary for calculating cost effectiveness within the care pathway because patients can enter the model with any treatment history,assuming they have at least had an inadequate response to laxative(s). Furthermore, AstraZeneca's model has been developed to build upon criticisms of existing health economic models in constipation (see Section 7.2.2, page 230 of the naloxegol STA submission for further detail), close agreement with participants at a clinical advisory board (please see the response to question 42 (a) in this document for further details) and external experts, including payers. Owing to this it is AstraZeneca's belief that the model submitted is more comprehensive than previously published models in OIC, for example by allowing for spontaneous movement between OIC and non-OIC health states if a patient is off treatment.

    Moreover, owing to the scenarios presented in the naloxegol STA submission listed in Table 16 below, AstraZeneca believe that these represent comparisons at different stages in the care pathway. Given that the submission demonstrates naloxegol is cost effective in nearly all scenarios it is believed that it is not a matter of where naloxegol is "most cost-effective in the care pathway" but rather that HCPs can make a personal decision where they feel it would be most appropriate to introduce naloxegol to an individual patient, based on their unique symptomatic profile, and history knowing naloxegol represents an efficacious and cost-effective option from 2nd line - presented in the naloxegol STA submission and listed in Table 16 below.

Table 16. Naloxegol Comparators and position in care pathway

Comparator	Position in care pathway
vs. placebo & bisacodyl	2nd line – comparator used as a proxy for PRN stimulant laxative use
vs. MNTX/OXN	From 2nd line, post inadequate response to at least one laxative class and within respective licensed indication
vs. placebo	Patients not on active therapy
vs. rectal interventions	Laxative refractory patients

39. Priority request: In the CSRs of KODIAC 4 and 5 (pages 104 and 106, respectively) it states: *"A complete analysis of the EQ-5D to calculate QALYs to support health economic analyses for payers is reported separately."* Please provide these reports.

Table 17. EQ-5D data split by individual domains across weeks 4 and 12 and treatment

		Naloxegol			Placebo		
		No problems	Moderate Problems	Severe Problems	No problems	Moderate Problems	Severe Problems
KODIAC 4							
Mobility	Week 0	41.59	57.52	0.88	42.24	57.76	0
	Week 4	46.43	53.57	0	49.56	50.44	0
	Week 12	58.51	41.49	0	45.83	53.13	1.04
Self-care	Week 0	80.53	19.47	0	76.72	23.28	0
	Week 4	82.14	17.86	0	75.22	24.78	0
	Week 12	81.91	18.09	0	79.17	19.79	1.04
Usual ivities	Week 0	38.05	59.29	2.65	35.34	60.34	4.31
	Week 4	41.96	53.57	4.46	41.59	49.56	8.85
	Week 12	43.62	52.13	4.26	38.54	55.21	6.25
Pain	Week 0	3.54	79.65	16.81	6.9	69.83	23.28
	Week 4	7.14	78.57	14.29	12.39	67.26	20.35
	Week 12	13.83	65.96	20.21	11.46	62.5	26.04
Anxiety and depress-ion	Week 0	65.49	33.63	0.88	56.9	39.66	3.45
	Week 4	65.18	33.04	1.79	65.49	27.43	7.08
	Week 12	74.47	22.34	3.19	58.33	35.42	6.25
KODIAC 5							
Mobility	Week 0	43.7	56.3	0	45.3	53.85	0.85
	Week 4	46.96	53.04	0	52.59	47.41	0
	Week 12	56.52	42.39	1.09	46.94	53.06	0
Self-care	Week 0	78.15	21.85	0	83.76	15.38	0.85
	Week 4	78.26	21.74	0	82.76	16.38	0.86
	Week 12	82.61	17.39	0	81.63	18.37	0
Usual activities	Week 0	42.86	52.1	5.04	36.75	58.12	5.13
	Week 4	47.83	47.83	4.35	43.1	51.72	5.17
	Week 12	53.26	42.39	4.35	41.84	55.1	3.06
Pain	Week 0	6.72	69.75	23.53	6.84	73.5	19.66
	Week 4	14.78	65.22	20	12.07	71.55	16.38
	Week 12	21.74	67.39	10.87	11.22	72.45	16.33
Anxiety and depress-ion	Week 0	57.98	33.61	8.4	58.97	37.61	3.42
	Week 4	60	33.04	6.96	60.34	38.79	0.86
	Week 12	76.09	20.65	3.26	57.14	38.78	4.08

Table 18. EQ-5D Visual Analogue Scale data across weeks 4 and 12 and treatment

	Naloxegol			Placebo		
	N	Mean	Standard deviation	N	Mean	Standard deviation
KODIAC 4						
Week 0	**113**	60.6	17.74	116	64.3	18.79
Week 4	**112**	63.6	16.74	113	65.8	19.18
Week 12	**94**	64.5	17.84	96	67.3	18.02
KODIAC 5						
Week 0	119	63.5	18.55	119	63.5	17.17
Week 4	115	64.9	18.97	116	65.0	17.56
Week 12	92	70.0	18.89	98	66.0	17.65

Table 19. EQ-5D utility data across weeks 4 and 12 and response

	OIC			Non OIC		
	N	Mean	Standard deviation	N	Mean	Standard deviation
KODIAC 4 and 5 combined						
Week 4	187	0.567	0.284	226	0.621	0.293
Week 12	124	0.558	0.315	212	0.639	0.289
Week 4 and 12 combined	311	0.564	0.296	438	0.630	0.291

Table 20. EQ-5D utility data across weeks 4 and 12 and treatment

	Naloxegol			Placebo		
	N	Mean	Standard deviation	N	Mean	Standard deviation
KODIAC 4 and 5 combined						
Week 0	232	0.570	0.288	233	0.557	0.295
Week 4	227	0.600	0.283	229	0.587	0.301
Week 12	186	0.646	0.289	194	0.570	0.317
Week 4 and 12 combined	413	0.621	0.286	423	0.579	0.310

Table 21. EQ-5D utility data across weeks 4 and 12, treatment and response

	Naloxegol			Placebo		
	N	Mean	Standard deviation	N	Mean	Standard deviation
OIC status in KODIAC 4 and 5 combined						
Week 4	67	0.571	0.243	120	0.565	0.305
Week 12	43	0.601	0.289	81	0.535	0.328
Week 4 and 12 combined	110	0.583	0.261	201	0.553	0.314
Non OIC status in KODIAC 4 and 5 combined						
Week 4	134	0.620	0.293	92	0.623	0.295
Week 12	123	0.665	0.291	89	0.602	0.284
Week 4 and 12 combined	257	0.642	0.293	181	0.613	0.289

40. On page 23, you state that *"Results are also presented for naloxegol 25 mg plus bisacodyl to demonstrate the cost-effectiveness of naloxegol when used in combination with a stimulant laxative. This scenario is considered most clinically relevant given the multi-factorial nature of constipation and clinical guidance obtained via an advisory board and AstraZeneca sponsored research"*.

a) Please clarify how this clinical guidance was identified (consensus, majority etc.)?

The question of whether or not OIC was a distinct condition in patients or confounded by other factors such as comorbidity, lifestyle and physical factors (ability to take tablets, etc) was discussed at the advisory board held on October 14th 2014. The advisory board panel felt that confounding factors needed to be taken into account when considering treatment options. The consensus was that it may be necessary to add a stimulant laxative to naloxegol to achieve maximum resolution of the constipation (for more details see OIC ad board report in the reference pack for the naloxegol STA submission).

b) In light of this statement, please comment on the most appropriate choice for the base case in the cost-effectiveness model? The statement suggests that naloxegol 25 mg vs. placebo is not the best choice for the base case.

Comparison of naloxegol to placebo was selected as the base case as it best reflects the design and endpoints of the KODIAC 4 and 5 trials. The base case is then built on to consider the use of bisacodyl in first the placebo arm and secondly the naloxegol arm. This conveys in a logical way how the comparisons within the KODIAC 4 and 5 trials are made and the respective ICERs of these comparisons.

However, though AstraZeneca believe that it was most appropriate to ground the health economic model with least unknowns/assumptions (the base case comparison of naloxegol 25mg vs placebo), owing to the "*multi-factorial nature of constipation and clinical guidance obtained via an advisory board and AstraZeneca sponsored research"* it remains the case that AstraZeneca maintain the most clinically relevant

scenario would be the naloxegol 25mg plus bisacodyl comparison to placebo plus bisacodyl.

41. **Priority request: In the section 6.5.4, page 88, table 17 and page 89, table 18 shows that the response rate of naloxegol differs between LIR and non-LIR patients, while the response rate of placebo is more or less similar between LIR and non-LIR patients. Consequently, the efficacy of naloxegol differs between the LIR and non-LIR population. In anticipation of the license, the cost-effectiveness analysis is restricted to the LIR population. Please provide the inputs and results of the cost-effectiveness analyses for all patients with OIC irrespective of response to previous laxatives as well as for the 2xLIR patients.**

    The population "All patients with OIC irrespective of response to previous laxatives" (i.e. the KODIAC ITT population) lies outside of the EC approved indication for naloxegol "*for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s)"* and therefore is not relevant to this appraisal on the grounds that the NICE Committee can only make recommendations on the use of the technology for the population in line with the marketing authorisation."

    As outlined in the response to Question 25 contained within this document, AstraZeneca do not believe it is necessary to provide data for 2xLIR patients.

42. **Priority request: Please provide the details of the methodology of all surveys conducted to obtain resource use data, populate and/or validate the model (GP Omnibus, 29 clinician, Advisory board, 3 KOLs) & BOI data in appendices? Please consider the following sub-questions when providing your answers:**
    a) **Specific information about the advisory meeting as described in section 10.24 is missing. Please provide more detailed information about the questions asked during the advisory meeting held on July 16-17, 2014.**

    <u>BOI Data</u>

    See Section 3 of Coyne et al BOI Study Report

    <u>Advisory Baord</u>

    The advisory board held between July 16th & 17th 2013 was presented with the approached adopted for the cost-effectiveness model, focusing on the following topics
    - Model structure
    - Natural history of OIC
    - Long-term response rates
    - Discontinuation
    - AEs
    - Cost inputs and resource use
    - Utility

The advisory board discussed both the methodological and clinical validity of the approaches adopted. No predetermined list of questions was specified that can be shared here.

Among the issues discussed by the advisory board, and referenced in the submission, are:

- Transient nature of OIC experience (Section 7.2.2)
- The use of non-response as proxy for treatment discontinuation (Section 7.2.8)
- Clinical plausibility of Transition A extrapolations (Section 7.3.7)
- Utility impact of adverse events (Section 7.4.8) and OIC (Section 7.4.10)

[redacted]

See Appendix 14 of original submission

[redacted]

[redacted]

3 KOLs

[redacted]

b) Please specify if experts participated in more than one survey/meeting(s)?

All research described in the response to Part A of question 42 with the exception of the July 16th & 17th Advisory Board and the 3 KOLs was anonymous. Owing to this AstraZeneca cannot definitively ascertain the true extent of any overlap. However, as per best practice for market research robust research screening was in place to try and ensure minimal overlap (e.g. asking if participants had a conflict of interest or had recently participated in research for opioid-induced constipation) but this is self-reported and so inherently relies on participant honesty.

43. Section 7.2.2 on page 237: it is mentioned that "Patients in the 'OIC' and 'non-OIC (untreated)' states use rescue therapy (e.g. laxatives) as required, with the laxative use in the 'non-OIC (untreated)' state being prophylactic." Please clarify how the laxative use in non-OIC (untreated) can be rescue therapy and prophylactic at the same time.

Patients in the "OIC" state use rescue therapy (e.g. laxatives) as required. Patients in the "non-OIC" (untreated) state would typically use laxatives prophylactically. However, due to the nature of the definition of non-OIC, where you require to have ≥ 3 SBMs in at least 3 out of the last 4 weeks, a patient could be deemed as being non-OIC but at that particular week could be experiencing a reduced number of SBMs (<3) and would be using laxatives as rescue therapy.

44. Priority request: Please explain why throughout the health economic analyses data have been pooled from KODIAC 4 and 5 rather than performing meta-analyses.

KODIAC 4 and 5 trials had identical study designs and inclusion/exclusion criteria and similar populations, drawn from non-overlapping centres. Because of this

AstraZeneca feels pooling the studies is the most efficient and reliable way to model the data in order to generate greater precision in the health economic analyses.

45. Please specify the y-axis (i.e. the measure of differences) on the graph in section 7.3.7 on page 252, figure 17, and explain the inclusion (in the key of the chart) of non-OIC (on treatment) patients (late responders) in this comparison:

The y-axis is the difference between naloxegol and placebo of the proportion of patients transitioning between health states at a given cycle.

A 5 year time horizon was selected as this was thought to reflect the upper end of the period of persistence of opioid use (Table 89 of the original submission). Running the model suggests that it reaches a steady state within this period, as demonstrated in Figure 17 of the original submission. This figure shows the difference over time of the proportion of patients transitioning from the different health states when comparing naloxegol with placebo. After 36 cycles or 3 years there are only a few patients transitioning and at 67 cycles or nearly 5 years there are no patients left transitioning. This shows that after 3 years the model stabilises.

46. In section 7.3.7, please provide diagnostic plots (cumulative log-hazard) with both treatment groups in one plot. Please explain why the same parametric function was chosen for naloxegol and placebo and provide the results of the statistical tests (or graphs) that justify the assumption of proportional hazards in the health economic model.

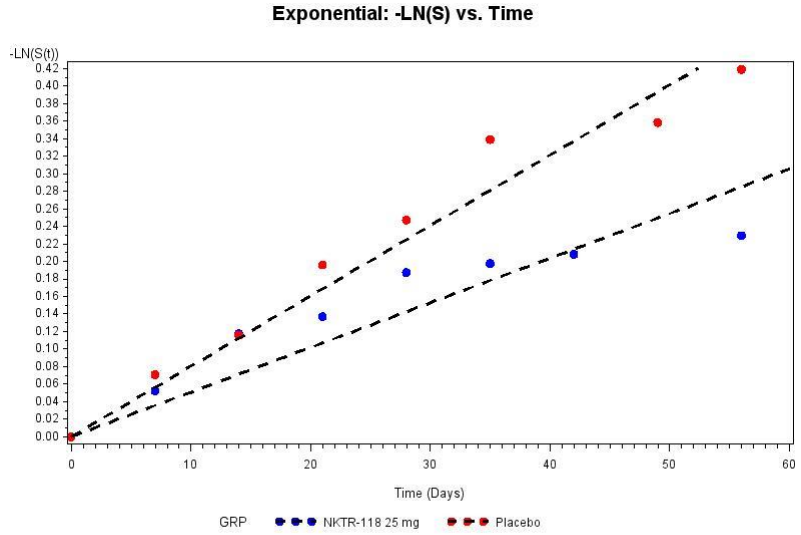
Diagnostic plots (cumulative hazard and log-hazard) with all treatment groups in one plot are provided below in Figure 4.

The choice to use the same type of function when modelling naloxegol and placebo was taken as it corresponded with DSU guidelines on survival analysis (reference 107 in the submission), which states that:

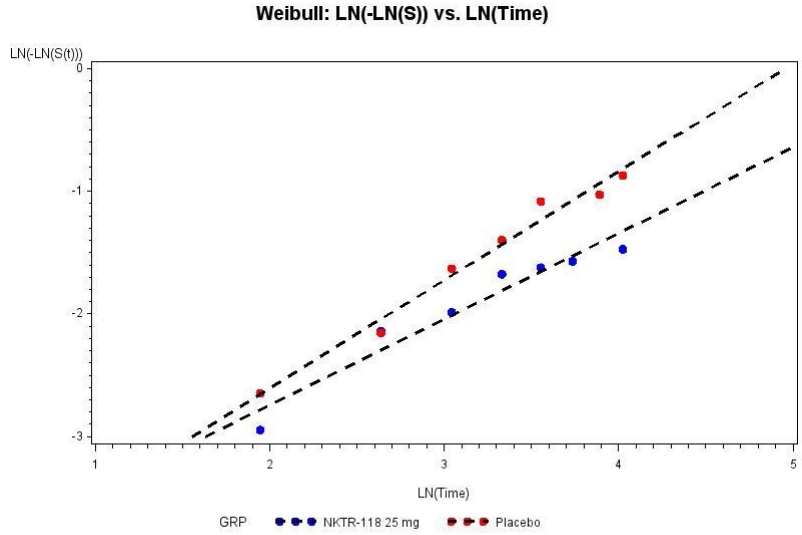
Where parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model, that is if a Weibull model is fitted to one treatment arm a Weibull should also be fitted to the other treatment arm. This allows a two dimensional treatment effect in that the shape and scale parameters can both differ between treatment arms, but does not allow the modelled survival for each treatment arm to follow drastically different distributions (pg 39-40).

It is important to note, however, that separate functions were generated for naloxegol and placebo populations, and AstraZeneca did not thus require the assumption of proportional hazard for the naloxegol and placebo comparison. The assumption of proportional hazards was applied to estimate the functions used to extrapolate OIC status for other comparator treatments (MNTX and OXN) for which there is no individual level data available to AstraZeneca. Thus, it was not possible to perform statistical analysis to support this assumption.

Figure 4. Cumulative Hazard and Log Hazard Diagnostic Plots for both naloxegol and placebo



Regression Equation:
lnst(GRP:NKTR-118 25 mg) = 0 + 0.005092*TIMEDY
lnst(GRP:Placebo) = 0 + 0.008029*TIMEDY



Regression Equation:
lnlnst(GRP:NKTR-118 25 mg) = -4.142514 + 0.699877*lnt
lnlnst(GRP:Placebo) = -4.370484 + 0.882245*lnt

47. In section 7.3.7, please provide more detail about the procedure to get to the per-cycle probabilities and whether the face-validity of these probabilities been checked with clinical experts.

Per cycle probabilities for all transitions A, B, and C are based on analysis of pooled KODIAC 4 & 5 trial data. For transition A, the best fitting statistical function was used to estimate transition probabilities, and for transitions B and C, constant probabilities were assumed.

These resulting functions showing changes in OIC-state status over time were shared with clinicians during an advisory board (see section 10.24 of the submission). The clinicians were able to validate the principle underlying the functions – for instance, that OIC status is variable and patients move between OIC and non-OIC status over time. However, they were uncertain about the precise magnitude of the probabilities that should be used to describe this variability. Consequently, multiple scenarios were run to explore the uncertainty in the transition probabilities employed in the model.

48. Please provide the following reference as referenced in section 7.4.2, page 264 of the submission:

- **Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and Wellness Survey. J Opioid Manag. 2009 May-Jun;5(3):137-44.**

  The reference is attached to this document

49. Please provide more information about the differences in quality of life between patients with and without OIC as this is not described in the poster by Annunziata et al.[5]

The study sample for the patient population reported in Annunziata et al. 2006 poster (attached to this document) is the same as that reported in the Bell 2009 reference (attached to this document). Among the total survey population (n=2,430), patients with OIC were found to have poorer scores on both the physical and mental components of the SF-8 Health Survey, compared to those without OIC. Full details can be seen in the text on page 5, Figure 3, Figure 4 of the Bell 2009 reference.

50. Priority request: Different definitions of OIC status have been used in the trial and in the model. Please clarify which definition was used to define OIC in the context of the utility analyses.

The model definition of OIC status was used to generate estimate of utility in the health states. Specifically, the following definitions were used to derive OIC and non-OIC status:

- *OIC: In the assessment "Week n", where "n" ranged between 4 and 12 inclusive, if any of the 2 observations in a 4-week rolling period (Weeks n-3, n-2, n-1, and n) were reported as SBM<3 subject was considered OIC.*
- *Non-OIC: In the assessment "Week n", where "n" ranged between 4 and 12 inclusive, if at least 3 out of 4 observations in a 4-week rolling period (Weeks n-3, n-2, n-1, and n) were reported as SBM≥3 subject was considered non-OIC.*

This 4-week rolling back definition was used to derive OIC and non-OIC status at Weeks 4, 5, 6, 7, 8, 9, 10, 11, and 12.

51. Priority request: The distinction in utilities between treatment and time is based upon an analysis using the change in utility score as the dependent variable (Table 103, page 266). Since the economic model does not specifically incorporate the change in utility, but the utility values itself, please provide a rerun of the analysis, now using absolute utility rather than change in utility as the dependent variable.

The analysis was not run for absolute utility, as the conventional approach to modelling longitudinal data is to use change from baseline score as the dependent variable while adjusting for each subject's baseline score. This adjustment ensures that each subject's randomly varying starting point (or intercept) is accounted for in the regression model. As a result, AstraZeneca do not believe that is it necessary to provide a rerun of the analysis using absolute utility.

52. The random mixed effect model includes OIC as an independent variable. Please clarify at what time point this OIC status was measured.

OIC status was derived as a time-dependent variable and could move between different statuses (i.e. OIC/non-OIC) at weeks 4 and 12. This type of time-dependent predictor setup allows the regression model to capture fluctuations among states and assess overall differences between OIC and non-OIC status over the follow-up.

53. Priority request: Please provide more details regarding the model selection as seen in table 103, e.g.

a) How was this model selected and which covariance structure was assumed?

Potential predictors for this model included time (weeks), age, gender, race, body mass index (BMI), duration of opioid use, treatment, baseline utility, and OIC status. At the initial stage, each of the variables listed above were examined in univariate regression models to assess the statistical significance of their association with outcome. Coefficients with a p-value of 0.1 or below were considered indicative of an association. A first multivariate model was then fitted by including the predictors identified in the previous step. This model was then trimmed down to retain only the significant/important variables. To ensure that AstraZeneca did not miss any clinically significant variables, AstraZeneca allowed key variables (e.g. study week and treatment) back into the trimmed multivariate model and re-assessed their significance.

A repeated measures mixed-effects (RMME) model (i.e. random intercept model) with unstructured covariance matrix structure was used to predict the change from baseline in utility score over time.

b) Were other interactions included?

Interaction of treatment with OIC status was additionally tested. No statistically significant results were observed.

c) Please also show the results including all interaction terms.

Table 22. Interaction Terms - LIR population

Solution for Fixed Effects								
Effect	**Visit**	**Treatment**	**OICStatus**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept				0.2938	0.03007	412	9.77	<.0001
Baseline score				-0.5050	0.03811	307	-13.25	<.0001
Treatment		Naloxegol		-0.01171	0.03472	307	-0.34	0.7362
Treatment		Placebo		0	.	.	.	.
Visit	Week 12			-0.02303	0.02113	307	-1.09	0.2765
Visit	Week 4			0	.	.	.	.
OIC status			nOIC	0.05305	0.02745	307	1.93	0.0542
OIC status			OIC	0	.	.	.	.
Treatment*Visit	Week 12	Naloxegol		0.06852	0.03015	307	2.27	0.0237
Treatment*Visit	Week 4	Naloxegol		0	.	.	.	.
Treatment*Visit	Week 12	Placebo		0	.	.	.	.
Treatment*Visit	Week 4	Placebo		0	.	.	.	.
Treatment*Status		Naloxegol	nOIC	-0.00366	0.04105	307	-0.09	0.9291
Treatment*Status		Naloxegol	OIC	0	.	.	.	.
Treatment*Status		Placebo	nOIC	0	.	.	.	.
Treatment*Status		Placebo	OIC	0	.	.	.	.

Table 23. Interaction Terms - LIR + Step 3 Opioid

Solution for Fixed Effects								
Effect	**Visit**	**Treatment**	**OICStatus**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept				0.2556	0.03611	289	7.08	<.0001
Baseline score				-0.4826	0.04443	214	-10.86	<.0001
Treatment		Naloxegol		0.009970	0.04329	214	0.23	0.8181
Treatment		Placebo		0	.	.	.	.
Visit	Week 12			-0.01638	0.02674	214	-0.61	0.5408
Visit	Week 4			0	.	.	.	.
OIC status			nOIC	0.05119	0.03336	214	1.53	0.1264
OIC status			OIC	0	.	.	.	.
Treatment*Visit	Week 12	Naloxegol		0.06162	0.03780	214	1.63	0.1045
Treatment*Visit	Week 4	Naloxegol		0	.	.	.	.
Treatment*Visit	Week 12	Placebo		0	.	.	.	.
Treatment*Visit	Week 4	Placebo		0	.	.	.	.
Treatment*Status		Naloxegol	nOIC	0.007174	0.05051	214	0.14	0.8872
Treatment*Status		Naloxegol	OIC	0	.	.	.	.
Treatment*Status		Placebo	nOIC	0	.	.	.	.
Treatment*Status		Placebo	OIC	0	.	.	.	.

An additional interaction effect of treatment and OIC status was tested in the models provided in Table 103 for both anticipated licensed population and anticipated licensed population + Step 3 opioids. The results did not yield any significant deviations from the estimates and p-values presented in the final models. The interaction term was consistently highly non-significant in both models and was therefore not included in the final model.

d) Additionally, can you please provide a test of the selected model versus a model without interactions?

The full model, excluding interactions is provided in the tables below.

Table 24. Utility regression analysis, all predictors (excluding interaction terms), LIR population, fixed effects

Effect		Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		0.3361	0.08020	402	4.19	<.0001
Baseline utility		-0.5085	0.03940	309	-12.90	<.0001
Time	Week 12 vs week 4	0.01025	0.01513	309	0.68	0.4986
Treatment	Nal 25 vs placebo	0.01797	0.02283	309	0.79	0.4319
OIC status	Non-OIC vs OIC	0.05178	0.02070	309	2.50	0.0129
Age		-0.00043	0.000995	309	-0.44	0.6634
Sex	Female v male	0.009934	0.02346	309	0.42	0.6723
Race	American Indian or Alaska native vs White	0.02698	0.2197	309	0.12	0.9023
Race	Asian vs White	0.1779	0.1274	309	1.40	0.1637
Race	Black or African American vs White	0.04059	0.03264	309	1.24	0.2147
Race	Other vs White	-0.02192	0.1033	309	-0.21	0.8322
Baseline BMI		-0.00142	0.001562	309	-0.91	0.3651
Duration of opioid use		-0.00004	0.000248	309	-0.17	0.8667

Table 25. Utility regression analysis, all predictors (excluding interaction terms), LIR population on step 3 opioids, fixed effects

Effect		*Estimate*	*Standard Error*	*DF*	*t Value*	*Pr > |t|*
Intercept		0.3029	0.09906	280	3.06	0.0024
Baseline utility		-0.4857	0.04610	216	-10.53	<.0001
Time	Week 12 vs week 4	0.01339	0.01893	216	0.71	0.4804
Treatment	Nal 25 vs placebo	0.04236	0.02757	216	1.54	0.1259
OIC status	Non-OIC vs OIC	0.05222	0.02542	216	2.05	0.0411
Age		-0.00007	0.001206	216	-0.06	0.9529
Sex	Female v male	0.009958	0.02795	216	0.36	0.7220
Race	American Indian or Alaska native vs White	0.05624	0.2210	216	0.25	0.7993
Race	Asian vs White	0.03405	0.2212	216	0.15	0.8778
Race	Black or African American vs White	0.02547	0.04581	216	0.56	0.5788
Race	Other vs White	-0.08321	0.1282	216	-0.65	0.5169
Baseline BMI		-0.00191	0.001929	216	-0.99	0.3239
Duration of opioid use		-0.00012	0.000289	216	-0.40	0.6862

54. Table 106 describes non-treatment specific inputs for OIC and non-OIC. Please explain why the utility of the OIC state is different to the utility of the OIC state as reported in Table 104 and 105. Please specify for table 106 the source in a similar way as in table 104 and 105.

The OIC utility estimate reported in Table 106 is based on pooled naloxegol and placebo data. The OIC utility estimate reported in Tables 104 and 105 is based on patients only in the placebo arm in the OIC state. A source column was added to Table 106 below to further clarify this point.

Table 26: Summary of utility inputs (non-treatment-specific, Dolan tariff)

State	Source (treatment arm, data point)	Anticipated licensed population (all)		Anticipated licensed population + Step 3 opioids	
		Mean	SE	Mean	SE
OIC	Naloxegol 25 mg and placebo, 4 and 12 weeks pooled	0.564	0.017	0.546	0.021
Non-OIC	Naloxegol 25 mg and placebo, 4 and 12 weeks pooled	0.630	0.014	0.610	0.017

Abbreviations: OIC, opioid-induced constipation; SE, standard error.

55. An alternative tariff has been used in a scenario analysis (MS page 269) with the argument that the underlying condition might cause patients to be in the worst health state and that the HRQOL is also evaluated without an additional decrement of being in the worst health state. Two questions arise with this assumption:

a) Patients with OIC almost certain have an underlying condition which influence HRQOL. The exclusion of the effect of this underlying condition means that only a specific aspect of HRQOL is measured instead of an overall assessment of HRQOL. Since the goal is to have a generic assessment of HRQOL including comorbidities and side effects, please further justify the rationale for using this alternative tariff.

The analysis provided is a sensitivity analysis only and was provided on the recommendation of a health economic expert reviewing AstraZeneca's model.

Due to the nature of the underlying condition experienced by patients suffering from OIC it was considered the emphasis of the generic tariff of EQ-5D for the UK, the Dolan tariff, on the dimension for pain and discomfort might have masked the effect of naloxegol. Owing to this, AstraZeneca looked at an alternative tariff to test this assumption, as a sensitivity analysis.

b) The Wittrup-Jensen tariff is a Danish tariff and within their study five health states were explicitly compared using the Danish and UK tariff. It was shown that in all these five health states, the Danish tariff resulted in larger utilities. Please provide the justification for why this tariff could be used in the UK population.

The analysis provided is a sensitivity analysis only and was provided on the recommendation of a health economic expert reviewing AstraZeneca's model.

AstraZeneca agree that the Danish tariff has not been validated for the UK population and acknowledge that it provides higher utility values, although at an incremental level, the difference between health state values would be more important to assess the impact on the model. However, the Wittrup-Jensen

tariff is used purely as a sensitivity analysis to investigate the point raised in the reponse to part (a) of this question and show further robustness of the cost-effectiveness estimate.

56. **Table 109 shows the results of quality of life estimated from the literature. The quality of life is separately reported for OIC and non-OIC. However, the definition of OIC differs from the definition used in the economic evaluation. In the study of Penning van Beest et al.3OIC is defined according to patient responses regarding constipation and the use of laxatives. As it is therefore questionable whether the OIC group of this study is comparable with the OIC group in the economic evaluation, please provide more justification for using the utility of this study in a scenario analysis.**

    AstraZeneca agree with this critique regarding the use of the Penning-van Beest3 estimates in the model. AstraZeneca have included a critique in the naloxegol STA submission (Page 269 of the naloxegol STA submission).

    The utility scenario based on Penning-van Beest et al. 3 study was only performed for completeness purposes. AstraZeneca would not propose favouring these inputs over those in the base case which is based on using EQ-5D data collected directly from KODIAC 4 & 5.

57. **Inclusion criteria of the systematic review of health-related quality of life data state that studies were restricted to patients with OIC. Please provide evidence that the quality of life in chronic constipation patients is different from the quality of life in OIC patients? If there is no difference, including studies evaluating quality of life in chronic constipation patients may increase the evidence base regarding quality of life, since only 6 studies were included in the review of HRQOL.**

    The inclusion criteria reflect the scope of the submission, which is patients with OIC. AstraZeneca, therefore, believe that the 6 included studies are the most appropriate. Furthermore, as highlighted in Question 55a, in restricting the search to OIC only, it ensures that underlying co-morbidities (i.e. this underlying causes requiring opioid use) have been controlled for as much as possible.

58. **Section 7.4.7 states that the utility inputs in the model were broadly similar to the utility values derived from the literature search, though it seems that the utility values used as inputs are consistently larger than the utility values in the literature. Please explain why these values should be considered as broadly similar.**

The literature search of published utility values returned a range of values for both the OIC and non-OIC states. Whilst some of these values differed considerably to those derived from the KODIAC trials (most notably the utility values reported by Penning-van Beest[3], and Van der Linden 2008[4] were considerably lower for patients in the OIC state than those reported in the KODIAC trials), other studies, such as Dunlop, 2012[5], returned values that were more similar.

The differences in utility values for patients with OIC/constipation observed by Penning-van Beest and Van der Linden may be due to the populations of these studies, which include patients with advanced illness, which is in contrast to the KODIAC trials, therefore resulting in utility values that were higher than those in the published literature. In fact, the KODIAC trials reported a much smaller difference in utility values between the OIC and non-OIC health states than is seen in the literature and so the use of these values in the economic model can be viewed as a conservative estimate of naloxegol's effectiveness, in terms of its impact on HRQL. A scenario analysis was completed using literature based estimates (Section 7.7.9, Table 134 of the naloxegol STA submission) which results in lower ICERs than in the base case, therefore use of slightly higher utility values may be considered conservative.

59. **In section 7.4.8, it is stated that the utility impact of AEs is captured by treatment-specific utility inputs. However, treatment-specific utility inputs were only used in the comparison of naloxegol with placebo (+ bisacodyl). Please explain why no utility impact of AEs was assumed in the comparison of naloxegol versus MNTX and OXN.**

No data was available for the utility decrements associated with AEs. Thus, these were captured by using treatment-specific utility inputs where these were available. These were not available for MNTX and OXN, and so the comparison with these treatments excluded AE utility decrements.

The Advisory Board held on July 16-17, 2013 concluded that adverse events are unlikely to have a significant impact on any of the ICERs.

60. **Priority request: Section 7.5.3 "No systematic search for resource use was completed. Clinicians were consulted to estimate the resource use associated with the management of constipation and associated adverse events for use in the economic model". Please explain why no search was conducted and why other professional groups, like nurses were not consulted.**

A specific systematic search was not conducted as these searches generally do not return data that are relevant to the healthcare setting in England and Wales. It was therefore felt that a more accurate estimate would be obtained by consulting clinicians, and AstraZeneca duly consulted a thousand GPs. As GPs are the owners

of patients' care it was felt that they were best placed to monitor cross-discipline care budgets, as opposed to nurses who are only responsible for one aspect of a patient's care. Thus it is AstraZeneca's opinion that consultation with clinicians provided the best estimates of resource use associated with the management of OIC and its associated adverse events.

61. Section 7.5.4 Please provide all the details regarding the clinical experts as requested in the template.

[redacted]

103. Page 287 (section 7.5.7). The mean expected cost per AE was calculated as the weighted average of patients with Grade 3/4 events (and the corresponding unit cost) and patients with Grade 1/2 events (at a cost of £0). These costs were then summated to provide an overall total AE costs. However, no data is provided regarding the rates at which Grade 3/4 events and Grade 1/2 events occur to track the calculations. Please provide these data.

The rates of adverse events and serious adverse events in the LIR population in KODIAC 4 and 5 trials combined are shown below. Table 27 considers the treatment period; weeks 1-12.

Table 27. Occurrence of adverse events in KODIAC 4 and 5 combined, weeks 1-12 (LIR Population)

Occurrence of adverse events in KODIAC 4 and 5 combined		Naloxegol	Placebo
Week 1-4	N	241	238
	Any AE	122	82
	Any SAE* (Grade 3 or 4)	3	3
Weeks 5-12	N	216	223
	Any AE	69	71
	Any SAE* (Grade 3 or 4)	5	8
Weeks 1-12	N	241	238
	Any AE	151	116
	Any SAE* (Grade 3 or 4)	8	10

*As adverse events were not classified according to nomenclature Grade 3 or 4, for the purposes of the health economic model submitted any SAE was considered to correspond to Grade 3 or 4 on a 1:1 basis.

104. Priority Request: Section 7.6.2. In the DSA, parameters are varied by ± 20%. However, the reported range could in reality be much larger or smaller for each parameter when confidence intervals (CI) are taken into account. Please provide a DSA with ranges based on 95% CI (instead of ± 20%).

Where 95% confidence intervals are available for model inputs, Table 28 below reports ICERs based on these estimates for the Naloxegol 25 mg vs placebo for the LIR patient population.

Before interpreting the results in Table 28, please note that the approach of varying OIC utility independently, without corresponding changes in the utility associated with non-OIC (on treatment) or non-OIC (untreated), should be treated with caution. By ignoring the correlations between these utility variables, the model may evaluate a scenario where utility associated with OIC may exceed those associated with improved health states, which is unrealistic in clinical terms.

Table 28: DSA results based on upper 95% CI and lower 95% CI input values, where available for parameter inputs (Naloxegol vs placebo, LIR population)

Parameter	Input values			ICER-QALY		
	Base case	Upper 95% CI	Lower 95% CI	Base case	Upper 95% CI	Lower 95% CI
Nal 25mg response for first cycle (week 0-4)	58.51%	64.73%	52.29%	£10,849	£10,321	£11,526
Placebo response for first cycle (week 0-4)	39.75%	45.95%	33.54%	£10,849	£11,371	£10,354
Nal 25mg: Transition A intercept	5.474	5.874	5.073	£10,849	£9,023	£14,085
Placebo: Transition A intercept	4.897	5.289	4.505	£10,849	£12,379	£9,930
Transition B	28.98%	37.34%	20.61%	£10,849	£11,523	£9,983
Transition C	20.94%	31.60%	10.29%	£10,849	£9,825	£
AE frequency / cycle, Nal 25mg	0.526	0.674	0.377	£10,849	£11,017	£10,680
AE frequency / cycle, Placebo	0.360	0.407	0.313	£10,849	£10,807	£10,890
Utility: OIC – cycles 1 & 2	0.553	0.596	0.510	£10,849	£11,255	£10,471
Utility: OIC – cycles 1 & 2– cycles 3+	0.553	0.596	0.510	£10,849	£12,697	£9,471
Utility, non-OIC (on treatment), Nal 25mg – cycles 1-2	0.620	0.669	0.571	£10,849	£9,567	£12,527
Utility, non-OIC (on treatment), Nal 25mg – cycles 3+	0.665	0.716	0.614	£10,849	£6,332	£37,863
Utility, non-OIC (on treatment), Placebo – cycles 1-2	0.613	0.654	0.572	£10,849	£11,717	£10,100
Utility, non-OIC (on treatment), Nal 25mg – cycles 3+	0.613	0.654	0.572	£10,849	£13,599	£9,024
Utility: Non-OIC (untreated) – cycles 1-2	0.613	0.654	0.572	£10,849	£10,888	£10,810
Utility: Non-OIC (untreated) – cycles 3+	0.613	0.654	0.572	£10,849	£14,137	£8,802

105. In section 7.7.2, figure 23 shows the number of patients in each health state over time for naloxegol. Was the assumption that all patients will be off naloxegol after 30 cycles verified by clinical experts?

It was not assumed that all patients would be off naloxegol after 30 cycles. This was the prediction of the model. This outcome was not validated with clinicians, as:

1. The corresponding changes in OIC status were validated with clinicians (see response to question 47)
2. The treatment discontinuations outcome were partly an artefact of the model assumption that patients would not go back onto naloxegol once they had discontinued

106. Sections 7.7.5 & 7.7.6(pages 297 and 298 of the MS): Could you please provide reasons why total costs of naloxegol (25mg) were £1,202 (table 122) and the same costs were £1,272 (table 123)? Furthermore, these differences in reporting are reflected on incremental cost differences as £185 and £256, respectively.

AstraZeneca confirm that the total cost of naloxegol in Table 122 and Table 123 should be £1,272.

107. Section 7.7.9 on page 312, table 132: Resource use of costs of managing constipation (in LIR population) indicates that differences in the GP omnibus survey (which was used in the base case) and BOI data (which was used in the scenario analyses) was 10 fold. Could you please explain the rationale of using GP omnibus survey values in the base case rather than the BOI? For example, which study provides a good proxy for quantification of costs of managing constipation in LIR population in the model, especially when clinical practice in the UK is considered?

The GP Omnibus results were used as the base case as AstraZeneca utilised the most conservative assumptions available for resource use. These cost estimates represent the lowest end of the cost range identified. Higher resource cost estimates would lower the ICER, and in certain scenarios result in naloxegol leading to an overall reduction in cost whilst increasing health benefit.

AstraZeneca believe that the GP Omnibus survey is sufficiently robust as the 1,000 UK based GPs surveyed accurately represent UK clinical practice and their responses were based on patients who have had an inadequate response to laxative(s) only owing to the phrasing of the questions included in the survey. Please see question 61 for further description of the research and the reference pack titled: AZN055205938 GP Omnibus - Chronic pain and OIC research (Draft) for examples of the questions included in the survey.

108. Section 7.7.9: Please provide the methodology on GP omnibus survey, as it is not included in any of the appendices.

Please see the response for question 61 in this document.

109. Section 7.8.1: The methods used to externally validate the model are very limited.

a) Did experts validate the face validity of the results?

There were no data sources against which the predictions of the model (e.g. changes in OIC status) could be externally validated. In lieu of this data two groups of experts were consulted:

a. Clinicians were consulted during an advisory board meeting (see the response to question 47 in this document for further details)
b. 3 expert health economists provided ongoing feedback on the model

Despite this validation, there is still uncertainty in, for instance, long-term OIC status. Consequently, significant scenario analysis was undertaken to explore the impact of this uncertainty.

b) Please provide a report about the technical validation that was performed externally.

An assessment of the technical validation of the economic model was undertaken by a senior modelling expert at a vendor company. The vendor's assessment report is attached.

In addition AstraZeneca collected the feedback of three independent external experts over time. However owing to this feedback being provided over different mediums (e.g. telephone), it is not possible to provide a technical report of their feedback.

110. Section 10.10.6 on page 383. Was a language restriction applied in the screening of the cost-effectiveness studies?

Yes, non-English language publications were excluded.

111. Section 10.25, table 183: Distribution of adverse events by treatment arm. Please specify the grade of listed adverse events in this table.

Table 183 shows the relative frequency of these six adverse events (sum to 100) across all grades of adverse event.

112. Section 10.28, appendix 26: Calculation of average age of cancer pain patients in the model was 72 years which was derived using data from the Office for National Statistics (ONS) for registrations of newly diagnosed cancer cases in England. On page 218: section 6.10.4, the mean age of cancer patients was indicated to be 70 years. Please provide clarification regarding the mean age of cancer patients used in the model.

In section 6.10.4, estimating the mean age of cancer patients to be 70 years is derived from personal communication from a clinician while the calculation of average age of cancer pain patients used as an input in the sensitivity analysis on Page 218 of the naloxegol STA submission is derived from data provided by the Office for National Statistics (ONS). The personal communication and the national data indicate a very similar age and AstraZeneca used the ONS value owing to it being considered the more robust, reliable, and nationally representative data source.

Section D: Literature searches

113. Priority request: On page 47 you state that the systematic review conducted in October 2013 was an update to an existing 2008 Cochrane review, but provide no reference. Please confirm if the review you are referring to is:

- **McNicol ED, Boyce D, Schumann R, Carr DB. Mu-opioid antagonists for opioid-induced bowel dysfunction. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006332. DOI: 10.1002/14651858.CD006332.pub2. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006332.pub2/abstract**

AstraZeneca confirm this is the correct citation

114. Priority request: According to page 47, "Laxatives were not included in this update as there was a lack of recent data and head to head studies versus naloxegol identified in the initial searches. It was therefore considered unlikely that any new data for laxatives would be available". Please provide more details justifying this approach.

The original Cochrane review did not include any terms for laxatives. This search was updated with laxative terms, without date restrictions to specifically search for relevant trials of laxatives (as described in the answer to Q75 below). The purpose of this search was to identify studies that compared two laxatives to each other, or a laxative versus placebo (as trials of a laxative versus a pharmaceutical treatment of interest would have been captured by the initial search). When this laxative specific search was conducted only one randomised trial was identified (Freedman 1997[7], which evaluated polyethylene glycol plus electrolytes vs lactulose) and it did not report any outcomes consistent with the other trials evaluated in the MTC, and could not be included in the analyses. Given this finding, when the August 2014 update specific to UK comparators was conducted, it was not considered necessary to continue searching for laxative/laxative vs placebo trials.

115. Priority request: Please confirm if the searches reported in section 6.8 (non-RCT) and linked section 10.6 were also screened to identify papers of interest to other sections i.e. RCTs and Adverse Events.

The searches reported in section 6.8 and 10.6 were not screened for papers of interest to other sections (i.e. RCTs and adverse events). However, two out the three full text studies that were excluded at second pass were RCTs. These were KODIAC 8 (long-term safety and tolerability of naloxegol in patients with OIC) and Webster 2013 (A phase 2, double-blind, randomised, placebo-controlled dose-escalation study to evaluate the efficacy, safety and tolerability of naloxegol in patients with opioid-induced constipation).[6] Both of these studies were already included elsewhere in the submission.

116. Priority request: Please confirm that the strategies reported in section 10.2 are the correct searches as they do not appear to match the search flow depicted on page 53.
If these are the correct searches:

a) Please provide clarification as to what the searches in 10.2 intended to retrieve and any additional strategies used for identifying papers on the required comparators for sections 6.1 and 6.7

b) Page 47 mentions a range of searches used to inform this review, including update searches for the 2008 Cochrane review. The searches detailed in appendix 10.2 do not appear to match all those detailed on page 47. Please provide all relevant strategies.

AstraZeneca confirm that there was an error in section 10.2, Appendix 2, as the search strategies used to identify RCTs were not fully represented in section 10.2, Appendix 2 of the naloxegol STA submission.
To identify relevant RCT evidence for the appraisal, three literature searches were run:

1. An update to the 2008 Cochrane Collaboration review, which was run in September 2012 initially and updated in October 2013 to identify relevant studies for all interventions of interest excluding laxatives as laxatives were not included in the Cochrane review.
2. A laxative-specific search run in October 2013 specifically to identify relevant studies assessing laxatives. These searches were designed to identify placebo-controlled trials of laxatives that were not identified as part of the original Cochrane review or the update of that review. Therefore, no date restrictions were applied to this search.
3. An update to the October 2013 systematic review conducted on August 21, 2014 to identify any recent studies relevant to the UK market that were also in line with the final scope of the current submission. The interventions included in the updated searches were methylnaltrexone and naloxone-oxycodone. Due to a lack of recent data identified in the 2013 searches, laxatives were not included in this update.

In addition to these searches, any papers meeting our inclusion criteria for OIC identified in the original Cochrane review were included in the review. Ultimately, three papers from the Cochrane review met the criteria for our review in OIC.

In error, appendix 10.2 only included the laxative-specific searches run in October 2013 (#2 above).

The key search strings and number of hits are presented below for the searches run in September 2012 and October 2013 to identify studies for all treatments of interest excluding laxatives (#1 above).

The search strings for the update conducted in August 2014 (#3 above) were identical to those presented below with the exception that the only intervention terms included were those relevant to two interventions: methylnaltrexone and naloxone-oxycodone. While line-by-line search yields were not documented during this search update, the total number of citations identified in the update were 181 in Embase, 66 in Cochrane, and 60 in Medline.

As stated on page 47 of the naloxegol STA submission submitted, a broad search was carried out in October 2013 (#1 & #2 above) to capture interventions used in

different markets including mu-receptor opioid antagonists, non-selective opioid antagonists, peripherally acting mu-opioid receptor antagonists (PAMORA), prokinetic 5HT4 receptor agonists, secretagogues, peptide agonists of guanylate cyclase-C receptors, laxatives, and other interventions such as ALKS 37 and bevenopran. Specific inclusion and exclusion criteria were then applied to the abstracts identified in order to include only interventions relevant to the UK and the scope of this appraisal (i.e. naloxegol, methylnaltrexone, naloxone-oxycodone and laxatives).

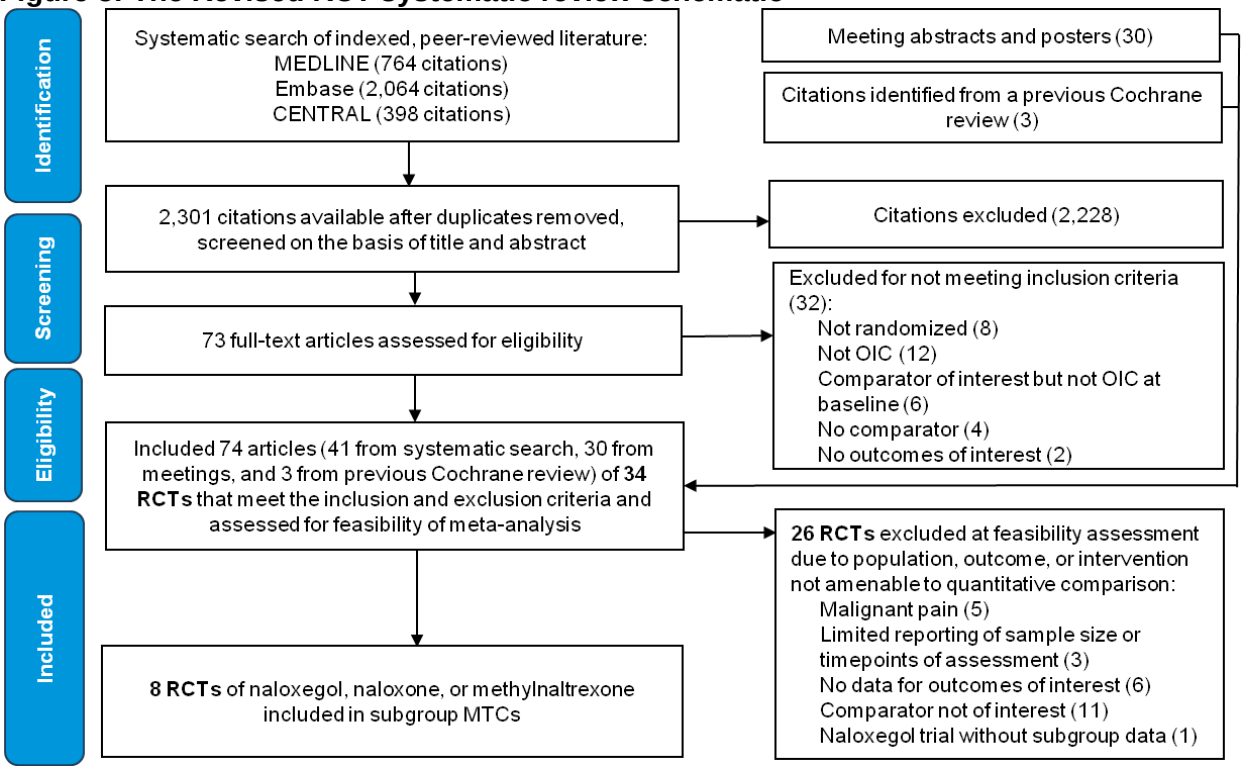
As described on page 52 of the naloxegol STA submission: "The RCT systematic review schematic is shown in Figure 2. Note that this diagram captures all searches conducted to date, including the systematic searches (conducted through October 2013) and the search update (conducted through August 2014) that included only key comparators of interest for these subgroup analyses (naloxone-oxycodone and methylnaltrexone) as described above in section 6.1.1.

Please note that Figure 2 in the naloxegol STA submission had initially showed search yields with duplicates removed within databases, in the top box. To clarify the search yield, figures are shown in Table 29 below and in the revised Figure 5 shown below.

Table 29. Search Yields within different databases

	MEDLINE	**Embase**	**Cochrane**
Sept 2012	443	1,230	106
Oct 2013	69	368	11
Laxatives (Oct 2013)	192	285	215
Aug 2014 (naloxone & methylnaltrexone only)	60	181	66
Total (duplicates not removed)	**764**	**2064**	**398**

Figure 5: The Revised RCT systematic review schematic



The following tables show the search strings and the number of hits for the searches conducted on September 4, 2012 and October 18, 2013 to identify relevant studies for all interventions of interest excluding laxatives as laxatives were not included in the Cochrane review (#1 above).

Table 30. MEDLINE Search Results (Cochrane search update)

#	MEDLINE Search Algorithm (Cochrane search update)	4 Sept 2012	18 Oct 2013
1	constipation OR ileus OR “gastrointestinal motility” OR “gastrointestinal transit” OR “gastrointestinal tract” OR “gastric emptying” OR “colonic diseases” OR (opioid[Title/Abstract] AND “bowel dysfunction”[Title/Abstract])	116065	122568
2	“narcotic antagonists” OR “opioid receptor” OR “opioid receptors” OR “opioid antagonist”[Title/Abstract] OR “opioid antagonists”[Title/Abstract] OR “pamora”[Title/Abstract] OR “pegylated naloxol conjugate”[Title/Abstract] OR secretagogue OR pentazocine[Title/Abstract] OR nalbuphine[Title/Abstract] OR buprenorphine[Title/Abstract] OR dezocine[Title/Abstract] OR butorphanol[Title/Abstract] OR methylnaltrexone[Title/Abstract] OR relistor[Title/Abstract] OR naloxone[Title/Abstract] OR narcan[Title/Abstract] OR nalone[Title/Abstract] OR narcanti[Title/Abstract] OR alvimopan[Title/Abstract] OR entereg[Title/Abstract] OR “adl 8 2698”[Title/Abstract] OR “adl 82698”[Title/Abstract] OR “ly 246736”[Title/Abstract] OR ly246736[Title/Abstract] OR naltrexone[Title/Abstract] OR antaxone[Title/Abstract] OR “pti 555”[Title/Abstract] OR celupan[Title/Abstract] OR morviva[Title/Abstract] OR revia[Title/Abstract] OR depade[Title/Abstract] OR vivitrol[Title/Abstract] OR nalmefene[Title/Abstract] OR nalmetrene[Title/Abstract] OR revex[Title/Abstract] OR cervene[Title/Abstract] OR arthrene[Title/Abstract] OR incystene[Title/Abstract] OR prucalopride[Title/Abstract] OR resolor[Title/Abstract] OR lubiprostone[Title/Abstract] OR amitiza[Title/Abstract] OR “ru 0211”[Title/Abstract] OR “td 1211”[Title/Abstract] OR “nktr 118”[Title/Abstract] OR linaclotide[Title/Abstract] OR tapentadol[Title/Abstract] OR nucynta[Title/Abstract] OR palexia[Title/Abstract] OR tapenta[Title/Abstract] OR targin[Title/Abstract] OR targinact[Title/Abstract] OR “alks 37”[Title/Abstract] OR adl5945[Title/Abstract] OR “adl 5945”[Title/Abstract]	56942	59092
3	#1 AND #2; Filters: Publication date from 2006/01/01 to 2013/01/01; Humans	443	--
3	#1 AND #2; Filters: Publication date from 05/28/2012 to 2014/01/01; Humans	--	69

Table 31. EMBASE Search Results (Cochrane search update)

#	EMBASE Search Algorithm (Cochrane search update)	4 Sept 2012	18 Oct 2013
1	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR 'allocated near/2 random' OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) OR placebo* OR 'prospective study'/de NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)	5,313,708	4,750,523
2	'constipation' OR 'constipation'/exp OR 'ileus'/exp OR 'gastrointestinal motility'/exp OR 'gastrointestinal transit'/de OR 'gastrointestinal tract'/exp OR 'gastric emptying'/exp OR 'colonic diseases, functional'/exp OR (opioid NEAR/2 'bowel dysfunction'):ab,ti	126,350	119,208
3	(non*selective NEAR/1 (opioid OR antagonists)):ab,ti OR 'narcotic antagonist'/exp OR 'opioid antagonist':ab,ti OR (opioid NEAR/1 receptor*):ab,ti OR 'opiate receptor'/exp OR 'delta opiate receptor'/de OR 'kappa opiate receptor'/de OR 'mu opiate receptor'/de OR 'pamora':ab,ti OR 'pegylated naloxol conjugate':ab,ti OR 'serotonin 4 agonist'/exp OR 'secretagogue' OR pentazocine:ab,ti OR nalbuphine:ab,ti OR buprenorphine:ab,ti OR dezocine:ab,ti OR butorphanol:ab,ti OR '17 methylnaltrexone'/exp OR methylnaltrexone:ab,ti OR relistor:ab,ti OR 'naloxone'/exp OR naloxone:ab,ti OR narcan:ab,ti OR nalone:ab,ti OR narcanti:ab,ti OR 'alvimopan'/exp OR alvimopan:ab,ti OR entereg:ab,ti OR 'adl 8 2698':ab,ti OR 'adl 82698':ab,ti OR 'ly 246736':ab,ti OR ly246736:ab,ti OR 'naltrexone'/exp OR naltrexone:ab,ti OR antaxone:ab,ti OR 'pti 555':ab,ti OR celupan:ab,ti OR morviva:ab,ti OR revia:ab,ti OR depade:ab,ti OR vivitrol:ab,ti OR 'nalmefene'/exp OR nalmefene:ab,ti OR nalmetrene:ab,ti OR revex:ab,ti OR cervene:ab,ti OR arthrene:ab,ti OR incystene:ab,ti	85,508	79,016
4	'prucalopride'/exp OR prucalopride:ab,ti OR resolor:ab,ti OR 'lubiprostone'/exp OR lubiprostone:ab,ti OR amitiza:ab,ti OR 'ru 0211':ab,ti OR 'td 1211':ab,ti OR 'nktr 118':ab,ti OR 'linaclotide'/exp OR linaclotide:ab,ti OR 'tapentadol'/exp OR tapentadol:ab,ti OR nucynta:ab,ti OR palexia:ab,ti OR tapenta:ab,ti OR targin:ab,ti OR targinact:ab,ti OR 'alks 37':ab,ti OR adl5945:ab,ti OR 'adl 5945':ab,ti	1,284	1,654
5	#3 OR #4	--	80,148
6	#1 AND #2 AND #5	--	2,642

7	#6 AND [humans]/lim	--	2,087
8	#3 OR #4 AND humans/lim AND [1-1-2006] NOT [1-1-2013]	1,230	--
8	#7 AND [embase]/lim AND [28-5-2012]/sd NOT [31-12-2013]/sd	--	368

Table 32. CENTRAL Search Results (Cochrane search update)

#	CENTRAL Search Algorithm (Cochrane search update)	4 Sept 2012	18 Oct 2013
1	MeSH descriptor Constipation explode all trees	779	813
2	MeSH descriptor Ileus explode all trees	108	117
3	MeSH descriptor Gastrointestinal Motility explode all trees	2327	2356
4	MeSH descriptor Gastrointestinal Transit, this term only	484	491
5	MeSH descriptor Gastrointestinal Tract explode all trees	8851	9088
6	MeSH descriptor Gastric Emptying explode all trees	1077	1097
7	MeSH descriptor Colonic Diseases, Functional explode all trees	668	694
8	(constipation) or (opioid NEAR/2 "bowel dysfunction"):ti,ab,kw	3219	3441
9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	13455	13945
10	MeSH descriptor Narcotic Antagonists explode all trees	775	816
11	MeSH descriptor Receptors, Opioid explode all trees	307	321
12	MeSH descriptor Receptors, Opioid, delta, this term only	5	5
13	MeSH descriptor Receptors, Opioid, kappa, this term only	52	52
14	MeSH descriptor Receptors, Opioid, mu, this term only	115	127
15	MeSH descriptor Serotonin 5-HT4 Receptor Agonists explode all trees	11	14
16	MeSH descriptor Naloxone explode all trees	1416	1470
17	MeSH descriptor Naltrexone explode all trees	612	649
18	(non*selective NEAR/1 (opioid OR antagonists)) OR "opioid antagonist" OR (opioid NEAR/1 receptor*) OR "pamora" OR "pegylated naloxol conjugate" OR "secretagogue" OR pentazocine OR nalbuphine OR buprenorphine OR dezocine OR butorphanol OR methylnaltrexone OR relistor OR naloxone OR narcan OR nalone OR narcanti OR alvimopan OR entereg OR "adl 8 2698" OR "adl 82698" OR "ly 246736" OR ly246736 OR naltrexone OR antaxone OR "pti 555" OR celupan OR morviva OR revia OR depade OR vivitrol OR nalmefene OR nalmetrene OR revex OR cervene OR arthrene OR incystene:ti,ab,kw	4737	5190

#	CENTRAL Search Algorithm (Cochrane search update)	4 Sept 2012	18 Oct 2013
19	(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18), from 2012 to 2013	962	251
20	(prucalopride OR resolor OR lubiprostone OR amitiza OR "ru 0211" OR "td 1211" OR "nktr 118" OR linaclotide OR tapentadol OR nucynta OR palexia OR tapenta OR targin OR targinact OR "alks 37" OR adl5945 OR "adl 5945"):ti,ab,kw	87	106
21	(#19 OR #20)	1039	351
22	(#9 AND #21)	157	119
23	(#22), from 2006 to 2013 in Cochrane Central Register of Controlled Trials	106	--
23	(#22), from 2012 to 2014 in Cochrane Central Register of Controlled Trials	--	11
23	(#22), from 2012 to 2015 in Cochrane Central Register of Controlled Trials	--	--

Please also note the corrected search yields for the laxative search in Embase (#2 above) presented below, for which an initial non-final version of the search strategy had been provided in the naloxegol STA submission.

Table 33. EMBASE Search Algorithm (Laxative Search)

#	EMBASE Search Algorithm (Laxative Search)	Hits
1	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR 'allocated near/2 random' OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) OR placebo* OR 'prospective study'/de NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)	4,750,523
2	'constipation' OR 'constipation'/exp OR 'ileus'/exp OR 'gastrointestinal motility'/exp OR 'gastrointestinal transit'/de OR 'gastrointestinal tract'/exp OR 'gastric emptying'/exp OR 'colonic diseases, functional'/exp OR (opioid NEAR/2 'bowel dysfunction'):ab,ti	11,208
3	(non*selective NEAR/1 (opioid OR antagonists)):ab,ti OR 'narcotic antagonist'/exp OR 'opioid antagonist':ab,ti OR (opioid NEAR/1 receptor*):ab,ti OR 'opiate receptor'/exp OR 'delta opiate receptor'/de OR 'kappa opiate receptor'/de OR 'mu opiate receptor'/de OR 'pamora':ab,ti OR 'pegylated naloxol conjugate':ab,ti OR 'serotonin 4 agonist'/exp OR 'secretagogue' OR pentazocine:ab,ti OR nalbuphine:ab,ti OR buprenorphine:ab,ti OR dezocine:ab,ti OR butorphanol:ab,ti OR '17 methylnaltrexone'/exp OR methylnaltrexone:ab,ti OR relistor:ab,ti OR 'naloxone'/exp OR naloxone:ab,ti OR narcan:ab,ti OR nalone:ab,ti OR narcanti:ab,ti OR 'alvimopan'/exp OR alvimopan:ab,ti OR entereg:ab,ti OR 'adl 8 2698':ab,ti OR 'adl 82698':ab,ti OR 'ly 246736':ab,ti OR ly246736:ab,ti OR 'naltrexone'/exp OR naltrexone:ab,ti OR antaxone:ab,ti OR 'pti 555':ab,ti OR celupan:ab,ti OR morviva:ab,ti OR revia:ab,ti OR depade:ab,ti OR vivitrol:ab,ti OR 'nalmefene'/exp OR nalmefene:ab,ti OR nalmetrene:ab,ti OR revex:ab,ti OR cervene:ab,ti OR arthrene:ab,ti OR incystene:ab,ti	79,016
4	'prucalopride'/exp OR prucalopride:ab,ti OR resolor:ab,ti OR 'lubiprostone'/exp OR lubiprostone:ab,ti OR amitiza:ab,ti OR 'ru 0211':ab,ti OR 'td 1211':ab,ti OR 'nktr 118':ab,ti OR 'linaclotide'/exp OR linaclotide:ab,ti OR 'tapentadol'/exp OR tapentadol:ab,ti OR nucynta:ab,ti OR palexia:ab,ti OR tapenta:ab,ti OR targin:ab,ti OR targinact:ab,ti OR 'alks 37':ab,ti OR adl5945:ab,ti OR 'adl 5945':ab,ti	1,654
5	Laxative OR purgative OR bisacodyl:ab,ti OR senna:ab,ti OR sennoside:ab,ti OR “polyethylene glycol 3350”:ab,ti OR docusate:ab,ti OR lactulose:ab,ti OR mannitol:ab,ti OR sorbitol:ab,ti OR “magnesium citrate”:ab,ti OR “sodium picosulfate”:ab,ti OR “magnesium hydroxide”:ab,ti OR psyllium:ab,ti OR methylcellulose:ab,ti OR polycarbophil:ab,ti	36,856
6	#1 AND #2 AND #5 AND placebo:ab,ti	294
7	#6 NOT (#3 OR #4) AND [humans]/lim	285

Lower priority questions:

117. Page 20 refers to the *"key KODIAC trial"*. Please state which of the KODIAC trials you are referring to and provide a reference for this.

AstraZeneca confirm that this should be amended to "key KODIAC 4 & 5 trials."

118. According to table 3, only English language studies were included. Please justify this approach.

The Cochrane review did not have language restrictions, but all of the studies from that review that met the criteria for our study were published in English. See the response to question 82 of this document for justification of this approach.

119. Figure 3 does not include reasons for exclusions for references excluded at 2nd pass. Please provide these reasons for exclusion.

The three studies that were excluded at second pass were excluded because they were RCTs (Figure 3 relates to the non-RCT SR).

120. Table 7 state that 167 sites were used for KODIAC 5. However, the detailed numbers in the same table do not add up to 167. Please provide the correct numbers.

AstraZeneca confirm that the table should state 116 centres.

121. Regarding the Medline search reported in 10.2:

a) Whilst 10.2 states that this was run on Ovid, both the search flow on page 53 and the syntax reported would suggest that this is a Pubmed search. Please provide clarification.

The MEDLINE searches were conducted in PubMed and not Ovid. AstraZeneca confirm that this should be corrected in Appendix 10.2 and Section 6.1.

122. The ERG are unclear regarding whether the first set of terms in each search line of the Medline strategy are MeSH or freetext, as these details don't appear in the strategy.

a) Is this a formatting error?

b) Please could you prove a clean copy of this strategy?

The search strategy is correct as is. As there were no overall limits to the search, in places where MeSH or tiab field was not specified, both were inherently captured.

123. Please explain the rationale of limiting the searches described in section 7.4.5 (HRQL) and detailed in section 10.12 to English language only and discuss what effect this may have had on your results.

Limiting searches to English language papers could introduce language bias, however, this was very limited and is unlikely to be significant in this systematic review because:

1. The relevant papers were mostly published in English – 95% in the results of searches
2. Evidence has shown that there is no systematic bias from the English-language restriction on systematic reviews. A recent study was conducted to investigate whether the exclusion of languages other than English may introduce a language bias and lead to inaccurate conclusions when conducting systematic review-based meta-analyses. A comprehensive literature search was conducted and found that there were no major differences between summary treatment effects in meta-analyses with English language restrictions and those that included languages other than English. The study therefore concluded that there was no evidence of any systematic bias from the use of English language restrictions in systematic review based meta-analyses in conventional medicine.[7]
3. As this systematic review focused on the relevant populations mostly in the UK, US and other European countries, the most relevant studies were published in English.

Appendix 1. 26 studies excluded from MTC at feasibility assessment step

Trial Name	Treatments	Reason for Exclusion
ALKS 37 Trial[1]	ALKS 37 vs placebo	Comparator not of interest
Jansen 2011[2]	Alvimopan vs placebo	Comparator not of interest
Irving 2011[3]	Alvimopan vs placebo	Comparator not of interest
VAMC Alvimopan Study[4]	Alvimopan vs placebo	Comparator not of interest
Webster 2008[5]	Alvimopan vs placebo	Comparator not of interest
Singla 2012[6]	Bevenopran vs placebo	Comparator not of interest
Freedman 1997[7]	Laxatives (polyethylene glycol + electrolytes vs lactulose)	No outcomes of interest
Cryer 2010[8]	Lubiprostone vs placebo	Comparator not of interest
Marciniak 2012[9]	Lubiprostone vs senna	No outcomes of interest/ comparator not of interest
OBD0632[10]	Lubiprostone vs placebo	Comparator not of interest
Jamal 2012[11]	Lubiprostone vs placebo	Comparator not of interest
Thomas 2008[12]	Methylnaltrexone vs placebo	Malignant pain
Anissian 2012[13]	Methylnaltrexone vs placebo	No outcomes of interest
Slatkin 2009[14]	Methylnaltrexone vs placebo	Malignant pain
UC Methylnaltrexone Study[15]	Methylnaltrexone vs placebo	No outcomes of interest
Naloxegol Phase II[16]	Naloxegol vs placebo	No LIR subgroup data available
Webster 2013[17]	Naloxegol vs usual care	No timepoints of interest (only reported outcomes at 52 weeks)
Lowenstein 2011[18]	Naloxone vs placebo	No timepoints of interest (did not provide the duration of the trial nor the timepoints at which outcomes were collected)
Ahmedzai 2011[19]	Naloxone vs placebo	Malignant pain
Leppert 2012[20]	Naloxone vs placebo	Malignant pain
CLB FNB Naloxone PR Study[21]	Naloxone vs placebo	No outcomes of interest/no timepoints of interest (CSBM response at 12 weeks only)
SJMC Naloxone Study[22]	Naloxone vs placebo	No outcomes of interest
UL Naloxone Study[23]	Naloxone vs placebo	Malignant pain
EMC Prucalopride Study [24]	Prucalopride vs placebo	Comparator not of interest
Theravance TD-1211 Study[25]	TD-1211 vs placebo	Insufficient sample size data for analysis/ comparator not of interest
Vickery 2013[26]	TD-1211 vs placebo	Comparator not of interest

1. DiPetrillo L, al. e. ALKS 37, A Novel, Peripherally-Restricted Opioid Receptor Antagonist, Demonstrates Efficacy in the Treatment of Opioid-Induced Bowel Dysfunction. Gastroenterology. 2011:S-136.
2. Jansen JP, Lorch D, Langan J, et al. A randomized, placebo-controlled phase 3 trial (Study SB-767905/012) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. J Pain. 2011;12(2):185-193.
3. Irving G, Penzes J, Ramjattan B, et al. A randomized, placebo-controlled phase 3 trial (Study SB-767905/013) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. J Pain. 2011;12(2):175-184.
4. Paulson DM, Kennedy DT, Donovick RA, et al. Alvimopan: an oral, peripherally acting, mu-opioid receptor antagonist for the treatment of opioid-induced bowel dysfunction--a 21-day treatment-randomized clinical trial. J Pain. 2005;6(3):184-192.

5. Webster L, Jansen JP, Peppin J, et al. Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain. Pain. 2008;137(2):428-440.
6. Singla N. CB-5945 0.25 mg Twice Daily is Associated with Significantly Increased Spontaneous Bowel Movement and Greater Proportion of Responders Compared with Placebo in Patients on Chronic Opioid Therapy for Noncancer Pain. Paper presented at: Digestive Disease Week,, 2012; San Diego, CA.
7. Freedman MD, Schwartz HJ, Roby R, Fleisher S. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: A double-blinded placebo-controlled trial. Journal of Clinical Pharmacology. 1997;37(10):904-907.
8. Cryer B, Katz S, Vallejo R, al. e. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Lubiprostone for the Treatment of Opioid-Induced Bowel Dysfunction in Patients With Chronic, Non-Cancer Pain. Gastroenterol Clin North Am. 2010:S-129.
9. Marciniak C, Toledo S, Jesselson M, et al. Lubiprostone compared to senna in the treatment of postoperative opioid-induced constipation following orthopedic procedures. American Journal of Gastroenterology. 2012;107:S695-S696.
10. Joswick T, Lichtlen P, Woldegeorgis F, Ueno R. Lubiprostone is Well Tolerated in Chronic Non-Cancer Pain Patients With Opioid-Induced Constipation in Three Phase 3, Randomized, Double-Blind, Placebo-Controlled Trials. Paper presented at: Digestive Disease Weak 2013, 2013; Orlando, Flordia, USA.
11. Jamal MM, Mareya S, Woldegeorgis F, Joswick T, Joswick RU. Lubiprostone Significantly Improves Treatment Response in Non-Methadone Opioid-Induced Bowel Dysfunction Patients with Chronic, Non-Cancer Pain: Results from a Phase 3, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Gastroenterology. 2012:S-144-S145.
12. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med. 2008;358(22):2332-2343.
13. Anissian L, Schwartz HW, Vincent K, et al. Subcutaneous methylnaltrexone for treatment of acute opioid-induced constipation: phase 2 study in rehabilitation after orthopedic surgery. J Hosp Med. 2012;7(2):67-72.
14. Slatkin N, Thomas J, Lipman AG, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. J Support Oncol. 2009;7(1):39-46.
15. Yuan CS, Foss JF, O'Connor M, et al. Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. JAMA. 2000;283(3):367-372.
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