in collaboration with:

Naloxegol for treating opioid-induced constipation

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Date completed	21/01/2015

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 13/124/01.

Declared competing interests of the authors
None.

Acknowledgements
None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in blue throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Wolff R, Al M, Zaim R, Lang S, Leunis A, Noake C, Ryder S, Worthy G, Stirk L, Armstrong N, Riemsma R, Severens JL, Kleijnen J. Naloxegol for treating opioid-induced constipation: a Single Technology Appraisal. York: Kleijnen Systematic Reviews Ltd, 2015.

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ABBREVIATIONS

AE	Adverse Event
AIC	Akaike information criterion
AiC	Academic in confidence
BIC	Bayesian information criterion
BFI	Bowel Function Index
BIC	Bayesian information criterion
BM	Bowel movement
BMI	Body Mass Index
BNF	British National Formulary
BOI	Burden of Illness
BPI-SF	Brief Pain Inventory Short Form
CADTH	Canadian Agency for Drugs and Technologies in Health
CBM	Complete bowel movements
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CiC	Commercial in confidence
CNS	Central nervous system
CPRD	Clinical Practice Research Data Link
CR	Controlled release
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
DAE	Discontinuation due to adverse events
DIC	Deviance information criterion
DSA	Deterministic sensitivity analyses
DSU	Decision support unit
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
FDA	U.S. Food and Drug Administration
GI	Gastrointestinal
GP	General practioner
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
IC	Indirect Comparison
ICER	Incremental Cost-effectiveness Ratio
ITT	Intention to Treat
LIR	Laxative inadequate response
LOCF	Last observation carried forward
LOE	Languages other than English
LY	Life year
MeSH	Medical Subject Heading
mITT	Modified intention to treat
mg	Milligram
MNTX	Methylnaltrexone
MTC	Mixed treatment comparison
N/A	Not applicable
NAS	Numerical analogue scale
NHS	National Health Services
NICE	National Institute for Health and Care Excellence

NIHR	National Institute for Health Research
NR	Not reported
NRS	Numerical Rating Scale
od	Once Daily
OIC	Opioid-induced constipation
OOWS	Objective Opiate Withdrawal Scale
OXN	Naloxone-oxycodone
PAC-SYM	Patient Assessment of Constipation Symptoms
PACOI	Patient Assessment of Opioid-Induced Constipation summary score
PAMORA	Peripherally acting mu-opioid receptor antagonist
PAS	Patient access scheme
PR	Prolonged release
PRN	Pro re nata (as required)
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QAD	Once every other day
QALY(s)	Quality-adjusted life year(s)
RCT	Randomised controlled trial
RePEc	Research Papers in Economics
RFBM	Rescue-free bowel movements
RMME	Repeated-measures mixed effects
SAE	Serious Adverse Events
SBM	Spontaneous bowel movement
SC	Subcutaneous
SCBM	Spontaneous complete bowel movement
SE	Standard error
SF-36	Short form 36
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SOC	Standard care
SOWS	Subjective Opiate Withdrawal Scale
STA	Single Technology Appraisal
TEAE	Treatment-emergent adverse event
TP	Transition probability
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organisation
WTP	Willingness-to-pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The patient population described in the final scope is *'adults with opioid-induced constipation'*. In contrast, the definition in the company's submission is narrower, ie *'adults with opioid-induced constipation who have had an inadequate response to laxative(s)'* which reflects the licensed indication granted by EMA in December 2014. Laxative inadequate response (LIR) was defined as *'opioid induced constipation symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days'*. This was based on [redacted]. It appears that the definition of LIR used by the company is a minimal definition of criteria for LIR.

The intervention described in the company's submission (*'naloxegol'*) matches the intervention described in the final scope.

The company's submission comparator criteria did not clearly include rectal interventions (suppositories or manual evacuation) nor was this included in the clinical effectiveness section although it was included in the scope.

Compared to the final scope some outcomes were not clearly considered and/or reported in the CS, eg effects on analgesic efficacy.

The company's submission did not include a specific section on equity considerations and *'no potential equality issues relating to naloxegol as a treatment for opioid-induced constipation'* were identified.

The ERG is not aware of any ongoing application for a patient access scheme (PAS). End of life criteria are not relevant for this project.

1.2 Summary of clinical effectiveness evidence submitted by the company

Direct evidence

The company's submission presented two identically designed, Phase III, randomised, placebo-controlled studies in patients with non-cancer related pain and opioid-induced constipation (OIC) (KODIAC 4 and 5). There was no direct evidence comparing naloxegol to any of the relevant comparators defined in the scope.

The primary outcome in both studies was the response to study drug, defined as ≥3 spontaneous bowel movements (SBMs) per week and a change from baseline of ≥1 SBM per week for at least nine out of the 12 study weeks and three out of the last four study weeks. Both trials included a pre-specified subpopulation of patients, the laxative inadequate response (LIR) group, which represents the licensed indication for naloxegol.

- Naloxegol 25 mg (recommended dose) resulted in significantly higher response rates in LIR patients compared with placebo in both trials (KODIAC 4, 48.7% versus 28.8% patients, respectively; p=0.002: KODIAC 5, 46.8% versus 31.4% patients, respectively; p=0.014).
- In both studies, naloxegol showed a consistent improvement in a range of secondary endpoints, eg time to first post-dose SBM, total SBMs per week, number of days per week with at least one SBM, use of rescue medication at least once over the treatment period.

- Three instruments (PAC-SYM, PAC-QoL, EQ-5D) showed advantages of naloxegol compared to placebo.

Safety data from the two RCTs (KODIAC 4 and 5) and two studies designed to primarily assess safety (KODIAC 7 and 8) demonstrated that naloxegol 12.5 mg and 25 mg was generally safe and well tolerated in OIC patients with non-cancer-related pain for up to 52 weeks of treatment.

- The majority of adverse events (AEs) reported were mild or moderate in intensity
- As expected there were no differences in AEs observed between the ITT and anticipated licensed population in KODIAC 4 and 5
- The most frequently reported AEs were gastrointestinal events (predominantly diarrhoea, abdominal pain, nausea, and flatulence) which was not unexpected given the nature of the disease and the pharmacological mechanism of action of naloxegol
- GI-related AEs occurred at a higher frequency in the naloxegol 25 mg treatment group compared with the naloxegol 12.5 mg and placebo groups
- There were no notable differences in the type or frequency of serious adverse events (SAEs) across treatment groups in the studies
- The incidence of discontinuations due to AEs was dose-related with a higher proportion of patients discontinuing in the naloxegol 25 mg treatment group compared with the naloxegol 12.5 mg and placebo groups
- The discontinuation rate observed with the longer-term use of naloxegol (52 weeks) was similar to that seen in the pivotal 12 week RCTs
- The most common AEs resulting in discontinuation were GI events

Indirect evidence

A mixed treatment comparison (MTC) was conducted to provide comparative evidence versus comparators of interest for the treatment of opioid-induced constipation (OIC) as defined in the scope, ie oral laxative treatment, methylnaltrexone, and naloxone-oxycodone. Comparators to naloxegol were methylnaltrexone and naloxone-oxycodone. Laxatives were not included as a comparator as the systematic review did not identify any laxative studies with outcomes of interest. In total, eight RCTs were considered for inclusion in the MTC analysis (two studies: naloxegol versus placebo, two studies: methylnaltrexone versus placebo, four studies naloxone-oxcodone versus placebo).

The company's submission found that only the naloxegol trials were able to provide data in the specific patient population of interest, ie LIR subgroup. 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 subgroup. As none of the other trials reported data specifically for the LIR subgroup, the MTC analysis uses the main enrolled trial populations to inform the analysis as per the pre-specified protocol. The trials identified in the systematic literature review and included in the MTC analyses varied substantially with respect to the definition and severity of OIC. Therefore, it is not expected that these subgroups of the KODIAC 4 and 5 trials represent populations substantially different from the included OIC trials, as a whole.

Based on the random-effects MTCs performed OIC, the evaluated treatments typically showed improved outcomes compared with placebo, reflecting the individual trial results. However, few of these subgroup analyses yielded statistically conclusive results. In part, this was due to the small evidence network including only comparators of interest for England and Wales.

- Naloxegol 25 mg had greater increases in SBMs over four weeks, and up to 12 weeks versus most doses of methylnaltrexone (with the exception of the 12 mg OD oral dose of methylnaltrexone)

- Naloxegol 12.5 mg and 25 mg had a higher odds of SBM response than the QAD schedule of subcutaneous methylnaltrexone 12 mg
- Naloxegol 25 mg had a higher odds of CSBM response than naloxone in a fixed ratio combination with oxycodone, in the anticipated licensed population + Step 3 opioids analysis
- Naloxegol 12.5 mg and 25 mg had a similar or lower rate of DAEs compared with all methylnaltrexone and naloxone regimens evaluated, except when the 25 mg dose was compared with the naloxone fixed ratio combination with oxycodone
- Naloxegol 12.5 mg trended towards a lower odds of TEAEs compared with subcutaneous methylnaltrexone

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The results from KODIAC 4 and KODIAC 5 trials (see 'direct evidence' above) were of naloxegol in comparison to placebo and therefore not relevant to the final scope. Note that no studies were identified for naloxegol versus any of the specified comparators.

The inclusion criteria used in the company's submission (CS) were not appropriate for a MTC analysis and this leads to a lack of clarity of how the studies were screened and selected for inclusion. The inclusion criteria for the intervention should have included all comparators of interest (as well as naloxegol) versus all comparators of interest. This may well have led to the inclusion of more studies and the network may have included some closed loops.

The differences in the inclusion specification of the 'population' between the scope and the CS report is likely to have reduced the number of included studies by limiting the naloxegol studies to the subgroup (LIR) in the CS. In addition this alteration of the scope leads to a difference between the population of the intervention and that of the comparator which is not appropriate (intervention is for LIR+ OIC, whilst comparator is for all OIC).

Twenty-six studies have been excluded after full text screening, some of which (three studies on mu-opioid receptor inhibitors, a study comparing naloxone with placebo and a study without LIR subgroup) should not have been excluded.

Insufficient details were presented for comparator study design, quality and data. These limitations prevent further analyses based on baseline characteristics (for pain intensity, opioid dose, duration of opioid use, duration of OIC, previous laxative use).

It should be noted that studies including patients with malignancies leading to opioid-induced constipation were not included. While this might allow better comparability, the presented evidence does not allow any firm conclusion regarding these patients.

Overall, there is no robust evidence of efficacy and safety between naloxegol and the comparators of interest.

1.4 Summary of cost-effectiveness submitted evidence by the company

The company developed a *de novo* model to assess the potential cost effectiveness of naloxegol (25 mg) and comparator regimens for the treatment of opioid-induced constipation (OIC). A decision tree followed by a Markov state-transition model (with four health states: OIC, non-OIC (on treatment), non-OIC (untreated) and death) was constructed in Microsoft Excel. The decision tree structure was used to assess response to treatment at week four. If patients achieve constipation relief, they were classified as responders and enter the Markov model in non-OIC (on treatment) health state. Non-responders at week four enter the Markov model in the OIC health state. From all health states, patients are at risk to die. The cycle length of the model is four weeks and the time horizon of the study is five years.

For naloxegol +/- rescue laxative and placebo +/- rescue laxative, the response rates were determined using the data from the KODIAC 4 and 5 trials. The company adopted a divergence from the clinical definition of response in the OIC and non-OIC health states. OIC, in the model, was defined as less than three spontaneous bowel movements (SMBs) per week in at least two out of the last four weeks. And non-OIC was defined as three or more SBMs per week in at least three out of the last four weeks. Moreover, response definition was based on any bowel movement (BM) when treatment includes a rescue laxative. For the comparison of naloxegol with other treatments (subcutaneous methylnaltrexone and naloxone-oxycodone) in the model, the response rates were determined by a mixed treatment comparison (MTC).

The health outcomes were expressed as cost per quality adjusted life year (QALY). Utility estimates were derived from the EQ-5D questionnaire, which was included in the KODIAC 4 and 5 trials at 0, 4 and 12 weeks. The average utility for patients in each health state is calculated while taking into account both treatment- and time-specific effects. The time-specific effects are only applied to patients on naloxegol treatment in the non-OIC health state. Due to absence of data, the comparison with MTC-based treatments does not incorporate treatment and time-specific utilities.

Costs of naloxegol were based on the recommended dosing (25 mg), where patients may discontinue treatment due to adverse events. The daily treatment costs were estimated, followed by per cycle costs. Two data sources were used for cost estimates in the model. In the base case, a GP survey (N=1,000) is used to estimate the utilisation of resources. No systematic literature review is conducted to explore resource utilisation in the model.

Costs and QALYs are discounted at 3.5%, according to the NICE reference case. The impact of parameter uncertainty is estimated in deterministic and probabilistic sensitivity analysis. Scenario analyses are run on key parameters, especially relating to the utility estimates. In addition, subgroup analyses are conducted for step three opioid (non-cancer) and cancer patients.

In the base case, the ICER for naloxegol compared to placebo is £10,849 per QALY gained for a five year time horizon. Based on the opinion of the company, the most clinically relevant comparisons are: 1) naloxegol 25 mg versus placebo in combination with bisacodyl (the ICER is £12,639 per QALY gained) 2) naloxegol 25 mg plus bisacodyl versus placebo in combination with bisacodyl (the ICER is £11,175 per QALY gained). The probalistic sensitivity analysis (PSA) results indicated that naloxegol 25 mg has a probability of 91% of being cost-effective (compared to placebo) at a willingness to pay threshold (WTP) of £20,000. The PSA results of other comparators are also acceptable at the same threshold. For the comparator 'rectal intervention', a cost minimisation analysis is conducted. Naloxegol 25 mg can be provided for 0.68 months for the same cost as a rectal intervention at patient's home.

The following scenario-analyses were performed by the company regarding the health-related quality of life (HRQoL) estimates in the model: treatment-specific utility inputs, health-state specific utility inputs, an alternative tariff and secondary literature. For costs, a scenario analysis is run using data collected as part of a burden of illness survey. The conclusions of the study were affected by two scenarios explored by the company: 12 week time horizon, resulted in ICERs of £20,020 for naloxegol 25 mg compared with placebo and £33,708 for naloxegol 25 mg compared with placebo plus bisacodyl. Naloxegol 25 mg remains dominant when compared with SC methylnaltrexone.

When a health-state specific utility input is employed (rather than treatment- and time-dependent utilities), the ICER for naloxegol 25 mg increases to £38,921 compared with placebo and £63,423 when compared with placebo plus bisacodyl.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent and is in line with the decision problem specified in the scope. Reviewing the overall evidence, the ERG confirmed that there was no existing cost-effectiveness model for naloxegol for the anticipated indication.

The ERG assessment indicated that the model was generally well presented and reported.

The population studied in the cost-effectiveness analysis is the same as the licensed indication but narrower than the population discussed in the final scope (ie adults with opioid-induced constipation). The ERG questions to what extent the trial definition of inadequate response to laxatives (ie taking at least one laxative class for a minimum of four days during the two weeks prior to the screening period) matches with clinical practice. However, explorative analysis showed that the outcomes hardly change when inadequate response is redefined as inadequate response from at least two classes of laxatives for ≥4 days in the two weeks prior to study entry or reported unsatisfactory laxation from ≥1 additional laxative class from the six month OIC history prior to screening.

On the other hand, the ERG agrees with the adopted response definition (three or more SBMs per week in at least three out of the last four weeks) instead of the clinical definition, in which also a change from baseline of one SBM is required. The advantage of the model definition of response is that it only incorporates absolute health states, not relative to baseline. However, HRQoL analysis indicates that the health state non-OIC is too broad to be homogeneous with regards to quality of life.

Furthermore, the impact of permitted switching between different treatments, which would help place naloxegol at a favourable position in the care pathway, is not addressed in the CS. The company indicated that permitted switching and the optimum position of naloxegol in the care pathway were not considered necessary. The ERG disagrees with the response received from the company.

The company indicated that the most clinically relevant scenario is the naloxegol (25 mg) plus bisacodyl in comparison with placebo plus bisacodyl. The comparison of naloxegol to placebo was selected in the base case analysis, since it was an appropriate regimen that reflects the design and endpoints of the KODIAC 4 and 5 trials. Hence, the company's consideration of the base case was based on the regimen choices with the least unknowns and assumptions (naloxegol 25 mg versus placebo).

However, the ERG would argue that naloxegol *minus* bisacodyl is neither clinically relevant nor consistent with the KODIAC 4 and 5 trials. Clinically it would seem implausible to prescribe naloxegol without bisacodyl (or some other rescue medication) given that rescue medication might be needed. As for the trial, rescue medication was permitted in all arms and therefore there was no such arm as naloxegol minus bisacodyl in the KODIAC 4 and 5 trials. However, by redefining a base case which fits the trial, ie naloxegol (25 mg) plus bisacodyl in comparison with placebo plus bisacodyl using SBM as measure of response, the ERG was able to show that this only increased the base case ICER by £65.

The inputs for the model are mainly derived from KODIAC 4 & 5 trials and literature. However, resource utilisation values are not based on a systematic search of the literature. In general, the ERG observed that there is uncertainty about the cost values that were used for adverse events (AEs) and cost parameters for constipation. AE calculations are not transparent, and the large difference between GP omnibus and the burden of illness (BOI) study lack explanation. The ERG believes that a literature search is vital to address the shortcomings of resource utilisation in the model.

Sensitivity analyses revealed that transition probabilities, costs and adverse events have little to no effect on the ICER. However, the utility estimates were influential on the cost-effectiveness results. Changing the utility assumptions had profound impact on the ICERs. In particular, the ICER is most sensitive to the in- or exclusion of a separate treatment effect for naloxegol on HRQoL. According to the ERG, the most plausible explanation is that the non-OIC (on treatment) state is too broad, thus including a heterogeneous group of patients. The most preferable approach to dealing with this would have been to refine the non-OIC (on treatment) state by splitting it in two states and deriving treatment unspecific, health state specific utility values. However, it is the ERG's view that in the absence of such a more refined Markov model, the current approach with treatment specific utilities is a reasonable alternative.

The cost-effectiveness results were generally robust. The ERG sensitivity and scenario analyses revealed that none resulted in ICERs that varied from the company's results in any meaningful way. However, the ERG requested to have a full MTC to have a comparable assessment of all ICERs. The company did not agree to perform a full MTC by including placebo from the KODIAC trials. Therefore, the cost-effectiveness results presented in this study are not comparable and given the conclusions formulated in section 1.4 the health economic outcomes of naloxegol versus methylnaltrexone and naltrexone/oxycodone should be interpreted with care.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out on all databases required by NICE. The host, date span and search dates were reported for all resources and the CS provided sufficient detail for the ERG to appraise the searches. Supplementary searches of conference abstracts and other relevant resources including trials databases, specialist and organisational websites, and the checking of references lists were undertaken by the company in order to find additional studies not retrieved by the main searches.

The model structure was based on a revised definition of response compared the one used in the clinical studies. Thus, the model was able to use absolute health states rather than health states relative to a baseline situation. EQ-5D data were available from the clinical studies to inform the utilities used in the model, thus providing good quality evidence for the cost-effectiveness analysis. Extensive sensitivity and scenario analyses were performed, showing the robustness of the results.

1.6.2 Weaknesses and areas of uncertainty

The searches provided in the Section 10.2 of the original CS, did not match the company's description of what had been undertaken in Section 6.1. Despite additional searches provided at clarification the ERG still has concerns regarding the comprehensiveness of searches for comparator treatments, however without the time to conduct and screen new searches the ERG is unable to say what effect these limitations may have had on the recall of results.

There is lack of direct evidence, ie of trials of naloxegol to any of the relevant comparators. The inclusion criteria used for the MTC were not appropriate for a MTC analysis and might well have missed relevant studies. There is a difference between the population of the intervention and that of the comparator which is not appropriate (intervention is for LIR + OIC, whilst comparator is for all OIC).

The main weakness of the cost-effectiveness analysis is the definition of intervention and comparator. The cost-effectiveness analysis compared naloxegol to placebo based on SBM and naloxegol (25 mg) plus bisacodyl to placebo plus bisacodyl based on BM. However, the ERG considers naloxegol *minus* bisacodyl neither clinically relevant nor consistent with the KODIAC 4 and 5 trials in which rescue medication was permitted in all arms. At the same time, for the comparison with bisacodyl, SBM

should be the basis for the response definition rather than BM. Resource utilisation values were based on an expert survey, whilst also data from a burden of illness (BOI) study were available. The large difference between these two lacks explanation, and this could have been done had the company performed a systematic search of the literature regarding resource use. The issues regarding the MTC described in the clinical assessment carry over into the cost-effectiveness analysis.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG was unable to replicate and check the results of the indirect and MTC analyses as the datasets used in the analyses were not provided in the CS.

The ERG performed the following exploratory and sensitivity analysis:

- New base case analysis based on naloxegol or placebo both plus rescue medication and SBM as outcome, in order to assess cost-effectiveness for the only correct comparison that can be made based on the data from the KODIAC 4 and 5. This analysis increased the ICER to £10,864, and increased the base case ICER by £65.
- Sensitivity analysis on response rate as proxy for the 2 x LIR population. Since only data on response could be found for the 2 x LIR population, and not for all other transition probabilities, we used the analysis with the adjusted response rate as a proxy for a full 2 x LIR assessment. This increased the ICER to £11,406.
- Threshold analysis on HR for transition non-OIC (on treatment) to OIC for methylnaltrexone and naloxone-oxycodone. In the model, the hazard ratios for the transition from non-OIC (on treatment) to OIC for methylnaltrexone and naloxone-oxycodone were approximated by the ratio of the four week response rate of these two comparators relative to that of naloxegol 25 mg. This was based on the assumption that the non-response rate after four weeks is likely to be related to the response rate at four weeks.

  For methylnaltrexone we found that for the whole range of hazard ratios naloxegol 25 mg is dominant. When naloxone-oxycodone is compared to naloxegol plus morphine, we find that for HR<1.2, naloxegol dominates naloxone-oxycodone. Once the HR is larger than 1.2, naloxegol would be considered cost-effective at the usual threshold. When we compare naloxone-oxycodone to naloxegol plus oxycodone, we find that at a HR of 0.45 the ICER would be £20,000 whereas at a HR of 0.85 the ICER would be £30,000.
- Analysis of structural uncertainty related to curve extrapolation. Given the wide variation in patients still in non-OIC (on treatment) after five years, we have looked at the impact of changing the parametric form of the time-to-event curve used to estimate the transition probability from non-OIC (on treatment) to OIC, with different combinations of distributions assumed for naloxegol and placebo instead of for each the same. We found that the various combinations let to ICERs between £8,000 and £13,000.

None of the additional clinical and economic analysis undertaken by the ERG resulted in central ICERs that varied from the company's results in any meaningful way.

2 BACKGROUND

This report provides a review of the evidence submitted by the company in support of naloxegol for treating opioid-induced constipation.

2.1 Critique of the company's description of underlying health problem

Health problem

'Opioid-induced constipation (OIC) is the most common, persistent and debilitating side-effect reported in patients receiving opioids to manage pain.[1] The analgesic effects of opioids are primarily exerted through mu-opioid receptors in the central nervous system (CNS).[2] However, when opioids bind to peripherally located mu-opioid receptors in the gastrointestinal (GI) tract, normal intestinal motility, sphincter tone and mucosal secretion into the GI tract is disrupted while fluid absorption from the GI tract is increased.[3] The result is an accumulation of hard, dry stools that are difficult to pass.[4] Other GI-related opioid-induced symptoms include abdominal pain, nausea, overflow diarrhoea and incontinence and faecal impaction.'[5]

'The NICE definition of constipation is unsatisfactory defecation due to infrequent bowel movements, difficult stool passage, or a feeling of incomplete evacuation.[6] According to The British Society of Gastroenterology, doctors define constipation as opening the bowels less than three times per week [7] which also constitutes one of the Rome III criteria for a diagnosis of constipation.'[8]

ERG Comment: Rome III criteria were established for functional bowel disorders of which functional constipation is one symptom and is defined as: straining at stool; passage of lumpy or hard stools; sensation of incomplete evacuation or anorectal obstruction; the need to use manual manoeuvres to facilitate defecation; and passing fewer than three stools per week.[8, 9]

'There is currently no universal definition of OIC as the condition and severity of symptoms can vary from one patient to the next. A recent consensus definition of OIC was developed by a working group of international clinical and basic science experts in pain medicine, palliative care, gastroenterology and gut neurobiology as follows [10]:

- *A change when initiating opioid therapy from baseline bowel habits that is characterised by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency.'*

The ERG believes the overview presented in section 2.1 of the company's submission (CS)[11] to be accurate, although it should be noted that the NICE definition of constipation was not supported by the reference. The ERG found the definition on a NICE website[12] and this was in agreement with the company. The lack of consensus on a definition for OIC appears to be correct.

The ERG believes that the quote *'OIC occurs in approximately 45–80% of patients receiving opioids for non-cancer pain'*[13-15], in Section 2.2, is misleading and the percentage should be 45-57%, according to the references quoted by the company and references identified by the ERG.[16] Therefore half of non-cancer pain sufferers given opioids will not develop OIC. The quote of *'at least 90% of patients receiving opioids for the management of cancer-related pain'* appears to be accurate and is supported by other reference sources.[16]

The ERG notes that the company has not discussed the underlying disease states that lead to opioid treatment of pain in non-cancer patients. These were identified by the ERG to include back pain, spinal osteoarthritis, and failed back surgery. It is important to note that patients suffering from cancer pain or non-cancer pain can have constipation due to multiple causes (dehydration, poor diet,

inactivity, spinal cord injuries, tumour activity) and this can lead to difficulties in correctly estimating the prevalence of OIC.[17, 18]

The ERG notes that opioid treatment for pain induces many side effects (nausea, vomiting, sedation, respiratory depression, miosis, euphoria, dysphoria, hypotension, urinary retention, and OIC) of which OIC is only one and therefore opioid antagonists will affect multiple side effects particularly those of the peripheral nervous system (hypotension, urinary retention, and OIC). Opioid-induced constipation compromises patient satisfaction with analgesic treatment.

2.2 Critique of the company's overview of current service provision

'Marketing authorisation from the European Medicines Agency is expected in December 2014'. '*Naloxegol is anticipated to be licensed for use in OIC patients who have had an inadequate response to laxative(s) (see section 1.5 for a definition of this patient population).'*

ERG Comment: Naloxegol was approved by the US Food and Drug Administration (FDA) in September 2014[19] and by the European Medicines Agency (EMA) in December 2014[20] therefore the ERG has not commented on Sections 1.5-1.14.

'*The aims of management in OIC are to improve symptoms, to achieve a complete bowel movement at least every 2–3 days without difficulty, and consequently to improve patient satisfaction and overall quality of life (CS section 2.5).'*

ERG comment: the CS presented an overview of the biological action of naloxegol in Section 1.2, which the ERG found to be accurate. It should be clarified that naloxegol has a preferential but not exclusive action in the peripheral nervous system.

ERG comment: the CS presented current treatment options for OIC in Section 2.1 (paragraph 7 onwards). Although they state that there is *'no clear consensus among UK physicians on treatment pathways for patients with OIC'* there are online recommendations by NICE for treatment of opioid induced constipation and palliative care constipation, which the CS subsequently refers to in Section 2.5.

Current recommendations provided by NICE for opioid-induced constipation[21] are based on the expert opinion of Goodheart and Leavitt 2006[22] and are as follows:

- Bulk-forming laxatives are not recommended. Their mode of action is to distend the colon and stimulate peristalsis but opioids prevent the colon responding with propulsive action. This may cause painful colic and rarely obstruction.
- Osmotic laxatives retain water in the stool making bowel evacuation easier and docusate also softens the stool.
- Stimulant laxatives overcome the reduced peristalsis due to the opioid.

If a person has opioid-induced constipation they are advised as follows:

- To increase the intake of fluid and fruit and vegetables if necessary.
- Avoid bulk-forming laxatives.
- Use an osmotic laxative (eg lactulose, macrogols) and a stimulant laxative (senna, sodium picosulfate, bisacodyl, dantron).
- Adjust the laxative dose to optimise the response.

The recommendations for palliative care constipation are summarised as follows[23] and were based on the expert opinion of Twycross and Wilcock 2011[24]:

- When introducing an opioid (or any other constipating drug), advise the person of the risks of constipation, and prescribe a stimulant laxative (such as senna or dantron-containing laxative) at the time of first prescription. Aim for a regular bowel movement, without straining, every 1–3 days. Add an osmotic laxative (such as lactulose or a macrogol) or a surface-wetting laxative (such as docusate, which also softens stools) if colic is a problem.
- Encourage an adequate fluid intake and fruit juice and fruit specifically.
- If the response to laxatives is insufficient, consider adding in a prokinetic agent such as metoclopramide, domperidone, or erythromycin 250–500 mg four times a day (off-label use). Do not use a pro-kinetic if the person has symptoms of colic.

Anticipated licensing

The CS states (Section 1.5) that '*In the pivotal trials for naloxegol to qualify as a laxative inadequate responder, patients had to have reported concurrent OIC symptoms of at least moderate severity (ie incomplete bowel movement, hard stools, straining or false alarms) while taking at least one laxative class for a minimum of 4 days during the two week period prior to the study screening period.*[25] *Thus, naloxegol is indicated for any patient with OIC after inadequate response of one laxative class.'* The CS further states (Section 2.1), that '*there is currently no accepted method for defining this subpopulation in clinical practice.* [redacted].[26] *See section 10.14 for further details on this survey*.'

ERG comment: The CS states that [redacted] From this questionnaire clinicians were asked their view of the definition for laxative inadequate response (LIR); *'opioid induced constipation symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days'*. The ERG noted that the results of this questionnaire were presented in the file 'Consolidated definition of laxative inadequate response' accompanying the CS. [redacted]. It remains unclear to the ERG (even after clarification was sought) how the CS came up with its definition for LIR. Clarification was requested from the company to identify what proportions of patients in the KODIAC trials were receiving high doses of bisacodyl. The evidence provided in Table 1 and Table 2 indicated that the majority of patients were receiving ≥15 mg/day rather than ≥30 mg/day. Based on all this evidence it would appear that the definition of LIR used by the company is a minimal definition of criteria for LIR.

Table 1: 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 2: 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)

According to the CS 'a *recent burden of illness study reported that 93% of patients had an inadequate response to laxatives, despite taking sufficient laxative therapy* [27]', the ERG was unable to verify this statement from original data. The CS indicates that when laxative(s) alone do not provide adequate pharmacological relief alternative treatments are available:

- Methylnaltrexone, a peripherally acting mu-opioid receptor antagonist (PAMORAs) for palliative care when laxatives are unsuccessful
- Naloxone-oxycodone (Targinact®), a combination of opioid and antagonist and only suitable for appropriate patients (those approved for oxycodone). Generally used after use of stimulant laxative but prior to manual intervention[28]
- Rectal interventions (eg suppositories and enemas).

The CS concludes that *'There is currently no guidance around the use of methylnaltrexone or naloxone-oxycodone.'*

ERG Comment: The ERG notes that the company does not describe the best patient response outcomes for assessing treatments of OIC. A review by Camilleri 2011[17] indicates that adverse events and severity scores (Patient Assessment of Constipation Symptoms, PAC-SYM) have been used for gastrointestinal tolerance. There is a clinician administered patient questionnaire (Bowel Function Index) used in cancer pain and non-cancer pain patients, based on a 0-100 scale. A new daily bowel function diary has also been produced in line with patient response outcomes following guidance from the FDA. It supports both patient relevant severity scores and composite endpoints (spontaneous bowel movement, SBM and spontaneous complete bowel movement, SCBM) preferred by reimbursement agencies. A SBM was defined as a bowel movement (BM) that occurred in the absence of laxative, enema, or suppository use within the preceding 24 hours. A SCBM is defined as a spontaneous bowel movement that was associated with a sense of complete evacuation.[29] According to the clinical study reports for KODIAC 4 and 5[30, 31],

[redacted]. The CS used the following outcomes to assess clinical effectiveness (see Sections 6.7 and 6.9 of the CS): spontaneous bowel movements, complete bowel movements (CBM), rescue medication, discontinuations due to adverse events (DAE) and treatment emergent adverse events (TEAE). Tables 81 and 82 of the CS list adverse events in KODIAC 4 and 5 (Table 3).

Compared to the final scope some outcomes were not clearly considered and/or reported in the CS, eg effects on analgesic efficacy, PAC-SYM and bowel function diary. Other outcomes, such as *'upper gastrointestinal symptoms including nausea'* (CS) are reported but not discussed in detail in spite of their low incidence.

Table 3: Adverse events in KODIAC 4 and 5

Adverse event (AE)	**KODIAC 4**			**KODIAC 5**		
	Placebo (n=213)	**Naloxegol 12.5 mg (n=211)**	**Naloxegol 25 mg (n=214)**	**Placebo (n=231)**	**Naloxegol 12.5 mg (n=230)**	**Naloxegol 25 mg (n=232)**
Any AE	100 (46.9)	104 (49.3)	131 (61.2)	136 (58.9)	137 (59.6)	160 (69.0)
Any AE with outcome death	0	2 (0.9)	0	0	0	0
Any SAE (including death)	11 (5.2)	11 (5.2)	7 (3.3)	12 (5.2)	14 (6.1)	8 (3.4)
Any AE causing treatment disc.	12 (5.6)	9 (4.3)	22 (10.3)	12 (5.2)	12 (5.2)	24 (10.3)
Abdominal distension	4 (1.9)	7 (3.3)	5 (2.3)	5 (2.2)	4 (1.7)	6 (2.6)
Abdominal pain	7 (3.3)	18 (8.5)	27 (12.6)	18 (7.8)	25 (10.9)	44 (19.0)
Abdominal pain upper	4 (1.9)	3 (1.4)	11 (5.1)	3 (1.3)	5 (2.2)	6 (2.6)
Anxiety	NR	NR	NR	4 (1.7)	5 (2.2)	4 (1.7)
Back pain	5 (2.3)	0	7 (3.3)	4 (1.7)	12 (5.2)	12 (5.2)
Blood thyroid stimulating hormone increased	NR	NR	NR	0	5 (2.2)	0
Diarrhoea	9 (4.2)	7 (3.3)	20 (9.3)	10 (4.3)	18 (7.8)	21 (9.1)
Dizziness	NR	NR	NR	5 (2.2)	8 (3.5)	3 (1.3)
Fall	5 (2.3)	3 (1.4)	3 (1.4)	3 (1.3)	6 (2.6)	1 (0.4)
Fatigue	NR	NR	NR	3 (1.3)	3 (1.3)	6 (2.6)
Flatulence	4 (1.9)	9 (4.3)	12 (5.6)	7 (3.0)	4 (1.7)	14 (6.0)
Headache	4 (1.9)	5 (2.4)	8 (3.7)	8 (3.5)	12 (5.2)	12 (5.2)
Hyperhidrosis	1 (0.5)	0	9 (4.2)	NR	NR	NR
Hypertension	NR	NR	NR	2 (0.9)	2 (0.9)	6 (2.6)
Nasopharyngitis	NR	NR	NR	1 (0.4)	2 (0.9)	7 (3.0)
Nausea	10 (4.7)	15 (7.1)	16 (7.5)	10 (4.3)	14 (6.1)	20 (8.6)
Pain in extremity	NR	NR	NR	1 (0.4)	5 (2.2)	7 (3.0)
Sinusitis	NR	NR	NR	2 (0.9)	3 (1.3)	7 (3.0)
Upper respiratory tract infection	6 (2.8)	6 (2.8)	6 (2.8)	6 (2.6)	3 (1.3)	5 (2.2)
Vomiting	7 (3.3)	3 (1.4)	6 (2.8)	6 (2.6)	7 (3.0)	14 (6.0)

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 4: Statement of the decision problem (as presented by the company)

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with opioid-induced constipation	Adults with opioid-induced constipation who have had an inadequate response to laxative(s)	As per anticipated licensed indication: the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).[25] *[NB: Please note footnote 1]*
Intervention	Naloxegol	As defined by scope	N/A
Comparator(s)	Oral laxative treatment without naloxegol For adults in whom oral laxative(s) have provided inadequate relief: Methylnaltrexone Naloxone-oxycodone Rectal interventions	For adults in whom oral laxative(s) have provided inadequate relief: Oral laxative(s) treatment without naloxegol (ie rescue medication is used as a proxy for stimulant laxative used PRN) Methylnaltrexone Naloxone-oxycodone Rectal interventions	As per anticipated licensed indication as above.
Outcomes	• Frequency of SBMs • Symptoms of constipation • Use of rescue medication or interventions • Response rate • Upper GI symptoms including nausea • Effects on analgesic efficacy • Adverse effects of treatment • HRQoL	As defined by scope	N/A
Economic analysis	Cost per QALY Time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services	As defined by scope	N/A

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	perspective.		
Subgroups to be considered	If the evidence allows, the following subgroup will be considered: • Adults for whom previous treatment with laxatives has been unsuccessful in providing adequate relief	Adults with opioid-induced constipation who have had an inadequate response to laxative(s) and who are receiving a Step 3 opioid as defined by the WHO pain ladder	The WHO analgesic ladder is an established pain management paradigm that classifies opioid medication into three steps, Step 3 being the strongest opioids. Patients with OIC who are prescribed a Step 3 opioid represent a clinically valid sub-group of patients who are likely to benefit from the introduction of naloxegol. NICE CG 140 states that constipation affects nearly all patients receiving strong opioid treatment.[6] Severe OIC as a consequence of taking strong opioids is particularly common in palliative care patients. the higher doses of opioids that are typically prescribed to reduce severe pain subsequently result in more severe adverse effects[32] Also a survey of 29 healthcare professionals confirmed that the more severe forms of OIC are likely to be linked to the use of strong opioids and that this is therefore a clinically relevant sub population.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation.	The decision problem addressed by this submission reflects the anticipated licensed indication for naloxegol	N/A

GI= gastrointestinal; HRQoL= Health related quality of life; N/A= not applicable; OIC= opioid-induced constipation; SBM= spontaneous bowel movement; WHO= World Health Organisation
1: The ERG noted a discrepancy regarding which population was used. While results for the intervention (naloxegol) have been reported for 'Adults with opioid-induced constipation who have had an inadequate response to laxative(s)' (LIR population), results for the whole population were given for the comparators (see comments on indirect and MTC analyses in Sections 4.4 and 4.5 for further details).

3.1 Population

The final scope described the patient population as follows: *'Adults with opioid-induced constipation'*.[33] In contrast, the definition in the company's submission is narrower, ie *'Adults with opioid-induced constipation who have had an inadequate response to laxative(s)'*.[11] This anticipated the licensed indication, granted by EMA in December 2014: *'Moventig is indicated for the treatment*

of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).'[20]

As detailed in Section 2.2 of this report, there is some uncertainty regarding the definition of laxative inadequate response (LIR) it would appear that the definition of LIR used by the company is a broad definition of criteria for LIR.

3.2 Intervention

The intervention described in the CS (*'naloxegol'*) matches the intervention described in the final scope.

According to EMA Summary of Product Characteristics (SmPC)[20], *'The recommended dose of Moventig is 25 mg once daily. When naloxegol therapy is initiated, it is recommended that all currently used maintenance laxative therapy should be halted, until clinical effect of naloxegol is determined. (...) It is recommended that Moventig is taken in the morning, for patient convenience to avoid bowel movements in the middle of the night. Moventig should be taken on an empty stomach at least 30 minutes prior to the first meal of the day or 2 hours after the first meal of the day'.* EMA recommends dose adjustments for

- patients with moderate or severe renal insufficiency, ie a starting dose of 12.5 mg once daily. Naloxegol should be discontinued *'if side effects impacting tolerability occur'.*
- patients taking moderate CYP3A4 inhibitors (eg diltiazem, verapamil), ie a starting dose of 12.5 mg once daily.

EMA does not recommend dose adjustments based on age, for patients with mild to moderate hepatic impairment, and patients with cancer-related pain. Safety and efficacy have not been established for patients with severe hepatic impairment and in children.

3.3 Comparators

The CS amended the wording used in the final scope (change underlined): *'for adults in whom oral laxative(s) have provided inadequate relief: Oral laxative(s) treatment without naloxegol (<u>ie rescue medication is used as a proxy for stimulant laxative used PRN)</u>; Methylnaltrexone; Naloxone-oxycodone; Rectal interventions'.*

As detailed in Section 4.1.2 of this report, it should be noted that Table 3 of the CS (*'Eligibility criteria used in search strategy for RCT evidence'*), also includes 'best supportive care' which was neither clearly defined nor was included in the scope for this population. The CS comparator criteria did not clearly include rectal interventions (suppositories or manual evacuation) nor was this included in the clinical effectiveness section although it was included in the scope.

3.4 Outcomes

The outcomes in the CS match the outcomes described in the final scope (*'frequency of spontaneous bowel movements; symptoms of constipation; use of rescue medication or interventions; response rate; upper gastrointestinal symptoms including nausea; effects on analgesic efficacy; adverse effects of treatment; health-related quality of life'*). However, as detailed in Section 2.2 of this report, some outcomes were not considered or discussed in the CS.

3.5 Other relevant factors

The CS did not include a specific section on equity considerations and *'no potential equality issues relating to naloxegol as a treatment for opioid-induced constipation'* were identified.

The ERG is not aware of any ongoing application for a patient access scheme (PAS). End of life criteria are not relevant for this project.

According to Section 4 of the CS, *'There is no restriction for its use in specific patient populations, thus unlike methylnaltrexone and naloxone-oxycodone, naloxegol is appropriate for use in a wider patient population'*. As described in Section 3.2 above, EMA recommends dose adjustments for patients with moderate or severe renal insufficiency and for patients taking moderate CYP3A4 inhibitors. Furthermore, safety and efficacy have not yet been established for patients with severe hepatic impairment and in children.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies, was used to inform this critique.[34] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[35] The ERG has presented only the major limitations of each search strategy in the main report. Further criticisms of each search strategy can be found in Appendix 1.

Clinical effectiveness

On page 47 the company stated that in order to identify randomised controlled trial (RCT) evidence, a systematic review was conducted in October 2013 in part as an update to a 2008 Cochrane review. No reference was given for the Cochrane review. In their response to clarification, the company confirmed that this was the 2008 review by McNicol et al.[36] The ERG requested clarification regarding the search strategies reported for this section, as those provided only appeared to search for one of the comparator groups: laxatives versus placebo. The company confirmed that there had been an error and that additional strategies had not been included in the original submission, these strategies were provided in the response to clarification.[37] The ERG noted a disparity in the reported scope of the laxative search within the response to clarification. In item 75 the company stated the search reported in the original submission was intended to retrieve *'placebo-controlled trials of laxatives that were not identified as part of the original Cochrane review or the update of that review'*[37], however in response to question 73 where the ERG queried the lack of an update for this search, the company responded *'The purpose of this search was to identify studies that compared two laxatives to each other, or a laxative versus placebo'*. This is contrary to the first statement and upon a second inspection the ERG can confirm that the strategy reported would only retrieve studies comparing laxative against placebo, not laxative versus laxative. Due to time constraints the ERG was unable to conduct and screen a new search for this group, so it is unclear what impact this omission may have had on results.

The additional searches, sent at clarification, provided details of an update search to the original Cochrane review conducted in September 2012 which was designed to retrieve pharmaceutical interventions of interest excluding laxatives. This search was further updated in October 2013. The company reported that relevant papers identified by the original Cochrane review were also included in the review.

According to the company a third update was conducted in August 2014 to identify any recent studies of methylnaltrexone and naloxone-oxycodone only. The company stated that the searches were identical to the Cochrane update, with the exception that only terms relevant for the interventions methylnaltrexone and naloxone-oxycodone were included. These strategies were not provided as the company reported that line-by-line search yields were not documented, however overall numbers were provided.

After examination of the searches sent at both clarification and in the original submission, the search terms for naloxegol appear limited, eg the terms naloxegol and moventig, do not appear to have been included in the strategies detailed in Section 10.2. The ERG queried if the searches reported in Sections 6.8 and 10.6 were screened for RCTs and adverse events. The company responded that *'the searches reported in section 6.8 and 10.6 were not screened for papers of interest to other sections (ie 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). Both of these studies were already included elsewhere in the submission.'[37]

Given this response the ERG reran and rescreened the Medline and Embase searches detailed in Section 10.6 for both RCTs and adverse events, however no additional includes were identified.

Also missing from the reported strategies was the final comparator group including enemas and disimpaction which did appear in the inclusion criteria in Section 10.2.6, however this is justified on page 39 of the submission where the company states '*Rectal interventions (enemas, suppositories): used as a rescue intervention when all other treatments have failed or been exhausted. As naloxegol is not intended for use in an acute rescue setting, but rather as a chronic treatment to directly target the cause of OIC in the GI tract, rectal interventions were not considered a relevant comparator in the current submission. Thus, AstraZeneca would position rectal interventions after failure of naloxegol treatment.'*[11]

Searches were carried out on all databases required by NICE. The host, search dates for the original and update searches were reported for all resources. Additional searches were reported, including conference proceedings and clinical study reports provided by the company.

Indirect and mixed treatment comparisons

Section 10.4 states *'The clinical search described in Section 6.1 and Section 10.2 was also designed to identify eligible studies for comparator interventions'*. In utilising the same strategies reported in Section 10.2 the same limitations as described above will have applied.

Adverse Events

Section 10.8 states *'A specific search strategy was not conducted for adverse events. However, the clinical systematic review described in section 6.1 and section 10.2 was also designed to identify eligible studies for adverse events associated with Naloxegol'*.[11] As previously stated, the ERG had queried whether the searches described in Section 10.6 were screened for adverse events as the strategies submitted for 10.2 both in the initial submission and in the response to clarification appear to omit key terms for naloxegol. The ERG reran and rescreened the Medline and Embase searches detailed in Section 10.6 for adverse events, however no additional relevant studies were identified.

Cost-effectiveness

Searches were carried out on all databases required by NICE. The host, date span and search dates were reported for all resources. Additional searches included hand searching the reference list of included studies, searches of conference proceedings, CEA registry and both the NICE, SMC and RePEc websites. Previous NICE technical appraisals and guidelines and SMC advice were also reviewed for relevant economic evaluations. The ERG was concerned that the economics filter utilised in the Medline and Embase searches appeared overly restrictive. The ERG reran the company's Embase search retrieving 189 results, the same search run with an alternative recognised economics filter[38] retrieved 917 results (Appendix 1). It is unlikely however that any economic studies for naloxegol would have been missed due to the additional searches carried out on NHS EED, Econlit and the supplementary searches detailed above. Without screening these new results the ERG is unable to say whether additional relevant information in comparator treatments would have been missed.

Measurement of health effects/HRQoL

Searches were carried out on all databases required by NICE. The host, date span and search dates were reported for all resources. Additional searches of conference proceedings, previous NICE and SMC submissions, RePEc, CEA Registry, EQ-5D website and the checking of reference lists were

also conducted. The ERG queried the use of a language limit and its possible impact on the recall of results, the company replied:

'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.*[39]
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.*[37]*'*

The ERG accepts the reasoning expressed in items 1 and 3, however on closer inspection the ERG do not agree with the statement in item 2 and note that the paper used to support the company's claim that it is appropriate to restrict to English language concludes *'There were conflicting findings about the methodological and reporting quality of English-language versus LOE* [languages other than English] *trials. These findings do not rule out the potential for language bias when language restrictions are used. Searches should include LOE studies when resources and time are available to minimize the risk of a biased summary effect.'*[39]

Summary of searching

Searches were carried out on all databases required by NICE. The searches documented were easily reproducible and the submission reported searches of several additional resources, including conference abstracts and other relevant resources including trials databases, specialist and organisational websites, and the checking of references lists. The searches documented in the initial CS contained some areas of weakness, only those relating to reproducibility or those potentially consequential to the recall of results were included in the points of clarification letter forwarded to the company by NICE. The company addressed all the points of concern raised by the ERG in their response to clarification. However, despite the additional searches provided at clarification the ERG still has concerns regarding the comprehensiveness of searches for comparator treatments. Unfortunately, the ERG does not have the time or recourses to conduct and screen new searches. Therefore, the implications of these limitations are not known.

4.1.2 Inclusion criteria

Both RCTs and non-RCTs were identified according to the criteria described in Table 5. Papers excluded were not documented in detail. Papers could be further excluded after this stage if they did not '*yield the final data set'* or were unsuitable for mixed treatment comparison (MTC) analyses.

ERG comment: the ERG critiqued whether the inclusion criterion of the CS deviated from that of the scope (Table 5). The ERG noted that the population criteria of the CS concentrates on the subgroup proposed in the scope of 'laxative inadequate responders' and not on the broader criteria of the scope, which is all patients with opioid-induced constipation. This was done to reflect the intended license population. Similarly, the outcomes of interest were broader in the scope than in the CS. The ERG noted that 'comparator' now includes 'best supportive care' which was neither clearly defined nor

was it included in the scope for this population. The CS comparator criteria did not clearly include rectal interventions (suppositories or manual evacuation) nor was this included in the clinical effectiveness section although it was included in the scope.

Table 5: The inclusion and exclusion criteria

	CS: Description	CS: Justification	ERG: CS criteria match the scope	ERG: Included studies match the criteria	ERG: Excluded studies match the criteria
Inclusion criteria					
Population	• Laxative inadequate responders (LIR) • LIR taking Step 3 opioids (LIR + Step 3 opioids) • Data for a broader OIC population was included when data for a specific LIR population was not available	Population is relevant to the anticipated licensed indication for naloxegol and to the subgroup outlined in the final scope (see section 5). The LIR subgroup is defined as follows: taking ≥1 laxative class for ≥4 days during the last two weeks while reporting concurrent OIC symptoms of at least moderate severity	Does not match the broader criteria of the scope (adults with opioid induced constipation). The criteria of the CS match the proposed subgroup analysis of the scope.	KODIAC 4 and KODIAC 5 meet the broad criteria of the scope, but only data relevant to the CS criteria were included. Michna 2011, Rauck 2012, Meissner 2009, Lowenstein 2009, Simpson 2008, Arsenault 2014 and KODIAC 16 all meet the broad criteria of the scope but do not match the CS criteria (they do not report LIR).	Unclear.
Interventions	• Naloxegol	Consistent with the final scope	Consistent	KODIAC 4, KODIAC 5 and KODIAC 16 meet the criteria. Michna 2011, Rauck 2012, Meissner 2009, Lowenstein 2009, Simpson 2008, and Arsenault 2014 do not meet the criteria (naloxegol not included).	Unclear.
Comparators	• Methylnaltrexone (oral and subcutaneous) • Naloxone-oxycodone • Best supportive care: OTC or laxatives, polyethylene glycols, enemas, and disimpaction • Placebo	Consistent with the final scope (please see section 5 for further information)	The CS has included best supportive care, without any detailed definitions for this.	All studies included a comparator of interest.	Unclear.
Outcomes	• Change in SBMs at 4 weeks	Consistent with the final	Does not match the	All studies included an	Unclear.

	• Change in SBMs at 4–12 weeks • Response rate defined as ≥3 SBMs/week over 4 weeks • Discontinuations due to adverse events • TEAEs • Proportion of patients with ≥3 complete SBMs/week over 4 weeks	scope and for use in the economic model (see section 5)	broader criteria of the scope (frequency of SBM, symptoms of constipation, use of rescue medication/interventions, response rate, upper GI symptoms, analgesic efficacy, TEAE, health related quality of life).	outcome of interest.	
Study design	Placebo- and active-controlled Phase II and III RCTs with at least one arm randomised to an intervention of interest alone or in combination with any other pharmacological agent	RCTs prioritised as per STA guidance.	N/A. Scope did not provide criteria for study design.	KODIAC 16 is a phase 1 non-RCT and therefore does not meet the CS criteria. All other studies were phase II or III and met the CS criteria.	Unclear.
Language restrictions	English language only	To reduce the number of hits and to identify studies in patient populations relevant to the UK setting	N/A. Scope did not provide criteria for language.	All studies were reported in English language.	Unclear.
Exclusion criteria					
Population	Patients without OIC or mixed populations in which outcomes for OIC patients are not reported separately	Not relevant to the final scope	N/A. Scope did not provide exclusion criteria.	All studies met the criteria.	Unclear.
Interventions	Studies that do not include a treatment arm with any of the selected μ-receptor opioid antagonists, agonist/antagonists, partial agonists, or laxatives	Not relevant to the final scope	N/A. Scope did not provide exclusion criteria.	All studies met the criteria.	Unclear.
Comparators	Studies that do not include a treatment arm with any of the selected comparators of interest	relevant to the final scope	N/A. Scope did not provide exclusion criteria.	All studies met the criteria	Unclear.
Outcomes	Studies lacking relevant data on any clinical efficacy,	Not relevant to the final scope	N/A. Scope did not provide exclusion criteria.	All studies met the criteria.	Unclear.

	safety, and tolerability outcomes of interest				
Study design	• animal, in vitro, pharmacokinetic, or pharmacodynamic studies • reviews (including systematic),letters to the editor, opinions, studies without abstracts • pooled analyses or meta-analyses • non-randomised studies • RCTs that were not Phase II or III	These types of records represent lower levels of evidence and were excluded to minimise potential sources of bias or represent evidence that is not appropriate for inclusion in this submission.	N/A. Scope did not provide exclusion criteria.	KODIAC 16 is an ongoing trial which is currently recruiting and therefore has no data.	Unclear.

ERG Comment: The ERG found some inconsistencies in how the inclusion and exclusion criteria were defined and adhered to. These are listed below:

- Table 43 of the CS lists eight studies that were used to conduct the MTC. All of these are placebo-controlled, namely two studies of naloxegol (KODIAC 4, KODIAC 5)[30, 31], two of methylnaltrexone (Michna 2011, Rauck 2012)[40,41], and four studies of naloxone (Arsenault 2014, Meissner 2009, Lowenstein 2009, Simpson 2008)[42-45]. This further confirms the observation (see Section 4.1.1) that no non-placebo comparisons, eg trials comparing naloxone versus methylnaltrexone, have been included. Such additional trials would have been able to contribute to the mixed-treatment comparison and could have led to different results.[46]
- The CS does not clearly report which studies were excluded at the full paper stage or studies that were not feasible for MTC. In Figure 2, 32 studies were excluded at the full paper stage, it is a concern that: eight studies were excluded for being non-randomised (not an exclusion criteria) and two studies were excluded because they did not report outcomes of interest. Twenty-six studies were excluded in the feasibility analysis.

  The company sent a list of the 26 studies in the clarification letter. This illustrates that 11 studies were excluded because the comparator was not of interest (ALKS 37, alvimopan, bevenopran, TD-1211, lubiprostone and prucalopride). The first three of these drugs are mu-opioid receptor inhibitors and should not have been excluded according to the scope. One study was excluded because the naloxegol data were not presented for the LIR subgroup. [47] However, in the studies included for comparators data were not presented for the LIR population either. Five studies were excluded because they were in a malignant pain population; this was not an exclusion criterion but they were likely excluded because the population would not be considered similar to that of the naloxegol studies which are in a non-malignant pain population. Nine studies were excluded due to outcome, follow-up or sample size; the ERG agreed with all these exclusions except for two studies, the Naloxegol Phase II study and the CLB FNB naloxone PR study.[47, 48] This study was excluded due to a lack of outcomes of interest and follow-up times, however the ERG noted that discontinuations due to adverse events (DAE) and treatment emergent adverse events (TEAE) were reported at 12 weeks which are all reported in the KODIAC trials and therefore MTC analyses would be possible at this time point for these outcomes.

Overall the inclusion criteria were not appropriate for a MTC analysis and this leads to a lack of clarity of how the studies were screened and selected for inclusion.

1. It is likely that including all interventions of interest to the MTC would likely result in the inclusion of more studies which could alter the overall findings.
2. As described above (second bullet point), some potentially relevant studies have been missed.
3. The differences in the inclusion specification of the ‘population’ between the scope and the CS report is likely to have reduced the number of included studies by limiting the naloxegol studies to the subgroup (LIR) in the CS. In addition this alteration of the scope leads to a difference between the population of the intervention and that of the comparator which is not appropriate (intervention is for LIR+ OIC, whilst comparator is for all OIC).

4.1.3 Critique of data extraction

No details were given for the data extraction of randomised controlled studies (outlined in Section 10.2.7 of the CS). Details were provided for non-randomised studies (outlined in Section 10.6.7 of the

CS) and were as follows: *'Relevant information was extracted into the STA template by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion'.*

ERG Comment: Details of extracted data were provided for KODIAC 4 and 5. However, insufficient details were provided in the CS for the comparator studies. Minimal details were presented for comparator study design, quality and data (Tables 43-45 of the CS). However no details were presented for baseline characteristics (eg age, disease severity, pain intensity, opioid dose, previous laxative use), it is unclear if the data were extracted and its absence does not allow assessment of the similarity of the studies included in the MTC (discussed further in section 4.3).

These limitations prevent further analyses based on baseline characteristics (for pain intensity, opioid dose, duration of opioid use, duration of OIC, previous laxative use).

4.1.4 Quality assessment

Nine trials were included in the CS. The quality assessments for KODIAC 4 and 5 were summarised in Table 13 (6.4.3) and more fully in Table 148 (Appendix 3) of the CS. The ERG made comments on these assessments based on Table 148 of the CS and the clinical study reports[30, 31], this information is summarised in Table 6, Table 7 and Table 8. Quality assessments for Michna 2011[40], Rauck 2012[41], Meissner 2009[43], Lowenstein 2009[44], Simpson 2008[45] and Arsenault 2014[42]) were summarised in Table 44 (6.7.2) and more fully in Appendix 5 (10.5.1) of the CS. The ERG made comments on these assessments based on the full paper publications. The non-RCT study (KODIAC 16)[49] was not assessed for quality (10.7, Appendix 7) nor included in the MTC.

ERG Comment: The ERG agrees with the company's assessment on most items. Two studies were reported as abstracts only and therefore the quality assessments were largely unclear (Rauck 2012 and Arsenault 2014).

Disagreements with the company assessment of study quality were as follows:

- Imbalances in drop-outs between groups: We noted that in three trials (KODIAC 5, Michna 2011, Meissner 2009) the placebo group had fewer discontinued patients and fewer discontinuations due to adverse events; or the different treatment arms reported different rates of discontinuation (Simpson 2008).
- Unclear risk of bias: For certain domains the ERG disagreed with the CS assessment because the ERG could find no evidence for the assessment and deemed it to be 'unclear risk of bias'.

Table 6: Summary of the quality assessment results for the pivotal RCTs (KODIAC 4 and KODIAC 5) and ERG critique

	KODIAC 4[30]	**ERG comment**	**KODIAC 5[31]**	**ERG comment**
Was randomisation carried out appropriately?	Yes	Low risk of bias	Yes	Low risk of bias
Was the concealment of treatment allocation adequate?	Yes	Low risk of bias	Yes	Low risk of bias
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Low risk of bias. It should be noted that placebo had lower lifetime opioid use (median of 60 months compared to 72-84)	Yes	Low risk of bias
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Low risk of bias	Yes	Low risk of bias
Were there any unexpected imbalances in drop-outs between groups?	No	Low risk of bias	No	High risk of bias. It should be noted that placebo had lower numbers of discontinued patients with n= 44 (AE= 12) compared to 25 mg naloxegol with n= 59 (AE= 24).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Low risk of bias	No	Low risk of bias
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Low risk of bias	Yes	Low risk of bias

Table 7: Summary of the quality assessment results for the methylnaltrexone studies included in the MTC and ERG critique

	methylnaltrexone			
	Michna 2011[40]	**ERG comment**	**Rauck 2012[41]**	**ERG comment**
Was randomisation carried out appropriately?	Yes	Low risk of bias	Not clear	Unclear risk of bias
Was the concealment of treatment allocation adequate?	Yes	Low risk of bias	Not clear	Unclear risk of bias
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Low risk of bias	Yes	Unclear risk of bias
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Low risk of bias	Not clear	Unclear risk of bias
Were there any unexpected imbalances in drop-outs between groups?	No	High risk of bias. Treatment arms both had n=28 discontinued, whereas for placebo n=16	Not clear	Unclear risk of bias
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Low risk of bias	No	Low risk of bias
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Low risk of bias (all patients who received at least 1 dose of study drug – mITT).	Not clear	Unclear risk of bias

Table 8: Summary of the quality assessment results for the naloxone studies included in the MTC and ERG critique

	naloxone							
	Meissner 2009[43]		**Lowenstein 2009[44]**		**Simpson 2008[45]**		**Arsenault 2014[42]**	
		ERG comment		**ERG comment**		**ERG comment**		**ERG comment**
Was randomisation carried out appropriately?	Yes	Unclear risk of bias	Not clear	Unclear risk of bias	Not clear	Unclear risk of bias	Not clear	Unclear risk of bias
Was the concealment of treatment allocation adequate?	Not clear	Unclear risk of bias	Yes	Unclear risk of bias	Not clear	Unclear risk of bias	Not clear	Unclear risk of bias
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Low risk of bias	Yes	Low risk of bias	Yes	Low risk of bias	Not clear	Unclear risk of bias
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Low risk of bias	Yes	Low risk of bias	Yes	Low risk of bias	Yes	Unclear risk of bias
Were there any unexpected imbalances in drop-outs between groups?	No	High risk of bias (fewer patients withdrew from placebo (12%) than treatment groups (17.6-22%).	No	Low risk of bias	No	High risk of bias (fewer patients withdrew from Oxycodone/ Naloxone PR (11.9%) than Oxycodone PR (16.9%). In particular discontinuation due to AE is lower in Oxycodone/ Naloxone PR (4.9%) than Oxycodone PR (11.3%)	Not clear	Unclear risk of bias
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Low risk of bias	No		No	Low risk of bias	Not clear	Unclear risk of bias
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Low risk of bias	Yes	Low risk of bias (all patients who received at least 1 dose of study drug and one assessment of primary outcome– mITT with LOCF).	Yes	Low risk of bias (all patients who received at least 1 dose of study drug – mITT).	Yes	Low risk of bias

4.1.5 Evidence synthesis

Both the direct meta-analysis and indirect meta-analysis results were obtained using the same mixed treatment comparison (MTC) analysis. Section 6.6.1 states that *'The direct meta-analysis examines the same comparisons as the MTC, without incorporating ancillary arms of the evidence network'*. This was used to compare each treatment with placebo. The direct meta-analysis was conducted in R using the metaphor package (version 1.6) and used a random effects Bayesian model. Fixed effect models were only used if there was a strong rationale for their use. Statistical heterogeneity was assessed using the I^2 statistic and was low for most outcomes apart from discontinuation due to adverse events, and treatment-emergent adverse events.

Comparisons between the different treatments were also made using a MTC analysis which was conducted using OpenBUGs. Details are given in Section 6.7.5 and the main analysis consisted of *'a 50,000 run-in iteration phase and a 50,000 iteration phase for parameter estimation using two chains. Convergence was confirmed through use of three-chain Brooks-Gelman-Rubin (BGR) plots and inspection of the ratios of mean change error to the standard deviations of the posteriors; values of greater than 5% are strong signs of convergence issues.'* As it was considered that there was methodological heterogeneity between the studies included in the MTC a random-effects model was thought to be *'especially appropriate'*. A global assessment of statistical heterogeneity for the MTC was made by considering the size of tau (the estimate of the between studies standard deviation). As for the direct meta-analysis, random effects models formed the base case, with fixed effects models used only in cases where there was a strong rationale. Model fit was assessed using the deviance information criteria (DIC), an analysis of residual deviance was not considered necessary due to the simplicity of the network.

In addition to the MTC analyses, indirect comparisons were performed using the Bucher method to compare pairs of treatments which were linked by a common comparator.

In all analyses there were two main populations used for the KODIAC 4 and 5 trials:

1. The anticipated licensed population (LIR)
2. The LIR plus Step 3 opioid population

ERG Comment: Forest plots were presented for all outcomes in Appendix 10.21. No details were given of the actual method used in the indirect comparison but given that the results are reported as credible intervals it appears that these results were also obtained from one of the Bayesian analyses.

The actual methods used for the meta-analysis are appropriate but they do seem to be overly complicated given the simplicity of the networks (all treatments are connected via placebo) and the small number of studies available for each outcome (between three and six). It was unclear why direct meta-analysis was performed using Bayesian methods in R, when these results could also have been obtained from the Bayesian model using OpenBUGs. There was no need to use both a MTC and indirect comparisons. Given that all treatments could be connected via placebo, an indirect comparison using the Bucher method would have been acceptable as a more simple analysis without additional MTC.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The clinical evidence was initially based on the two KODIAC trials 4 and 5. These are described in Section 6, pages 45-133 of the CS. Both trials compare 12.5 mg and 25 mg naloxegol and placebo. Meta-analysis was performed for both drug doses in comparison to placebo and the results are presented in Tables 41 and 42 of the CS.

ERG Comment: This approach is sensible given that placebo is the comparator in both trials. However, it should be noted that the final scope did not define placebo to be a relevant comparator.

It is also important to note that the cost-effectiveness section compares naloxegol with placebo. In addition, it compares 'naloxegol plus rescue bisacodyl' versus 'placebo plus rescue bisacodyl'. As explained in Section 5.2.4, the ERG would argue that the treatments plus rescue bisacodyl correspond better to the trial arms.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

'*8 RCTs were identified for inclusion in the MTC'* (KODIAC 4[30], KODIAC 5[31], Michna 2011[40], Rauck 2012[41], Meissner 2009[43], Lowenstein 2009[44], Simpson 2008[45], Arsenault 2014[42]) and one non-RCT (KODIAC 16)[49] was included. Details of the eight RCTs are given in Table 43 of the CS, whilst the non-RCT trial was detailed in Table 6 of the CS.

ERG Comment (similarity of population): The population of each included trial was outlined in Tables 43 and 47 of the CS. Overall the studies were similar; the studies were of non-malignant pain largely due to back pain. It would have been advantageous to further analyse population on the basis of baseline characteristics (for pain intensity, opioid dose, duration of opioid use, duration of OIC, previous laxative use). The ERG checked the study reports for this data but no characteristics were consistently reported between trials to make this useful. Further scrutiny of the trials indicated that Meissner et al[43] reported results from cancer pain in approximately 3% of patients. It is unclear why this trial has been included since malignant pain was used as an exclusion criterion for feasible studies. The percentage of patients is probably low enough for this to not be a concern to the overall results. In KODIAC 4 and 5 the population of patients is clearly stated as '*data for the LIR and LIR+3 step opioid subgroup is [sic!] included in the MTC' (Table 43).* However the ERG note that in Table 45 the quoted results were for the whole ITT set population and not the LIR subgroup. LIR subgroup data for naloxegol should be compared to LIR subgroups in the comparators; however it appears that data for both naloxegol and comparators are derived from the whole population and are therefore similar (see comments on indirect and MTC analyses in Sections 4.4 and 4.5 for further details).

ERG Comment (similarity of posology): The treatment regimen for each trial was outlined in Table 43 of the CS. There was minimal information so the ERG prepared further details as outlined in Table 9. There are two naloxegol trials which have identical regimens. The ERG would not combine Michna 2011 in the MTC because as a subcutaneous injection, it is not considered similar to the other trials in which administration was oral.[50] Four trials were included of naloxone in combination with oxycodone. The dosing of naloxone was not clearly presented as it depended on the optimum analgesic effect of oxycodone (usually set at 40-80 mg/day), however the intended dosing regimens appeared similar. The definition of rescue treatment varied between the trials. Not enough information was reported to judge the similarity of rescue treatment. For most trials, laxatives were stopped previous to the trial but allowed as rescue during treatment. Two trials did not report rescue treatments (Arsenault 2014 and Rauck 2012). Two trials reported rescue treatment with oxycodone, presumably for pain relief (Meissner 2009, Lowenstein 2009). The other trials reported the use of bisacodyl.

Table 9: Similarity of posology

	Run in period?	**Treatment/Dose**	**Frequency of opioid inhibitor**	**SC/ oral**	**Concomitant opioids**	**Concomitant laxatives / rescue treatments**
KODIAC 4	Regimen stability was confirmed during the 2-week OIC confirmation period. All laxatives and other bowel regimens (prune juice and herbal products) were stopped during the 2-week OIC confirmation and the 12-week treatment period.	naloxegol 12.5 mg OD naloxegol 25 mg OD placebo OD	Once daily	oral	Stable maintenance opioid regimen (30 - 1000 mg of oral morphine or equivalent).	Bisacodyl (if a BM had not occurred within at least 72 hours of the last recorded BM).
KODIAC 5	Regimen stability was confirmed during the 2-week OIC confirmation period. All laxatives and other bowel regimens (prune juice and herbal products) were stopped during the 2-week OIC confirmation and the 12-week treatment period.	naloxegol 12.5 mg OD, naloxegol 25 mg OD placebo OD	Once daily	oral	Stable maintenance opioid regimen (30 - 1000 mg of oral morphine or equivalent).	Bisacodyl (if a BM had not occurred within at least 72 hours of the last recorded BM).
Michna 2011	No	methylnaltrexone 12 mg OD, methylnaltrexone 12 mg QAD, placebo OD	Once daily or once every two days.	sc	NR	Rescue laxatives were permitted during the study if the patient had no bowel movement for 3 consecutive days, at which point bisacodyl tablets (1 dose, up to 4 tablets orally). The incidence of rescue laxative use: placebo group = 61.7%, MNTX OD =38.7%, MNTX QAD =, 49.3%.

	Run in period?	Treatment/Dose	Frequency of opioid inhibitor	SC/ oral	Concomitant opioids	Concomitant laxatives / rescue treatments
Rauck 2012	No	methylnaltrexone 150 mg methylnaltrexone 300 mg methylnaltrexone 450 mg placebo	4 weeks daily, then 8 weeks PRN dosing	oral	NR	NR
Meissner 2009	Individuals were titrated and stabilised at an oxycodone PR dose of 40, 60 or 80 mg/day over 2 weeks. Patients on stable oxycodone PR 40, 60 or 80 mg/day entered a 1 week run in.	-naloxone 10 mg + 40-80mg oxycodone OD, -naloxone 20 mg + 40-80mg oxycodone OD, -naloxone 40 mg + 40-80mg oxycodone OD, -placebo + 40-80mg oxycodone	Once daily	oral	yes	Rescue medication was restricted to a maximum of five intakes of 10 mg oxycodone per week.
Lowenstein 2009	The run-in period (7 – 28 days) was designed to titrate oxycodone PR to an effective analgesic dose (60 – 80 mg oxycodone PR/day), convert patients to the study laxative (bisacodyl).	-Naloxone-PR mg + oxycodone PR OD (1:2) -Placebo + oxycodone PR OD	Once daily	oral	yes	Use of oxycodone immediate-release was permitted as rescue medication, (every 4 h as needed). Patients taking >2 doses of rescue medication/ day had their oxycodone PR dose up-titrated. Up-titration in a double-dummy manner to 120 mg/day oxycodone PR during the double-blind phase was permitted.
Simpson 2008	patients had their pre-study opioid converted to oxycodone PR and titrated to optimum analgesic effect, and were also converted to the standard laxative regimen using oral bisacodyl (7-28 days).	-Naloxone-PR mg + oxycodone PR (1:2) -Placebo + oxycodone PR	NR	oral	Yes	Bisacodyl.

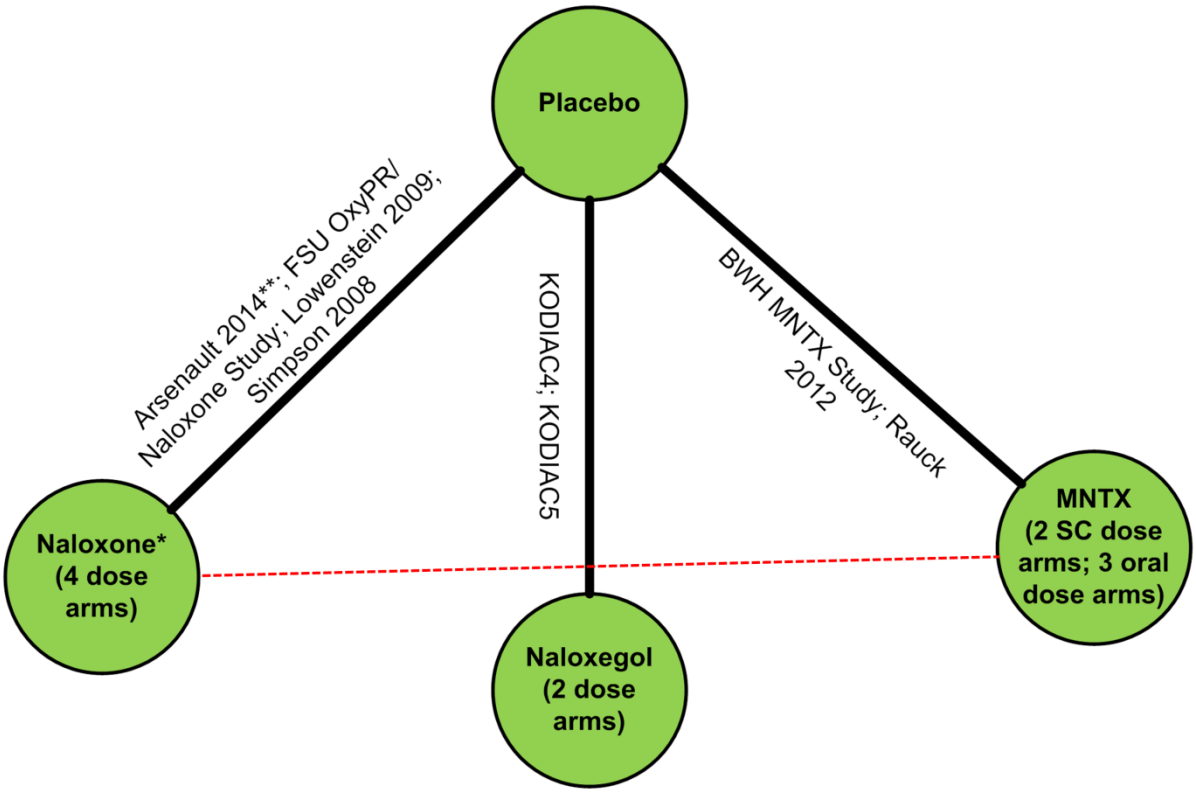
	Run in period?	**Treatment/Dose**	**Frequency of opioid inhibitor**	**SC/ oral**	**Concomitant opioids**	**Concomitant laxatives / rescue treatments**
Arsenault 2014	2-week run-in period, the daily dose of CR oxycodone was optimized (moderate pain and <=2 rescue IR oxycodone doses/day) to 60 or 80mg q12h	-Naloxone + oxycodone CR -Placebo + oxycodone CR	Twice a day	oral	Yes	NR
CR= controlled release; MNTX= methylnaltrexone; OD= once daily; PR= prolonged release; PRN= pro re nata (as required); QAD= once every other day; sc= subcutaneous						

4.4 Critique of the indirect comparison and/or multiple treatment comparison

ERG Comment (proposed network): The ERG noted that the network in Figure 11 of the CS is correct. However it should be noted that the studies to inform this network were not identified properly. The inclusion criteria for the intervention should have included all comparators of interest (as well as naloxegol) versus all comparators of interest. This may well have led to the inclusion of more studies and the network may have included some closed loops.

An example is given in Figure 1 which is a modified version of Figure 11 of the CS. While the original network (black lines) only allows indirect comparisons of active treatments via placebo, potential identification of head-to-head comparisons between two active treatments (in this example: MNTX versus naloxone) would allow to combine direct evidence (the red line) and indirect evidence (via placebo) in a mixed-treatments comparison.

Figure 1: MTC subgroup analysis network diagram (modified from CS)



ERG comment (feasible analyses and similarity of outcome and follow-up): To check the proposed feasibility of indirect and MTC analysis in the CS, the ERG assessed the similarity of the trials, eg whether equivalent outcomes were combined at equivalent follow-up times. A table of all outcomes reported in the included trials and follow-up times was prepared (Table 10). According to Table 45 of the CS only the following analyses were possible: mean change from baseline of SBM (4-12 weeks), SBM response (percentage with ≥3 SBM/week) at four weeks, SCBM response (percentage with ≥3 SCBM/week) at four weeks, discontinuation due to AE (4-12 weeks), and percentage with TEAE (four weeks). It is evident that symptoms of constipation, use of rescue medication/ interventions, upper GI symptoms (including nausea), analgesic efficacy or HRQoL were not analysed.

The ERG assessed whether the summary of results used to conduct the MTC comparisons was correct (Table 45). The ERG reproduced the table and commented on whether the extractions were accurate,

reported the outcome definition and follow-up times available. If additional results were available from trials not reported in Table 45 the ERG indicated these results as shown in Table 11.

This indicated the ERG agreed the following analyses were possible and reported in the CS:

- Mean change from baseline in SBMs/week (4–12 weeks), but note this should indicate a four week follow-up not 4-12, and is for the total population not the LIR.
- SBM response ((≥3 SBM/week) over four weeks (percentage) – note that the ERG could not find the reported results for KODIAC 4 in the clinical study report (CSR), the results the ERG found had higher percentage which followed the same pattern between treatment arms, therefore this should not overly influence the results. Also results were extracted from the full set not the LIR.

The following analyses showed discrepancies between the available data and the results reported:

- SCBM response (≥3 SCBM/week) at four weeks (percentage) – The definitions for SCBM response differs between KODIAC 4 and 5 (percentage days in week with ≥1 SCBM) and the other trials (patients >3 SCBMs/week) and therefore should not be combined. Note results were extracted from the full data set not the LIR subgroup in KODIAC 4 and 5.
- DAEs, 4-12 weeks (percentage): This analysis is feasible, but since the data for the KODIAC trials is at 12 weeks it could only be compared to the other 12 week trials (Lowenstein 2009, Simpson 2008), using the Bucher method.
- TEAE, four weeks (percentage) – the ERG could not find four week results for TEAE for the KODIAC trials and only found data relating to 12 weeks for this outcome. Therefore a Bucher analysis would be possible at 12 weeks when the KODIAC trials are compared with Lowenstein 2009.

ERG Comment (indirect and MTC analyses): the ERG was unable to replicate and check the results of the indirect and MTC analyses as the datasets used in the analyses were not provided in the CS. Table 45 states that it is a summary of the results used to conduct the comparisons but the data do not match the data given in other tables (eg Table 170 for proportion of patients with SBM response) nor does Table 45 make it clear which populations the data are for (LIR, or LIR with Step 3 opioids). It appears that this table applies to the ITT population and not those used in the MTC analysis. Therefore, we are unable to verify the accuracy of the reported results.

A further point regards the choice of fixed or random effects models. A table was presented which compares the deviance information criterion (DIC) for the fixed and random effects MTC models for each analysis (Table 56). Smaller DIC values indicate the more preferable model and based on this table the fixed effect model would be preferred (although the differences were generally very small), however the submission stated that *'based on the results of the DIC analysis, a random effects analysis was chosen over a fixed effects model'*. Their conclusion contradicts the reported DIC values. Both fixed and random effects model results were presented in the appendices however these were only for the comparisons with placebo, and not between treatments. Therefore it was not possible to assess how the choice of model affected the results comparing different treatments.

Table 10: Table of the outcomes requested in the scope and the outcomes reported within trials, as assessed by ERG

	Follow-up weeks	**Frequency of SBM**	**Symptoms of constipation**	**Use of rescue medication or interventions**	**Response rate**	**Upper GI symptoms including nausea**	**Effects on analgesic efficacy**	**Treatment AE**	**HRQoL**
KODIAC 4	4, 12	Mean days/ wk with > 1 SBM* Mean days/ wk with > 1 SCBM	Mean degree of straining mean stool consistency PAC-SYM	Mean weekly bisacodyl dose. n patients using an enema	>3 SBM*/wk Time to first post-dose SBM	GI AEs (including abdominal pain, nausea, and flatulence), 12 weeks.	Mean VAS pain score. Daily opioid dose.	AE. SAE. Death. Discontinuations due to AE. Multiple individual AE.	EQ-5D PAC-QOL
KODIAC 5	As for KODIAC 4								
Michna 2011	4	RFBM within 4 hrs of the first dose. Active injections/ patient with a RFBM within 4 hrs. Time to first RFBM. Weekly number of RFBMs.	Bristol Stool Form Scale scores straining, completeness of evacuation	Use of rescue laxatives		GI AEs (including abdominal pain, nausea, and diarrhoea)	SOWS OOWS	Treatment emergent AE. SAE. Discontinuations due to AE.	PAC-QOL
Rauck 2012	4	RFBM by 24h post first dose				Abdominal pain, nausea, flatulence and diarrhoea.			

	Follow-up weeks	Frequency of SBM	Symptoms of constipation	Use of rescue medication or interventions	Response rate	Upper GI symptoms including nausea	Effects on analgesic efficacy	Treatment AE	HRQoL
Meissner 2009	4		Bowel Function Index (BFI) stool frequency.	Mean (±SD) number of days with laxative number of patients taking laxatives.			Mean pain intensity (NAS score).	AE. Severe AE. Deaths. Discontinuations due to AE.	
Lowenstein 2009	4, 12	Median and % SCBM	Bowel Function Index (BFI). PAC-SYM.	Laxative use.		GI AEs (including abdominal pain, nausea)	Daily average Pain Intensity Scale (NRS). Mean supplemental analgesic use.	Discontinuations due to AE. TEAE.	
Simpson 2008	4,12	Mean number SCBM/week	Bowel Function Index (BFI) painful, burning and incomplete bowel movements (PACOI)	frequency of laxative and rescue medication		GI AEs (including abdominal pain, nausea, and diarrhoea)	Mean Pain Intensity Scale (NRS). BPI-SF.	Discontinuations due to AE. SAE.	
Arsenault 2014	5	>=3 SCBM	BFI	-	-	-	Mean VAS pain score.	SAE.	-

	Follow-up weeks	**Frequency of SBM**	**Symptoms of constipation**	**Use of rescue medication or interventions**	**Response rate**	**Upper GI symptoms including nausea**	**Effects on analgesic efficacy**	**Treatment AE**	**HRQoL**
Analysis possible			PAC-SYM outcomes match.	Specific outcomes do not match.		KODIAC 4 abdominal pain, nausea, Table 31. 12wks Vs. Lowenstein, Simpson. Others may be possible	Possible for VAS score, other outcomes do not match.	TEAE Vs. Michna	PAC-QOL not possible since Michna does not give sd for change from baseline.

*A SBM was defined as a BM without the use of rescue laxatives
BPI – SF= Brief Pain Inventory Short Form; BFI= Bowel Function Index; NAS= numerical analogue scale; NRS= Numerical Rating Scale; OOWS= Objective Opiate Withdrawal Scale; PACOI= Patient Assessment of Opioid-Induced Constipation summary score; RFBM= rescue-free bowel movements; SAE= serious adverse events; SOWS= Subjective Opiate Withdrawal Scale; VAS= Visual Analogue Scale

Table 11: ERG Assessment of summary of results from studies used to conduct the comparisons

Outcome	**naloxegol**		**methylnaltrexone**		**naloxone-oxycodone**			
	KODIAC 4[30]	**KODIAC 5[31]**	**Michna 2011[40]**	**Rauck 2012[41]**	**Meissner 2009[43]**	**Lowenstein 2009[44]**	**Simpson 2008[45]**	**Arsenault 2014[42]**
Mean change from baseline in SBMs/week (4–12 weeks)	Extractions: correct Definition: mean number of SBMs per week, change from baseline. Full set ITT Follow-up: **4**, 12 weeks	Extractions: correct Definition: mean number of SBMs per week, change from baseline. Full set ITT Follow-up: **4**, 12 weeks	Extractions: correct Definition: adjusted mean change from baseline in the number of weekly RFBMs m ITT Follow-up: **4** weeks	Extractions: NR Definition: ≥ 1/week RFBM change from baseline. Follow-up: **4** weeks	NR	NR	NR	NR
SBM response[†] over 4 weeks (%)	Extractions: couldn't find. P810 of CSR reports: 35.5% placebo, 52.6% 12.5mg, 59.3% 25mg. Definition: >3 SBMs/ week Full set ITT Follow-up: **4**, 12 weeks	Extractions: couldn't find. P866 of CSR reports: 38.4% placebo, 49.1% 12.5mg, 48.7% 25mg. Definition: >3 SBMs/ week Full set ITT Follow-up: **4**, 12 weeks	Extractions: correct Definition: > 3 RFBM/week mITT Follow-up: **4**weeks	NR	NR	NR	NR	NR
SCBM response[‡] at 4 weeks (%)	Extractions: correct Definition: percent number of days/ week with SCBM Full set ITT Follow-up: **4**, 12 weeks	Extractions: incorrect 25mg should be 30.3% Definition: percent number of days/ week with SCBM Full set ITT Follow-up: **4**, 12 weeks	NR	NR	NR	Extractions: correct Definition: % patients >3 SCBMs / week. LOCF Follow-up: **4**	Extractions: correct Definition: % patients ≥3 SCBMs / week. Follow-up: **4**	Extractions: correct Definition: % patients >=3 SCBM. ITT Follow-up: **5**

Outcome	naloxegol		methylnaltrexone		naloxone-oxycodone			
	KODIAC 4[30]	**KODIAC 5[31]**	**Michna 2011[40]**	**Rauck 2012[41]**	**Meissner 2009[43]**	**Lowenstein 2009[44]**	**Simpson 2008[45]**	**Arsenault 2014[42]**
DAEs, 4-12 weeks (%)	Extractions: correct Definition: Any AE leading to discontinuation. Full safety set Follow-up: 12 weeks	Extractions: correct Definition: Any AE leading to discontinuation. Full safety set Follow-up: 12 weeks	Extractions: correct Definition: discontinued due to AE. ITT Follow-up: **4** weeks	NR	Extractions: correct Definition: withdrawn due to AE. ITT Follow-up: **4** weeks	Extractions: correct Definition: discontinued due to AE. ITT Follow-up: **12** weeks	Extractions: correct Definition: discontinued due to AE. ITT Follow-up: **12** weeks	NR
TEAEs, 4 weeks (%)	Extractions: couldn't find. P1009 of CSR reports: 45.5% placebo, 47.9% 12.5mg, 60.3% 25mg. Definition: AE during treatment. Full safety set Follow-up: 12 weeks	Extractions: couldn't find. P1064 of CSR reports: 56.3% placebo, 56.5% 12.5mg, 66.4% 25mg. Definition: AE during treatment. Full safety set Follow-up: 12 weeks	Extractions: extraction s are possible but weren't performed. Definition: Treatment-emergent adverse events. Follow-up: 4 weeks	NR	Extractions: extraction s are possible but weren't performed. Definition: adverse events by absolute naloxone dose during the maintenance phase. Follow-up: 4 weeks	Extractions: extraction s are possible but weren't performed. Definition: Treatment-emergent adverse events. Follow-up: 12 weeks	NR	NR

AE= adverse event; CSR= clinical study report; DAE= Discontinuation due to adverse events; ITT= intention to treat; mITT= modified intention to treat; LOCF= last observation carried forward; NR= not reported; RFBM= rescue-free bowel movements; SBM= spontaneous bowel movement; SCBM= spontaneous complete bowel movement; TEAE= treatment-emergent adverse event

4.5 Additional work on clinical effectiveness undertaken by the ERG

It has already been noted that the data described in Table 45 of the CS refer to the ITT whole population of the KODIAC trials and yet the results for the analysis clearly indicate the data were derived from the LIR population (Tables 50-52). The CS does not clearly indicate the input data for the MTC (either whole ITT population or LIR subpopulation), therefore it is difficult to clarify which trials and which data were used to perform the analyses. To check what analyses were performed the ERG tried re-performing the MTC using both the LIR and the ITT whole population from the KODIAC trials together with the relevant comparators but was unable to replicate and check the results of the indirect and MTC analyses as the datasets used in the analyses were not provided in the company's submission (see ERG comment on indirect and MTC analyses in Section 4.4 for further details).

To clarify this point, we present quotes from the CS below.

Evidence of intended analysis of LIR subpopulation in MTC:

- Page 134 (Section 6.7.2), aim of MTC analysis: *'Populations of interest included laxative inadequate responders (the anticipated licensed population [LIR] and anticipated licensed population who are taking Step 3 opioids (anticipated licensed population + Step 3 opioids).'*
- Page 135 (Section 6.7.2), description of Table 43 in the CS: *'A summary of the methodology of the relevant RCTs included in the MTC subgroup analyses is presented in Table 43.'*
- Table 43 (page 136), patient population: *'OIC patients with non-malignant pain. Only data from the LIR and LIR + 3 step opioid subgroup is included in the MTC'* (KODIAC 4 and 5). No subgroups mentioned in the description of the other six studies.
- Figure 11 (page 140): *'MTC subgroup analysis network diagram'*
- Tables 50-55 (page 150-155), footnote: *'Populations included in comparisons were main trial populations for methylnaltrexone and naloxone and the LIR population for naloxegol.'*

Evidence of use of whole ITT population for MTC:

- Table 45 (page 140), summary of results: Data given in this table for KODIAC 4 and 5 was verified to be the whole ITT population from the CSR of KODIAC 4 and 5.
- Page 146 (Section 6.7.4), summary of data used in the analysis: *'The review found that only the naloxegol trials were able to provide data in the specific patient populations of interest (ie 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 (See Section 6.2.1).'*

4.6 Conclusions of the clinical effectiveness section

The results of clinical effectiveness presented in the executive summary all described the results from KODIAC 4 and KODIAC 5 trials and were therefore of naloxegol in comparison to placebo. The executive summary did not summarise those of the mixed treatment comparison. The results of the mixed treatment comparison (Tables 51 and 52 of the CS) indicate that naloxegol (12.5 or 25 mg) has similar efficacy to methylnaltrexone and fixed ratio combination naloxone (SBM, SCBM). The authors of the CS emphasised that the results from the MTC were limited by the use of different populations (LIR versus whole population) for the intervention and comparator.

Overall: There is no robust evidence of efficacy and safety between naloxegol and the comparators of interest.

5 COST-EFFECTIVENESS

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Objective of cost-effectiveness review

The objective of the cost-effectiveness review in the CS was to identify cost-effectiveness/cost-utility studies from the literature for naloxegol and comparator regimens for the treatment of opioid-induced constipation. The search strategies for the cost-effectiveness review are discussed in detail in Section 4.1.1.

5.1.2 Inclusion/exclusion criteria used in the study selection

The in- and exclusion criteria of the study selection could not be found in chapter 7 (cost-effectiveness) of the CS. The study selection criteria are presented in Appendix 10.2.6.

5.1.3 Included/excluded studies in the cost-effectiveness review

In total, 252 publications were identified. Upon removal of duplicate papers, 231 titles and abstracts were reviewed. Two hundred and twenty-one publications were excluded. Ten were ordered for full paper review, of which six were excluded, resulting in four relevant papers for final inclusion. In addition, one relevant SMC advice document[51] was identified and included. The identified studies evaluated interventions and comparators relevant to the submission and reported an ICER/cost per QALY. The economic evaluations were conducted in the UK, Belgium and the Netherlands. Of the five studies data extracted, two were available as full paper economic evaluations[52, 53], two were conference abstracts[54, 55] and one was a SMC advice document[51] obtained from the SMC website. A summary of all identified studies is presented in Appendix 2.

Reviewing the overall evidence, no economic evaluation was identified for naloxegol for the treatment of opioid-induced constipation. To address the lack of any published evidence for the cost-effectiveness of naloxegol, a *de novo* analysis was carried out. Table 12 depicts an overview of the included studies in the cost-effectiveness review.

Table 12: An overview of the included studies in the cost effectiveness review

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Sensitivity analyses
Gerlier L 2009, Netherlands[55], Belgium (Abstract)	Decision analytical model	Naloxone-oxycodone vs. oxycodone alone	Patients with moderate/severe non-cancer pain.	QALY gain	Incremental drug cost:	Incremental cost-effectiveness ratio at 12 months	Sensitivity analysis indicated that the proportion of patients experiencing at least one episode of OIC during a four week treatment period was the most sensitive parameter.
	Societal perspective Netherlands and Belgium		Age NR	Netherlands 0.0026	Netherlands €115	Belgium €25,421/QALY	PSA indicated that at a willingness to pay threshold of €20,000/QALY in the Netherlands and €30,000/QALY in Belgium, the probability of OXN being cost-effective was 58% and 63%, respectively.
	Time horizon: three and 12 months No discounting applied Clinical data from OXN3001 trial			Belgium 0.0026	Belgium €153	Netherlands €12,786/QALY Incremental cost-effectiveness ratio at three months OXN dominant vs. OXY in the Netherlands (data	

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Sensitivity analyses
	Utilities: SF-36 Deterministic and probabilistic sensitivity analysis conducted					not shown) Belgium €16,389/QALY	
Earnshaw SR 2010[53], Netherlands (full paper)	Decision analytical model Payer perspective of Netherlands Time horizon <12months	Methylnaltrexone bromide plus SOC vs. SOC	Advanced illness patients (cancer, cardiovascular disease, chronic obstructive disease and Alzheimer's disease) Median age: 71 years	QALYs gained 0.02 (MNTX plus SOC vs. SOC)	Total costs(drug costs + other medical costs) MNTX: €7151 SOC alone: €6170	Incremental cost per QALY MNTX + SOC vs. SOC: €40,865	The most influential parameter in the one-way sensitivity analyses was nurse time for management of constipation, which was varied ±30% but still fell within the €80,000 cost per QALY threshold PSA showed that at a threshold of €50,000/QALY and €80,000/QALY, the probability of MNTX being cost-effective was 61% and 93%, respectively

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Sensitivity analyses
	No discounting Clinical data from (NCT00402038) Utilities: EQ-5D One way sensitivity analyses and PSA conducted						
Dunlop W 2013[54], UK (abstract)	Model: NR UK NHS perspective Clinical data from an RCT Utilities: BFI to EQ-5D Deterministic sensitivity analyses	Naloxone-oxycodone vs. oxycodone alone	Patients with moderate/severe non-cancer pain, patients with moderate/severe cancer pain.	QALYs gained 0.0524 (OXN vs. OXY)	Incremental cost of OXN vs. OXY : £409.60	Incremental cost-effectiveness ratio OXN vs. OXY: £7,821.80	Deterministic sensitivity analyses yielded ICERs below £30,000 for all parameters
Dunlop W 2012[52], UK (full paper)	Cohort model (type of model is not clearly stated) UK NHS perspective	Naloxone-oxycodone vs. oxycodone alone	Patients with moderate/severe non-malignant pain	QALYs gained 0.0273 (OXN vs. OXY)	Total costs (pain therapy+ laxatives+ other resource costs) OXN: £873.07	Incremental cost-effectiveness ratio OXN vs. OXY £5841.56	Deterministic sensitivity analyses showed that varying the key parameters of the model resulted in an ICER of less than £8000 in all scenarios Sensitivity analyses on the cost of constipation used data from non-UK studies, which resulted in OXN as dominant,

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Sensitivity analyses
	Time horizon 301 days Clinical data from RCT Utilities: mapping from SF-36 to EQ-5D Deterministic and Probabilistic sensitivity analyses were conducted The base case analysis estimated constipation costs based on a survey of UK primary physicians only, and did not clearly define the treatment duration and the resource use				OXY: £713.39		indicating that if the cost of OIC is sufficiently high OXN could be cost saving to the UK The PSA showed that at a threshold of £20,000 the probability that OXN was cost-effective was 97%

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Sensitivity analyses
	The model assumed that QoL and BFI remained constant after the 12th week, whereas BFI data from the extension phase of the study showed improvement up till12 months of treatment						
SMC submission Targinact® 2009[51]	Decision analytical model UK NHS perspective Time horizon: one year Clinical data from RCT Utilities: different sources including EQ-5D Sensitivity analyses conducted The health states are defined in terms of use of laxatives rather than constipation. The analysis used utilities from different sources that were not	Naloxone-oxycodone vs. oxycodone alone	Patients with severe pain	QALYs gained 0.02 (OXN vs. OXY)	Net Total cost OXN: £93 OXY: NR	Cost per QALY OXN vs. OXY: £4,712 per QALY	Sensitivity analysis was conducted with utility values obtained from SF-36 data collected during the trial, which resulted in cost per QALY of £6,184.

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Sensitivity analyses
	comparable with one another						

BFI= Bowel Function Index; EQ-5D= European Quality of Life-5 Dimensions; ICER= Incremental Cost-effectiveness Ratio; MNTX= Methylnaltrexone; NHS= National Health Services; NR= not reported; OIC= Opioid-induced constipation; OXN= Naloxone-oxycodone; OXY= oxycodone; PSA= probabilistic sensitivity analysis; QALY= quality-adjusted life year(s); RCT= randomised controlled trial; SF-36= Short form 36; SOC= standard care; UK= United Kingdom

5.1.4 Conclusions of the cost-effectiveness review

No specific conclusions from the economic review were provided in the CS. The ERG asked whether a language restriction was applied in the screening of the cost-effectiveness studies in the clarification letter (Section C, Question 69). The company confirmed that non-English language publications were excluded from the analysis.

ERG Comment: The ERG agrees with the conclusions of the company that none of the selected studies were relevant for the decision problem.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 13 presents a summary of the *de novo* economic model developed by the company. The ERG has assessed the company's economic evaluation using the Philips et al checklist for assessing the quality of the decision analytic models.[56] This is shown in Appendix 3 and is used to assist the narrative critique in the following sections.

Table 13: Summary of the company's economic evaluation

	Approach	Source/Justification	Source (in the CS)
Model	Decision-tree(4 weeks) followed by a Markov structure	The cycle length was based on the dosing interval for naloxegol. Time horizon was 5 years.	Section 7.2
States and events	OIC non-OIC(on treatment) non-OIC(untreated) Death	The Markov model consists of four health states: OIC; non-OIC (on treatment), non-OIC (untreated) and death, where OIC and non-OIC are defined as: OIC: less than 3 spontaneous bowel movements (SBMs) per week in at least 2 out of the last 4 weeks, Non-OIC: 3 or more SBMs per week in at least 3 out of the last 4 weeks (where treatment included rescue bisacodyl, treatments were compared based on likelihood of any bowel movements (BMs), otherwise, response was defined based on SBMs). Hence, the model defines health states in terms of constipation status.	Section 7.2
Comparators	Placebo, Placebo+bisacodyl, Methylnaltrexone, Naloxone-Oxycodone, Rectal interventions	Based on current treatment options in the UK.	Section 7.2
Natural history	Based on decision tree analysis and Markov structure.		Section 7.2
Treatment effectiveness	Treatment response is influential when patients enter Markov model.	Response rate of the treatment group (for base case) was obtained from the KODIAC 4&5 trials. Duration of response for naloxegol 25mg and placebo was based on the KODIAC 4&5 trial data.	Section 7.3
Adverse events	Grade 3/4 AEs were assumed to be incurred in cycle 1 only.	Only Grade 3/4 adverse events were included. The utility impact of AEs is captured by treatment-specific utility inputs. 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).	Section 7.4
Health related QoL	Utility values were obtained using EQ-5D from the KODIAC 4 & 5 trials.	As time- and treatment-dependent utility inputs were only available for naloxegol 25 mg, a health-state only (non-time- and non-treatment-specific) utility input was estimated for the comparison with SC methylnaltrexone and naloxone-oxycodone This was also used in a scenario of the model for naloxegol 25 mg versus placebo.	Section 7.4
Resource utilisation and costs	Treatment cost (ie technology costs of naloxegol, monitoring costs and other) and health state cost (ie incremental costs of constipation, treatment costs, opioid costs, adverse events)	Based on UK reference costs and literature.	Section 7.5
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case	Section 7.2
Subgroups	Anticipated licensed population + Step 3	Adults with opioid-induced constipation who have had an inadequate response to	Section 7.9

	Approach	Source/Justification	Source (in the CS)
	opioids (non-cancer) & cancer	laxative(s) and who are receiving a Step 3 opioid as defined by the WHO pain ladder	
Sensitivity analysis	One-way deterministic sensitivity analysis, scenario analyses and probabilistic sensitivity analysis	Ranges based on confidence intervals, standard errors and assumptions.	Section 7.6
CS= Company's submission; EQ-5D= European Quality of Life-5 Dimensions; NICE= National Institute for Health and Care Excellence; OIC= Opioid-induced constipation; SBM= Spontaneous bowel movement; UK= United Kingdom; WHO= World Health Organization			

5.2.1 NICE reference case checklist

Table 14: Summary of the company's economic evaluation

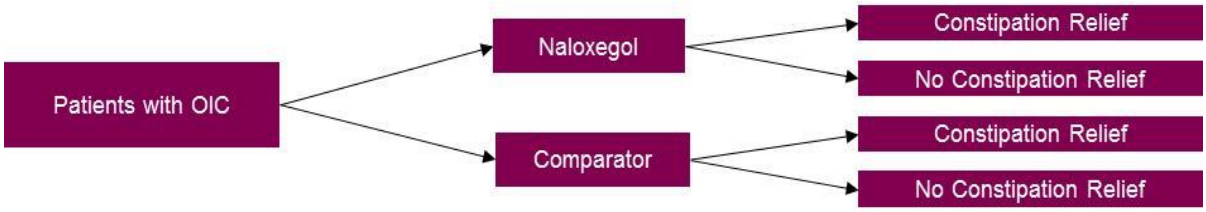
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	The NICE scope defined: *Adults with opioid-induced constipation*	No	Limited to: *Adults with opioid-induced constipation who have had an inadequate response to laxative(s)* due to license.
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes	
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	Time horizon is 5 years.
Synthesis of evidence in outcomes	Systematic review	Partially	No systematic search was conducted for resource use.
Measure of health effects	QALYs	Yes	
Source of data for measurement HRQoL	Reported directly by patients and or carers	Yes	
Source of preference data for valuation of changes in HRQoL	Sample of public	Yes	
Discount rate	Annual rate of 3.5 on costs and health effects	Yes	
Equity weighting	No special weighting	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	
HRQoL= Health-related Quality of Life; MTC= mixed treatment comparison: NHS= National Health Services; NICE= National Institute for Health and Care Excellence; PSS= Personal Social Services; QALY= Quality-adjusted life year			

5.2.2 Model structure

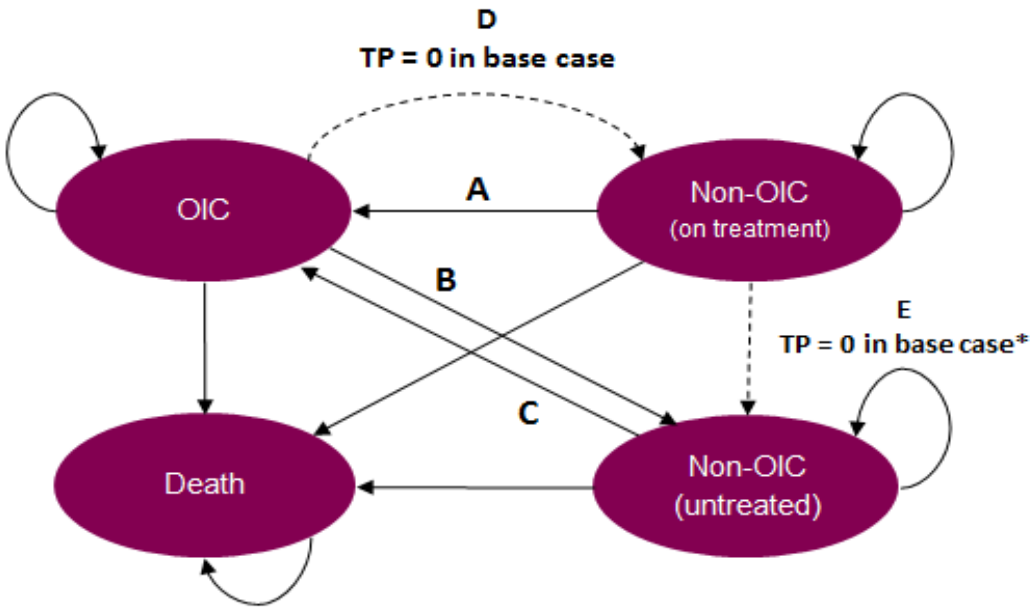
The company constructed a decision-analytic model to assess the cost-effectiveness of naloxegol. The model consists of a decision-tree structure for the first four weeks of treatment, with patients being classified as responders, if they have achieved constipation relief and as non-responders if they have not. This decision tree is followed by a Markov structure, with a cycle length of four weeks, and time horizon up to a maximum of five years. Patients who have responded to treatment by week four will begin the Markov model in 'non-OIC (on treatment)' state. Non-responders at week four will start the Markov phase in the 'OIC' health state.

Figure 2: Model structure as constructed by the company

Decision Analytic Schematic (week 0-4)



Markov model structure, after week 4



*Except for patients on SC MNTX for whom treatment is limited to 16 weeks, per licence. After 4 cycles (16 weeks), all non-OIC (on treatment) patients receiving this drug move to the non-OIC (untreated) health state.

MNTX= methylnaltrexone; OIC= opioid-induced constipation; SC= subcutaneous; TP= transition probability

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

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

The company adopted this divergence from the clinical definition as it is claimed to correspond with an internationally accepted definition of constipation and because it facilitates a simplification of the model design by allowing the estimation of utility and resource use as a function of constipation status, rather than a change in that status.

Table 15: States into which patient transition in the model

Initial health state	States patients can transition to	Comments
Patients entering the Markov model	'Non-OIC (on treatment)' state ie remain constipation-free	Patients on SC MNTX can also transition from the 'non-OIC (on treatment)' state to the 'non-OIC (untreated)' state, in accordance to the SPC that SC MNTX has not been studied for more than a 16 week duration (as detailed further in section 7 in the CS). That is, SC MNTX patients are assumed to discontinue treatment if: i) they are non-responders within the first 16 weeks (and so move to the 'OIC' state) or ii) they are still responders at 16 weeks (and move to the 'non-OIC (untreated)' state
	'OIC' state ie treatment failure and relapse (transition A)	
	Death	
Patients in the 'OIC' health state	'OIC state ie continue to experience OIC	In the base case, patients are assumed to not move from the 'OIC' state to the 'non-OIC (on treatment)' state. That is, once patients have stopped responding to treatment and discontinued, they cannot go back onto the treatment.
	'Non-OIC (untreated)' state (transition B)	
	Death	
Patients in the 'non-OIC (untreated)' state	'OIC state' ie relapse (transition C)	
	Death	
CS= Company's submission; MNTX= methylnaltrexone; OIC= opioid-induced constipation; SC= subcutaneous		

ERG Comment: The ERG agrees with the definition of response used in the economic evaluation. In general, health economic models should use absolute health states rather than health states relative to a baseline situation. However, as will later be discussed in the section about health related quality of life (Section 5.2.7), it is likely that the health state non-OIC is too broad to be homogeneous regarding quality of life. In the current definition only nine SBMs should occur over a 28-day period to be classified as a responder (ie move to the non-OIC on treatment state). But patients who have 28 SBM in these 28 days are in the same health state and thus are assumed to have the same quality of life as those with only nine SBM. This appears unlikely to the ERG. In Section 5.2.7, we will further discuss this issue in relation to the validity of the outcomes.

5.2.3 Population

The population for the model was defined as the licensed population for naloxegol, ie: treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s). In the pivotal RCTs for naloxegol, to qualify as a laxative inadequate responder, patients had to have reported concurrent OIC symptoms of at least moderate severity (ie incomplete bowel movement, hard stools, straining or false alarms) while taking at least one laxative class for a minimum of four days during the two weeks prior to the screening period of the study.[30, 31] Thus, naloxegol is indicated for any patient with OIC after inadequate response to one laxative class. For subgroup analysis, step 3 opioid patients were considered. Step 3 opioids are for the management of moderate to severe pain and patients receive strong opioids (eg morphine, methadone, oxycodone, buprenorphine, hydromorphone, and fentanyl) based on the WHO pain ladder.[57]

ERG Comment: The population studied in the cost-effectiveness is the same as the licensed indication but more narrow than the population discussed in the final scope (ie adults with opioid-

induced constipation). However, the question arises to what extent the trial definition of inadequate response to laxatives (ie taking at least one laxative class for a minimum of four days during the two weeks prior to the screening period) matches with clinical practice. While for some types of laxatives its effectiveness can be reasonably assessed after four days (ie bisacodyl), other types would require a slightly longer period of use before its effectiveness can be fully assessed (ie lactulose). To assess the impact of a stricter definition of inadequate response to laxatives it would have been of interest to assess the model outcomes when input was restricted to the 2xLIR populations, ie patients with inadequate response from at least two classes of laxatives for ≥4 days in the two weeks prior to study entry or reported unsatisfactory laxation from ≥1 additional laxative class from the six month OIC history prior to screening. We therefore requested in the clarification letter (Question 41) 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. However, the company responded that did not believe it to be necessary to provide data for 2xLIR patients.[37] In response to Question 25, the company responded with a list of reasons for their rejection of our request, such as the fact that the studies has not been powered to detect differences in the 2xLIR group and the companies believe that the 'All LIR' population was the most clinically relevant to the population listed in the scope as: 'For adults in whom oral laxatives have provided inadequate relief'. The ERG regrets this decision not to provide the 2xLIR input data in order to explore what impact the patient history with regards to laxatives has on the outcomes. In Section 5.3, the ERG will present a simple analysis based on the 2xLIR response rates as reported in the CSR.

5.2.4 Interventions and comparators

The CS studies the cost-effectiveness of naloxegol 25 mg versus placebo in the base case, since placebo was the comparator in the pivotal clinical trials. Various other comparators were defined:

- Placebo in combination with bisacodyl (where bisacodyl is used as a proxy for stimulant laxative use)
- methylnaltrexone
- naloxone-oxycodone

The model comparison was also presented for naloxegol 25 mg plus bisacodyl to demonstrate the cost-effectiveness of naloxegol when used in combination with a stimulant laxative.

In addition, an indirect comparison with rectal interventions in the form of a cost minimization analysis was conducted to address the number of months of naloxegol treatment that could be given for the cost of one rectal intervention. The company's comparators and endpoints as used in the model are set out in Table 16.

Table 16: Summary of the company's model comparators

Treatment	Comparator	Comments	Source	End-Point	Definition of response	Base Case or Scenario	Populations
Naloxegol 25 mg	Placebo	Patients not on active therapy	Trial	SBM	≥3 SBMs/ week in 3 of the last 4 weeks	Base Case	Anticipated Licensed population Anticipated Licensed population + Step 3 Opioids
	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)	Scenario	Anticipated Licensed population Anticipated Licensed population + Step 3 Opioids
	SC MNTX 12mg QAD	As per scope	MTC	SBM	≥3 SBMs/ week in each of the last 4 weeks	Scenario	Anticipated Licence Anticipated Licensed population + Step 3 Opioids
	OXN 59.3mg/29.7mg	As per scope	MTC	CSBM	≥3 CSBMs/ week in each of the last 4 weeks	Scenario	Anticipated Licensed population + Step 3 Opioids
	Rectal Interventions	As per scope	Assumptions	NA	NA	Cost Minimisation Scenario	Anticipated Licensed population Anticipated Licensed population + Step 3 Opioids
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	Scenario	Anticipated licensed population Anticipated Licensed

Treatment	Comparator	Comments	Source	End-Point	Definition of response	Base Case or Scenario	Populations
							population + Step 3 Opioids
BMs= Total Bowel Movements, Defined as all bowel movements, CSBMs= Complete Spontaneous Bowel Movements, Defined as spontaneous bowel movements with completeness of evacuation; MNTX= methylnaltrexone; MTC= mixed treatment comparison; NA= not available; OXN= naloxone-oxycodone; SBMs= Spontaneous Bowel Movements. Defined as a BM without the use of rescue medication administered in the last 24 hours; SC= subcutaneous							

The ERG requested in the clarification letter (Section C, Question 38) from the company to consider the impact of permitted switching between different treatments, which would help place naloxegol at a favourable position in the care pathway. The company indicated that permitted switching and the optimum position of naloxegol in the care pathway were not considered necessary. It was indicated that the company's model was constructed to reflect health states rather than laxative status. In addition, it was stated that there is insufficient data available for laxatives to develop a robust model. Table 17 depicts naloxegol's position in the care pathway provided by the company in the clarification letter.

Table 17: Naloxegol's position in the care pathway provided by the company

Naloxegol vs. comparators	Position in care pathway
Naloxegol vs. placebo + bisacodyl	2nd line – comparator used as a proxy for PRN stimulant laxative use
Naloxegol vs. MNTX/OXN	2nd line, post inadequate response to at least one laxative class and within respective licensed indication
Naloxegol vs. placebo	Patients not on active therapy
Naloxegol vs. rectal interventions	Laxative refractory patients
MNTX= Methylnaltrexone; PRN= Pro re nata (as required); OXN= Naloxone-oxycodone	

ERG Comment: Throughout the CS, naloxegol is compared with placebo. Clearly, placebo as used in the pivotal clinical trials should be seen as patients not on active therapy. To avoid confusion, we will also denote the usual care comparator by placebo in our assessment of the CS. Given the multifactorial nature of constipation, the ERG asked in the clarification letter (Section C, Question 40) for the consideration of the most clinically relevant comparator. The company indicated that the advisory board panel's opinion was to take confounding factors (comorbidity, lifestyle, ability to take tablets) into consideration when considering treatment options. The consensus statement was that '*it may be necessary to add a stimulant laxative to naloxegol to achieve maximum resolution of the constipation'*. The company indicated that the most clinically relevant scenario is the naloxegol (25 mg) plus bisacodyl in comparison with placebo plus bisacodyl. The company stated the comparison of naloxegol to placebo was selected in the base case analysis, since it was an appropriate regimen that reflects the design and endpoints of the KODIAC 4 and 5 trials. The base case was then built on to consider the use of bisacodyl with both the placebo and naloxegol in the model (as the most clinically relevant scenario). Hence, the company's consideration of the base case was based on the regimen choices with the least unknowns and assumptions (naloxegol 25 mg versus placebo).

However, the ERG would argue that naloxegol *minus* bisacodyl is neither clinically relevant nor consistent with the KODIAC 4 and 5 trials. Clinically it would seem implausible to prescribe naloxegol without bisacodyl (or some other rescue medication) given that rescue medication might be needed. As for the trial, rescue medication was permitted in all arms and therefore there was no such arm as naloxegol minus bisacodyl. Indeed, as Table 93, pages 245-251 of CS, shows, the response rate for naloxegol (referred to as 'Naloxegol 25 mg') was estimated using the SBM rate from the trial as opposed to naloxegol plus bisacodyl ('Naloxegol 25 mg + rescue bisacodyl') for which any BM was used. Given that the model states are defined according to SBMs the former is the appropriate measure of response. However, given that patients in the naloxegol arms were permitted and did take rescue medication, one cannot use the trial data to estimate the effect of naloxegol alone. Indeed, one can easily imagine how the ability to turn to rescue medication might actually be necessary to

increase the rate of SBMs even when having taken rescue bisacodyl in the last 24 hours prior to a BM precludes counting this BM as an SBM (Table 86 footnote, page 233 CS). Consider the case where a BM has not occurred within the last 72 hours: according to the trial protocol (Table 7, page 58 CS), rescue bisacodyl can now be taken. If it is taken and a BM results then at least 24 hours must elapse before any BM can be counted as a SBM, but at least a SBM can now occur. Without rescue bisacodyl it would be unlikely for any BM, let alone a SBM to occur. This would also apply to the so-called *'placebo'* arm which represents patients not on active therapy' (page 22): standard care would probably better be described as including rescue bisacodyl, which is consistent with the placebo arm of the trials. The issue is that the probability of a BM is not independent over time; not having had a SBM in a few days most likely decreases the probability of an SBM occurring.

A further related problem is that rescue bisacodyl is assumed to not be permitted in the model whilst in the *'non-OIC on-treatment'* health state *'…unless defined as part of the treatment regimen…'*,ie in the naloxegol or placebo plus rescue bisacodyl arms of the model (page 285 of the CS) However, this is inconsistent with the definition of response that is at least three SBMs per week in three of the last four weeks (Table 86, page 233 CS). One can imagine how response can be achieved even if rescue bisacodyl has been used in any given week given that three days (72 hours) have to have elapsed since the last BM, which might have been a SBM and that only another one day (24 hours) have to have elapsed following a BM after taking rescue bisacodyl before any subsequent BM can be counted as a SBM. Up to three days or more would remain in that week for no more than three further SBMs to occur in order to count that week as 1 of the 3 needed to achieve response (page 285).

Therefore, the ERG would argue that:

1) the intervention defined in the scope (page 43) as 'naloxegol' is most consistent with the 'naloxegol plus rescue bisacodyl' arm of the model,
2) the comparator defined in the scope as 'Oral laxative treatment without naloxegol' is most consistent with the 'placebo plus rescue bisacodyl' arm of the model,
3) the effectiveness of these treatment should be that estimated in the trials in terms of SBM rate and not BM rate,
4) the cost of this treatment should include a cost of rescue bisacodyl in the non-OIC on-treatment state in the naloxegol plus rescued bisacodyl arm of the model as observed in the naloxegol arm of the trials,
5) the cost of rescue bisacodyl in the non-OIC on-treatment state in the 'placebo' arm of the model should also be estimated from the placebo arm of the trials.

In summary the company does present results for naloxegol plus rescue bisacodyl, although they have been estimated using the wrong response rate, ie based on BM instead of SBM. It is also compared correctly, although in a scenario analysis, to 'placebo plus rescue bisacodyl', which is in effect standard care, although it does not include other types of oral laxatives. Therefore, the most appropriate results in the CS are those based on this scenario analysis and not the base case results. If the correct response rate had been used it is likely that the ICER would in fact go down for naloxegol plus rescue bisacodyl versus rescue bisacodyl only given that the relative risk versus placebo plus rescue bisacodyl of response (see Table 90, page 245 CS) based on SBMs is higher (about 1.46) than based on BMs (about 1.20). Of course, there still remains no comparison with any other oral laxative.

5.2.5 Perspective, time horizon and discounting

The analysis performed in the CS was conducted from the NHS and personal social services perspective in England and Wales using a time horizon of five years, with 3.5% per annum discounting, applied for costs and QALY outcomes. For sensitivity analyses, the model allows shorter time horizons, three months, one year and three years, respectively. The model cycle length was four weeks, which corresponded to the first time-point that estimates of treatment response were available. A half-cycle correction was applied.

ERG Comment: The ERG concludes that the discount rate and study perspectives are in-line with the NICE reference case. In the clarification letter, ERG asked (Section C, Question 45) about the justification of the time horizon. It was stated by the company that a five year time horizon was selected as this was thought to reflect the upper end of the period of persistence of opioid use (Table 89 in the CS). Figure 17 in the CS shows that it reaches a steady state within this period. After 36 cycles or three years there are only a few patients transitioning and at 67 cycles or nearly five years there are no patients left transitioning. This shows that after three years the model stabilises. In addition, data from an analysis of the Clinical Practice Research Data Link (CPRD) database[58] showed that, for patients with at least 182 days of continuous opioid exposure, the mean duration of opioid use in patients receiving opioids for non-cancer pain and cancer pain management is approximately 18 months and 15 months, respectively.[58] Hence, in the population of interest, the ERG considers the five year time horizon acceptable.

5.2.6 Treatment effectiveness and extrapolation

The model starts with a four week period in which the response to treatment is determined. Patients having a response enter the Markov model in the non-OIC (on treatment) state whereas the non-responders enter in the OIC state. Patients in the non-OIC (on treatment) health state can relapse to OIC state or die. Patients in the OIC health state can stay in that state, have a spontaneous recovery and move to non-OIC (untreated) or die. Patients in the non-OIC state were followed until time-to-next OIC state. The transition probabilities that correspond to each health state are included in Table 18.

Table 18: Summary of transition probabilities

Transition probability	Definition	Source	Comments

A	Non-OIC (on treatment) to OIC ie Treatment failure (cycle 2 onwards)	KODIAC 4 and 5 trial data	Type of curves used for extrapolation:
			• proportional hazard model:
			  o exponential functions
			  o Weibull functions
			• non-proportional hazard model
			  o lognormal,
			  o log logistic
			  o exponential functions
			The trial data on which these function were fitted (KODIAC 4 and 5) were only available for naloxegol 25 mg and placebo patients

B	OIC to non-OIC (untreated) Patients who had entered the 'OIC' state either at Week 4 or via transition A were followed until the	Analysis of the anticipated licensed population (LIR) patients in the placebo arm of the KODIAC 4 and KODIAC 5 datasets	Placebo data was analysed because the model assumes that patients are not on treatment in the 'OIC' and 'non-OIC (untreated)' states. This is why the same transition B and C estimates were used across the treatments included in the model.

Transition probability	Definition	Source	Comments
	time when they next became non-OIC		
C	Proportion of patients who move from non-OIC (untreated) to OIC per cycle Patients in the non-OIC state were followed until time-to-next OIC state		
D	OIC to non-OIC (on treatment)		Set to zero
E	non-OIC (on treatment) to non-OIC (untreated)		Set to zero
LIR= laxative inadequate responder; OIC= opioid-induced constipation			

For naloxegol +/- bisacodyl and placebo +/- bisacodyl the response rates were determined using the data from the KODIAC 4 and 5 trials. For the comparison of naloxegol versus SC methylnaltrexone and naloxone-oxycodone, the outcomes of a MTC were used.

Response was defined based on any bowel movement (BM) when treatment includes rescue bisacodyl; for the other treatment options response is based on spontaneous bowel movements (SBM, ie a BM without the use of rescue laxative in the last 24 hours).

Trial-based response estimates were generated in two ways. In the base case, the intent-to-treat (ITT) principle was applied, with the baseline N being used as the denominator to generate the response rate. Second, in a scenario analysis, the number of patients at risk (for whom observations were available at week four) was used as to generate the response rate.

Tables 19 and 20 summarise the response rate at week four calculated using the methods described above. The response rates estimated with the MTC were lower (eg naloxegol 25 mg: 45.9%) than those taken directly from the trial (naloxegol 25 mg: 58.5%). This was because the definition of response adopted in the MTC was more stringent than that in the trial.

Table 19: Proportion of patients in 'non-OIC (on treatment)' state at week 4, trial-based

	ITT		Patients at risk	
Technology	**Licensed population**	**Licensed population + step 3 opioids**	**Licensed population**	**Licensed population + step 3 opioids**
	Mean (SE)	**Mean (SE)**	**Mean (SE)**	**Mean (SE)**
Naloxegol 25 mg†	58.51% (3.17%)	62.50% (3.65%)	65.58% (3.24%)	70.51% (3.65%)
Naloxegol 25 mg + rescue bisacodyl‡	72.20% (2.89%)	73.86% (3.31%)	79.09% (2.74%)	82.80% (3.01%)
Placebo†	39.75% (3.17%)	38.75% (3.85%)	42.41% (3.30%)	41.33% (4.02%)
Placebo + rescue bisacodyl‡	60.25% (3.17%)	61.25% (3.85%)	61.80% (3.18%)	62.42% (3.87%)

†Response is defined as patients with ≥3 SBMs/week (%) over at least 3 out of past 4 weeks
‡Response is defined as patients with ≥3 BMs/week (%) over at least 3 out of past 4 weeks
ITT= intent-to-treat; SE= standard error

Table 20: Proportion of patients in 'non-OIC (on treatment)' state at Week 4, MTC analysis

	Licensed population		Licensed population + step 3 opioids	
	Mean	**SE**	**Mean**	**SE**
Naloxegol 25 mg	45.87%	7.66%	53.99%	9.18%
SC MNTX QAD	38.40%	9.74%	37.82%	10.97%
OXN	-	-	46.01%	6.59%

MNTX= methylnaltrexone; OXN= naloxone-oxycodone; QAD= every other day; SC= subcutaneous; SE= standard error

The clinical data employed in estimating response differed from that of the clinical inputs in the model. The definition of response adopted in the economic analysis intentionally focuses on absolute constipation status alone, without a measure of change in bowel movements from baseline.

The next step is the estimation of the time until patient move from non-OIC (on treatment) to OIC. This is estimated using the trial data of the KODIAC 4 and 5.

Figure 3 shows the KM curve as observed in the trial and the predicted curves for proportions of patients remaining in the non-OIC (treated) health state over time in the naloxegol 25 mg arm (transition A). This figure depicts extrapolation results to 300 days, applying the curve fitted on Weeks 4–12 data from Week 4. Figure 4 shows similar prediction for placebo.

For the extrapolation of the KM curves, the following parametric functions were considered: exponential, Weibull, gamma, Gompertz, log-normal and loglogistic.

Based on diagnostic plots and the Akaike's Information Criteria (AIC) and Bayesian Information Criterion (BIC) the exponential and log-normal distribution may fit the data best. Curves were fitted separately for naloxegol 25 mg and placebo, to allow for the possibility that changes in constipation status followed a different distribution in the two arms. Though,

the selection process resulted in the same function being used for naloxegol 25 mg and placebo. Table 21 shows the AIC and BIC of these fitting functions.

Table 21: Functions used to estimates transition from non-OIC (on treatment) to OIC, anticipated licensed population

Function	Exponential	Weibull	Log-logistic	Log-normal	Gamma	Gompertz
Naloxegol 25 mg						
AIC	176.242	177.974	177.210	174.642	180.761	176.109
BIC	179.005	183.498	182.734	180.166	189.047	181.633
Placebo						
AIC	143.611	145.033	144.344	142.784	143.219	144.363
BIC	145.902	149.614	148.925	147.365	150.091	148.944
AIC= Akaike's Information Criteria; BIC= Bayesian Information Criterion						

Four functions were selected for inclusion in the model – exponential, Weibull, log-logistic and log-normal. Given that estimates of statistical fit and clinical opinion failed to identify an obviously preferred function, and that no data was identified against which to externally validate the extrapolations, the exponential function was selected for using the base case as the most parsimonious of the available functions.

The trial data on which these function were fitted (KODIAC 4 and 5) were only available for naloxegol 25 mg and placebo patients. Therefore, the company assumed that functions for other treatments (methylnaltrexone and naloxone-oxycodone) could be estimated based on the naloxegol 25 mg curve, assuming proportional hazards to naloxegol, and using hazard ratios (HRs) estimated from the MTC (Section 6.7 of the CS). In the base case, these HRs were approximated as the ratio of the four week response rate of the comparator relative to that of naloxegol 25 mg on the basis that non-response after four weeks is likely to be related to the response rate at four weeks (Table 22). In a scenario analysis, the HR was set to 1.

Table 22: Hazard ratios compared to naloxegol 25 mg used to estimate transition non-OIC (on treatment) to OIC

Comparator	Anticipated licensed population	Anticipated licensed population + Step 3 opioids
SC MNTX QAD	0.84	0.70
OXN	1.07	0.85
LIR= laxative inadequate response; MNTX= methylnaltrexone; OXN= naloxone-oxycodone; QAD= every other day; SC= subcutaneous		

Figure 3 shows the predicted curves for proportions of patients remaining in the non-OIC (treated) health state over time in the naloxegol 25 mg arm (transition A). This figure depicts extrapolation results up to 300 days, applying the curve fitted on Weeks 4–12 data from Week 4. Figure 4 shows similar prediction results for placebo.

Figure 3: Extrapolation of response predictions (up to 300 days), naloxegol 25 mg, anticipated licensed population

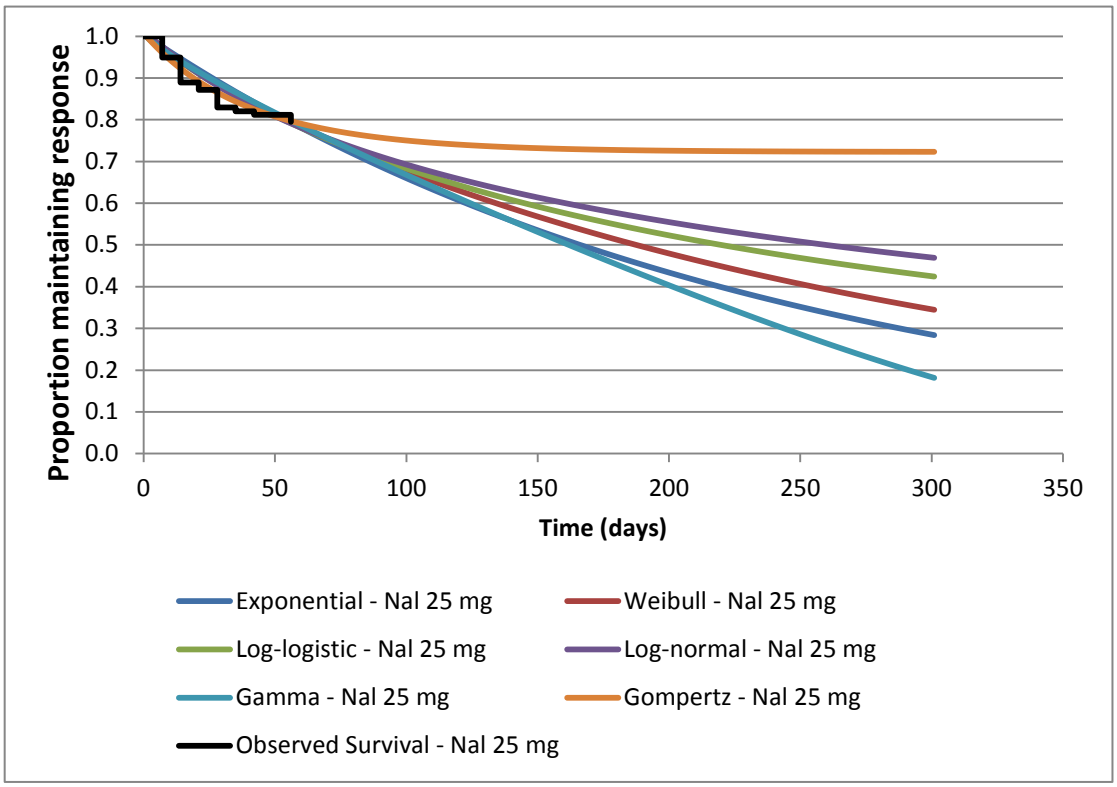
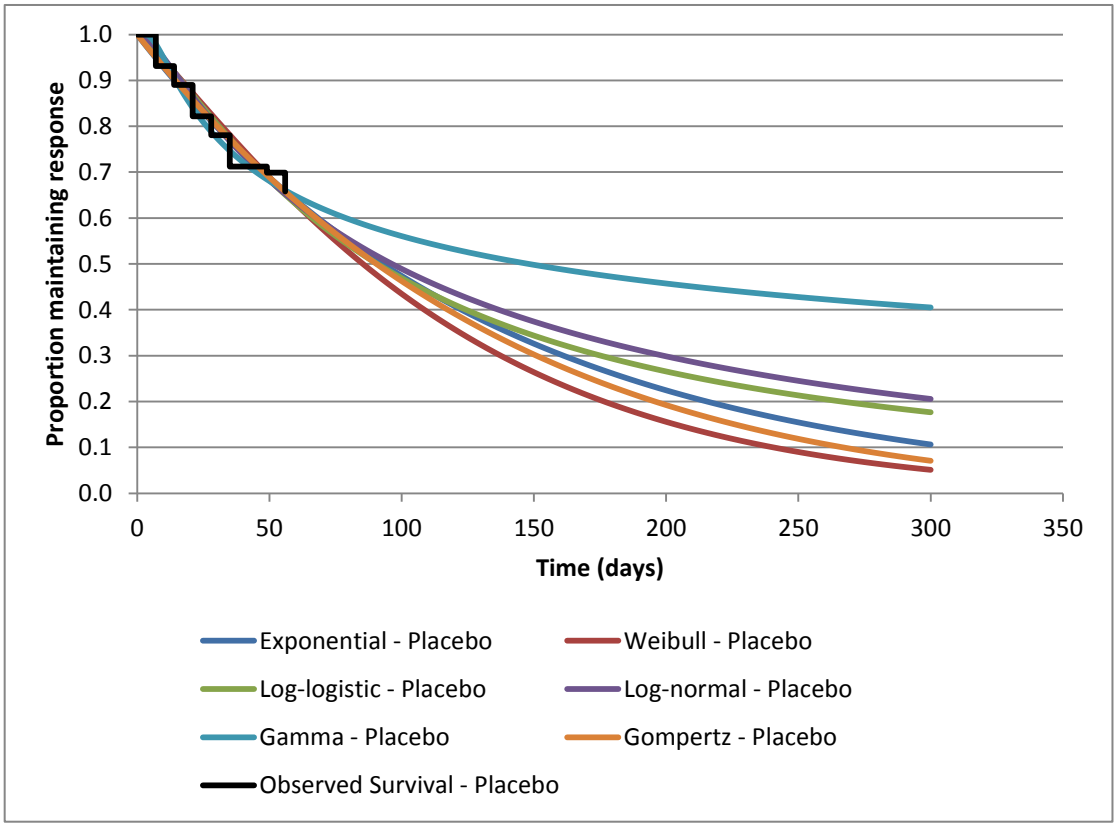


Figure 4: Extrapolation of response predictions (up to 300 days), placebo, anticipated licensed population



Several alternatives for estimation of the transition probability from non-OIC (on treatment) to OIC were also explored by the company. The first was based on the discontinuation data from the 52-week long term safety study (KODIAC 8). This approach was used to exploit the longer duration observed by KODIAC 8 compared with the KODIAC 4 and 5 studies, as well as to account for the possibility that the definition of response included in the base case analysis may be more strict than patients themselves would apply when considering whether treatment is efficacious enough to continue.

During the 52 weeks of the trial, 185 of the 506 patients who received naloxegol 25 mg discontinued treatment. The three most common reasons for such discontinuation were patient decision (n=62); AEs (n=49); and lost to follow-up (n=36). Only three patients discontinued due to a loss of therapeutic effect. Based on this a constant probability for transition from non-OIC (on treatment) to OIC (3.43% per cycle) was derived.

On the basis that discontinuation after four weeks is likely to be related to the response rate at four weeks, transition probabilities for other treatments were estimated by multiplying the naloxegol 25 mg transition probability by the inverse of the relative risk of response for the treatment versus naloxegol 25 mg.

A second alternative approach to the estimation of the transition probability from non-OIC (on treatment) to OIC was to use estimates of the proportion of patients on the 'OIC' and 'non-OIC (on treatment)' states at 4, 8 and 12 weeks from the KODIAC 4 and 5 trials without extrapolating beyond this trial period. This was intended to represent a worst case response scenario. Table 23 summarises the proportion of patients remaining in 'non-OIC (on treatment)' state used in the model. This analysis was only undertaken for naloxegol 25 mg, naloxegol 25 mg plus rescue bisacodyl, placebo, and placebo plus rescue bisacodyl, as the necessary required data were not available for other treatments.

Table 23: Proportion of patients remaining in 'non-OIC (on treatment)' state at week 4, 8, 12 (anticipated licensed population)

	anticipated licensed population			**anticipated licensed population + Step 3 opioids**		
Treatment	**Week 4**	**Week 8**	**Week 12**	**Week 4**	**Week 8**	**Week 12**
Naloxegol 25 mg[†]	58.51%	55.60%	55.19%	62.50%	56.25%	55.11%
Naloxegol 25 mg + bisacodyl[‡]	72.20%	64.32%	61.83%	73.86%	65.34%	61.93%
Placebo[†]	39.75%	43.93%	41.42%	38.75%	44.38%	43.75%
Placebo + bisacodyl[‡]	60.25%	55.65%	53.97%	61.25%	56.35%	56.88%

[†]Response is defined as patients with ≥3 SBMs/week (%) over at least 3 out of past 4 weeks.
[‡]Response is defined as patients with ≥3 BMs/week (%) over at least 3 out of past 4 weeks.

Finally, in a third scenario estimates of the proportion of patients in the 'non-OIC (on treatment)' state from the KODIAC 4 and 5 trials was used, which assumed that patients in

the 'non-OIC (on treatment)' state at 12 weeks stayed in this state for the remainder of the model.

Estimates for the transition from OIC to non-OIC (untreated) and from non-OIC (untreated) to OIC state were generated from analysis of anticipated licensed population patients in the placebo arm of the KODIAC 4 and KODIAC 5 datasets. The placebo data was analysed because the model assumes that patients are not on treatment in the 'OIC' and 'non-OIC (untreated)' states. This also explains why the same transition estimates were used across the treatments included in the model.

For the transition OIC to non-OIC (untreated), patients who had entered the 'OIC' state either at week four or via transition from non-OIC (on treatment) to OIC were followed until the time when they next became non-OIC. For the transition non-OIC (untreated) to OIC state, patients in the non-OIC state were followed until time-to-next OIC state. The numerators (events) and denominators (number at risk) for each transition were used to compute four week transition probabilities utilised in the economic model.

Table 24: 4 week transition probabilities between non-OIC (untreated) and OIC (source: analysis of KODIAC 4 and 5)

	Mean	**SE**
Transition OIC to non-OIC (untreated)	28.98%	4.27%
Transition non-OIC (untreated) to OIC	20.94%	5.44%
OIC= Opioid-induced constipation; SE= standard error		

Finally, for the transition to death the same mortality rate, based on the UK general population, was applied to all health states. Mortality was calculated based on UK life table for the years 2008–2010.[59] The yearly probability of death used in the model was the one corresponding to the average age of patients. The exponential function was used to calculate cycle probability of mortality.

Naloxegol, other treatments, and constipation health states are not expected to have an impact on mortality.

ERG Comment: In the clarification letter (Section C, Question 46) the ERG asked why same parametric function to estimate transition probabilities between non-OIC (treated) and OIC was chosen for naloxegol and placebo. It was indicated by the company that 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.[60] It was also stated that separate functions were generated for naloxegol and placebo populations. 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. As there is quite some variation in the extrapolated part of the curves, we considered it relevant to explore what happens to the ICER if different functional forms are selected for naloxegol and placebo. In Section 5.3 we present the results of such analysis.

In the base case analysis, the HRs for methylnaltrexone and naloxone-oxycodone were approximated as the ratio of the four week response rate of the comparator relative to that of naloxegol 25 mg on the basis that non-response after four weeks is likely to be related to the response rate at four weeks. While the ERG agrees that a correlation is likely between

response rate and rate of transition from non-OIC (on treatment) to OIC, we are not convinced that this relation is strictly 1 on 1. To test this assumption, the ERG explored the rate ratio of the response rates of naloxegol 25 mg and placebo, and compared this to the hazard ratio of naloxegol and placebo. Since for both groups an exponential curve was assumed for the transition from non-OIC (on treatment) to OIC, the hazard ratio is constant over time. We found that the rate ratio was 0.68 whilst the hazard ratio was 0.56. From this, we might deduct that the assumption is not unreasonable in the absence of any other data, but clearly leads to uncertainty. We have therefore performed a threshold analysis on the hazard ratios that is presented in Section 5.3.

It is important to realise that various definitions of bowel movement have been used to define OIC and response. For the comparison of naloxegol versus placebo without rescue laxatives response and OIC are defined based on spontaneous bowel movements, ie where no laxative has been used in the past 24 hours. On the other hand, for the comparison of naloxegol plus laxatives versus placebo plus laxatives, all bowel movements are part of the response estimation. In the comment part of Section 5.2.4 it was explained why the ERG considers this a faulty approach. For the comparison of naloxegol versus methylnaltrexone and naloxone-oxycodone, it is less clear which definitions of bowel movement were used to define response as presented in Table 20. This means that all uncertainties as described in Section 4.4 regarding the indirect comparisons carry over into the model. However, the ERG expects the impact of this uncertainty to be limited.

5.2.7 Health related quality of life

Base case

Quality of life utilities were derived from the EQ-5D questionnaire which was included in the KODIAC4 and 5 trials at 0, 4 and 12 weeks. Since previous studies showed a significantly lower HRQoL in patients with OIC than those without OIC,[61, 62] it was expected that patients who experience relief from OIC would also experience a HRQoL improvement. This assumption was tested by a repeated-measures mixed effects (RMME) model for the change of utility in the pooled KODIAC 4 and 5 data. The company ran the model separately for the anticipated licensed population and anticipated licensed population on Step 3 opioids. The model also assessed whether an independent treatment effect of naloxegol (compared to placebo) on HRQoL could be observed. The selected RMME model included the following independent variables: time, treatment, baseline utility, OIC status and an interaction between treatment and time. It was found that baseline utility, OIC status and the interaction between treatment and time were significantly associated with change in utility score. Based on these findings the company decided to incorporate treatment-specific and time-specific utility estimates in the base-case analysis. Note that the RMME model was only used to justify this decision, the model was not used to estimate the utilities per health state themselves. In response to Question 53 in the clarification letter, the company explained that besides the included explanatory variables, other predictors were also assessed, ie age, gender, race, BMI and duration of opioid use. However, these did not contribute to the model significantly.

In the CS, it is explained that the treatment effect on utility was further validated by the observed difference in change in SBMs between naloxegol and placebo in both KODIAC 4 and 5 trials. In the KODIAC 4 trial the change from baseline was 4.2 and 3.4 for naloxegol and placebo respectively. For KODIAC 5 these numbers were 4.9 and 3.7.

The utility values used in the base-case analysis were based upon the Dolan tariff[63, 64] and were calculated as the average utility for patients in each health state while taking into

account the treatment and time-specific effect. As it was assumed in the model that naloxegol treatment was only administered in the non-OIC state, the time-specific effects were only applied to patients on naloxegol treatment in the non-OIC state. Consequently, three different utility values for the non-OIC (on treatment) were identified in the base-case analysis:

1. Non-OIC (on naloxegol treatment) cycles 1 and 2
2. Non-OIC (on naloxegol treatment) cycles 3 onwards
3. Non-OIC (on placebo)

The utility value used in cycle 1 and 2 was derived from the EQ-5D questionnaire at week four. Results from week 12 were used to estimate the utility values for cycle 3 onwards. The combined results of week 4 and 12 were used for the non-OIC (on placebo). The utility values for the non-OIC (no treatment) and OIC did not differ between cycle and treatment. These utility values were calculated from the EQ-5D questionnaires at both week 4 and 12 for patients treated with placebo in the KODIAC 4 and 5 trials as it was assumed that naloxegol treatment was not administered to patients in these health states.

The comparison of naloxegol with subcutaneous methylnaltrexone and naloxone-oxydone did not incorporate treatment and time-specific utilities due to the absence of specific HRQoL data for methylnaltrexone and naloxone-oxycodone.

Scenario analysis

The following scenario-analyses were performed by the company regarding the HRQoL estimates in the model (see Table 25 for all the values used):

- Treatment-specific utility inputs (non-time specific): the utility in the non-OIC state differed between naloxegol and placebo, but was constant over time for both treatment arms.
- Health-state specific utility inputs: no distinction was made in the utility of the non-OIC state in patients treated with naloxegol or placebo.
- Alternative tariff: an alternative tariff (Wittrup-Jensen tariff)[65] was used which did not incorporate an additional decrement for being in the worst state. This tariff was used because it is assumed that the underlying condition of patients with OIC will cause patients to be at the worst level on one of the domains of the EQ-5D and that it will not change with a variation in OIC status.
- Secondary literature. The systematic review identified one study that estimated utilities in patients who were prescribed opioids.[66] The utilities in patients with non-advanced illnesses were used in the scenario-analysis as this group best matched the model's patient population. Only health-state specific utilities could be derived from this study. Several disadvantages of the study have been identified on which it was decided to include the data from this study in a scenario-analysis instead of the base-case analysis. The reported disadvantages included i) the inclusion of any constipation, not specific OIC, ii) the cross-sectional nature of the study and iii) only median utilities were reported. Furthermore, it was unknown which tariff was used to estimate utilities.

Adverse events

No direct estimates of the impact of AEs on utility were available to be included in the model. Clinicians advised that AEs were unlikely to have a significant impact on the HRQoL.

However, the utility impact of AEs in the naloxegol and the placebo treatments may be expected to be captured by the treatment-specific utility inputs.

Quality-of-life data used in cost-effectiveness analysis

A summary of the HRQoL values in both the full anticipated licensed population and the anticipated licensed population is shown in Table 25.

Table 25: Summary of quality of life values for cost-effectiveness analysis

	State	**Utility value, mean (SE)**		**Reference to section in CS**
		Anticipated licensed population (all)	Anticipated licensed population + Step 3 opioids	
Base-case				
Naloxegol versus placebo	Non-OIC (on naloxegol), cycle 1 and 2	0.620 (0.025)	0.594 (0.030)	Table 104
	Non-OIC (on naloxegol), cycle 3 onwards	0.665 (0.026)	0.679 (0.030)	Table 104
	Non-OIC (on placebo)	0.613 (0.021)	0.572 (0.027)	Table 104
	Non-OIC (no treatment)	0.613 (0.021)	0.572 (0.027)	Table 104
	OIC	0.553 (0.022)	0.537 (0.027)	Table 104
Naloxegol versus MNTX or OXN	Non-OIC	0.630 (0.014)	0.610 (0.017)	Table 106
	OIC	0.564 (0.017)	0.546 (0.021)	Table 106
Scenario-analysis				
Naloxegol versus placebo				
Treatment-specific, non-time specific	Non-OIC (on naloxegol)	0.642 (0.018)	0.634 (0.021)	Table 105
	Non-OIC (on placebo)	0.613 (0.021)	0.572 (0.027)	Table 105
	Non-OIC (no treatment)	0.613 (0.021)	0.572 (0.027)	Table 105
	OIC	0.553 (0.022)	0.537 (0.027)	Table 105
Health-state specific	Non-OIC	0.630 (0.014)	0.610 (0.017)	Table 106
	OIC	0.564 (0.017)	0.546 (0.021)	Table 106
Alternative tariff (treatment and time-specific utilities)	Non-OIC (on naloxegol), cycle 1 and 2	0.691 (0.019)	0.672 (0.022)	Table 107
	Non-OIC (on naloxegol), cycle 3 onwards	0.724 (0.020)	0.733 (0.023)	Table 107
	Non-OIC (on placebo)	0.686 (0.015)	0.652 (0.020)	Table 107
	Non-OIC (no treatment)	0.686 (0.015)	0.652 (0.020)	Table 107
	OIC	0.643 (0.015)	0.632 (0.020)	Table 107
Naloxegol versus MNTX or OXN				
Alternative tariff	Non-OIC	0.648 (0.012)	0.638 (0.015)	Table 108
	OIC	0.698 (0.010)	0.681 (0.012)	Table 108
Naloxegol versus placebo or MNTX or OXN				
		Median (CI)		
Secondary literature	Non-OIC	0.65 (0 .22-0.78)		Table 109
	OIC	0.31 (0.17-0.73)		Table 109
CI= confidence interval; MNTX= methylnaltrexone; OXN= naloxone-oxycodone; SE= standard error				

ERG Comment: It was found in the results section of the CS that the ICER is most sensitive to the in- or exclusion of a separate utility for naloxegol and placebo in the non-OIC state. The ICER was £10,849 if both a treatment and time-effect was included compared to £38,921 if these effects were excluded. The initial submission provided evidence for this effect based upon a repeated measures mixed effect model. However, the RMME model only shows an effect of the interaction between treatment and time and not an individual treatment effect. Although it seems plausible that an independent treatment effect of naloxegol on HRQoL may be present, the provided evidence is not completely convincing. If there is indeed a treatment effect on utility, the most plausible explanation is that the non-OIC (on treatment) state is too broad as it can include patients with exactly three SBM per week but also patients with seven SBM per week, thus including a heterogeneous group of patients. The most preferable approach to dealing with this would have been to refine the non-OIC (on treatment) state by splitting it in two states and deriving treatment unspecific, health state specific utility values. However, it is the ERG's view that in the absence of such a more refined and transparent Markov model, the current approach with treatment specific utilities is a reasonable alternative.

In the base-case analysis, the utility value for the OIC state was derived from patients treated with placebo, because it was assumed that patients in the OIC state did not receive treatment. Therefore, the HRQoL in the OIC state is treatment-independent. Consequently, this utility should also be used for the health-state specific utilities used in the comparison with methylnaltrexone and naloxone-oxycodone and in the scenario-analysis with health-state specific utilities. Nevertheless, the utility estimated in both patients treated with naloxegol and placebo was larger, thus decreasing the utility difference between OIC and non-OIC. This means that the current ICER for naloxegol in comparison with methylnaltrexone and naloxone-oxycodone is conservative.

An alternative tariff has been used in a scenario analysis (in the CS, 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. The company stated in the clarification letter (Section C, Question 55) that due to the nature of the underlying condition experienced by patients suffering from OIC it was considered that 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, the company looked at an alternative tariff to test this assumption, as a sensitivity analysis.

Consequently, in the sensitivity analysis, the Wittrup-Jensen tariff resulted in higher utilities. The justification provided in the clarification letter by the company is as follows:

The Danish tariff provides higher utility values, although at an incremental level, the difference between health state values would be considered more important. Hence, the Wittrup-Jensen tariff is used purely as a sensitivity analysis to investigate robustness of the cost-effectiveness estimate.

The ERG considers the alternative tariff irrelevant for two reasons. First, the rationale for using utilities from the EQ-5D is to incorporate quality of life decrements of comorbidities and side effects in the assessment of HRQoL. Consequently, it is not valid to correct for the relatively severe health condition of patients taking opioids. Secondly, the alternative tariff is

a Danish tariff and the comparisons shown in the Wittrup-Jensen paper[65] between the UK tariff and the Danish tariff shows that the latter is higher for all five health states that are reported on. Thus, it is not reasonable to assume that the UK population values health states the same as the Danish population.

5.2.8 Resources and costs

Costs of treatment

For active treatments, the unit costs of drugs (per pill or per vial) were derived from the British National Formulary (BNF) database.[67] The unit cost for the administration of SC methylnaltrexone was taken from the Personal Social Services Research Unit (PSSRU) costs of health and social care.[68] For placebo, the treatment cost is assumed to be zero. For placebo and bisacodyl arm, costs include the rescue bisacodyl component based on observed use in the KODIAC 4 and 5 trials. Dosing regimens, as informed by product labels[69] or clinical trial publications[30, 31] were used to estimate the doses (in mg) required to treat patients with OIC. The daily treatment costs were estimated, followed by the calculation of treatment costs per cycle (28 days), which was used in the model. For SC methylnaltrexone, the costs associated with administering subcutaneous injections were also included, as part of the treatment costs.

Table 26: Unit costs associated with the technology in the economic model

Items	**Naloxegol 25 mg**	**Naloxegol 25 + bisacodyl**	**SC MNTX QAD**	**OXN**	**Placebo**	**Placebo + bisacodyl**
Technology cost per pill or vial	£ 1.84 25 mg pill	£ 1.84 25 mg Naloxegol pill £ 0.04 / 5 mg bisacodyl pill	£ 21.05/ 12 mg vial	£ 1.51/ 25 mg pill	-	£ 0.04 / 5 mg bisacodyl pill
Technology cost per 4 weeks	£51.52	£51.81	£294.70	£ 125.54	-	£ 0.29
Administration unit cost	-	-	£ 22.48	-	-	-
Administration cost per 4 weeks	-	-	£ 314.75	-	-	-
Total cost per 4 weeks	**£51.52**	**£51.72†**	**£609.45**	**£ 125.54**	**£ 0**	**£ 0.29**

MNTX= methylnaltrexone; OXN= naloxone-oxycodone; QAD= once every other day; SC= subcutaneous
†: in the CS this cost was £51.81. However, in the electronic model this lower, correct, estimate is used

Health-state costs

The incremental cost of managing constipation was included in the health states. Patients were assumed to incur the non-laxative costs of constipation only in the OIC state. Laxative medications were incorporated into the model in three ways.

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

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

Two data sources were used to estimate costs related to constipation. [redacted] (Appendix 10.27, in the CS) and [redacted].

[redacted]

Table 27 presents the detailed results of the GP omnibus survey and the BOI study for the LIR population. Table 28 and Table 29 present the aggregated results for both the LIR and the LIR + step 3 opioid population.

Table 27: Costs of managing constipation (in LIR population)

Resource use	Unit cost	GP Omnibus Survey (base case)			BOI data (scenario)		
		Average frequency per cycle	Duration of care in days	Weighted cost per cycle	Average frequency per cycle	Duration of care in days	Weighted cost per cycle
Inpatient care	£1631.81	0.0000	0.0000	£0.00	0.0346	4.6657	£263.63
Outpatient care	£349.98	0.0100		£3.50	0.2770		£96.94
Emergency care	£116.50	0.0100	1.0000	£1.17	0.0282	1.0000	£3.29
GP visit	£45.70	0.3900		£17.82	0.0110		£0.50
Nurse visit in GP surgery	£18.36	0.1300		£2.39	0.0016		£0.03
Nurse visit at home	£71.08	0.0000		£0.00	0.0016		£0.11
GP telephone	£23.55	0.2900		£6.83	0.2900		£6.83

Resource use	Unit cost	GP Omnibus Survey (base case)			BOI data (scenario)		
		Average frequency per cycle	Duration of care in days	Weighted cost per cycle	Average frequency per cycle	Duration of care in days	Weighted cost per cycle
consultation							
Rescue therapy-enema	£35.54	0.0000		£0.00	0.0000		£0.00
Rescue therapy-manual evacuation	£149.85	0.0000		£0.00	0.0000		£0.00
Haemorrhoid stapling	£125.05	0.0000		£0.00	0.0000		£0.00
Endoscopy	£161.07	0.0000		£0.00	0.0000		£0.00
Colonoscopy	£282.83	0.0000		£0.00	0.0000		£0.00
Abdominal X-ray	£28.72	0.0000		£0.00	0.0000		£0.00
Urea and Electrolytes tests	£1.00	0.0000		£0.00	0.0000		£0.00
Full blood count	£3.00	0.0000		£0.00	0.0000		£0.00
Liver function tests	£1.00	0.0000		£0.00	0.0000		£0.00
Total				[redacted]			[redacted]

Table 28: The incremental cost of constipation (base case - GP omnibus survey), per cycle (2014 £)

Cost items	Anticipated licensed population			Anticipated licensed population + Step 3 opioids		
	OIC	Non OIC (on treatment)	Non OIC (untreated)	OIC	Non OIC (on treatment)	Non OIC (untreated)
Non-laxative cost	£31.70	0	0	£36.90	0	0
Laxatives	£4.12	0	£3.14	£4.08	0	£3.12

OIC, opioid-induced constipation.
Source: GP omnibus survey. Appendix 10.27 in the CS

Table 29: The incremental cost of constipation (scenario- BOI survey), per cycle (2014 £)

Cost items	Anticipated licensed population			Anticipated licensed population + Step 3 opioids		
	OIC	Non OIC (on treatment)	Non OIC (untreated)	OIC	Non OIC (on treatment)	Non OIC (untreated)
Non-laxative cost	£371.32†			£1,709†		

LIR= laxative inadequate response; OIC= opioid-induced constipation.
†The higher OIC costs identified is driven by inpatient stay
Source: BOI survey

Table 30 summarises the opioid costs included in the model for the analysis of the naloxegol 25 mg arm when compared with naloxone-oxycodone. In the 'non-OIC (on treatment)' state, patients receiving naloxone-oxycodone do not incur additional opioid costs, since the opioid oxycodone is a component of naloxone-oxycodone (unit costs of oxycodone are already accounted for in Section 7.5.5 in the CS).

Table 30: Opioid use costs per cycle (2014 £)

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

OIC, opioid-induced constipation; OXY, oxycodone.
[‡§]Only applied when comparing naloxegol 25 mg and naloxone-oxycodone.
[§]Only applicable for naloxegol 25 mg arm. Patients receiving naloxone-oxycodone do not incur additional opioid cost, since oxycodone is a component of naloxone-oxycodone.

Adverse Events Costs

According to the company, the mean expected cost per AE was calculated as the weighted average of patients with Grade 3/4 events (based on corresponding unit costs) and patients with Grade 1/2 events (at a cost of £0). These costs were then summed to provide the total AE costs. As Grade 3/4 AEs in KODIAC 4 and 5 trials were very limited, AE costs were not influential in the model. All AE costs are assumed to be incurred only in the first cycle (Table 31).

Table 31: Summary of costs of adverse events included in the economic model (first-cycle)

	Cost of adverse events per cycle (Cycle 1)
Naloxegol 25 mg	£19.31
Naloxegol 25 mg and bisacodyl	£19.31
Placebo	£11.50
Placebo and bisacodyl	£11.50
SC MNTX QAD	£17.75
OXN	£13.92

MNTX= methylnaltrexone; OXN= naloxone-oxycodone; SC= subcutaneous; QAD= every other day

The ERG asked the company in the clarification letter (Section C, Question 62) to provide the occurrence of Grade 3/4 events and Grade 1/2 events. The rates of adverse events and serious adverse events in the licensed population in KODIAC 4 and 5 trials combined are shown below in Table 32. As adverse events were not classified according to nomenclature Grade 3 or 4, for the purposes of the health economic model submitted any severe adverse event (SAE) was considered to correspond to Grade 3 or 4 on a 1:1 basis.

Table 32: 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

ERG Comment: The ERG was surprised to see that the company had not performed a systematic search of relevant resource data for the UK, as requested in the STA template under Section 7.5.3. The company also did not provide a rationale for this omission in their submission, but in their response to the clarification letter (Section C, Question 60) they state: '*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.'*

Whilst it may be true that a more accurate estimate would be obtained by consulting clinicians, the large difference between the cost estimates provided by the GP omnibus and the BOI study shows that in this specific case data from literature would have been very helpful to assess the validity of the diverse outcomes.

This difference between GP omnibus cost estimates (Table 28) and the BOI cost estimates (Table 29) is 10 fold. The company did not provide any explanation regarding the substantial differences observed between the two data sources. However, they did state in their response to the clarification letter (Section C, Question 66) that they used the GP outcomes as they were more conservative; the higher cost estimates would lower the ICER. They also stated that the GP Omnibus survey is sufficiently robust to be used as a base case.

The ERG agrees with the assessment that the GP Omnibus survey is robust. However, the ERG also considers the BOI study robust, which raises the question how this difference could be explained. In the absence of an answer to this question, it is reassuring to see that had the BOI estimates been used, naloxegol would have been dominant compared to placebo, placebo plus bisacodyl, and methylnaltrexone (Table 133 of CS).

For the adverse events (AEs) cost calculations, the methods employed were not transparent. The ERG was not able to reproduce AE cost calculations, which were incorporated in the model (in the first-cycle). For example, using Tables 181 (unit costs) and 182 (resource use frequency) from the CS, the ERG tried to reproduce the adverse event costs presented in Table 184 of the CS. For the AE abdominal pain, one of the items of resource use is inpatient care. According to three clinical experts, 5.37% of patients with OIC would use this 1.49 times per event. At a cost of £1,606.98 per stay, this would result in costs of £129 on average per patient with abdominal pain. However, Table 184 of the CS reports an average cost of £0.08. On the other hand, using the same approach we find an average cost for outpatient care of £14.40, which is exactly the same value as in Table 184. Checking all types

of care for abdominal pain we observe that approximately half of the ERG calculations match those in Table 184 whereas the other half differs substantially. The ERG was not able to find a plausible explanation for this. In order to assess the impact of this uncertainty, the ERG increased the adverse event costs by a factor of 3. This led to a marginal increase of the ICERs by 5%.

5.2.9 Cost-effectiveness results

The structure of the various cost-effectiveness analyses that were performed by the company is depicted in Table 33. The structure adopted to present the model results reflects the relevance of the comparators and the nature of available data. The use of different sources of evidence means that the ICERs generated for each comparator are not comparable.

Table 33: Structure of the cost-effectiveness results section

Analysis	Population	Comparators	Section of CS
Base case	Anticipated licensed population (non-cancer)	• Placebo	7.7.1-7.7.8
Additional comparator treatments		• Placebo+ bisacodyl • SC MNTX	7.7.9
Assessment of structural uncertainties		• Placebo • Placebo+ bisacodyl • SC MNTX	
Validation			7.8
Subgroup analysis	Anticipated licensed population + Step 3 opioids (non-cancer)	• Placebo • Placebo+ bisacodyl • SC MNTX • OXN	7.9
	Cancer		
LIR= laxative inadequate response; MNTX= methylnaltrexone; OXN= oxycodone plus naloxone; SC= subcutaneous			

Base-case analysis

In the base case, the model inputs were based on the KODIAC 4 and 5 trial data. However, the response rates used in the model and those reported in the clinical effectiveness section are different. The clinical analysis included both a measure of absolute constipation status and minimum change in bowel movements from baseline. In contrast, the definition of response adopted in the economic analysis focuses on the absolute constipation status alone. Hence, the cost-effectiveness model results are more optimistic than the clinical trial outcomes. A summary of the comparison of response rates used in the model versus clinical data is depicted in Table 34.

Table 34: Comparison of response rates used in the model versus clinical trial data

Outcome	Treatment	• Clinical trial ('observed')	• Economic analysis • ('modelled')
Response rate at 4 weeks	Naloxegol 25 mg	56.8%†	58.51%‡
	Placebo	36.4%†	39.75%‡

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

Table 35 depicts health outcomes and costs accrued by patients on naloxegol 25 mg and placebo. The model assumption of QALYs accrued over time is driven by three factors: change in OIC status, the impact of naloxegol 25 mg on non-OIC health state and time horizon. The technology costs and AE costs increase with the use of naloxegol 25 mg. There is a reduction in costs of managing constipation with naloxegol 25 mg (as a consequence of reduction in time spent in OIC health state). Consequently, naloxegol 25 mg increases costs by £256 per patient over a five year time horizon.

Table 35: Summary of QALYs and costs by health state & resource use by category of costs (anticipated licensed population)

Item	Naloxegol 25 mg	Placebo	Absolute increment	% absolute increment
QALYs and costs by health state				
OIC – LY	1.85	1.95		
OIC – QALY	1.02	1.08		
OIC – cost	862.6	909.1		
Non-OIC (on treat) – LY	0.39	0.16		
Non-OIC (on treat) – QALY	0.26	0.10		
Non-OIC (on treat) – cost	315.6	7.55		
Non-OIC (untreat) – LY	2.29	2.43		
Non-OIC (untreat) - LY	1.41	1.49		
Non-OIC (untreat) - LY	94.0	99.6		
Cost by category				
Technology cost† (£)	£ 302	£ 0	£ 231	-
Constipation management cost (£)	£ 957	£ 1,009	£ -52	-5.2%
Adverse event cost (£)	£ 14.11	£ 7.55	£ 6.56	86.9%
Total	£ 1,272	£ 1,016	£ 256	18.3%

LY= life year; OIC= opioid-induced constipation; QALY= quality adjusted life year
†Including administration cost

Although it does not impact mortality, as life years accrued by naloxegol (25 mg) and placebo patients are the same, naloxegol 25 mg resulted improvements in HRQoL.

The ICER for naloxegol compared to placebo is £10,849 per QALY gained for a five year time horizon (Table 36). Based on the opinion of the company, the most clinically relevant comparisons are;

- Naloxegol 25 mg versus placebo in combination with bisacodyl. The ICER is £12,639 per QALY gained
- Naloxegol 25 mg plus bisacodyl versus placebo in combination with bisacodyl. The ICER is £11,175 per QALY gained

Table 36: Base case results – absolute (anticipated licensed population)

Technologies	LY	QALY	costs (£)	Incr. LY	Incr. QALY	Incr. costs (£)	ICER (£) (QALYs)
Placebo	4.534	2.663	£1,016				
Naloxegol 25 mg	4.534	2.686	£1,272	0.000	0.024	£256	£10,849
LY, life year; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio							

ERG Comment: The ERG observed an inconsistency in reporting total costs of naloxegol 25 mg and incremental costs in the CS. In the clarification letter (Section C, Question 65), the company acknowledged these differences in the base case costs and indicated that the total costs of naloxegol 25 mg should be £1,272 (Section 7.7.5, 7.7.6). The corresponding incremental cost amounts to £256 (instead of £185). The definitions of clinical and safety inputs of the economic model are not fully comparable with the clinical effectiveness section of the report. In particular, definitions of response parameters are higher as a result of the change in definition. The ERG agrees with the changes made for the economic model, so as to avoid health state definitions that rely on a change from baseline.

Table 37: Model inputs which by definition differ from those reported in the clinical section

Cost-effectiveness Model Inputs	Divergence From the Clinical Effectiveness Section
Definition of OIC	Base Case: Less than three spontaneous bowel movements (SBMs) per week in at least two out of the last four weeks
Definition of non-OIC	Base Case: Three or more SMBs per week in at least three out of the last four weeks
Assessment of response	Response in the CE model focuses on absolute constipation status alone, without measure of change in bowel movements from baseline.
Adverse Events	The utility impact of AEs is captured by treatment-specific utility inputs in non-OIC health state. (only in the first cycle of the model)

More importantly, the ERG already described why they consider the comparison of naloxegol versus placebo to be irrelevant (Section 5.2.4); a treatment without the option of rescue medication is highly implausible in clinical practice and the SBM observed in the trial cannot be seen as independent from the use of rescue medication in the trial. As mentioned in Section

5.2.4, the ERG considers the comparison naloxegol plus bisacodyl versus placebo plus bisacodyl based on SBM as response the only comparison that can be made. Therefore Section 5.3 presents this analysis.

When disregarding the above crucial issue, the ERG considers the base case analysis presented by the manufacturer too limited, in the sense that for all comparators together a full incremental analysis should have been performed. In this case that means that for the LIR population naloxegol 25 mg should have been compared to naloxegol plus bisacodyl, placebo, placebo plus bisacodyl and methylnaltrexone. We therefore requested in the clarification letter (Section B, Question 37) from the company to provide a full MTC analysis for the model including placebo, placebo plus bisacodyl and naloxegol plus bisacodyl, ie an expansion of the current MTC to include all comparators. The company wrote in their response that they did not believe it was required to provide the MTC analysis requested as the KODIAC 4 and 5 trials provide a direct estimate of the comparative efficacy of naloxegol plus bisacodyl versus placebo plus bisacodyl, eliminating a need for this comparator.

However, by not providing this full MTC, the manufacturer has now produced two sets of ICERs which are incomparable.

5.2.10 Sensitivity analyses

The company assessed the various uncertainties in the economic evaluation through deterministic sensitivity analysis, scenario analysis and probabilistic sensitivity analysis. While the first two show which parameters and assumption have the largest impact on the model outcomes, the latter shows the overall uncertainty around the ICER.

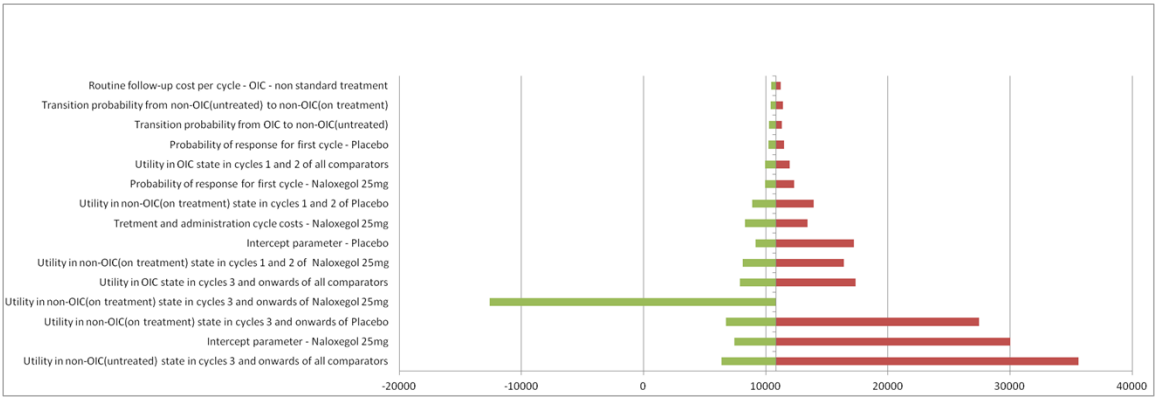
Deterministic sensitivity analyses

Univariate sensitivity analyses were conducted in the CS to test the sensitivity of the results (ICER) for plausible variation of input parameters. Parameter values were varied ±20% to the base case value and the results were displayed in a tornado diagram.

Table 38: Base case values used in the deterministic sensitivity analysis

Variable	Relative Variation	Rationale
Treatment response	±20%	A common variation in parameter inputs was included in the DSA to determine the relative sensitivity of model outcomes to different model inputs. Exploration of uncertainty in parameter inputs was assessed through the PSA (Section 7.7, in the CS).
Extrapolation function, intercept parameter	±20%	
Transition B	±20%	
Transition C	±20%	
Utility in non-OIC	±20%	
Utility in OIC	±20%	
Cost in non-OIC	±20%	
Cost in OIC	±20%	
Frequency of adverse events	±20%	
DSA= Deterministic sensitivity analyses; OIC= opioid-induced constipation; PSA= probabilistic sensitivity analysis		

Figure 5: Base case tornado diagram



Abbreviations: OIC= opioid-induced constipation
†In the DSA, utility in non-OIC (untreated) and OIC states for cycles 1 and 2 are analysed separately from utility in non-OIC (untreated) and OIC states for cycle 3.

Based on the tornado diagram results, five parameters were identified that had an impact on the ICER. A threshold analysis was conducted to assess the input values that generate a base case ICER of £20,000. Table 39 shows five influential parameters on the ICER (anticipated licensed population).

Table 39: Threshold analysis results, naloxegol 25 mg versus placebo (anticipated licensed population)

Input†	**Base case value**	**Parameter value to give an ICER =£20,000.**
Utility in non-OIC (on treatment) state in cycles 3 and onwards of naloxegol 25 mg	0.665	0.632
Utility in non-OIC(untreated) state in cycles 3 and onwards of all comparators	0.613	0.694
Utility in non-OIC(on treatment) state in cycles 3 and onwards of Placebo	0.613	0.706
Intercept parameter - Naloxegol 25mg	5.473	4.692
Utility in OIC state in cycles 3 and onwards of all comparators	0.553	0.668

OIC= opioid-induced constipation
† In the DSA, utility in non-OIC (untreated) and OIC states for cycles 1 and 2 are analysed separately from utility in non-OIC (untreated) and OIC states for cycle 3.

The ERG requested in the clarification letter (Section C, Question 63) to re-run the DSA with ranges based on the 95% CI of parameters (instead of ± 20%). Table 40 below depicts ICERs based on the 95% CI estimates for the LIR patient population. DSA indicates that most influential input parameter in the model is HRQoL. Only when treatment- and time-specific utility inputs are varied, a significant impact on the ICER is observed, both for the DSA based on a SE of 20% of the mean or 95% CI.

Table 40: ICERs based on the 95%CI estimates for the LIR patient population

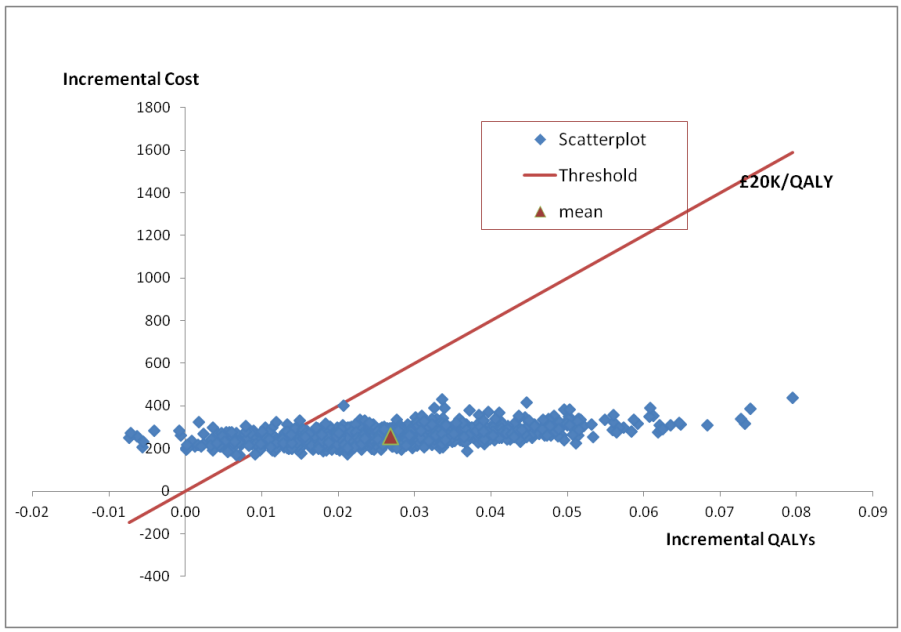
Parameter	Input values			ICER-QALY		
	Base case	Upper 95% CI	Lower 95% CI	Base case	Upper 95% CI	Lower 95% CI
Nal 25mg response for first cycle (week 0-4)	58.51%	64.73%	52.29%	£10,849	£10,321	£11,526
Placebo response for first cycle (week 0-4)	39.75%	45.95%	33.54%	£10,849	£11,371	£10,354
Nal 25mg: Transition 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	£ 12,691
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

AE= adverse event; CI= confidence interval; NAL= naloxegol; OIC= opioid-induced constipation

Probabilistic sensitivity analyses

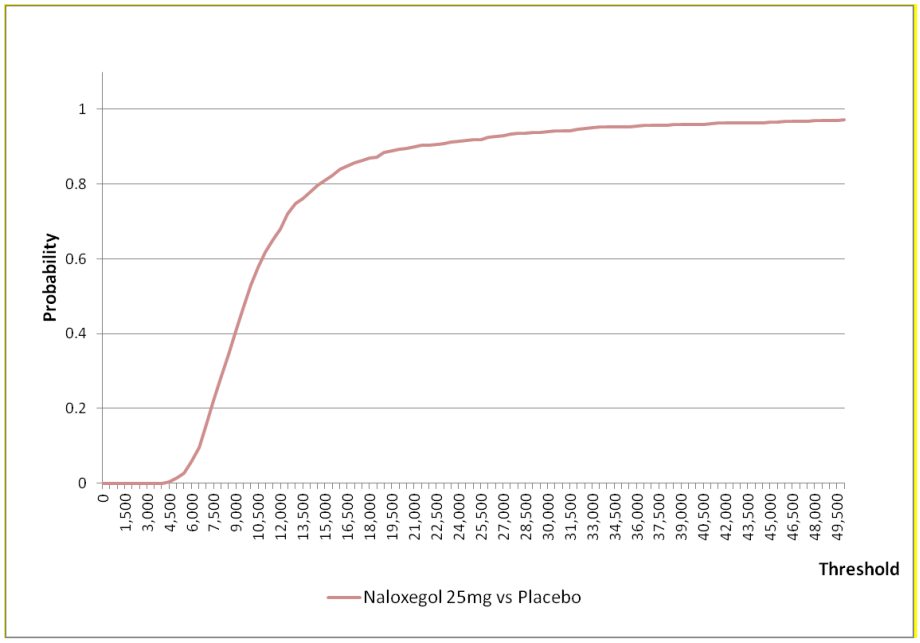
A probabilistic sensitivity analysis (PSA) was performed in the company's submission to assess the uncertainty of input parameters of the economic model. Probability distributions were specified for the input parameters and cost-effectiveness results associated with simultaneously selecting random values from those distributions were generated. Table 118 from the CS summarises the parameters included in the PSA and the distributions used to determine their values. These parameters were considered for PSA based on their known SE, if and whenever available, around the base case estimate. A SE of 5% of the mean was assumed for the purpose of PSA where the SE is unknown. PSA was run using 10,000 simulations.

Figure 6: Base case PSA scatter plot for naloxegol 25 mg vs. placebo, anticipated licensed population (10,000 simulations)



Abbreviations: QALY= quality adjusted life year.

Figure 7: Base case cost-effectiveness acceptability curve (CEAC) for naloxegol 25 mg vs. placebo, anticipated licensed population



For the base case, PSA results indicated that naloxegol 25 mg has a probability of 91% of being cost-effective (compared to placebo) at a willingness to pay threshold of £20,000.

Base case analyses of additional comparator treatments

A. Naloxegol 25 mg (plus bisacodyl) compared with placebo plus bisacodyl

The higher response of naloxegol 25 mg plus bisacodyl compared with placebo plus bisacodyl, leads to higher proportion of patients to enter the *'non-OIC'* (on treatment) health state. Consequently, the point at which the model reaches a steady state is delayed. Naloxegol 25 mg and naloxegol 25 mg plus rescue bisacodyl generate QALY gains when compared with placebo plus bisacodyl. Hence, the resulting ICERs are favourable for naloxegol 25 mg. The cost of placebo plus bisacodyl is lower than the cost of placebo alone. This is because the cost increase of adding bisacodyl is offset by the cost reduction of managing constipation, which is a consequence of the higher response achieved by bisacodyl.

Table 41: Base case results: additional comparators (anticipated licensed population)

Technologies	Total LY	Total QALY	Total costs (£)
Naloxegol 25 mg	4.534	2.686	£1,272
Naloxegol 25 mg + bisacodyl	4.534	2.693	£1,313
Placebo + bisacodyl	4.534	2.665	£1,000
LY= life years; QALY= quality adjusted life year			

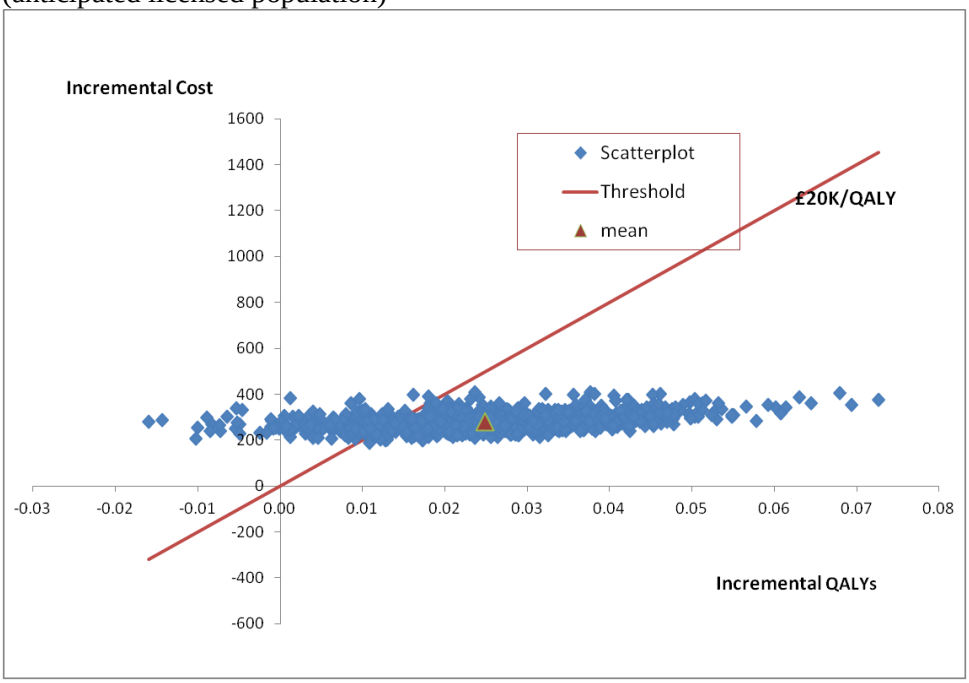
Table 42: Base case results: additional comparators (anticipated licensed population)

Treatment	Comparator	Incremental LY	Incremental QALY	Incremental costs (£)	ICER (£) (QALYs)
Naloxegol 25 mg	Placebo + bisacodyl	0.000	0.022	£272	£12,639
Naloxegol 25 mg + bisacodyl	Placebo + bisacodyl	0.000	0.028	£313	£11,175
ICER= incremental cost effectiveness ratio; LY= life years; QALY= quality adjusted life year					

The PSA and CEAC results suggest that ICER for naloxegol 25 mg, when compared with placebo plus bisacodyl is acceptable at the willingness-to-pay (WTP) threshold of £20,000.

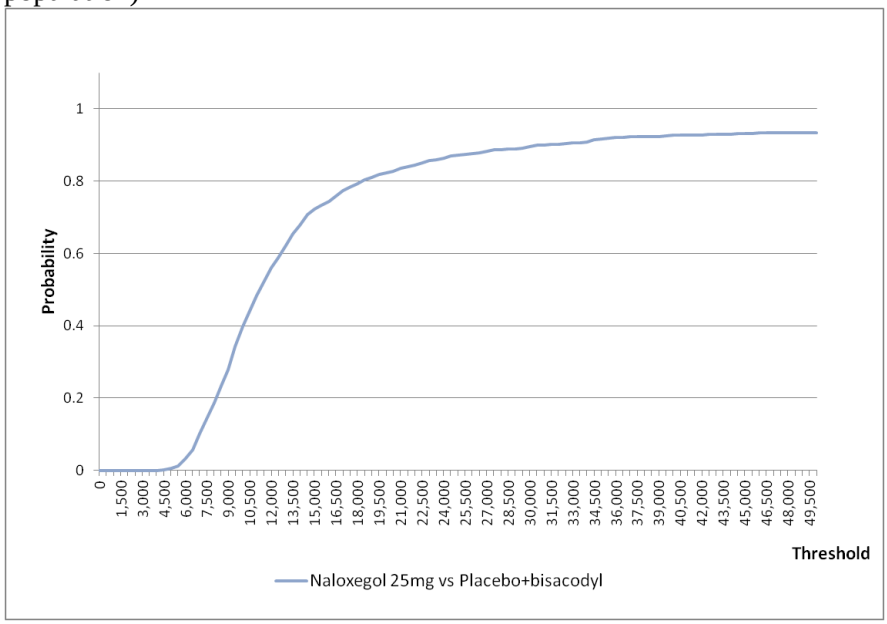
Naloxegol 25 mg has a probability of 83% of being cost-effective when compared with placebo plus bisacodyl (willingness-to-pay (WTP)= £20,000) Figure 8 and Figure 9 depict the cost-effectiveness scatter plot and acceptability curve for naloxegol 25 mg versus placebo plus bisacodyl (anticipated licensed population).

Figure 8: Cost-effectiveness scatter plot for naloxegol 25 mg compared with placebo plus bisacodyl (anticipated licensed population)



Abbreviations: QALY= quality adjusted life year.

Figure 9: CEAC for naloxegol 25 mg compared with placebo plus bisacodyl (anticipated licensed population)



Naloxegol 25 mg plus bisacodyl has a probability of 87% of being cost-effective when compared with placebo plus bisacodyl (WTP= £20,000). The cost-effectiveness scatter plot and acceptability curve for naloxegol 25 mg plus bisacodyl versus placebo plus bisacodyl (anticipated licensed population) is almost the same as for naloxegol 25 mg compared with placebo plus bisacodyl.

B. Naloxegol 25 mg compared with SC methylnaltrexone QAD

The proportion of patients in the OIC state with SC methylnaltrexone is exacerbated by the stopping rule, which causes patients to stop SC methylnaltrexone after 16 weeks. Naloxegol 25 mg generates higher QALYs in this analysis than the naloxegol 25 mg versus placebo comparison. This is because the response data is obtained from MTC. The treatment costs of SC methylnaltrexone are higher, which leads to cost savings when compared with naloxegol 25 mg. The resulting ICER is dominant, favouring naloxegol 25 mg.

Table 43: Naloxegol 25 mg compared with SC methylnaltrexone QAD (anticipated licensed population)

Technologies	Total LY	Total QALY	Total costs (£)
Naloxegol 25 mg	4.534	2.732	£1,236
SC MNTX QAD	4.534	2.729	£2,198
LY= life year; MNTX= methylnaltrexone; QAD= every other day; QALY= quality adjusted life year; SC= subcutaneous			

Table 44: Naloxegol 25 mg compared with SC methylnaltrexone QAD (anticipated licensed population)

Treatment	Comparator	Incremental LY	Incremental QALY	Incremental costs (£)	ICER (£) (QALYs)
Naloxegol 25 mg	SC MNTX QAD	0.000	0.004	-£962	Naloxegol Dominant
ICER, incremental cost-effectiveness ratio; LY, life year; MNTX, methylnaltrexone; QAD, every other day; QALY, quality adjusted life year; SC, subcutaneous					

The PSA and CEAC results suggest that ICER for naloxegol 25 mg, when compared with SC methylnaltrexone is acceptable at the willingness-to-pay (WTP) threshold of £20,000; at that threshold naloxegol 25 mg has a probability of 100% of being cost-effective when compared with SC methylnaltrexone.

C. Cost minimisation analysis of naloxegol 25 mg in comparison with rectal interventions

A cost minimisation analysis was conducted to calculate how many months of naloxegol 25 mg treatment could be given for the cost of one rectal intervention. The unit costs of manual evacuation are presented in Table 45. According to the company's survey, the length of time required to perform a manual evacuation in the community setting is 0.5 hours. The unit costs associated with this scenario and the expected number of months of naloxegol 25 mg treatment expected per cost of one rectal intervention are shown in Table 46.

Naloxegol 25 mg can be provided for 0.68 months for the same cost as a rectal intervention at patient's home. Similarly, naloxegol 25 mg can be provided for 43.02 months, if the rectal intervention is performed at an inpatient care unit.

Table 45: Unit costs of manual evacuation based on time required to perform the procedure

Intervention	Unit cost	Unit cost (based on time)	Reference
Community setting			
Nurse hourly cost	£70.00	£ 35.00	PSSRU 2013, section 10.1. community nurse cost per hour of home visiting including travel
Hospital setting			
Outpatient care	£310.00	£ 310.00	NHS Reference Cost 2012/2013 procedure FZ90a, abdominal pain with intervention, general medicine
Inpatient care	£2,216.33	£2,216.33	NHS Reference Cost 2012/2013 Average of elective and non-elective procedure FZ90a, abdominal pain with intervention, gastroenterology
Drug cost			
Naloxegol 25 mg	£51.52	£51.52	Company Cost per 28 day cycle. £55.20 for a pack of 30 tablets, £1.84 per day

Table 46: Number of months of naloxegol 25 mg treatment expected per cost of one single intervention

Intervention	Number of months of treatment with naloxegol
Manual evacuation at patient home	0.68
Outpatient care	6.02
Inpatient care	43.02

Subgroup analyses

Subgroup analysis was performed to assess naloxegol 25 mg for the anticipated licensed population on step 3 opioids. This analysis was conducted for non-cancer patients with OIC who were laxative inadequate responders at baseline (demonstrated ≥4 days of laxative use during the 14 days prior to the study screening period and on step 3 opioids (according to the WHO pain ladder.[57] The proportion of patients in each health state corresponds to the base case population (Section 7.7.2, in the CS).

For the comparison of naloxone-oxycodone in which naloxegol 25 mg is taken in combination with oral morphine, naloxegol 25 mg is dominant. When naloxegol 25 mg is taken in combination with oxycodone, the ICER is £30,054. The PSA and CEAC results suggest that ICER for naloxegol 25 mg (OXY), when compared with naloxone-oxycodone has a probability of 46% of being cost-effective (WTP= £20,000).

Table 47: Subgroup analyses results (anticipated licensed population + Step 3 opioids)

Treatment	Comparator	Incremental QALY	Incremental costs (£)	ICER (QALY) (£), treatment vs. comparator	Prob. ICER <£20000
Naloxegol 25 mg	Placebo	0.043	£260	£6,015	99%
Naloxegol 25 mg	Placebo + rescue bisacodyl	0.042	£280	£6,687	97%
Naloxegol 25 mg + Rescue laxatives	Placebo + rescue bisacodyl	0.050	£312	£6,219	98%
Naloxegol 25 mg	SC MNTX QAD	0.006	-£918	Naloxegol Dominant	100%
Naloxegol 25 mg (morphine)†	OXN	0.0026	-£4,097	Naloxegol Dominant	100%
Naloxegol 25 mg (OXY)‡	OXN	0.0026	£78	£30,054	45%

ICER= incremental cost effectiveness ratio; MNTX= methylnaltrexone; OXN= naloxone-oxycodone; OXY= oxycodone; QAD= every other day; QALY= quality adjusted life year
†Source: IMS Health[28]
‡Average dose of oxycodone = 59.3 mg. Source: [42, 44, 45]

Scenario analyses

A large number of structural assumptions were examined in the CS to explore the impact on model outcomes. The results of these analyses are reported in the company's submission Tables 130-135.

The results (ICERs) of the different utility scenarios are displayed in Table 48.

Table 48: Utility inputs scenarios (anticipated licensed population)

Scenario	**ICER (£) (QALYs) for naloxegol 25 mg vs.**		
	Placebo	**Placebo + bisacodyl**	**SC MNTX QAD**
Base case (vs. placebo)†	£10,849	£12,639	
Base case (vs. SC MNTX)‡			Naloxegol Dominant
Treatment-specific health state utility, distinguishing utility used in Cycle 1 and 2 versus remaining model cycles (trial data, Wittrup-Jensen tariff)	£14,925	£17,365	
Treatment-specific health state utility (pooled 4 and 12 week trial data, Dolan tariff	£14,693	£17,725	
Health state specific (trial data, Dolan tariff)	£38,921	£63,423	
Health state specific (trial data, Wittrup-Jensen tariff)			Naloxegol Dominant
Health state specific (secondary literature[66]	£7,555	£12,312	Naloxegol Dominant

ICER, incremental cost-effectiveness ratio; LY, life year; MNTX, methylnaltrexone; QAD, every other day; QALY, quality adjusted life year; SC, subcutaneous
†A treatment, time and OIC specific utility input is used in the base case comparison with placebo
‡A OIC specific utility is used in the base case comparison with SC MNTX

Table 49: Transition non-OIC (on treatment) to OIC scenarios, anticipated licensed population

Scenario	**Time horizon**	**ICER (£) (QALYs) for naloxegol 25 mg vs.**		
		Placebo	**Placebo + bisacodyl**	**SC MNTX QAD**
Base case	5 years	£10,849	£12,639	Naloxegol Dominant
Exponential	1 year	£11,804	£14,349	Naloxegol Dominant
	3 years	£10,882	£12,696	Naloxegol Dominant
Weibull	1 year	£10,703	£ 12,522	Naloxegol Dominant
	3 years	£9,510	£10,602	Naloxegol Dominant

Scenario	Time horizon	ICER (£) (QALYs) for naloxegol 25 mg vs.		
		Placebo	Placebo + bisacodyl	SC MNTX QAD
	5 years	£9,420	£10,464	Naloxegol Dominant
Log logistic	1 year	£11,011	£13,326	
	3 years	£9,130	£10,419	
	5 years	£8,633	£9,700	
Log normal	1 year	£10,903	£13,253	
	3 years	£8,835	£10,034	
	5 years	£8,281	£9,219	
K8 constant discontinuation	1 year	£11,742	£15,651	Naloxegol Dominant
	3 years	£10,066	£12,514	Naloxegol Dominant
	5 years	£9,655	£11,771	Naloxegol Dominant
12 week response maintained	1 year	£12,743	£15,886	
	3 years	£11,283	£13,647	
	5 years	£11,016	£13,250	
No extrapolation	12 weeks	£26,431	£43,400	
Hazard ratio = 1				Naloxegol Dominant

ICER, incremental cost-effectiveness ratio; LY, life year; MNTX, methylnaltrexone; QAD, every other day; QALY, quality adjusted life year; SC, subcutaneous.

ERG Comment: For the PSA, the company had used a default standard error of 5% of the mean wherever no standard errors were available. The ERG considers 5% rather small for many parameters and therefore reran the PSA with a standard error of 20% of the mean. In addition, the model did not define a range for the HR of methylnaltrexone and naltrexone-oxycodone. We therefore applied the 20% SE as well for these parameters. This additional uncertainty does not impact the base case ICER, but now the probability of naloxegol being cost-effective compared to placebo reduces from 91% to 84% at a threshold of £20,000. The same is true for all other CEACs presented by the company, in all instances the probability of being cost-effective drops a few percentage points.

The scope of the STA is adults with OIC and is thus broader than the population included in the *de novo* economic model. Section 7.9.5 in the CS considers the generalisability of the cost effectiveness analysis for non-cancer patients to cancer patients. The ERG thinks it is questionable to assume that efficacy (as demonstrated in previous studies of methylnaltrexone and naloxone-oxycodone, in Section 1.4 in the CS), safety and utility estimates (as they include a time and treatment effect

interaction) could be kept similar for cancer pain patients. For simplicity reasons, the company maintained the efficacy, AE rates and all transition probabilities (A, B, C, D and E) the same as non-cancer population. Hence, the ERG does not believe that the current model is generalisable to cancer patients based on current model inputs & assumptions.

Based on the extensive set of sensitivity and scenario analyses performed by the company only two scenarios that changed the conclusions of the study findings were:

1. The worst case scenario, 12 week time horizon, resulted in ICERs of £20,020 for naloxegol 25 mg compared with placebo and £33,708-for naloxegol 25mg compared with placebo plus bisacodyl. Naloxegol 25 mg remains dominant when compared with SC methylnaltrexone.
2. When a health-state specific utility input is employed (rather than treatment- and time-dependent utilities), the ICER for naloxegol 25 mg increases to £38,921 compared with placebo and £63,423 when compared with placebo plus bisacodyl.

5.2.11 Model validation and face validity check

The following steps were undertaken to validate the model:

i. The assumptions of the model were checked by clinical experts during an advisory board meeting.

ii. The modelling methodology was reviewed by three health economists.

iii. An assessment of the technical validity of the model was undertaken by the agency contracting the model, to test accuracy of the programming and the extraction of data inputs.

In the clarification letter, (Section C, Question 68), the ERG stated that the methods used to externally validate the model were not obvious. The company indicated that there were no data sources against which the predictions of the model (eg changes in OIC status) could be externally validated. In lieu of this information, clinicians were consulted during an advisory board meeting and expert health economists provided ongoing feedback on the model. In addition, it was indicated that technical validation of the economic model was undertaken by a senior modelling expert at a vendor company.

ERG Comment: The ERG thoroughly checked the technical validity and found no major issues. The ERG considers it unfortunate that clinical experts were not asked to comment on the model outcomes with regards to the time patients stay in the non-OIC (on treatment) health state. After only two years all patients have left this health state, which is not surprising for the placebo group but is for the naloxegol group.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

New base case analysis based on rescue medication and SBM

Table 50 presents the analysis as suggested by the ERG, that is rescue bisacodyl is permitted, and the response is based on SBM. The ICER has increased by only £65 per QALY gained, as the only difference between this analysis and the base case presented by the manufacturer is the inclusion of costs of bisacodyl, which amounts to £0.20 and £0.029 per cycle for naloxegol and placebo respectively.

Table 50: Base case results – absolute (anticipated licensed population)

Technologies	LY	QALY	costs (£)	Incr. LY	Incr. QALY	Incr. costs (£)	ICER (£) (QALYs)
Placebo + rescue bisacodyl	4.534	2.663	£1,017				

Technologies	LY	QALY	costs (£)	Incr. LY	Incr. QALY	Incr. costs (£)	ICER (£) (QALYs)
Naloxegol 25 mg + rescue bisacodyl	4.534	2.686	£1,273	0.000	0.024	£256	£10,864
LY, life year; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio							

Sensitivity analysis on response rate as proxy for the 2xLIR population

In Table 51 we show the response rates at four weeks as extracted from the CSRs for both the LIR and the 2xLIR population. The 2xLIR population consists of patients who had inadequate response from at least two classes of laxatives for ≥4 days in the two weeks prior to study entry or reported unsatisfactory laxation from ≥1 additional laxative class from the six month OIC history prior to screening.

With this data, we calculated a pooled response rate for the 2xLIR population. Note that in this table, the clinical definition of response is used, that is, a response means that is defined as ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least nine out of the 12 study weeks and three out of the last four study weeks.

It is clear from the response rates in Table 51 that per treatment group, the impact of limiting the population is not very large. However, the difference in response rate between the two groups has altered substantially, from 20.4% for the LIR population to 13.5% for the 2xLIR population.

Table 51: Response rates at four weeks for LIR and 2xLIR population (as extracted from the CSRs)

	placebo			**naloxegol 25 mg**		
KODIAC 4	n	responders	response rate	n	responders	response rate
LIR	118	40	33.9%	117	72	61.5%
2xLIR	42	16	38.1%	57	31	54.4%
KODIAC 5	n	responders		n	responders	
LIR	121	47	38.8%	124	65	52.4%
2xLIR	48	20	41.7%	42	22	52.4%
Pooled	n	responders		n	responders	
LIR	239	87	36.4%	241	137	56.8%
2xLIR	90	36	40.0%	99	53	53.5%

We therefore did an exploratory analysis to see how much this would impact the ICER. Also, since for this population the sample size is reduced, we also performed a PSA to assess the uncertainty around the ICER.

For this analysis, we used the response rates from Table 51 and also derived the standard errors (5%). We assumed that all other input parameters would be the same, as we have no 2xLIR data to inform the various transition probabilities in the Markov model. The results are presented in

Table 52. It is clear that the ICER is only slightly increased compared to the base case ICER of £10,849. When uncertainty is taken into account the probability of the ICER being below £20,000 is 80% while the probability of being below £30,000 is 89% (for the base case these percentages are 85% and 93%, respectively).

Table 52: Scenario analysis (naloxegol 25 mg versus placebo in the 2xLIR population)

	QALY	Cost	incr QALY	incr Cost	ICER
Placebo	2.663	£1,016			
Naloxegol	2.684	£1,258	0.0212	£242	£11,406

Threshold analysis on HR for transition non-OIC (on treatment) to OIC for methylnaltrexone and naloxone-oxycodone

In the model, the hazard ratios for the transition from non-OIC (on treatment) to OIC for methylnaltrexone and naloxone-oxycodone (Table 22) were approximated as the ratio of the four week response rate of these two comparators relative to that of naloxegol 25 mg. This was based on the assumption that the non-response rate after four weeks is likely to be related to the response rate at four weeks.

Since this relation is unlikely to be strictly one-on-one, we explored at which hazard ratio naloxegol is no longer cost-effective.

For methylnaltrexone we explored both the anticipated licensed population and the anticipated licensed population plus step 3 opioids. Here we found that for the whole range of hazard ratios (ie from 0.01 to 100), naloxegol 25 mg is dominant. This is because methylnaltrexone is only recommended for 16 weeks of treatment; after 16 weeks, patients in the model move from non-OIC (on treatment) to non-OIC (untreated).

For naloxone-oxycodone we only explored the anticipated licensed population plus step 3 opioid as this combination already contains a step 3 opioid.

When naloxone-oxycodone is compared to naloxegol plus morphine, we find that for HR<1.2, naloxegol dominates naloxone-oxycodone. Once the HR is larger than 1.2, naloxone-oxycodone becomes more effective whilst being more costly than naloxegol. However, even for a HR of 100, naloxegol would still be considered cost-effective with an ICER of £99,000 (as the ICER is in the SW quadrant of the CE-plane, the ICER should be larger than the threshold ICER).

When we compare naloxone-oxycodone to naloxegol plus oxycodone, we find that at a HR of 0.45 the ICER would be £20,000 whereas at a HR of 0.85 the ICER would be £30,000. This latter threshold of the HR is exactly the current base case value used in the model.

Analysis of structural uncertainty related to curve extrapolation

In Table 53 the company has explored the impact of changing the parametric form of the time-to-event curve used to estimate the transition probability from non-OIC (on treatment) to OIC. In that analysis, curves are changed to another distribution, but each time placebo and naloxegol use the same parametric distribution. Given the wide variation in patients still in non-OIC (on treatment) after five years, we have here explored the impact when different combinations of distributions are assumed.

The model allows calculation with four distributions: exponential, Weibull, lognormal and loglogistic.

With these four, we performed a total of 12 analyses. We looked each time at the comparison naloxegol versus placebo and naloxegol plus bisacodyl versus placebo plus bisacodyl. We found that in only two cases did the ICER increase noticeably, in all other cases it remained more or less the same or decreased to around £8,000. Table 53 shows the results when we assume an exponential distribution for the naloxegol group and a lognormal distribution for the placebo group. Table 54 shows similar results, in this table a loglogistic distribution is assumed for the placebo group.

Table 53: Transition non-OIC (on treatment) to OIC scenario: naloxegol exponential - placebo lognormal

exp - lognormal	QALY	Cost	incr QALY	incr Cost	ICER	av time on treatment (weeks)	time till no one on treatment (weeks)
Placebo	2.665	£996				15.48	220
Naloxegol	2.686	£1,272	0.021	£276	£13,143	23.1	160
Placebo + bisacodyl	2.668	£970				22.44	220
Naloxegol + bisacodyl	2.693	£1,313	0.025	£343	£13,720	28.04	160

Table 54: Transition non-OIC (on treatment) to OIC scenario: naloxegol exponential - placebo loglogistic

exp - loglogistic	QALY	Cost	incr QALY	incr Cost	ICER	av time on treatment (weeks)	time till no one on treatment (weeks)
Placebo	2.665	£ 999				14.72	220
Naloxegol	2.686	£ 1,272	0.021	£ 273	£ 13,000	23.1	160
Placebo + bisacodyl	2.668	£ 975				21.28	220
Naloxegol + bisacodyl	2.693	£ 1,313	0.025	£ 338	£ 13,520	28.04	160

5.4 Conclusions of the cost-effectiveness section

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent and is in line with the decision problem specified in the scope. Reviewing the overall evidence, the ERG confirmed that there was no existing cost-effectiveness model for naloxegol for the anticipated indication.

The ERG assessment indicated that the model was generally well presented and reported.

The population studied in the cost-effectiveness is the same as the licensed indication but narrower than the population discussed in the final scope (ie adults with opioid-induced constipation). The ERG questions to what extent the trial definition of inadequate response to laxatives (ie taking at least one laxative class for a minimum of four days during the two weeks prior to the screening period) matches with clinical practice. However, explorative analysis showed that when inadequate response is redefined as at least two laxative classes previously, the outcomes hardly change.

However, explorative analysis showed that the outcomes hardly change when inadequate response is redefined as inadequate response from at least two classes of laxatives for ≥4 days in the two weeks prior to study entry or reported unsatisfactory laxation from ≥1 additional laxative class from the six month OIC history prior to screening.

On the other hand, the ERG agrees with the adopted response definition (three or more SBMs per week in at least three out of the last four weeks) instead of the clinical definition, in which also a change from baseline of one SBM is required. The advantage of the model definition of response is that it only incorporates absolute health states, not relative to baseline. However, HRQoL analysis

indicates that the health state non-OIC is too broad to be homogeneous with regards to quality of life. In the current definition only nine SBMs should occur over a 28 day period to be classified as a responder (ie move to the non-OIC on treatment state). But patients who have 28 SBM in these 28 days are in the same health state and thus are assumed to have the same quality of life as those with only nine SBM. This appears unlikely to the ERG.

Furthermore, the impact of permitted switching between different treatments, which would help place naloxegol at a favourable position in the care pathway, is not addressed in the CS. The company indicated that permitted switching and the optimum position of naloxegol in the care pathway were not considered necessary. The ERG disagrees with the response received from the company.

The company indicated that the most clinically relevant scenario is the naloxegol (25 mg) plus bisacodyl in comparison with placebo plus bisacodyl. The company stated the comparison of naloxegol to placebo was selected in the base case analysis, since it was an appropriate regimen that reflects the design and endpoints of the KODIAC 4 and 5 trials. The base case was then built on to consider the use of bisacodyl with both the placebo and naloxegol in the model (as the most clinically relevant scenario). Hence, the company's consideration of the base case was based on the regimen choices with the least unknowns and assumptions (naloxegol 25 mg versus placebo).

However, the ERG would argue that naloxegol *minus* bisacodyl is neither clinically relevant nor consistent with the KODIAC 4 and 5 trials. Clinically it would seem implausible to prescribe naloxegol without bisacodyl (or some other rescue medication) given that rescue medication might be needed. As for the trial, rescue medication was permitted in all arms and therefore there was no such arm as naloxegol minus bisacodyl in the KODIAC 4 and 5 trials. However, by redefining a base case which fits the trial, ie naloxegol (25 mg) plus bisacodyl in comparison with placebo plus bisacodyl using SBM as measure of response, the ERG was able to show that this only increased the base case ICER by £65.

The inputs for the model are mainly derived from KODIAC 4 and 5 trials and literature. However, resource utilisation values are not based on a systematic search of the literature. In general, the ERG observed that the uncertainty is about the cost values that were used for adverse events (AEs) and cost parameters for constipation. AE calculations are not transparent, and the large difference between GP omnibus and the BOI study lack explanation. The ERG believes that a literature search is vital to address the shortcomings of resource utilisation in the model.

Sensitivity analyses revealed that transition probabilities, costs and adverse events have little to no effect on the ICER. However, the utility estimates were influential on the cost-effectiveness results. Changing the utility assumptions had profound impact on the ICERs. In particular, the ICER is most sensitive to the in- or exclusion of a separate treatment effect for naloxegol on HRQoL. According to the ERG, the most plausible explanation is that the non-OIC (on treatment) state is too broad, thus including a heterogeneous group of patients. The most preferable approach to dealing with this would have been to refine the non-OIC (on treatment) state by splitting it in two states and deriving treatment unspecific, health state specific utility values. However, it is the ERGs view that in the absence of such a more refined Markov model, the current approach with treatment specific utilities is a reasonable alternative.

The cost-effectiveness results were generally robust. The ERG sensitivity and scenario analyses revealed that none resulted in central ICERs that varied from the company's results in any meaningful way. However, the ERG requested to have a full MTC to have a comparable assessment of all ICERs. The company did not agree to perform a full MTC by including placebo from the KODIAC trials. Therefore, the cost-effectiveness results presented in this study are not comparable and given the

conclusions formulated in Section 4.4 the health economic outcomes of naloxegol versus methylnaltrexone and naltrexone/oxycodone should be interpreted with care.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

None of the additional clinical and economic analysis undertaken by the ERG resulted in central ICERs that varied from the company's results in any meaningful way.

7 OVERALL CONCLUSIONS

The two main trials presented in the company's submission (KODIAC 4, KODIAC 5) were RCTs comparing naloxegol with placebo. No direct evidence from head-to-head trials to any of the comparators defined in the final scope was available. Furthermore, studies included for indirect comparisons assessed different populations, as detailed in Section 4.1.2 of this report.

In anticipation of the license by EMA, the population was defined as *'adults with opioid-induced constipation who have had an inadequate response to laxative(s)'*. However, the definition of LIR remains unclear to the ERG (as detailed in Section 2.2 of this report). The eligible population in the CS is based on a broad definition of LIR in OIC rather than the total OIC population (as referred to in the scope). External validity of results would have been more seriously compromised had a more restrictive definition of LIR been used but, nevertheless it is evident that important evidence may have been overlooked by restricting searches to any definition of LIR.

Compared to the final scope some outcomes were not clearly considered and/or reported in the CS, eg effects on analgesic efficacy.

It should be noted that studies including patients with malignancies leading to opioid-induced constipation were not included. While this might allow better comparability, the presented evidence does not allow any firm conclusion regarding these patients.

As detailed in Section 4.1.1 of this report, the ERG still concerns regarding the comprehensiveness of searches for comparator treatments. In addition, studies comparing two comparators to each other which could have been contributed to a MTC have not been included. Unfortunately, the ERG does not have the time or recourses to conduct and screen new searches. Therefore, the implications of these limitations are not known.

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent and is in line with the decision problem specified in the scope. The ERG assessment indicated that the model was generally well presented and reported.

The company used the comparison of naloxegol to placebo as the base case analysis, since it was deemed an appropriate regimen that reflects the design and endpoints of the KODIAC 4 and 5 trials.

However, the ERG considers this a faulty choice, as naloxegol *minus* bisacodyl is neither clinically relevant nor consistent with the KODIAC 4 and 5 trials (as rescue medication was permitted in all arms). However, by redefining a base case which fits the trial, ie naloxegol (25 mg) plus bisacodyl in comparison with placebo plus bisacodyl using SBM as measure of response, the ERG was able to show that this only increased the base case ICER by £65.

The various sensitivity and scenario analyses revealed that the ICER is relatively robust against changes in most input values but quite sensitive to changes in the utility vales applied to the non-OIC health states. Using treatment and time independent utility values increased the ICER significantly, from £10,849 to £38,921. However, the ERG considers the treatment and time dependent utility values more valid for the current assessment, given the rather heterogeneous health state non-OIC.

7.1 Implications for research

There is an apparent lack of RCTs in patients with laxative inadequate response (LIR) comparing naloxegol with any of the relevant comparators defined in the final scope, ie oral laxative treatment without naloxegol; peripheral mu-opioid receptor antagonists (methylnaltrexone); opioid analgesic and opioid receptor antagonist combinations (naloxone-oxycodone); rectal interventions (eg suppositories and enemas). These trials would not only allow direct comparisons of two or more

treatments but would also contribute to MTC for this clinical problem and would allow a full incremental analysis of the cost-effectiveness.

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APPENDIX 1: ERG SEARCH STRATEGIES

The ERG undertook the following search to investigate whether the Economic filter utilised in the Medline & Embase searches reported in Section 10.10 may have been overly restrictive.

Database: Embase (Ovid SP): 1974-2015/1/12

Searched: 13.01.2015

1 'constipation'.mp. 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 NEAR2 'bowel dysfunction'.ti,ab. (65399)
2 (Constipation or Dyschezia or obstipation or "rectal constipation" or "slow transit constipation").ti,ab. (26588)
3 (non*selective adj2 opioid antagonists).ti,ab. (9)
4 exp narcotic antagonist/ (54293)
5 opioid antagonist.ti,ab. (3204)
6 (opioid adj2 receptor*).ti,ab. or exp opiate receptor/ (37019)
7 delta opiate receptor/ (4805)
8 kappa opiate receptor/ or mu opiate receptor/ (12076)
9 pamora.ti,ab. (8)
10 pegylated naloxol conjugate.ti,ab. (0)
11 exp serotonin 4 agonist/ or secretagogue/ (793)
12 (pentazocine or nalbuphineor buprenorphine or dezocine or butorphanol).ti,ab. (4146)
13 exp 17 methylnaltrexone/ (681)
14 (methylnaltrexone or relistor).ti,ab. (375)
15 exp naloxone/ (36776)
16 (naloxone or narcan or nalone or narcanti).ti,ab. (23540)
17 exp alvimopan/ (531)
18 (alvimopan or entereg or adl 8 2698 or adl 82698 or ly 246736 or ly246736).ti,ab. (211)
19 exp naltrexone/ (11499)
20 (naltrexone or antaxone or pti 555 or celupan or morviva or revia or depade or vivitrol).ti,ab. (6678)
21 exp nalmefene/ (973)
22 (nalmefene or nalmetrene or revex or cervene or arthrene or incystene).ti,ab. (353)
23 or/3-22 (81471)
24 exp prucalopride/ (651)
25 (prucalopride or resolor).ti,ab. (310)
26 exp lubiprostone/ (654)
27 (lubiprostone or amitiza or "ru 0211" or td 1211 or nktr 118).ti,ab. (331)
28 exp linaclotide/ (400)
29 linaclotide.ti,ab. (268)
30 exp tapentadol/ (685)
31 (tapentadol or nucynta or palexia or tapenta or targin or arginact or alks 37 or adl5945 or 'adl 5945).ti,ab. (461)
32 or/24-31 (2183)
33 (Laxative or purgative or bisacodyl or senna or sennoside or polyethylene glycol 3350 or docusate or lactulose or mannitol or sorbitol or magnesium citrate or sodium picosulfate or magnesium hydroxide or psyllium or methylcellulose or polycarbophil).ti,ab. (40050)
34 (naloxegol or MOVANTIK or moventig or NKTR-118).mp. (63)
35 exp naloxegol/ (47)

36 laxative.mp. or exp laxative/ (122436)
37 (suppositor* or enema*).mp. (26462)
38 "manual evacuation".mp. (66)
39 (cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp. (2864)
40 exp "cost benefit analysis"/ (66093)
41 ((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp. (67814)
42 (cost utility analys* or (cost-utility adj1 analys*)).mp. (6555)
43 "cost utility analysis"/ or economic evaluation/ (14933)
44 ((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp. (105024)
45 "cost effectiveness analysis"/ (102787)
46 or/39-45 (172174)
47 ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp. (22204)
48 ("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp. (49927)
49 exp decision theory/ or "decision tree"/ (7734)
50 decision tree.mp. (8895)
51 economic model.mp. (1930)
52 (markov or deterministic).mp. (25649)
53 ((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp. (214924)
54 ((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp. (681)
55 (incremental-cost or incremental cost).mp. (9440)
56 ("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp. (12840)
57 or/48-56 (301681)
58 47 and 57 (6720)
59 46 or 58 (172954)
60 1 or 2 (65631)
61 or/33-38 (171771)
62 23 or 32 or 61 (252488)
63 59 and 60 and 62 (189) Original company search strategy
64 health-economics/ (34113)
65 exp economic-evaluation/ (220054)
66 exp health-care-cost/ (212147)
67 exp pharmacoeconomics/ (170813)
68 or/64-67 (494246)
69 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (639804)
70 (expenditure$ not energy).ti,ab. (25202)
71 (value adj2 money).ti,ab. (1471)
72 budget$.ti,ab. (25423)
73 or/69-72 (664853)
74 68 or 73 (942161)
75 letter.pt. (864853)
76 editorial.pt. (462134)
77 note.pt. (578543)
78 or/75-77 (1905530)
79 74 not 78 (852409)
80 (metabolic adj cost).ti,ab. (941)
81 ((energy or oxygen) adj cost).ti,ab. (3242)
82 ((energy or oxygen) adj expenditure).ti,ab. (21091)
83 or/80-82 (24429)
84 79 not 83 (847170)
85 exp animal/ (19684531)

86 exp animal-experiment/ (1822652)
87 nonhuman/ (4426163)
88 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (4915004)
89 or/85-88 (21093242)
90 exp human/ (15373570)
91 exp human-experiment/ (332721)
92 90 or 91 (15375000)
93 89 not (89 and 92) (5719199)
94 84 not 93 (781617)
95 60 and 62 and 94 (917) Company strategy run with alternative economics filter

ERG Economic filter:
Centre for Reviews and Dissemination. Search strategies: NHS EED EMBASE using OvidSP (economics filter) [Internet]. York: Centre for Reviews and Dissemination; 2014 [accessed 2.6.14]. Available from:
http://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedembase

Further critique of company's searches

All strategies

- Limited use of truncation, brand names & synonyms ie Constipation instead of constipat$. The use of MeSH and Emtree may have mitigated the effect of some of these omissions, but without rerunning searches the ERG is unable to say what impact this may have had on the recall of results.

Clinical Effectiveness (6.1 & 10.2)/ MTC (6.7 & 10.4)

- In the response to clarification the company confirmed that the Medline search was run on Pubmed not Ovid as initially reported

Cost Effectiveness (7.1 & 10.10)

- In the Medline search Lines #16 & #17 the inclusion of the drug Naloxone appear to be redundant as this also appears in lines #13 & #14. In the case of #16 & #17 it appears that this should have read as Naltrexone. As it is included in the remaining strategies it is unlikely to have impacted on the overall recall of results

HRQoL (7.4.5 & 10.12)
Failure to combine line #26: ("quality adjusted" or "disability adjusted") in both the Medline & Cochrane searches, however it is unlikely that this would have impacted on the overall recall of results

APPENDIX 2: SUMMARY LIST OF COST-EFFECTIVENESS EVALUATIONS

None of the included studies evaluated the cost-effectiveness of naloxegol. Four studies evaluated the cost-effectiveness of naloxone-oxycodone (OXN) versus oxycodone alone (OXY)[51, 52, 55] and a single study[53] evaluated the cost-effectiveness of methylnaltrexone bromide (MNTX) plus standard care (SOC) versus SOC alone. All studies used a time horizon of ≤1 year. Two studies, Gerlier 2009[55] and Dunlop 2013[54] evaluated the cost-effectiveness of OXN versus OXY in Belgium/Netherlands and the UK, respectively. However, both were conference abstracts and were not available for full paper review. Due to insufficient data reported in these abstracts, the modelling methods and inputs used, they were excluded from the analysis. Earnshaw 2010[53] evaluated the cost-effectiveness of MNTX versus SOC in OIC patients in the Netherlands. The healthcare system in the Netherlands was deemed to be different than that of the England and Wales, and was excluded.

Of the two remaining UK studies, one presented a cohort model[52] and another used a decision analytical model[51]. The two models took a UK NHS payer perspective, and both evaluated the cost-effectiveness of naloxone-oxycodone compared with oxycodone alone.[51] The clinical data used in the models were sourced from RCTs. In the SMC for naloxone-oxycodone (Targinact®) model[1, 27], the health states were defined in terms of use of laxatives, and utilities were used from different sources that were not comparable with one another. Dunlop 2012 et al[52] used two health states in their model; constipated and non-constipated in both treatment groups. The constipated state was modelled by defining normal bowel functioning as a BFI score ≤28.8. The model used SF-36 utility data collected from a trial and mapped to EQ-5D.

In general, the two studies though relevant to decision making in England and Wales did not address the cost effectiveness of naloxegol. The cost-effectiveness analysis submitted to the SMC for naloxone-oxycodone (Targinact®) in patients with severe pain did not gain acceptance, as the economic evidence submitted by the company was not, in the SMC's assessment, robust enough. Dunlop et al 2012[52] demonstrated an improved methodology in their model by using utility data from trial rather than published literature. However, an important limitation of this model is the method of estimation of the cost of OIC. The base case analysis estimated constipation costs based on a survey of perceptions of UK primary physicians, and did not clearly define treatment duration or resource use. It is therefore possible that the UK costing data could have underestimated the true cost of OIC.

APPENDIX 3: PHILLIPS ET AL CHECKLIST

Results of assessing the company's report based on the checklist by Phillips et al

1. Is there a clear statement of the decision problem?

Yes, the decision problem is clearly stated.

2. Is the objective of the evaluation and model specified consistent with the stated decision problem?

Yes.

3. Is the primary decision-maker specified?

Yes.

4. Is the perspective of the model stated clearly?

Yes.

5. Are the model inputs consistent with the stated perspective?

Yes

6. Has the scope of the model been stated and justified?

Yes.

7. Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?

Yes.

8. Is the structure of the model consistent with a coherent theory of the health condition under evaluation?

Yes.

9. Are the sources of data used to develop the structure of the model specified?

Yes

10. Are the causal relationships described by the model structure justified appropriately?

Yes

11. Are the structural assumptions transparent and justified?

Yes.

12. Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?

Yes.

13. Is there a clear definition of the options under evaluation?

No, comparator treatment options are presented as scenarios.

14. Have all feasible and practical options been evaluated?

Yes.

15. Is there a justification for the exclusion of feasible options?

NA.

16. Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?

Yes.

17. Is the time horizon of the model sufficient to reflect all important differences between options?

Yes. A time horizon of 5 years deemed sufficient.

18. Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?

Yes.

19. Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?

Yes, though the non-OIC health state might be too broad.

20. Is the cycle length defined and justified in terms of the natural history of disease?

Yes.

21. Are the data identification methods transparent and appropriate given the objectives of the model?

Yes

22. Where choices have been made between data sources, are these justified appropriately?

Yes,
[redacted].

23. Has particular attention been paid to identifying data for the important parameters in the model?

Yes.

24. Has the quality of the data been assessed appropriately?

No, the quality assessment was not undertaken for all data in the model.

25. Where expert opinion has been used, are the methods described and justified?

Yes, but the explanations are provided mostly in the clarification letter.

26. Is the data modelling methodology based on justifiable statistical and epidemiological techniques?

Yes

27. Is the choice of baseline data described and justified?

Yes.

28. Are transition probabilities calculated appropriately?

Not. Neither sources nor ratio calculations were appropriate.

29. Has a half-cycle correction been applied to both cost and outcome?

Yes.

30. If not, has this omission been justified?

NA.

31. If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?

Yes.

32. Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?

Yes.

33. Have alternative extrapolation assumptions been explored through sensitivity analysis?

Yes.

34. Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?

No.

35. Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?

No.

36. Are the costs incorporated into the model justified?

No. There was a substantial difference between costs used in the base case and the scenario analysis.

37. Has the source for all costs been described?

Yes, but mostly in the clarification letter.

38. Have discount rates been described and justified given the target decision-maker?

Yes.

39. Are the utilities incorporated into the model appropriate?

Yes.

40. Is the source for the utility weights referenced?

Yes.

41. Are the methods of derivation for the utility weights justified?

Yes.

42. Have all data incorporated into the model been described and referenced in sufficient detail?

No.

43. Has the use of mutually inconsistent data been justified (ie are assumptions and choices appropriate)?

No.

44. Is the process of data incorporation transparent?

No. The incorporation of transition probabilities in the model was not transparent.

45. If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?

Yes.

46. If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?

Yes

47. Have the four principal types of uncertainty been addressed?

No.

48. If not, has the omission of particular forms of uncertainty been justified?

No.

49. Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?

Yes.

50. Is there evidence that structural uncertainties have been addressed via sensitivity analysis?

Yes. Several alternative scenarios have been run for different structural assumptions in order to explore their impact on the model outcomes.

51. Has heterogeneity been dealt with by running the model separately for different subgroups?

Yes

52. Are the methods of assessment of parameter uncertainty appropriate?

Yes.

53. If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?

No. They were clearly stated but not justified. Moreover, in the CS parameter values were varied ±20% to the base case value. In response to the clarification letter (Section C – Question 63), the univariate sensitivity analysis was performed with parameter variation based on 95% confidence intervals.

54. Is there evidence that the mathematical logic of the model has been tested thoroughly before use?

Yes

55. Are any counterintuitive results from the model explained and justified?

Yes

56. If the model has been calibrated against independent data, have any differences been explained and justified?

NA

57. Have the results of the model been compared with those of previous models and any differences in results explained?

NA. The Company developed a *de novo* model to assess the potential cost effectiveness of naloxegol. None of the previous models (identified by literature search) were relevant for the decision problem.