NICE National Institute for Health and Care Excellence

Slides for all- contain no ACIC

Naldemedine for treating opioid-induced constipation

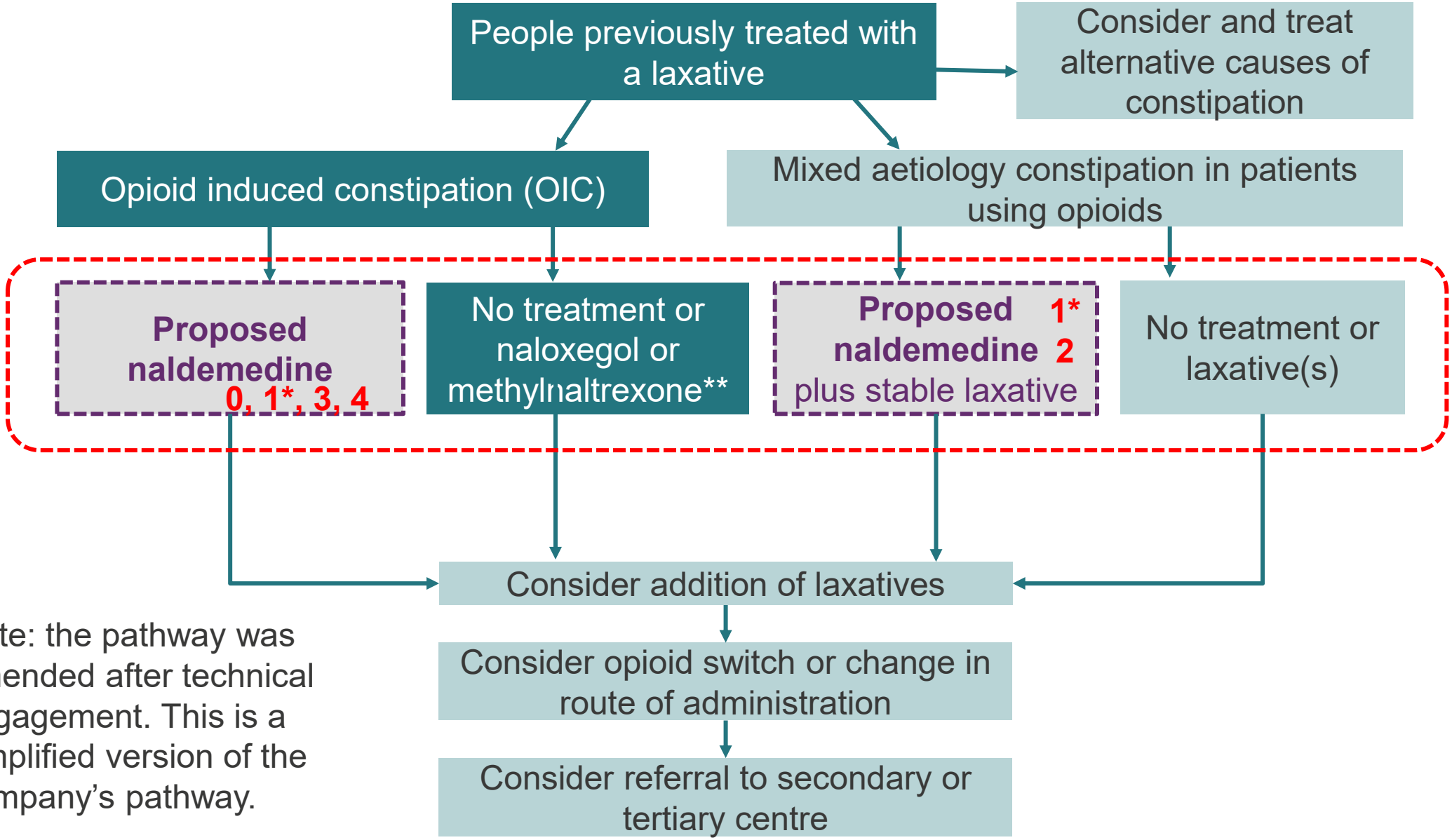
Lead team presentation

Chair: Stephen O'Brien and Peter Selby
Lead team: Michael Chambers, Mudasar Mushtaq, Ugochi Nwulu
ERG: Kleijnen Systematic Reviews
Technical team: Anita Sangha, Alexandra Filby, Frances Sutcliffe
Company: Shionogi
ACM1: 18 March 2020

Naldemedine (Rizmoic, Shionogi)

Marketing authorisation	Naldemedine is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative.
Mechanism of action	Peripheral acting mu opioid receptor antagonist (PAMORA)
Administration	Oral tablet
Price	The list price of a 28-tablet pack of naldemedine is £41.72. The cost of a course of treatment will depend on the duration of opioid therapy resulting in OIC requiring treatment. No patient access scheme.

Treatment pathway



Note: the pathway was amended after technical engagement. This is a simplified version of the company's pathway.

Notes:
Dashed red line indicates pathway included in model. Numbers in red refer to key subpopulations modelled by company
*Subpopulation 1 is a proxy for naldemedine versus no treatment in both pathways (OIC and mixed aetiology constipation)
**Methylnaltrexone predominantly used in a palliative care setting

Background

Comparators	Placebo
Clinical trials	• 4 double blind, randomised trials comparing naldemedine to placebo (**COMPOSE -1, -2, -3 and -4**) • 3 supportive, single arm, open-label safety studies (COMPOSE -5, -6 and -7) • All patients had prior treatment with a laxative • All trials permitted the use of rescue laxatives
Key trial results (primary outcome)	Statistically significant improvement in proportion of SBM responders: COMPOSE -1; naldemedine: 48%, placebo: 35% COMPOSE -2; naldemedine: 53%, placebo: 34% COMPOSE -4; naldemedine: 71%, placebo: 34% COMPOSE -3: Measures of treatment-emergent adverse events.
Comparison with placebo	Direct comparison. All statistically significant differences for COMPOSE-1, -2 and -4.
Model	Decision tree for first 4-week cycle. Markov model from second cycle.

COMPOSE 1 and 2:. Responders were defined as patients with ≥9/12 positive-response weeks and ≥3 positive-response weeks out of the last four weeks. A positive response week was defined as ≥3 SBM/week and ≥1 SBM/week increase from baseline.
COMPOSE -4: Responders were defined as patients with ≥3 SBMs/week and an increase of ≥1 SBM/week from baseline

Key subpopulations modelled by company

Subpopulation		Intervention (I)	Comparator (C)	Source
0	• OIC • Non-cancer patients	Naldemedine ± rescue laxative	Placebo ± rescue laxative	COMPOSE-1 & -2 (ITT)
1	• OIC and mixed aetiology constipation • Non-cancer patients	Naldemedine ± laxative ± rescue laxative	Placebo ± laxative ± rescue laxative	COMPOSE-3 (ITT)
2	• Mixed aetiology constipation • Non-cancer patients	Naldemedine + stable laxative ± rescue laxative	Placebo + stable laxative ± rescue laxative	COMPOSE-3 (ITT stable laxative subgroup)
3	• OIC • Non-cancer patients	Naldemedine ± rescue laxative	Naloxegol ± rescue laxative	ITC from Luthra et al. 2018
4	• OIC • Cancer patients	Naldemedine ± rescue laxative	Methylnaltrexone (SC) ± rescue laxative	ITC based on COMPOSE-4 and Bull et al. 2015

OIC = opioid-induced constipation, ITT = intention-to-treat analysis, ITC = indirect treatment comparison, LIR = laxative inadequate response, SC = subcutaneous injection.

Patient and carer perspectives

Referenced from the company submission (no patient expert submissions available):

- OIC is often under-diagnosed and undertreated, with healthcare professionals often underestimating the severity of constipation as perceived by the patient.
- National Health and Wellness Survey: OIC negatively impacts pain management, productivity, and health-related quality of life (HRQoL).
- Cross-sectional survey: Despite use of 2 or more laxatives for OIC, symptoms often remain. Constant cycling between laxatives results in patient dissatisfaction and lower quality of life.

Referenced from the literature (no patient expert submissions available):

- OIC is persistent and can become more distressing than the associated condition
- Qualitative studies: have identified themes of psychological distress, treatment burden and reluctance to use opioids
- Social media posts: also attest to the impact of diet, need for treatment, emotional impact and the need to change opioid treatment.

Kennedy-Martin, T. and Brewer, S., 2017. Patient-reported outcomes of opioid-induced constipation as identified through social media. Value in Health, 20(9), p.638

Dhingra, L., Shuk, E., Grossman, B., Strada, A., Wald, E., Portenoy, A., Knotkova, H. and Portenoy, R., 2013. A qualitative study to explore psychological distress and illness burden associated with opioid-induced constipation in cancer patients with advanced disease. Palliative Medicine, 27(5), pp.447-456.

Clinical evidence

	COMPOSE-1 (n=545)	COMPOSE-2 (n=550)	COMPOSE-3 (n=1,240)	COMPOSE-4 (n=193)
Population	Adults with OIC and non-cancer chronic pain	Adults with OIC and non-cancer chronic pain	Adults with OIC and non-cancer chronic pain	Adults with OIC and cancer pain
Setting/Location	8 UK, 12 rest of Europe, 48 USA	54 in USA; 15 in Europe	20 UK, 30 rest of Europe, 133 USA, 8 Canada, 3 Australia, 1 South Africa	70 sites in Japan
Intervention (0.2mg/day)	Naldemedine Duration:12 wks	Naldemedine Duration: 12 wks	Naldemedine Duration: 52 wks	Naldemedine Duration: 2 wks
Comparator	Placebo	Placebo	Placebo	Placebo
Prior treatment	Opioids for ≥3 mths; stable opioids ≥1 mth before screening and not using laxatives or willing to discontinue	Opioids for ≥3 mths; stable opioids ≥1 mth before screening and not using laxatives or willing to discontinue	Opioids for ≥3 mths; stable opioids ≥1 mth before screening. Patients with stable laxative not excluded	Stable daily opioids for ≥2 wks before screening. Patients with stable laxative not excluded
Primary outcomes	Proportion of SBM responders	Proportion of SBM responders	Measures of TEAEs	Proportion of SBM responders

Clinical evidence

	COMPOSE-1 (n=545)	COMPOSE-2 (n=550)	COMPOSE-3 (n=1,240)	COMPOSE-4 (n=193)
Other outcomes	Changes in COWS, SOWS and NRS scores; BM frequency; and PAC-SYM and PAC-QOL scores			Changes in frequency of SBM, CSBM and SBM without straining and in COWS and NRS scores

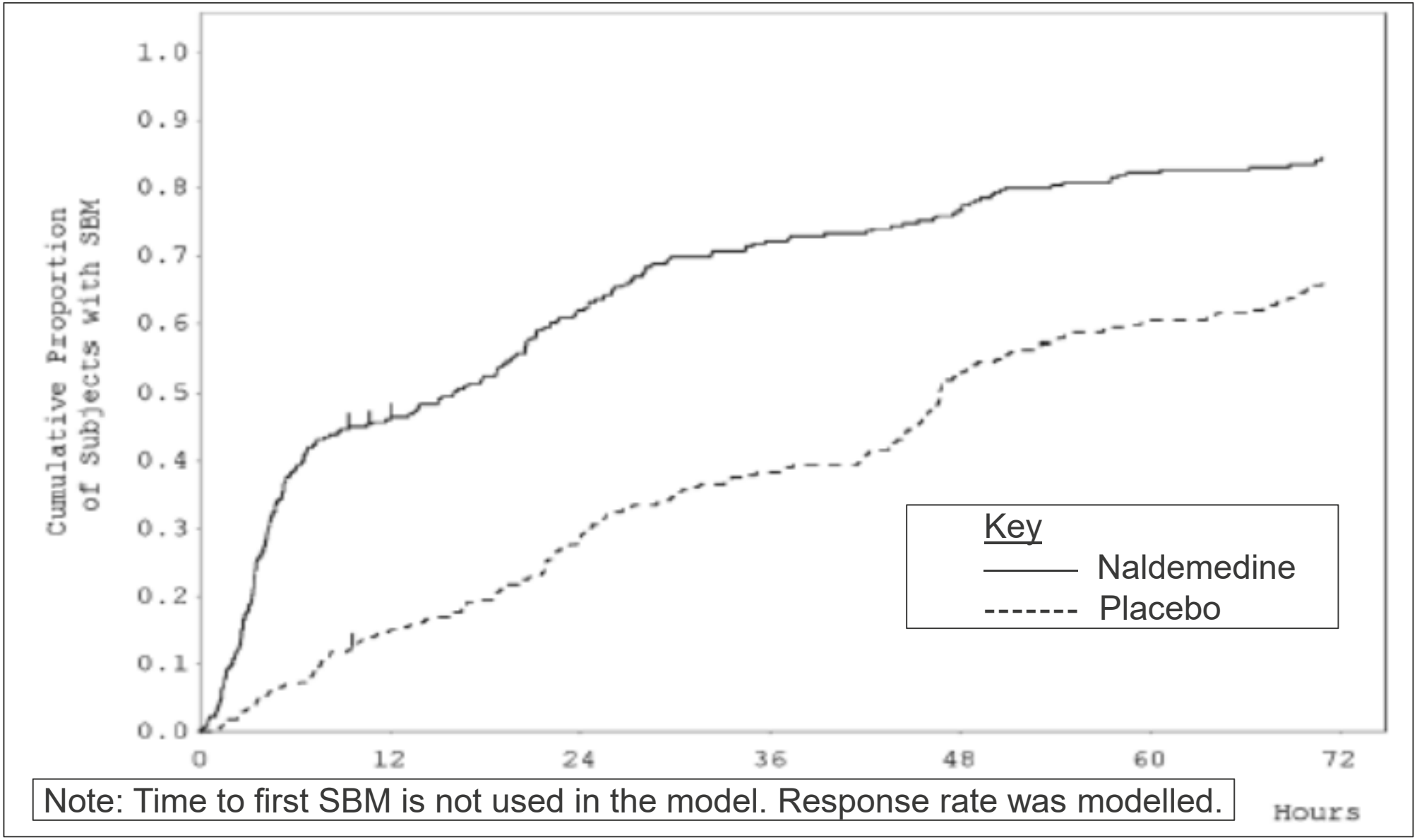
BM = bowel movement, COWS = clinical opiate withdrawal scale, CSBM = Complete spontaneous bowel movement, NRS = numerical rating scale, PAC-QOL = Patient Assessment of Constipation Quality of Life, PAC-SYM = Patient Assessment of Constipation Symptoms, SBM = spontaneous bowel movement, SOWS = subjective opiate withdrawal scale

Clinical evidence

	COMPOSE-1		COMPOSE-2		COMPOSE-3		COMPOSE-4	
Population	Non-cancer		Non-cancer		Non-cancer		Cancer	
Treatment group	Naldemedine (n = 271)	Placebo (n = 272)	Naldemedine (n = 271)	Placebo (n = 274)	Naldemedine (n = 621)	Placebo (n = 620)	Naldemedine (n = 97)	Placebo (n = 96)
SBM responders n (%)	**130 (48)**	**94 (35)**	**145 (53)**	**92 (34)**	NA		**69 (71)**	**33 (34)**
Change (95% CI)	**13.0% (4.8, 21.2) p=0.0020**		**18.9% (10.8, 27.0); p<0.0001**				**36.8% (23.7, 49.9); p<0.0001**	
Increase in frequency of SBMs, n/week (SE)	3.42 (0.19)	2.12 (0.19)	3.56 (0.17)	2.56 (0.17)	3.92 (0.18)	2.92 (0.19)	5.16 (0.53)	1.54 (0.54)
Change (95% CI)	1.30 (0.77, 1.83) p<0.0001		1.40 (0.92, 1.88); p<0.0001		1.00 (0.49, 1.51); p<0.0001		3.62 (2.13, 5.12); p<0.0001	

Clinical evidence

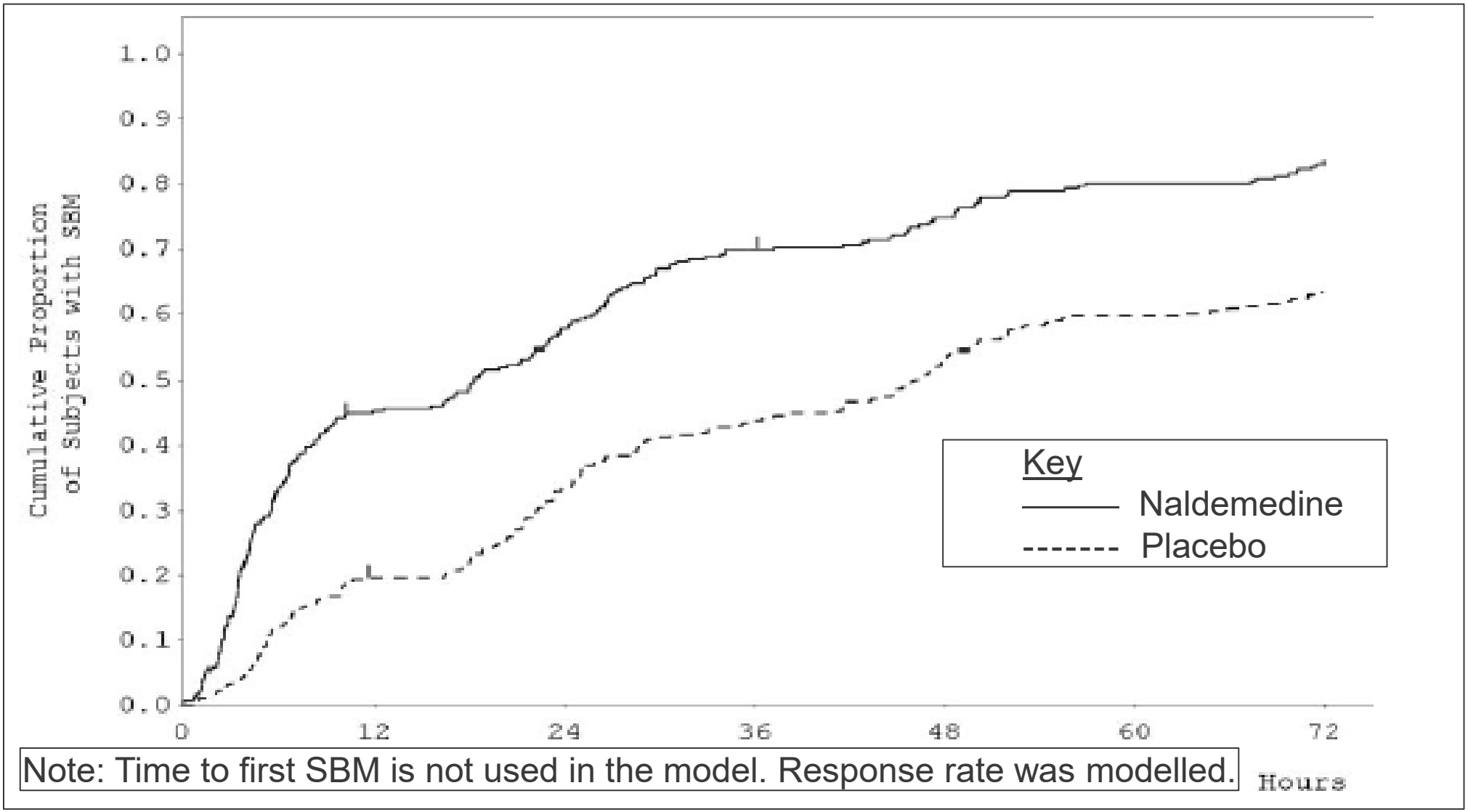
Kaplan-Meier curve of time to first SBM- intent to treat population for COMPOSE-1



Note: Time to first SBM is not used in the model. Response rate was modelled.

Clinical evidence

Kaplan-Meier curve of time to first SBM- intent to treat population for COMPOSE-2



Note: Time to first SBM is not used in the model. Response rate was modelled.

Clinical evidence

3 single-arm, open-label supportive studies

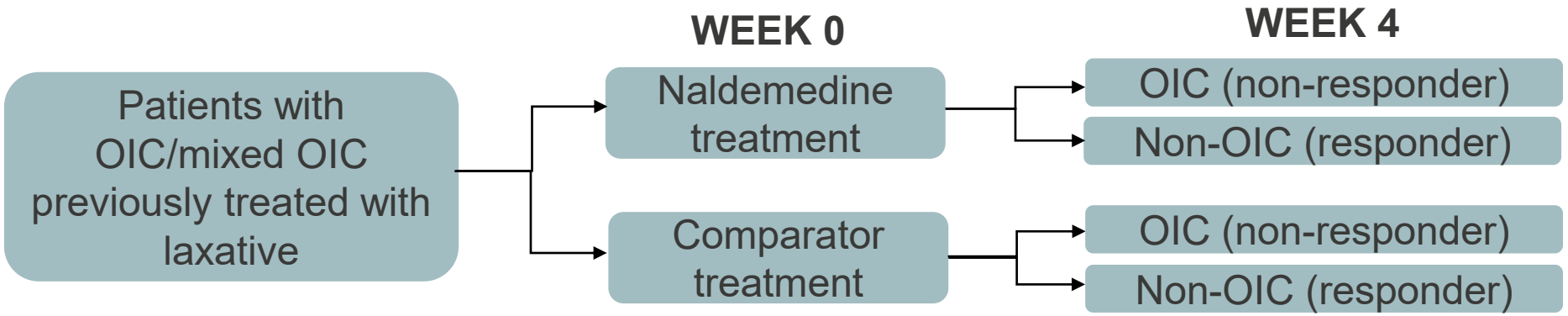
	COMPOSE-5 (n=131) (extension of COMPOSE-4)	COMPOSE-6 (n=43)	COMPOSE-7 (n=10)
Population	Adults with OIC and cancer pain	Adults with OIC and non-cancer chronic pain	Adults with OIC and non-cancer chronic pain, treated with PR oxycodone.
Setting/location	70 sites in Japan	21 sites in Japan	9 sites in Japan
Intervention	Naldemedine 0.2mg/day for 12-weeks	Naldemedine 0.2mg/day for 48-weeks	Naldemedine 0.2mg/day for 48-weeks
Primary outcomes	Measures of TEAEs	Measures of TEAEs	Measures of TEAEs

PR = prolonged release, OIC = opioid-induced constipation, TEAEs = treatment emergent adverse events

Company's model structure

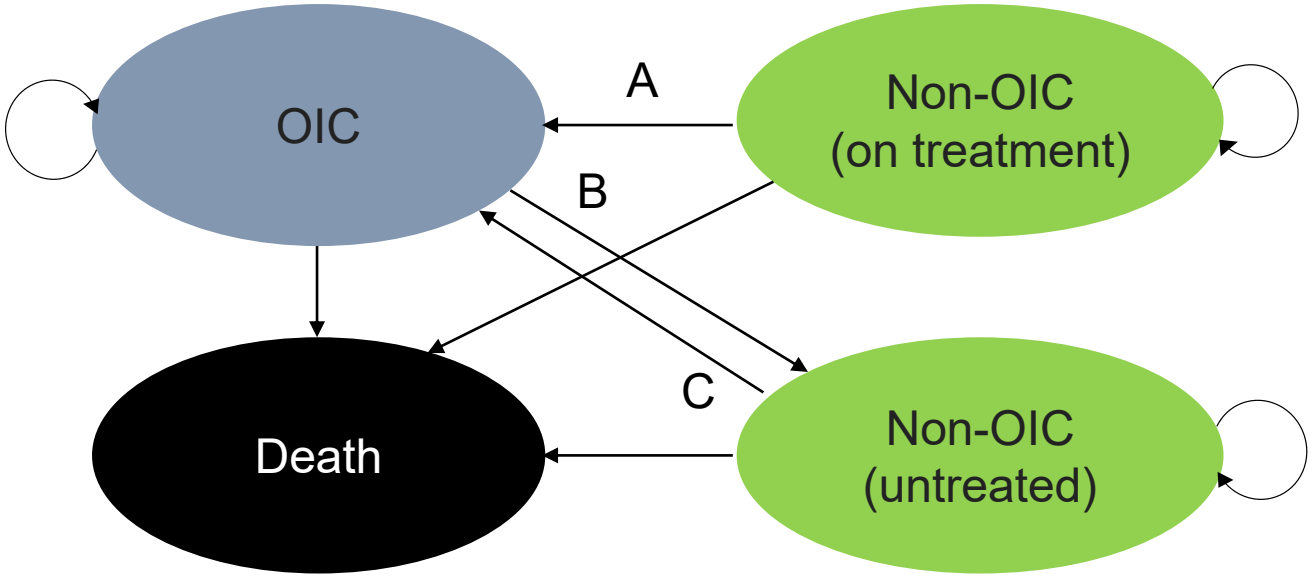
Structure based on model considered in technology appraisal 345; naloxegol for opioid induced constipation:

1. Decision-tree structure for first model cycle (response assessment)



2. Markov structure from second model cycle:

- Cycle length of 4 weeks
- Time horizon up to a maximum of 5 years
- Patients enter the Markov model at either OIC or non-OIC (on treatment) health states



OIC= <3 SBMs per week in at least 2 of the weeks per 4-week cycle

Non- OIC= ≥3 SBMs per week in at least 3 of the weeks per 4-week cycle.

Key subpopulations modelled by company

Subpopulation		Intervention (I)	Comparator (C)	Source
0	• OIC • Non-cancer patients	Naldemedine ± rescue laxative	Placebo ± rescue laxative	COMPOSE-1 & -2 (ITT)
1	• OIC and mixed aetiology constipation • Non-cancer patients	Naldemedine ± laxative ± rescue laxative	Placebo ± laxative ± rescue laxative	COMPOSE-3 (ITT)
2	• Mixed aetiology constipation • Non-cancer patients	Naldemedine + stable laxative ± rescue laxative	Stable laxative ± rescue laxative	COMPOSE-3 (ITT stable laxative subgroup)
3	• OIC • Non-cancer patients	Naldemedine ± rescue laxative	Naloxegol ± rescue laxative	ITC from Luthra et al. 2018
4	• OIC • Cancer patients	Naldemedine ± rescue laxative	Methylnaltrexone (SC) ± rescue laxative	ITC based on COMPOSE-4 and Bull et al. 2015

OIC opioid-induced constipation, ITT intention-to-treat analysis, ITC indirect treatment comparison, LIR laxative inadequate response, SC subcutaneous injection.

Other subpopulations modelled by company

As agreed at technical engagement, the technical team did not consider these other subpopulations further:

Naldemedine without rescue laxative in patients with non-cancer pain

Subpopulation		Intervention	Comparator	Source
5	• Subpopulation 0 without rescue laxative for naldemedine	Naldemedine	Placebo ± rescue laxative	COMPOSE-1 & -2 (non-randomised subgroup)
6	• Mixed aetiology constipation • Non-cancer patients	Naldemedine + stable laxative	Placebo ± rescue laxative	COMPOSE-3 (non-randomised stable laxative subgroup)
7	• OIC • Non-cancer patients	Naldemedine	Naloxegol 25mg	ITC based on COMPOSE -1 & -2, KODIAC 4 & 5

Naldemedine with rescue laxative in patients with cancer pain

Subpopulation		Intervention	Comparator	Source
8	• OIC • Cancer patients	Naldemedine ± rescue laxative	Placebo ± rescue laxative	COMPOSE-4 and COMPOSE-5

KODIAC 4 and 5 trials were considered in technology appraisal 345; naloxegol for treating opioid-induced constipation.

Key issues considered at technical engagement	Status
1 – Is mixed aetiology constipation an appropriate subpopulation? a) Is it within the scope of the appraisal? b) Is combination therapy appropriate?	Resolved
2 – Treatment pathway a) Is the positioning of naldemedine clear in the pathway? b) What definition of LIR has been included in the model?	Resolved
3 – Subpopulations to be considered a) Should rescue medication be included? b) Should subpopulation 4 include all patients on naldemedine or be restricted to those patients with LIR?	Resolved
4 – Indirect treatment comparisons • Are the indirect treatment comparisons comparing naldemedine to naloxegol and to methylnaltrexone acceptable for decision-making?	Unresolved uncertainty*
5 – Generalisability of COMPOSE trials a) Are the studies generalisable to the UK population? b) Are the baseline characteristics reflective of England? c) Would naldemedine be equally effective for treating OIC in patients with cancer pain compared with non-cancer pain?	Resolved
6 – Extrapolation of treatment response • Are the justifications for the distributions chosen acceptable? • Is the lognormal or Gompertz distribution more appropriate in subpopulations 0 and 3?	Unresolved uncertainty*

*unresolved based on the information provided by the company

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
1 a	The company have patients with mixed aetiology constipation (which includes OIC). The ERG queried whether this is within the scope of this appraisal.	The marketing authorisation does not state that naldemedine cannot be used in mixed aetiology constipation, but that it can be used with or without laxatives.	Mixed aetiology constipation is a suitable subpopulation to include in this appraisal.	✓
1 b	The comparator modelled for mixed aetiology constipation is combination laxative therapy. Clinical expert opinion indicated a singular conventional laxative would initially be used in clinical practice.	Combination standard laxatives are recommended in mixed aetiology constipation, where initial laxative therapy has been tried.	Combination therapy is a suitable comparator following prior laxative treatment.	✓

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
2a	The company positioning of naldemedine for laxative refractory and laxative inadequate response (LIR) is not clear in the treatment pathway.	Pathway is too complex and presents an artificial divide between laxative refractory and LIR patients. The positioning of naldemedine should not be distinct to naloxegol and methylnaltrexone.	The positioning of naldemedine in the treatment pathway is now clear in the company's revised pathway.	Not applicable
2b	The definition of LIR used in the economic model is not clear. The ERG noted that the definition of LIR is different between the COMPOSE and KODIAC studies, and noted other potential differences between these trials, including baseline comparability and other definitions used in the studies.	The company clarified that the definition of LIR used in the model is based on that used in the COMPOSE clinical study reports.	The definition of LIR used in the model is now clear. It is not clear if this matches up with clinical data and so subpopulation 7 should be interpreted with care.	**Unknown impact** **Issue is no longer relevant**

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
3 a	All COMPOSE trials permitted the use of rescue laxatives. The company modelled subpopulations 6 and 7 for a subset of patients who used naldemedine without rescue laxative. The ERG noted that these subpopulations without rescue medication were defined post-hoc and did not include the correct patient selection. The ERG also noted that it is highly unlikely that in clinical practice patients will be told not to use rescue medication.	Rescue laxatives should be included in the subpopulations. The company have provided subpopulations 1, 2 and 3 which include ± rescue laxative use across both arms.	Subpopulations 1, 2 and 3 include the ITT population and can be considered relevant for decision-making.	✓

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
3 b	The ERG noted that in subpopulation 4, the naldemedine group was not restricted to patients with laxative inadequate response (LIR), which was a requirement for treatment with the comparator - methylnaltrexone. The ERG suggest that, based on the non-cancer population, it is plausible that there is likely to be little difference in effectiveness between LIR and non-LIR subgroups in the cancer population.	The company state that no criteria was set for LIR in the COMPOSE-4 study to create this subpopulation. The company consider naldemedine to offer comparable efficacy in non-cancer and cancer pain patients. As such, the company note that naldemedine has shown effectiveness in both LIR and non-LIR subgroups (COMPOSE-1 and -2).	LIR is an artificial definition not used in clinical practice and has been removed from treatment pathway. Subpopulation 4 can be considered relevant for decision-making.	✓ **Issue is no longer relevant**

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
5	UK setting: COMPOSE -1 and -3 trials included sites in the UK. COMPOSE -4 and the open-label studies were conducted in Japan. Cancer/non-cancer pain: COMPOSE-4 and -5 were conducted in cancer patients. All other COMPOSE trials were in non-cancer patients. Baseline characteristics: The ERG clinical expert stated that there may be differences in bowel movements and opioid use at baseline in the COMPOSE -1, -2 and -3 trials and UK clinical practice.	Treatment response would not be different for UK population compared with Japanese patients. Clinical expert opinion from the company suggests that naldemedine should offer comparable efficacy in non-cancer and cancer pain patients.	The results of the COMPOSE trials can be generalised to the UK. Naldemedine is likely to be equally effective in people with non-cancer and cancer pain who have OIC.	Not applicable

Issues unresolved after technical engagement

	Summary	Stakeholder responses	Included in updated base case?	Remaining uncertainties	Impact on ICER
4	The company did not provide the methods used to combine the data from the trials used in the ITCs for subpopulations 4 and 7. The ERG were unable to assess the appropriateness of the ITC analyses or verify the results.	The company did not provide any further information at technical engagement. The company do not have the input data for the ITC used to inform subpopulation 3a.	✓	It is not clear if the data and methods used to inform the ITCs are appropriate for decision-making. ERG – results of the ITCs should be interpreted with care.	 **Subpopulation 3: small impact*** **Subpopulation 4: small impact****

***ERG:** naldemedine dominates if RR is <0.99. If RR>1 ICER over £20,000
****ERG:** methylnaltrexone is substantially more expensive than naldemedine so that even if methylnaltrexone is much more effective the ICER (in the SW-quadrant) would still be cost-effective

Issues unresolved after technical engagement

	Summary	Stakeholder responses	Included in updated base case?	Remaining uncertainties	Impact on ICER
6	The company did not provide external validation for their choice of preferred curves to model loss of treatment response. For subpopulations 0 and 7, the ERG consider the Gompertz model to be more appropriate than the lognormal distribution, based on clinical opinion which suggests that loss of response is likely to plateau at a certain level.	The company state that for all subpopulations, the choice of survival distribution has a minimal impact on the ICER. No external validation report was provided by the company.	✓	The clinical plausibility of the time-to-event curves is not known. ERG - impact of the choice of the curve has minimal impact on the ICER	 **Small impact** Use of Gompertz distribution reduces the ICER

The parametric survival curves for each subpopulation, based on the company's original model, can be found in the company response to clarification.

Issues for consideration after technical engagement

1. Are subpopulations 0 to 4 reflective of how naldemedine would be used in clinical practice and do they consider all relevant comparators used in the NHS?

2. Given the uncertainties in the data used to inform the subpopulations modelled, are the analyses appropriate for decision-making?

New issue 1: Key subpopulations modelled in the pathway

Brief summary

- The company have modelled subpopulation 1, considering it a proxy for a comparison of naldemedine + standard of care (SoC) versus SoC (± rescue laxative across both arms) in both OIC and mixed aetiology populations.
- The company have also modelled subpopulation 0, 2, 3 and 4 which include ± rescue laxative use across both arms.
- The ERG considers that subpopulations 0, 1, 2 and 3 include the correct patient selection and considers the results of these subpopulations to be reliable.

Subpopulation	Intervention (I)	Comparator (C)
0 - OIC	Naldemedine ± rescue laxative	Placebo ± rescue laxative
1 - OIC and mixed aetiology constipation (includes OIC)	Naldemedine ± laxative ± rescue laxative	Placebo ± laxative ± rescue laxative
2 - Mixed aetiology constipation (includes OIC)	Naldemedine + stable laxative ± rescue laxative	Stable laxative ± rescue laxative
3 - OIC + LIR	Naldemedine ± rescue laxative	Naloxegol ± rescue laxative
4 - OIC + LIR	Naldemedine ± rescue laxative	Methylnaltrexone ± rescue laxative

Are subpopulations 0 to 4 reflective of how naldemedine would be used in clinical practice and do they consider all relevant comparators used in the NHS?

New issue 2: Key uncertainties in the data modelled

Brief summary

- There are uncertainties in the data used to inform the subpopulations modelled:
  - The ERG were unable to assess the appropriateness of the ITC analyses or verify the results. For subpopulation 4, the ERG note that the uncertainty in the result of the ITC is expected to have very small impact on the ICER.
  - The ERG also note that for subpopulation 3, the uncertainty in the result of the ITC is expected to have a small impact on the ICER.
  - The company did not provide external validation for their choice of preferred curves to model loss of treatment response. The ERG notes that the choice of curve has a minimal impact on the ICERs for all the subpopulations.

Given the uncertainties in the data used to inform the subpopulations modelled, are the analyses appropriate for decision-making?

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Choice of utility values	EQ-5D was not administered in the COMPOSE trials, so utility values from NICE TA345 were imputed: • The company used treatment-specific utilities for the non-OIC (on treatment) health state. • ERG found insufficient evidence for an independent treatment effect on HRQoL, however their clinical expert did not expect differences in quality of life between naldemedine and naloxegol populations. • ERG consider that the current approach is a reasonable alternative and was accepted in NICE TA345.	The ERG note that the ICER is sensitive to the assumption of treatment-specific utilities. Use of health state specific utilities, increased the company's base case ICERs for subpopulations 0, 1 and 2 in some cases to between £20,000 - £30,000 (see slide 32).

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Adverse event rates	Unclear in the model how adverse event rates in the model were derived	Likely to be very small
Mortality rates	Unclear in the model whether UK or USA specific mortality rates were used	Unknown but likely to be small impact

Innovation

- Company considers naldemedine to be innovative
- Technical team considers that all relevant benefits associated with the drug are adequately captured in the model.

Equality considerations

- None identified
- Are there any equality issues?

Cost effectiveness results – key subpopulations

Subpopulation/scenario	Inc costs (£)	Inc QALYs	ICER (£/QALY)
Company base case (Subpopulation 0)	£275.11	0.022	£12,556
Issue 6: ERG use of a Gompertz distribution (instead of lognormal)	£834.37	0.070	£11,903
Company base case (Subpopulation 1)	£838.46	0.067	£12,489
Company base case (Subpopulation 2)	£788.59	0.083	£9,462
Company base case (Subpopulation 3)	£73.72	0.02	£3,649
Company base case (Subpopulation 4)	-£3,356	0.014	Naldemedine is dominant

Cost effectiveness results – other subpopulations

Subpopulation/scenario	Inc costs (£)	Inc QALYs	ICER (£/QALY)
Company base case (Subpopulation 5)	£392.92	0.044	£8,942
Company base case (Subpopulation 6)	£775.25	0.083	£9,287
Company base case (Subpopulation 7)	£95.21	0.022	£4,260
Issue 6: ERG use of a Gompertz distribution (instead of lognormal)	£99.26	0.046	£2,145
Company base case (Subpopulation 8)	£545.01	0.060	£9,059

Cost effectiveness results – Sensitivity analysis - utility

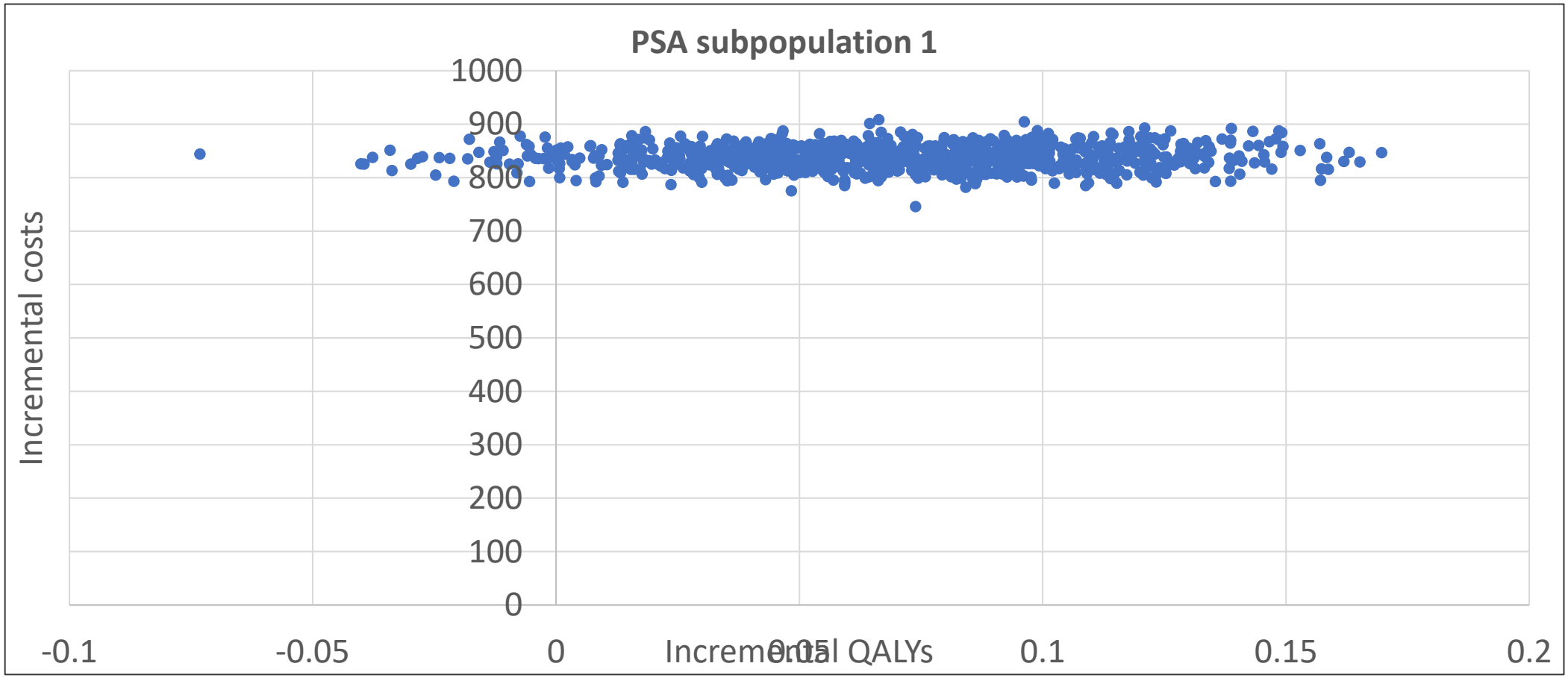
ERG noted that the 2 parameters which impact the base case ICER for this subpopulation are the utilities for the non-OIC (on treatment) health state, for naldemedine and the comparator.

Impact of choice of utility values on ICER (£/QALY)

	Treatment- specific utility values	Health state-specific utility values
Subpopulation 0	£12,556	£28,000
Subpopulation 1	£12,489	£27,000
Subpopulation 2	£9,462	£15,000

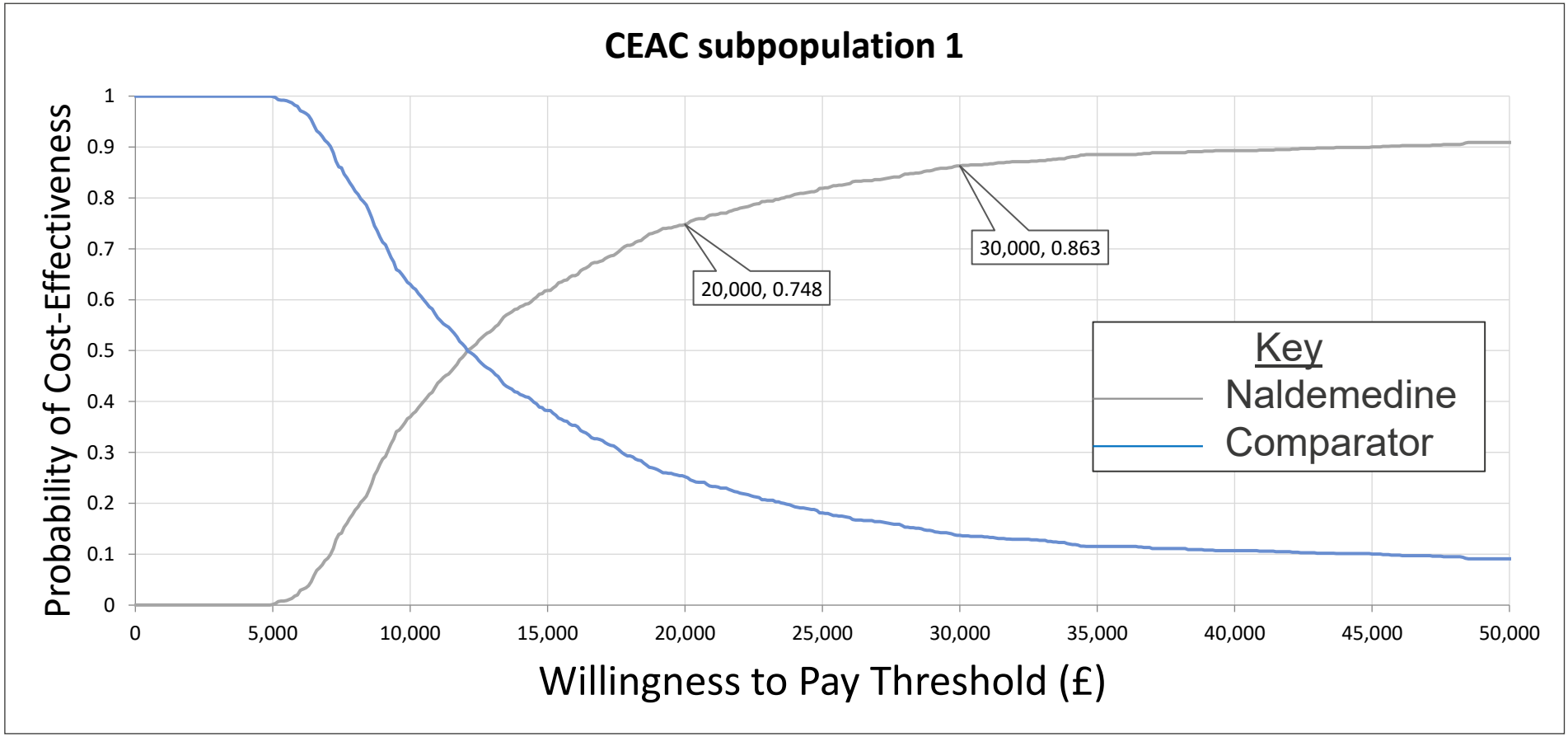
Probabilistic sensitivity analysis for subpopulation 1

- The ERG conducted a probabilistic sensitivity analysis for subpopulation 1
- ICERs largely fall in the north-east quadrant of the cost-effectiveness plane.



Probabilistic sensitivity analysis for subpopulation 1

- The ERG used incremental costs and QALYs obtained from PSA to calculate the cost-effectiveness acceptability curve (CEAC)
- In subpopulation 1, naldemedine has a probability of being cost effective of 74.8% and 86.3% at thresholds of £20,000 and £30,000, respectively.



Issues for consideration after technical engagement

1. Are subpopulations 0 to 4 reflective of how naldemedine would be used in clinical practice and do they consider all relevant comparators used in the NHS?

2. Given the uncertainties in the data used to inform the subpopulations modelled, are the analyses appropriate for decision-making?