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Naloxegol for treating opioid-induced constipation

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Contents

List of Tables ... 4
List of Figures ... 11
Abbreviations ... 14
Executive summary ... 18
Section A – Decision problem ... 26
1 Description of technology under assessment ... 26
2 Context ... 32
3 Equality ... 40
3.1 Identification of equality issues ... 40
4 Innovation ... 41
5 Statement of the decision problem ... 43
Section B – Clinical and cost effectiveness ... 45
6 Clinical evidence ... 45
6.1 Identification of studies ... 47
6.2 Study selection ... 48
6.3 Summary of methodology of relevant RCTs ... 57
6.4 Critical appraisal of relevant RCTs ... 78
6.5 Results of the relevant RCTs ... 79
6.6 Meta- analysis ... 127
6.7 Indirect and mixed treatment comparisons ... 134
6.8 Non-RCT evidence ... 174
6.9 Adverse events ... 175
6.10 Interpretation of clinical evidence ... 210
7 Cost-effectiveness ... 220
7.1 Published cost-effectiveness evaluations ... 221
7.2 De novo analysis ... 229
7.3 Clinical parameters and variables ... 243
7.4 Measurement and valuation of health effects ... 263
7.5 Resource identification, measurement and valuation ... 278
7.6 Sensitivity analysis ... 286
7.7 Results ... 292
7.8 Validation ... 314
7.9 Subgroup analysis ... 315
7.10 Interpretation of economic evidence ... 330
Section C – Implementation ... 332
8 Assessment of factors relevant to the NHS and other parties ... 332

9 References 337
10 Appendices 346
10.1 Appendix 1 346
10.2 Appendix 2: Search strategy for Section 6.1 (Identification of studies) 347
10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4) 354
10.4 Appendix 4: Search strategy for Section 6.7 (Indirect and mixed treatment comparisons) 357
10.5 Appendix 5: Quality assessment of comparator RCT(s) in Section 6.7 (Indirect and mixed treatment comparisons) 358
10.6 Appendix 6: Search strategy for Section 6.8 (Non-RCT evidence) 364
10.7 Appendix 7: Quality assessment of non-RCT(s) in Section 6.8 (Non-RCT evidence) 368
10.8 Appendix 8: Search strategy for Section 6.9 (Adverse events) 369
10.9 Appendix 9: Quality assessment of adverse event data in Section 6.9 (Adverse events) 370
10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1) 371
10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1) 384
10.12 Appendix 12: Search strategy for Section 7.4 (Measurement and valuation of health effects) 387
10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5) 396
10.14 Appendix14: Methodology of 29 clinician survey 397
10.15 Appendix 15: Methodology of 34 participant survey 400
10.16 Appendix 16: KODIAC 4 and 5, ITT analysis set results 402
10.17 Appendix 17: Guidelines for determination of laxative response status 409
10.18 Appendix 18: OpenBUGS model for the MTC analysis (section 6.7.5) 410
10.19 Appendix 19: Square output tables of the MTC analysis 412
10.20 Appendix 20: Random and fixed effects model results for the MTC and direct meta-analysis 421
10.21 Appendix 21: Forest plots for the MTC analysis 433
10.22 Appendix 22: non-RCT studies identified in the systematic review 434
10.23 Appendix 23: Efficacy results from KODIAC 7 437
10.24 Appendix 24: Advisory board 438
10.25 Appendix 25: Estimation of AE management cost 439
10.26 Appendix 26: Diagnostic plots for transition A 445
10.27 Appendix 27: Health state cost data inputs 451
10.28 Appendix 26: Calculation of average age of cancer pain patients in the model 458

List of Tables

Table 1: Base-case cost-effectiveness results ... 23
Table 2: Unit costs of technology being appraised ... 29
Table 3: Eligibility criteria used in search strategy for RCT evidence ... 50
Table 4: Eligibility criteria used in search strategy for non-RCT evidence ... 51
Table 5: List of relevant RCTs ... 55
Table 6: List of relevant non-RCTs ... 56
Table 7: Methodology of the pivotal RCTs (KODIAC 4 AND KODIAC 5) ... 57
Table 8: Eligibility criteria in the pivotal RCTs (KODIAC 4 and KODIAC 5) ... 60
Table 9: Characteristics of the anticipated licensed population in the pivotal RCTs (KODIAC 4 and KODIAC 5) across randomised groups ... 62
Table 10: Characteristics of the ITT analysis set in the pivotal RCTs (KODIAC 4 and KODIAC 5) across randomised groups ... 64
Table 11: Primary and secondary outcomes of the pivotal RCTs (KODIAC 4 and KODIAC 5) ... 66
Table 12: Summary of statistical analyses in the pivotal RCTs (KODIAC 4 and KODIAC 5) ... 69
Table 13: Summary of the quality assessment results for the pivotal RCTs (KODIAC 4 and KODIAC 5) ... 78
Table 14: Summary of the primary efficacy outcome for Weeks 1–12 (ITT analysis set) 83
Table 15: Response rates for Week 1–12 in the anticipated licensed population in KODIAC 4 and 5 (ITT analysis set) ... 85
Table 16: Time to first post-dose SBM for the anticipated licensed population in KODIAC 4 and KODIAC 5 (ITT analysis set) ... 86
Table 17: Summary of efficacy endpoints by baseline laxative response in KODIAC 4 (anticipated licensed population and non-LIR group, ITT analysis set) ... 88
Table 18: Summary of efficacy endpoints by baseline laxative response in KODIAC 5 (anticipated licensed population and non-LIR group, ITT analysis set) ... 89
Table 19: Summary of enema use in the anticipated licensed population ... 90
Table 20: Summary of patients with MID changes from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population (ITT analysis set) ... 92
Table 21: Summary of change from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population (KODIAC 4, ITT set) ... 94
Table 22: Summary of change from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population (KODIAC 5, ITT set) ... 95
Table 23: Summary of patients with MID changes from baseline in PAC-QoL domain scores at Week 12 in the anticipated licensed population (KODIAC 4 and 5, ITT analysis set) ... 96
Table 24: Summary of change from baseline in PAC-QoL domain scores at 12 weeks in the anticipated licensed population (KODIAC 4, ITT analysis set) ... 99
Table 25: Summary of change from baseline in PAC-QoL domain scores at 12 weeks in the anticipated licensed population (KODIAC 5, ITT analysis set) ... 100

Table 26: Summary of efficacy endpoints in anticipated licensed population + Step 3 opioids (KODIAC 4, ITT analysis set) 101

Table 27: Summary of efficacy endpoints in anticipated licensed population + Step 3 opioids (KODIAC 5, ITT analysis set) 101

Table 28: Key secondary outcomes and improvements in the symptoms of OIC in the anticipated licensed population + Step 3 opioids group (KODIAC 4 and 5, ITT analysis set) 104

Table 29: Summary of enema use in anticipated licensed population + Step 3 opioids (KODIAC 4 and 5) 106

Table 30: Summary of patients with MID changes from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population + Step 3 opioids (ITT analysis set) 108

Table 31: Summary of change from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population + Step 3 opioids (KODIAC 4 - ITT set) 110

Table 32: Summary of change from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population + Step 3 opioids (KODIAC 5 - ITT set) 111

Table 33: Summary of patients with MID changes from baseline in PAC-QoL domain scores at Week 12 in the anticipated licensed population + Step 3 opioids (ITT analysis set) 112

Table 34: Summary of change from baseline in PAC-QoL domain scores at 12 weeks in the anticipated licensed population + Step 3 opioids (KODIAC 4, ITT analysis set)..... 115

Table 35: Summary of change from baseline in PAC-QoL domain scores at 12 weeks in the anticipated licensed population + Step 3 opioids (KODIAC 5, ITT analysis set)..... 116

Table 36: EQ-5D responses in KODIAC-4 and KODIAC-5 in the anticipated licensed population 117

Table 37: EQ-5D responses in KODIAC 4 and KODIAC 5 in the anticipated licensed population +Step 3 opioid group 118

Table 38: Methodology and efficacy outcomes from study 07-IN-NX003 121

Table 39: Methodology and key findings from the BOI study 124

Table 40: Summary of I^2 statistic values 128

Table 41: Results from direct meta-analysis in the anticipated licensed population – treatment vs placebo 131

Table 42: Results from direct meta-analysis in the anticipated licensed population with Step 3 opioids – treatment vs placebo 132

Table 43: Summary of the studies used to conduct the MTC 136

Table 44: Summary of the quality assessment results for the studies included in the MTC 138

Table 45: Summary of results from studies used to conduct the comparisons 140

Table 46: Summary of the trials used to conduct the comparisons 141

Table 47: Study characteristics potentially contributing to clinical heterogeneity 144

Table 48: Summary of the data used in the MTC 147

Table 49: Results from MTC of mean change in SBMs per week from baseline to 4-12 weeks – treatment vs placebo 149

Table 50: Results from MTC in the anticipated licensed population – treatment vs placebo† 155

Table 51: Results from MTC in the anticipated licensed population – naloxegol 12.5 mg vs comparators† 156

Table 52: Results from MTC in the anticipated licensed population – naloxegol 25 mg vs comparators† 157

Table 53: Results from MTC in the anticipated licensed population + Step 3 opioids subpopulation – treatment vs placebo† 158

Table 54: Results from MTC in the anticipated licensed population+ Step 3 opioids subpopulation – naloxegol 12.5 mg vs comparators† 159

Table 55: Results from MTC in the anticipated licensed population + Step 3 opioids subpopulation – naloxegol 25 mg vs comparators 160

Table 56: DIC values for random vs fixed effects models 161

Table 57: Summary of Bayesian MTC results for the random and fixed-effects model in the anticipated licensed population –comparators vs placebo 162

Table 58: Summary of Bayesian MTC results for the random and fixed-effects model in the anticipated licensed population + Step 3 opioids – comparator vs placebo 164

Table 59: Estimates of random effects variance from Bayesian MTC 166

Table 60: Results from Bucher indirect comparisons in the anticipated licensed population – naloxegol 12.5 mg vs comparators 168

Table 61: Results from Bucher indirect comparisons in the anticipated licensed population – naloxegol 25 mg vs. comparators 169

Table 62: Results from Bucher indirect comparisons in the anticipated licensed population with Step 3 opioids – naloxegol 12.5 mg vs. comparators 170

Table 63: Results from Bucher indirect comparisons in the anticipated licensed population with Step 3 opioids – naloxegol 25 mg vs comparators 171

Table 64: Methodology of KODIAC 7 176

Table 65: Methodology of KODIAC 8 177

Table 66: Eligibility criteria in KODIAC 7 179

Table 67: Eligibility criteria in KODIAC 8 180

Table 68: Characteristics of the ITT population in KODIAC 7 180

Table 69: Characteristics of the safety analysis population in KODIAC 8 181

Table 70: Primary and secondary outcomes of KODIAC 7 183

Table 71: Primary and secondary outcomes of KODIAC 8 184

Table 72: Summary of statistical analyses in KODIAC 7 185

Table 73: Quality assessment results for KODIAC 7 and KODIAC 8 190

Table 74: Summary of adverse events in KODIAC 7 (Safety analysis set) 191

Table 75: Adverse events occurring in ≥2% of patients in any treatment group, by preferred term, in KODIAC 7 (Safety analysis set) 193

Table 76: Summary of adverse events in KODIAC 8 (Safety analysis set) 195

Table 77: Adverse events occurring in ≥2% of patients in any treatment group, by preferred term, in KODIAC 8 (Safety analysis set) 197

Table 78: Summary of adverse events in KODIAC 4 and KODIAC 5 (Safety analysis set) 200

Table 79: Summary of adverse events in KODIAC 4 by baseline laxative response.... 201

Table 80: Summary of adverse events in KODIAC 5 by baseline laxative response.... 201

Table 81: Adverse events occurring in ≥2% of patients in any treatment group, by preferred term, in KODIAC 4 (Safety analysis set) 202

Table 82: Adverse events occurring in ≥2% of patients in any treatment group, by preferred term, in KODIAC 5 (Safety analysis set) 204

Table 83: Analysis of MID change from baseline to NRS pain Week 1-12 in KODIAC 4 and KODIAC 5 (Safety analysis set)..... 206

Table 84: Summary of patient willingness to take drug again in KODIAC 4 and KODIAC 5 (Safety analysis set) 208

Table 85: Summary list of other cost-effectiveness evaluations..... 226

Table 86: Comparators used in the model..... 233

Table 87: Transition Probabilities Summary 235

Table 88: Further Model Transitions Description 236

Table 89: Key features of analysis..... 240

Table 90: Proportion of patients in ‘non-OIC (on treatment)’ state at Week 4, trial-based (all anticipated licensed population patients) 244

Table 91: Proportion of patients in ‘non-OIC (on treatment)’ state at week 4, trial-based (anticipated licensed population + step 3 opioids) 244

Table 92: Proportion of patients in ‘non-OIC (on treatment)’ state at Week 4, MTC analysis 244

Table 93: Summary of variables applied in the economic model (anticipated licensed population) (costs in 2014 £) 246

Table 94: Summary of variables applied in the economic model (anticipated licensed population + Step 3 opioids) (costs in 2014 £)..... 248

Table 95: Summary of approaches used to measure transition A (X indicates where the extrapolation scenario was applied) 251

Table 96: Functions used to estimates transition A, anticipated licensed population (Weeks 4–12)..... 253

Table 97: Hazard ratios used to estimate transition A (source: MTC) 257

Table 98: Proportion of patients remaining in ‘non-OIC (on treatment)’ state at Week 4, 8, 12 (anticipated licensed population) 258

Table 99: Proportion of patients remaining in ‘non-OIC (on treatment)’ state at Week 4, 8, 12 (anticipated licensed population + Step 3 opioids)..... 259

Table 100: Transition probabilities B and C (source: analysis of KODIAC 4 and 5) 259

Table 101: List of assumptions used in the economic model..... 261

Table 102: Summary of utility inputs (X indicates where the method was reported)..... 264

Table 103: Random mixed effect model for change from baseline in utility..... 265

Table 104: Summary of utility inputs (treatment and time-specific, Dolan tariff)..... 266

Table 105: Summary of utility inputs (treatment-specific, Dolan tariff) 267

Table 106: Summary of utility inputs (non-treatment-specific, Dolan tariff) 268
Table 107: Summary of utility inputs (treatment and time-specific, Wittrup-Jensen tariff) 268
Table 108: Summary of utility inputs (non-treatment-specific, Wittrup-Jensen tariff) 269
Table 109: Summary of utility input 269
Table 110: Included HRQL studies 274
Table 111: NHS codes associated with management of OIC 279
Table 112: Unit costs associated with the technology in the economic model (2014 £) 282
Table 113: The incremental cost of constipation (base case), per cycle (2014 £) 284
Table 114: The incremental cost of constipation (scenario), per cycle (2014 £) 284
Table 115: Opioid use costs per cycle (2014 £)† 285
Table 116: Adverse events costs† (2014 £) 285
Table 117: Relative variations on base case values used in the deterministic sensitivity analysis 287
Table 118: Values and distributions used in the probabilistic sensitivity analysis, anticipated licensed population (costs in 2014 £) 288
Table 119: Values and distributions used in the probabilistic sensitivity analysis, anticipated licensed population + Step 3 opioids (costs in 2014 £) 289
Table 120: Structure of the results section 292
Table 121: Summary of model results compared with clinical data (anticipated licensed population) 293
Table 122: Summary of QALYs and costs by health state and resource use by category of cost (anticipated licensed population) 295
Table 123: Base case results – absolute (anticipated licensed population) 296
Table 124: Base case results - incremental (anticipated licensed population) 296
Table 125: Threshold analysis for five parameters to which the ICER is most sensitive, naloxegol 25 mg versus placebo (anticipated licensed population) 298
Table 126: Scenario analysis results (anticipated licensed population) 302
Table 127: Scenario analysis results (anticipated licensed population) 302
Table 128: Scenario analysis results (anticipated licensed population) 306
Table 129: Scenario analysis results (anticipated licensed population) 306
Table 130: Transition A scenarios, anticipated licensed population (see section 7.3.7 for a description of the scenarios) 308
Table 131: Transition D (OIC – non-OIC [on treatment] and transition E (non-OIC [on treatment] – non-OIC (untreated) scenarios (anticipated licensed population) 309
Table 132: Resource use costs of managing constipation 310
Table 133: Non-laxative costs of managing constipation (anticipated licensed population) 312
Table 134: Utility inputs scenarios (anticipated licensed population) 313
Table 135: Treatment response scenarios (anticipated licensed population) 314

Table 136: Subgroup results (anticipated licensed population + Step 3 opioids) 319

Table 137: Unit costs of manual evacuation 327

Table 138: Unit costs of conducting manual evacuation based on time required to perform the procedure 327

Table 139: Number of months of naloxegol 25 mg treatment expected per cost of one single intervention 328

Table 140: Generalisability to cancer patients of the results of the economic analysis undertaken for non-cancer patients 330

Table 141: Estimation of patients eligible for treatment, licensed population 332

Table 142: Estimation of patients eligible for treatment, anticipated licensed population + Step 3 opioids 332

Table 143: Estimated displaced medicine cost – methylnaltrexone (Relistor®) 333

Table 144: Estimated displaced medicine cost – naloxone-oxycodone (Targinact®).... 333

Table 145: Estimated displaced medicine cost – laxatives 334

Table 146: Patients treated with naloxegol each year, anticipated licensed population 335

Table 147: Patients treated with naloxegol each year, anticipated licensed population + Step 3 opioids 335

Table 148: Quality assessment of pivotal RCTs (KODIAC 4 and KODIAC 5) 354

Table 149: Quality assessment of studies designed to primarily assess safety (KODIAC 7)..... 355

Table 150: Quality assessment of studies designed to primarily assess safety (KODIAC 8)..... 356

Table 151: Qualitative questions used in the 29 clinician survey 398

Table 152: Quantitative questions used in the 29 clinician survey 399

Table 153: Key secondary outcomes in KODIAC 4 and KODIAC 5 (ITT analysis set) . 403

Table 154: Analysis of response rate incorporating symptom data for Weeks 1–12 in KODIAC 4 and KODIAC 5 (ITT analysis set) 405

Table 155: OIC symptom-related secondary outcomes from Weeks 1–12 in KODIAC 4 and KODIAC 5 (ITT analysis set) 408

Table 156: Bayesian MTC results grid for the mean change in SBMs from baseline to the average over four weeks in the anticipated licensed population (mean difference [95% CrI]) 413

Table 157: Bayesian MTC results grid for the mean change in SBMs from baseline to the average over four to twelve weeks in the anticipated licensed population (mean difference [95% CrI]) 414

Table 158: Bayesian MTC results grid for the proportion of patients with SBM response in the anticipated licensed population (median OR [95% CrI]) 415

Table 159: Bayesian MTC results grid for the proportion of patients with CSBM response in the anticipated licensed population (median OR [95% CrI]) 415

Table 160: Bayesian MTC results grid for the proportion of patients with DAEs in the anticipated licensed population (median OR [95% CrI])..... 416

Table 161: Bayesian MTC results grid for the proportion of patients with TEAEs in the anticipated licensed population (median OR [95% CrI])..... 416

Table 162: Bayesian MTC results grid for the mean change in SBMs from baseline to the average over four weeks in the anticipated licensed population + Step 3 opioids (mean difference [95% CrI]) 417

Table 163: Bayesian MTC results grid for the mean change in SBMs from baseline to the average over four to twelve weeks in the anticipated licensed population + Step 3 opioids (mean difference [95% CrI]) 418

Table 164: Bayesian MTC Results Grid for the Proportion of Patients with SBM Response in the LIR with Step 3 Opioids Population (Median OR [95% CrI]) 418

Table 165: Bayesian MTC results grid for the proportion of patients with CSBM response in the anticipated licensed population + Step 3 opioids (median OR [95% CrI]) 419

Table 166: Bayesian MTC results grid for the proportion of patients with DAEs in the anticipated licensed population + Step 3 Opioids (median OR [95% CrI]) 419

Table 167: Bayesian MTC results grid for the proportion of patients with TEAEs in the anticipated licensed population + Step 3 opioids (median OR [95% CrI]) 420

Table 168: Bayesian MTC results for the mean change in SBMs per week from baseline to average over 4 weeks in the anticipated licensed population 421

Table 169: Bayesian MTC results for the mean change in SBMs per week from baseline to average over 4 to 12 weeks in the anticipated licensed population 422

Table 170: Bayesian MTC results for proportion of patients with SBM response in the anticipated licensed population 423

Table 171: Bayesian MTC results for proportion of patients with CSBM response in the anticipated licensed population 424

Table 172: Bayesian MTC results for proportion of patients with DAEs in the anticipated licensed population 425

Table 173: Bayesian MTC results for proportion of patients with TEAEs in the anticipated licensed population 426

Table 174: Bayesian MTC results for the mean change in SBMs per week from baseline to average over 4 weeks in the anticipated licensed population + Step 3 opioids 427

Table 175: Bayesian MTC results for the mean change in SBMs per week from baseline to average over 4 to 12 weeks in the anticipated licensed population + Step 3 opioids 428

Table 176: Bayesian MTC results for proportion of patients with SBM response in the anticipated licensed population + Step 3 opioids 429

Table 177: Bayesian MTC results for proportion of patients with CSBM response in the anticipated licensed population + Step 3 opioids 430

Table 178: Bayesian MTC results for proportion of patients with DAEs in the anticipated licensed population + Step 3 opioids 431

Table 179: Bayesian MTC Results for proportion of patients with TEAEs in the anticipated licensed population + Step 3 opioids 432

Table 180: Methodology of KODIAC 16 434

Table 181: Unit costs of medical resource use items used in adverse event management 440

Table 182: Medical resource use frequency per adverse event† 441

Table 183: Distribution of adverse events by treatment arm for which grade? 443

Table 184: Adverse events costs 444

Table 185: Constipation related resource use in the OIC state, excluding laxatives (Source: GP Omnibus Survey) 451

Table 186: Laxative use in the OIC state (source: GP Omnibus Survey) 452

Table 187: Change in laxative use with constipation relief (source: GP Omnibus Survey) 452

Table 188: Constipation related resource use in the OIC state, excluding laxatives 453

Table 189: Profile of Opioid Use for Naloxegol 25 mg 454

Table 190: Unit Cost inputs 455

List of Figures

Figure 1: Mechanism of action of naloxegol 27

Figure 2: Schematic for the systematic review of RCT evidence 53

Figure 3 Schematic for systematic review of non-RCT evidence 54

Figure 4: KODIAC 4 study flow chart 74

Figure 5: KODIAC 5 study flow chart 75

Figure 6: Analysis of response rate for Weeks 1–12 in KODIAC 4 (ITT analysis set) 84

Figure 7: Analysis of response rate for Weeks 1–12 in KODIAC 5 (ITT analysis set) 84

Figure 8: Response rates for Weeks 1–12 in the anticipated licensed population in KODIAC 4 and 5 (ITT analysis set) 86

Figure 9: Change from baseline to Week 12 in number of patients in each EQ-5D domain level in the anticipated licensed population in (A) KODIAC 4 and (B) KODIAC 5 119

Figure 10: Change from baseline in number of patients in each EQ-5D domain level in the anticipated licensed population +Step 3 opioid group in (A) KODIAC 4 and (B) KODIAC 5 120

Figure 11: MTC subgroup analysis network diagram 141

Figure 12: KODIAC 7 flow chart 187

Figure 13: KODIAC 8 flow chart 188

Figure 14: Schematic for the systematic review of cost-effectiveness evidence 223

Figure 15: Decision Analytic Schematic (Week 0-4) 231

Figure 16: Markov model structure, after week 4 234

Figure 17: Difference over time of patient transition between health states between naloxegol 25 mg and placebo 251

Figure 18: Predicted versus observed responders, naloxegol 25 mg, anticipated licensed population 254

Figure 19: Extrapolation of response predictions (up to 300 days), naloxegol 25 mg, anticipated licensed population 254

Figure 20: Predicted versus observed responders, placebo, anticipated licensed population 255

Figure 21: Extrapolation of response predictions (up to 300 days), placebo, anticipated licensed population 256

Figure 22: Schematic for the systematic review of HRQL evidence 272
Figure 23: Number of naloxegol 25 mg patients in each health state over time (anticipated licensed population) 294
Figure 24: Number of placebo patients in each health state over time (anticipated licensed population) 294
Figure 25: Tornado diagram for DSA results (ICER) of naloxegol 25 mg vs placebo (anticipated licensed population), parameters varied by ± 20% 297
Figure 26: PSA Scatterplot for naloxegol 25 mg vs placebo, anticipated licensed population (10,000 simulations)..... 298
Figure 27: CEAC for naloxegol 25 mg vs placebo, anticipated licensed population 299
Figure 28: Proportion of naloxegol 25 mg patients in each health state over time (anticipated licensed population) 300
Figure 29: Proportion of naloxegol 25 mg + bisacodyl patients in each health state over time (anticipated licensed population)..... 301
Figure 30: Proportion of placebo + bisacodyl patients in each health state over time (anticipated licensed population) 301
Figure 31: Scatter plots for naloxegol 25 mg versus placebo + bisacodyl (anticipated licensed population) 303
Figure 32: CEAC for naloxegol 25 mg versus placebo + bisacodyl (anticipated licensed population) 303
Figure 33: Scatter plots for naloxegol 25 mg + bisacodyl versus placebo + bisacodyl (anticipated licensed population) 304
Figure 34: CEAC for naloxegol 25 mg + bisacodyl versus placebo + bisacodyl (anticipated licensed population) 304
Figure 35: Proportion of naloxegol 25 mg patients in each health state over time (anticipated licensed population) 305
Figure 36: Proportion of SC methylnaltrexone QAD patients in each health state over time (anticipated licensed population)..... 305
Figure 37: Scatterplot for Naloxegol 25 mg versus SC methylnaltrexone QAD (anticipated licensed population) 307
Figure 38: CEAC for naloxegol 25 mg versus SC methylnaltrexone QAD (anticipated licensed population) 307
Figure 39: Proportion of naloxegol 25 mg patients in each health state over time (anticipated licensed population + Step 3 opioids) – trial data analysis..... 316
Figure 40: Proportion of naloxegol 25 mg patients in each health state over time (anticipated licensed population + Step 3 opioids) - MTC 316
Figure 41: Proportion of naloxegol 25 mg + bisacodyl patients in each health state over time (anticipated licensed population + Step 3 opioids) 317
Figure 42: Proportion of placebo patients in each health state over time (anticipated licensed population + Step 3 opioids) 317
Figure 43: Proportion of placebo + bisacodyl patients in each health state over time (anticipated licensed population + Step 3 opioids)..... 318
Figure 44: Proportion of SC methylnaltrexone QAD patients in each health state over time (anticipated licensed population + Step 3 opioids) 318

Figure 45: Proportion of naloxone-oxycodone patients in each health state over time (anticipated licensed population + Step 3 opioids) 319

Figure 46: Scatterplot for naloxegol 25 mg vs placebo (anticipated licensed population + Step 3 opioids) 321

Figure 47: Scatterplot for naloxegol 25 mg versus placebo + bisacodyl (anticipated licensed population + Step 3 opioids) 321

Figure 48: Scatterplot for naloxegol 25 mg + bisacodyl versus placebo + bisacodyl (anticipated licensed population + Step 3 opioids) 322

Figure 49: Scatterplot for naloxegol 25 mg versus SC methylnaltrexone QAD (anticipated licensed population + Step 3 opioids) 322

Figure 50: Scatterplot for naloxegol 25 mg (+ morphine) versus naloxone-oxycodone (anticipated licensed population + Step 3 opioids) 323

Figure 51: Scatterplot for naloxegol 25 mg (+ OXY) versus naloxone-oxycodone (anticipated licensed population + Step 3 opioids) 323

Figure 52: CEAC for naloxegol 25 mg vs. placebo (anticipated licensed population + Step 3 opioids) 324

Figure 53: CEACs for naloxegol 25 mg versus placebo + bisacodyl (anticipated licensed population + Step 3 opioids) 324

Figure 54: CEACs for naloxegol 25 mg + bisacodyl versus placebo + bisacodyl (anticipated licensed population + Step 3 opioids) 325

Figure 55: CEACs for naloxegol 25 mg versus SC methylnaltrexone (anticipated licensed population + Step 3 opioids) 325

Figure 56: CEAC for naloxegol 25 mg (+ morphine) versus OXN (anticipated licensed population + Step 3 opioids) 326

Figure 57: CEAC for naloxegol 25 mg (+ OXY) versus naloxone-oxycodone (anticipated licensed population + Step 3 opioids) 326

Figure 58: Kaplan-Meier curve of comparison to first post-dose SBM without the use of rescue medication in KODIAC 4 (ITT analysis set) 404

Figure 59: Kaplan-Meier curve of comparison to first post-dose SBM without the use of rescue medication in KODIAC 5 (ITT analysis set) 404

Figure 60: Determination of laxative response status 409

Figure 61: Diagnostic plot for Naloxegol 25 mg: exponential 445

Figure 62: Diagnostic plot for Naloxegol 25 mg: Weibull 446

Figure 63: Diagnostic plot for Naloxegol 25 mg: Loglogistic 446

Figure 64: Diagnostic plot for Naloxegol 25 mg: lognormal 447

Figure 65: Diagnostic plot for Placebo: Exponential 448

Figure 66: Diagnostic plot for Placebo: Weibull 448

Figure 67: Diagnostic plot for Placebo: Loglogistic 449

Figure 68: Diagnostic plot for Placebo: Lognormal 450

Abbreviations

AAPM	American Academy of Pain Medicine
AE	Adverse event
AIC	Akaike's Information Criteria
ALKS	Alkermes
ALT	Alanine aminotransferase
APS	American Pain Society
ARR	Absolute risk reduction
AST	Aspartate aminotransferase
AUC	Assessment of area under the plasma concentration-time curve
BBB	Blood brain barrier
BD	Twice daily
BFI	Bowel function index
BGR	Brooks-Gelman-Rubin
BIC	Bayesian Information Criteria
BL	Baseline
BLRSQ	Baseline Laxative Response Status Questionnaire
BM	Bowel movement
BMI	Body mass index
BNF	British National Formulary
BOI	Burden of illness
BSS	Bristol Stool Scale
BSW	Global Assessment of Treatment, Benefit, Satisfaction, and Willingness to Continue
CEAC	Cost-effectiveness acceptability curves
CFB	Change from baseline
CG	Clinical guideline
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CSBM	Complete spontaneous bowel movement
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale

CV	Cardiovascular
DAE	Discontinuation due to adverse event
DDW	Digestive Disease Week
DSA	Deterministic sensitivity analysis
DIC	Deviance information criterion
ECG	Electrocardiogram
eDiary	Electronic diary
EMA	European Medicines Agency
EQ-5D	EuroQol 5 Dimension
ERG	Evidence Review Group
ESRD	End-stage renal disease
FDA	Food and Drug Administration
FLACC	Face, legs, activity, cry, consolability
FRC	Fixed ratio combination
GI	Gastrointestinal
GP	General practitioner
HCRU	Healthcare resource use
HES	Hospital episodes statistics
HRQL	Health-related quality of life
HS	Health state
HSUV	Health state utility values
IASP	International Association for the Study of Pain
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
INB	Incremental net benefit
IQR	Interquartile range
ITT	Intent-to-treat
IVRS	Interactive voice response system
LAR	Laxative adequate responder
LIR	Laxative inadequate responder
LP	Licensed population
LUR	Laxative unknown responder

LY	Life year
LYG	Life years gained
MACE	Major adverse cardiovascular events
MD	Mean difference
MED	Morphine equivalent dose
MEU	Morphine equivalent dose units
mHS	Modified Himmelsbach scale
MID	Minimally important difference
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
MNTX	Methylnaltrexone
MOR	Mu-opioid receptor
MRT	Mean residence time
MTC	Mixed treatment comparison
N/A	Not applicable
NHS	National Health Service
NKTR-118	Naloxegol
NR	Not reported
NRS	Numeric Rating Scale
OA	Osteoarthritis
OD	Once daily
OED	Oxycodone equivalent dose
OIC	Opioid-induced constipation
OR	Odds ratio
OTC	Over the counter
OXN	Oxycodone plus naloxone
OXY	Oxycodone
PAC-QoL	Patient Assessment of Constipation Quality of Life
PAC-SYM	Patient Assessment of Constipation Symptoms questionnaire
PAMORA	Peripherally acting mu-opioid receptor antagonist
PBAC	Pharmaceutical Benefits Advisory Committee
PK	Pharmacokinetics
PNS	Peripheral nervous system
PP	Per-protocol

PR	Prolonged release
PRN	As required
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QAD	Every other day
QALY(s)	Quality adjusted life year(s)
RCT	Randomised controlled trial
RMME	Repeated measures mixed effects
RR	Relative Risk
SAE	Serious adverse event
SBM	Spontaneous bowel movement
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short form 36
SG	Standard gamble
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SOC	Standard of care
SPC	Summary of product characteristics
STA	Single technology appraisal
TEAE	Treatment emergent adverse event
TTO	Time trade off
VAS	Visual analogue scale
WHO	World Health Organisation

Executive summary

Burden of disease

Opioid-induced constipation is one of the most common and debilitating side-effects of opioid treatment, leading to severe discomfort and impaired quality of life.

Definitions of constipation in England and Wales include opening the bowels fewer than three times per week (1) and unsatisfactory defecation as a consequence of infrequent bowel movements (BM) and straining to pass a BM (4). Opioid-induced constipation (OIC) results from the binding of opioid agonists to mu-opioid receptors in the gastrointestinal tract to reduce motility, secretion, and sphincter tone (5).

OIC is the most widely-recognised side effect reported in patients receiving opioids for pain management (6) and available literature suggests that OIC affects 45–80% of patients treated for non-cancer pain (7-9) and at least 90% of those treated for cancer pain (10). This condition is extremely debilitating for the patient, resulting in diminished quality of life and overall well-being (7). Indeed, constipation is rated as the most "bothersome" opioid-related side effect by 81% of patients (7), while straining to pass a BM is regarded by 58–82% of patients as the most troubling side-effect (7, 11). The symptoms of OIC can be so severe and disabling that the patient may reduce the dose or even cease their pain medication in order to facilitate having a BM (7, 12, 13). Consequences of long-term constipation can include rectal pain, bowel obstruction, a ruptured bowel and in rare instances, death (14).

Current management and unmet need

There is currently no consensus treatment pathway in the UK for patients with OIC. Treatment decisions are based on individual patient symptom profiles. There are limited options for patients who have had an inadequate response to laxative(s) who require a clinically beneficial and chronic oral treatment option that directly targets the underlying cause of their condition.

Despite the burden of OIC on patients, there is currently no clear consensus on the appropriate treatment pathway for patients with OIC in England and Wales. Treatment decisions are typically based on individual patient symptom profiles. This may be due in part to the multifactorial nature of constipation eg. dehyrdration, mobility in addition to OIC (15).

Laxative(s) are typically used as an initial treatment option for OIC in clinical practice. While laxative(s) may alleviate the symptoms of OIC, they do not specifically target the underlying cause of the condition. At least 25% of patients with OIC report that they are unsatisfied with the laxative(s) available to them (8, 11) and less than 50% of patients report that they achieve the desired laxative outcome, such as BMs, at least half of the time (16). In addition, [redacted] of patients with OIC report that being able to have one more spontaneous bowel movement (SBM) per week is "extremely important" to them, regardless of their number of SBMs per week at baseline (17).

Patients who have had an inadequate response to one or more laxative(s) (laxative inadequate responders[LIR]) and are still experiencing OIC have no option for a specific targeted therapy unless they have advanced illness or are eligible for oxycodone.

Methylnaltrexone (Relistor®) is a peripherally acting mu-opioid receptor antagonist administered by subcutaneous injection. Its use is restricted to patients with advanced medical illness under palliative care whose response to usual laxative therapy has not been sufficient (18). Naloxone-oxycodone (Targinact®) is a combination therapy where the opioid antagonist naloxone is added to the opioid oxycodone (19). It has limited use due to dose restrictions to ensure the correct ratio of naloxone to oxycodone; the ratio of naloxone to oxycodone is based on the ability of naloxone to cross the blood brain barrier and potentially reduce pain relief. It has also been prohibited from use by many local health authorities in the absence of robust evidence demonstrating that it is cost-effective when prescribed as a fixed dose in combination versus oxycodone monotherapy plus concomitant laxative use (20-22). Once all treatment options have been exhausted, patients with OIC may require rectal interventions to alleviate their condition (i.e. suppositories, enema, manual evacuation) which are often unpleasant and distressing (23).

Current evidence demonstrates that there are no effective treatment options that fully meet the needs of all OIC patients. LIR patients represent an important population of OIC patients with a high unmet need for a clinically beneficial and chronic oral treatment option that directly targets the underlying cause of their condition.

Naloxegol (Moventig™)

Naloxegol offers OIC patients who have had an inadequate response to laxative(s) an effective treatment option that specifically targets the underlying cause of their constipation, unlike conventional laxative(s). Naloxegol is the first oral, once daily, peripherally acting mu-opioid receptor antagonist that can be dosed independently of the patient's opioid.

Naloxegol is anticipated to be licensed for the treatment of OIC in adult patients who have had an inadequate response to laxative(s) and is intended for use as part of a holistic approach to constipation management. This includes using stimulant laxatives as required and behavioural and other pharmacological interventions where few treatment options currently exist. Naloxegol is a pegylated derivative of the mu-opioid receptor antagonist naloxone with minimal ability to penetrate the blood brain barrier at clinically relevant doses, where it could potentially reduce the pain-relief effects of the opioid. Naloxegol preferentially binds to mu-opioid receptors in the gastrointestinal (GI) tract, disrupting the agonist action of opioids on these receptors that lead to OIC without impacting the central analgesic effects of opioids on the central nervous system.

Compared to currently available treatments:

- Naloxegol offers physicians and patients flexibility in dosing as, unlike other treatment options, such as naloxone-oxycodone, it can be used independently of the opioid prescribed.
- Naloxegol requires no up-titration, unlike conventional laxatives, and thus is simpler to manage for both patients and physicians.
- Naloxegol is an oral, daily treatment that offers patients:
    - more convenient management of their OIC in contrast to current treatment options, such as methylnaltrexone, which as a subcutaneous injection would normally be administered by a healthcare professional (24).

    - a convenient way for patients to effectively manage their OIC, without impacting significantly on a, potentially already, high pill burden associated with the treatment of their underlying condition. In addition, the single daily dose may be less than the volume of currently available laxatives required to achieve highest tolerated effective doses.

- Potential to improve patient adherence: OIC can adversely affect adherence to opioid pain-management regimens impacting pain management. Reducing OIC without impacting on the analgesic effects of the opioid is likely to improve patient adherence to opioid treatment and improve pain control as a barrier to optimal use has been removed.

Naloxegol received CHMP positive opinion on September 25, 2014. Marketing authorisation from the European Medicines Agency is expected in December 2014.

Naloxegol will be supplied as 12.5 mg and 25 mg film-coated tablets (30 tablets per pack), with a recommended dose of 25 mg once daily. A price range has been submitted, however, the list price is anticipated to be £55.20 per pack. The price for 28 days of treatment is anticipated to be £51.52.

A price range has been submitted owing to uncertainty based on not yet having marketing authorisation and thus no agreement with the Department of Health on price.

It is anticipated that naloxegol will be prescribed for as long as a patient remains on opioid therapy.

Place in therapy

Patients who develop OIC that is not adequately relieved by currently available laxative(s) have a clear unmet clinical need. Laxative inadequate response may be defined as, in line with the key KODIAC trial and anticipated license: OIC symptoms (i.e. incomplete BM, hard stools, straining, or false alarms) of at least moderate severity while taking at least one laxative class for a minimum of four days.

In line with the anticipated licensed indication, naloxegol could fit into the treatment pathway as:

- An alternative treatment option to existing laxative(s) for patients who have had a laxative inadequate response to at least one laxative class

- An alternative treatment option for patients who are experiencing inadequate response provided by laxative(s) who would be suitable for methylnaltrexone or naloxone-oxycodone, that is, those who have advanced illness and are receiving palliative care or are suitable for oxycodone

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

Clinical evidence

Naloxegol demonstrates significant improvements in the clinical symptoms of OIC and patient quality of life.

The efficacy of naloxegol has been demonstrated in two identically designed, Phase III, randomised, placebo-controlled studies in patients with non-cancer related pain and OIC (KODIAC 4 and 5). The primary outcome in both studies was the response to study drug, defined as ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 study weeks. A key feature of KODIAC 4 and 5 was the inclusion of a pre-specified subpopulation of patients, the laxative inadequate response (LIR) group, which represents the anticipated licensed indication for naloxegol (KODIAC 4, n=350; KODIAC 5, n=370 across all treatment arms in the LIR group). The LIR population in these studies was defined as patients who had reported taking at least one laxative class for a minimum of four days within the two-week period prior to the screening visit concurrent with at least moderately severe symptoms of OIC (i.e. incomplete BMs, hard stools, straining or false alarms). To enable robust comparisons of naloxegol versus placebo, KODIAC 4 and 5 were powered to detect statistically significant differences in response to study drug in the LIR population.

In the LIR population (please note all data below is in this population):

- Naloxegol 25 mg (recommended dose) resulted in significantly higher response rates in LIR patients compared with placebo in both trials (KODIAC 4, 48.7% vs 28.8% patients, respectively; p=0.002: KODIAC 5, 46.8% vs 31.4% patients, respectively; p=0.014).
- In both studies, naloxegol showed a consistent improvement in a range of secondary endpoints that assessed all clinically relevant aspects of OIC:
    - Naloxegol resulted in shorter time to first post-dose SBM compared with placebo in both trials (KODIAC 4, 5.4 hours versus 43.4 hours in the naloxegol 25mg and placebo groups, respectively: KODIAC 5, 12.8 hours versus 38.2 hours in the naloxegol 25 mg and placebo groups, respectively
    - Naloxegol was associated with an increase in the total SBMs per week in both studies (KODIAC 4, 4.7, and 3.4 in the naloxegol 25 mg and placebo groups, respectively: KODIAC 5, 4.8, and 3.5 in the naloxegol 25 mg and placebo groups, respectively).
    - The number of days per week with at least 1 SBM was greater in the naloxegol treatment groups in the anticipated licensed population compared with placebo (KODIAC 4; 3.9 and 2.9 days in the naloxegol 25 mg and placebo groups, respectively: KODIAC 5; 3.9, and 3.0 days in the naloxegol 25 mg and placebo groups, respectively).
    - Use of rescue medication at least once over the treatment period was greater in the placebo groups compared with the naloxegol treatment groups in the anticipated licensed population in both studies (KODIAC 4; 56.4%, and 76.3% of naloxegol 25 mg and placebo patients, respectively: KODIAC 5; 62.9% and 76.9% of naloxegol 25 mg and placebo patients, respectively).

Naloxegol treatment was associated with symptomatic improvement and enhanced quality of life as measured across three patient reported outcome instruments.

- In both KODIAC 4 and 5, in the LIR population, naloxegol treatment was associated with greater reductions across all domains in Patient Assessment of Constipation symptoms (PAC-SYM) compared with placebo, indicating improvement in symptoms.
- In both studies, patients receiving naloxegol in the LIR population demonstrated greater reductions across all domains in the Patient Assessment of Constipation Quality of Life questionnaire (PAC-QoL) questionnaire compared with placebo, indicating improved quality of life.
- The EQ-5D scores collected in both studies demonstrate that there is a trend towards a greater number of patients reporting no problems across the domains and fewer patients reporting moderate problems who are receiving naloxegol compared with placebo.

Naloxegol is well-tolerated.

The safety profile of naloxegol has been well characterised in more than 850 patients in KODIAC 4 and KODIAC 5, and is further supported by the results of KODIAC 7, a 12 week safety extension study of KODIAC 4. Longer-term safety data presented in KODIAC 8 demonstrates that naloxegol was well-tolerated for up to 52 weeks of treatment with an adverse event (AE) profile that was generally consistent with that observed in the pivotal RCTs. The majority of AEs in all studies were mild to moderate in intensity. In all studies, the most frequently reported AEs associated with naloxegol treatment were GI symptoms (abdominal pain, diarrhoea, and nausea), the majority of which occurred within the first 7 days of starting treatment and resolved within one week. Due to the nature of the condition under investigation and the pharmacological action of the medicinal product, AEs of this nature could be expected.

Cost-effectiveness of naloxegol

Naloxegol is a cost-effective treatment option in the UK for patients with OIC who have experienced an inadequate response to laxative(s).

Model Structure: a de novo model was constructed to compare the cost-effectiveness of naloxegol based on the patients enrolled in KODIAC 4 & 5 for the treatment of adult patients with OIC who have had an inadequate response to laxative(s). The model was comprised of a decision-tree structure for the first 4 weeks of treatment, followed by a Markov structure over a time horizon of up to a maximum of 5 years.

This approach was taken in order to accurately represent the course of the condition and of treating OIC. The approach is in-line with models previously created, as well as the feedback upon them, for OIC and similar conditions (22, 25-27).

Comparators: the model compares naloxegol 25 mg (recommended dose) with:

- Placebo (which represents patients not on active therapy)
- Placebo in combination with bisacodyl (where bisacodyl is used as a proxy for stimulant laxative use as required)
- Methylnaltrexone

- Naloxone-oxycodone

Results are also presented for naloxegol 25 mg plus bisacodyl to demonstrate the cost-effectiveness of naloxegol when used in combination with a stimulant laxative. This scenario is considered most clinically relevant given the multifactorial nature of constipation and clinical guidance obtained via an advisory board and AstraZeneca sponsored research (28-30).

In the absence of robust data enabling an indirect comparison with rectal interventions, a cost minimisation analysis calculated how many months of naloxegol treatment could be given for the cost of one rectal intervention.

Base Case Results: in the base case analysis (the inputs of which are based on the KODIAC 4 & 5 data) the ICER for naloxegol vs placebo is £10,849 per QALY gained for a 5 year time horizon.

However it is the opinion of AstraZeneca that the most clinically relevant comparisons are;

- Naloxegol 25 mg vs 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

Please see Table 1 for a table of results for each comparator considered in the base case analysis:

Table 1: Base-case cost-effectiveness results

	Naloxegol 25 mg (+ bisacodyl)	**Placebo (vs Naloxegol 25 mg)**	**Placebo + bisacodyl (vs Naloxegol 25 mg)**	**Placebo + bisacodyl (vs Naloxegol 25 mg + bisacodyl)**
Technology acquisition costs	£302 (£361)	£0.00	£1.00	£1.00
Other costs	£971 (£951)	£1,016	£999	£999
Total costs	£1,272 (£1,313)	£1,016	£1,000	£1,000
Difference in total costs	N/A	£256	£272	£313
LYG	4.534 (4.534)	4.534	4.534	4.534
LYG difference	N/A	0.000	0.000	0.000
QALYs	2.686 (2.693)	2.663	2.665	2.665
QALY difference	N/A ()	0.024	0.0215	0.028
ICER	N/A ()	£10,849	£12,639	£11,175

Abbreviations: LYG, life years gained; QALYs, quality adjusted life year(s); ICER, incremental cost-effectiveness ratio.

Scenarios and Sensitivity Analyses: a large number of sensitivity and scenario analyses were completed in order to demonstrate the robustness of the model to changes in the model parameters and assumptions. These included analyses on treatment effect, extrapolation assumptions, utility and cost assumptions and in nearly all

of these sensitivity analyses naloxegol was found to be cost-effective at a willingness to pay threshold of <£20,000.

A probabilistic sensitivity analysis was undertaken for the base case comparison with placebo. Derived from this, naloxegol 25 mg has a probability of 91% of being cost-effective at a willingness to pay threshold of <£20,000.

Naloxegol was found to be dominant vs methylnaltrexone and naloxone-oxycodone, when naloxegol is used with oral morphine. In addition to these results, compared with rectal interventions, naloxegol can be provided for 0.68 months for the same cost as a rectal intervention given at the patient's home and for 43.02 months if the rectal intervention is given in an inpatient care hospital setting

Conclusion

- **Patients taking opioids who develop OIC as a consequence currently have limited treatment options when conventional laxative(s) prove insufficient in alleviating the condition, which results in debilitating symptoms that can adversely affect adherence to opioid treatment and negatively impact quality of life.**
- **Naloxegol provides an oral treatment option that directly targets the cause of OIC and can be used with existing opioid treatment at any dose, unlike current treatments available. This gives patients a simple, flexible and convenient treatment option for the management of their OIC.**
- **The pivotal RCTs demonstrate that:**
    - **Naloxegol has proven efficacy in those patients with substantial unmet need; patients with LIR. Naloxegol was associated with an increase in the 4-5 total SBMs per week in KODIAC 4 and 5 studies. OIC patients report that an increase of even one more SBM per week is meaningful to them (17).**
    - **Naloxegol is the first opioid antagonist to have demonstrated efficacy in this LIR population.**
- **Naloxegol is associated with symptomatic improvement and enhanced quality of life. Patients with OIC are already burdened due to their underlying condition, and naloxegol offers significant improvement in the symptoms of OIC, including a reduction in straining, regarded by a substantial proportion of patients as one of their most troubling side-effects.**

- **Naloxegol is a cost-effective treatment option in the UK for patients with OIC who have experienced an inadequate response to laxative(s).**

In summary, naloxegol is an efficacious, tolerable and cost-effective peripherally acting mu-opioid antagonist for the treatment of patients with an inadequate response to laxative(s) that provides an alternative treatment with added benefits compared with the limited options available. Naloxegol should form part of an integrated management approach to OIC that may also include behavioural and other pharmacological interventions.

Section A – Decision problem

1 Description of technology under assessment

1.1 *Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.*

Brand name: Moventig™

Approved name: naloxegol

Therapeutic class: naloxegol is a peripherally acting mu-opioid receptor antagonist (PAMORA), ATC code: A06AH03

1.2 *What is the principal mechanism of action of the technology?*

Opioids exert their main analgesic effects primarily via agonist activity at mu-opioid receptors which are widely distributed throughout the central nervous system (CNS) (31). However, many of the common side-effects associated with opioid use, such as impaired gastrointestinal (GI) motility, are as a result of activation of peripherally located mu-opioid receptors in the GI tract(31). Binding of opioids to these receptors results in dysmotility, reduced fluid secretion and impairment of sphincter tone (Figure 1). Together, these effects contribute to the constipating side-effects of opioids (32).

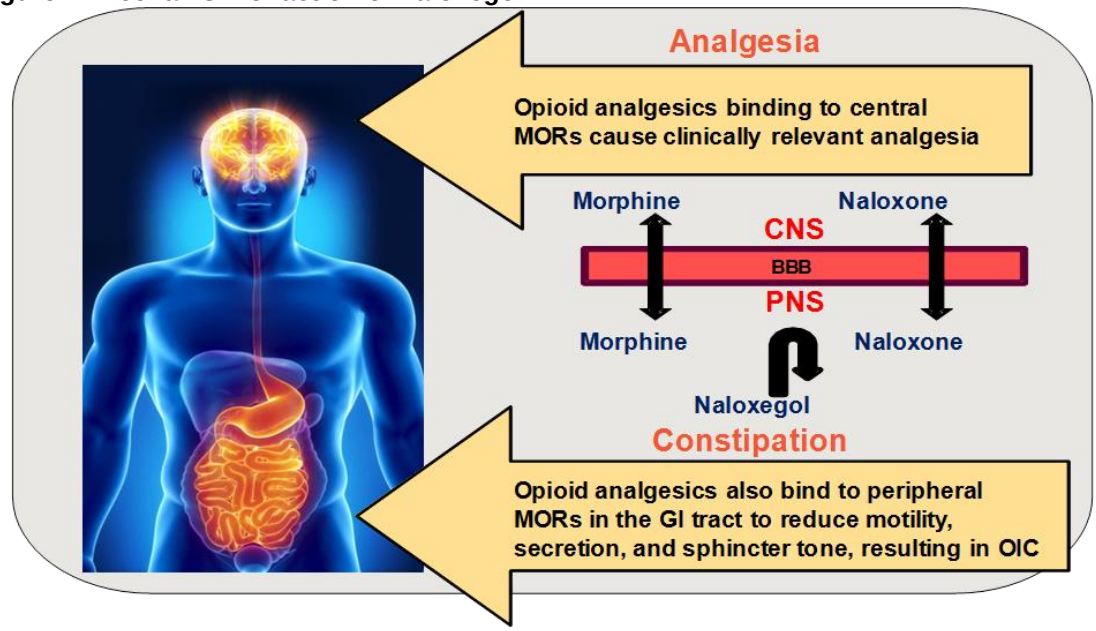
Naloxegol is an orally administered pegylated derivative of the mu-opioid receptor antagonist naloxone with limited ability to cross the blood brain barrier at clinically relevant doses (33). Pegylation of the parent molecule confers the following beneficial properties:

1. Naloxegol is a substrate of the P-glycoprotein (P-gp) transporter. Due to the substrate properties of P-gp transporters, the ability of naloxegol to cross the blood brain barrier is minimal
2. Pegylation of naloxone results in increased molecular weight and thus reduced passive permeability across membranes, including the blood brain barrier
3. Pegylation increases the bioavailability of the molecule

Unlike conventional laxatives, naloxegol targets the underlying causes of opioid-induced constipation (OIC) by preferentially binding to mu-opioid receptors in the GI tract, thus displacing opioids from these receptors, i.e. the agonist action of opioids on mu-opioid receptors that results in OIC is disrupted (32).

Due to the limited ability of naloxegol to permeate the blood brain barrier, the antagonistic effects of naloxegol are essentially restricted to mu-opioid receptors located outside of the CNS. As a result, naloxegol alleviates OIC without reducing the central analgesic effects of opioids.

Figure 1: Mechanism of action of naloxegol



Abbreviations: BBB, blood brain barrier; CNS, central nervous system; GI, gastrointestinal; MOR, mu-opioid receptor; OIC, opioid-induced constipation; PNS, peripheral nervous system.

1.3 ***Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).***

CHMP positive opinion was granted on September 25, 2014 and marketing authorisation from the European Medicines Agency is expected in December, 2014.

1.4 ***Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).***

The EPAR opinion has yet to be received and a copy will be provided to NICE upon receipt. The main points from the regulatory discussions are provided below:

The absence of relevant data on the treatment of OIC in cancer pain patients

In the absence of data on the treatment of OIC in cancer pain patients, the CHMP asked AstraZeneca to justify the extrapolation of the available efficacy and safety data in OIC non-cancer patients to the treatment of OIC patients with cancer pain. In assessing the available evidence, the CHMP considered that AstraZeneca had attempted to conduct a Phase III, multicentre, global study dedicated to assessing the efficacy and safety of naloxegol in patients with cancer related pain and OIC (KODIAC 6). However, severe recruitment difficulties meant the study had to be terminated early with only 14 of the required 366 patients randomised. An additional non-interventional burden of illness study also proved challenging with only 23 of the projected 130 cancer pain patients enrolled after nearly 9 months. Data collection is currently on-going for this cohort.

It was also discussed that there is no published evidence that opioid receptor pharmacology, density or location in cancer pain patients is substantially different from that of non-cancer pain patients. Thus, AstraZeneca presented their position that there is no scientific rationale to expect the pharmacodynamic properties of naloxegol to differ in patients with cancer pain to those with non-cancer pain. This is supported by data from other peripherally acting mu-opioid receptor antagonist (PAMORAs) which showed no decrease in efficacy in patients with OIC and cancer pain compared with patients with OIC and non-cancer pain: two Phase III studies using methylnaltrexone administered subcutaneously to treat patients with OIC and advanced illness (59% and 81% had cancer pain; (34, 35)) and one Phase II study using oral oxycodone/naloxone prolonged-release to treat OIC patients with moderate/severe cancer pain (36). Furthermore, in one of the studies (35) a logistic regression analysis of methylnaltrexone-treated patients found that rescue-free laxation within 4 hours of the first dose did not vary according to diagnosis (cancer/non-cancer). In addition, there were no substantial differences in the safety profiles of these drugs in patients with cancer pain compared with patients with non-malignant pain (35, 36).

AstraZeneca acknowledged that additional safety data for naloxegol in cancer pain patients should be collected on an ongoing basis and committed to conducting a further observational study in cancer pain patients as part of the risk management plan. However, it was AstraZeneca's position that these patients, who not only suffer the discomfort associated with their malignancies and the side-effects of the therapies used to treat them but also the additional comorbidity of OIC, should not be deprived of the option to seek potential benefit from naloxegol. Following consideration of the evidence, the CHMP granted a positive opinion for naloxegol with a licence that does not exclude patients with OIC and cancer pain subject to the post-approval safety study.

It is anticipated that naloxegol will only be contraindicated in the following patients with cancer pain:

- Patients with underlying cancer who are at a heightened risk of gastrointestinal (GI) perforation, such as those with;
  - underlying malignancies of the GI tract or peritoneum
  - recurrent or advanced ovarian cancer
  - vascular endothelial growth factor inhibitor treatment

1.5 *What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.*

The anticipated indication for naloxegol is the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).

In the pivotal RCTs for naloxegol (presented in section 6.3), to qualify as a laxative inadequate responder, patients had to have reported concurrent OIC symptoms of at least moderate severity (i.e. 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 (33). Thus, naloxegol is indicated for any patient with OIC after inadequate response of one laxative class.

1.6 ***Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.***

There are no ongoing studies and no additional studies anticipated to be completed over the next 12 months.

1.7 ***If the technology has not been launched, please supply the anticipated date of availability in the UK.***

The anticipated date of availability in the UK is [redacted]

1.8 ***Does the technology have regulatory approval outside the UK? If so, please provide details.***

On September 16, 2014, naloxegol was approved by the US Food and Drug Administration (FDA) for the treatment of OIC in adults with chronic non-cancer pain (37).

1.9 ***Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?***

Scottish Medicines Consortium: planned submission in May 2015.

The All Wales Medicines Strategy Group has been contacted by AstraZeneca and has been informed that naloxegol is currently being assessed by NICE under the Single Technology Appraisal process.

1.10 ***For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.***

Table 2: Unit costs of technology being appraised

Pharmaceutical formulation	Each film-coated tablet contains naloxegol oxalate equivalent to 25 mg naloxegol. A 12.5 mg dose is also available
Acquisition cost (excluding VAT)	Naloxegol is supplied as 12.5 mg and 25 mg film-coated tablets (30 tablets per pack), with a recommended dose of 25 mg once daily. The list price for a 30 tablet pack of 25 mg or 12.5 mg tablets is anticipated to be £55.20 equating to a daily cost of £1.84. Please note that a price range has been submitted owing to uncertainty based on not yet having marketing authorisation and thus no agreement with the Department of Health. Although a range has been provided the £1.84 price should be used for the purposes of the evaluation
Method of administration	Oral
Doses	The recommended dose is 25 mg. A 12.5 mg dose is available for patients requiring necessary dose adjustments (see below)

Dosing frequency	Naloxegol should be taken once daily either on an empty stomach at least 30 minutes before the first meal of the day or 2 hours after the first meal of the day
Average length of a course of treatment	It is anticipated that naloxegol will be prescribed for as long as the patient remains on opioid therapy. Data from an analysis of the CPRD database 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 (30, 89). *Additional screening criteria were applied including ensuring patients had at least one year of data prior to index date (and posterior to practice "up-to-standard" date), were naive to opioid prior to index date, older than 18 and excluding patients with less than 5 year of follow-up and still on index treatment at the end of follow-up
Average cost of a course of treatment	The price for 28 days of treatment is £51.52
Anticipated average interval between courses of treatments	Naloxegol is intended for chronic use and is to be taken alongside opioid therapy. in the event the patient no longer requires laxation and naloxegol is discontinued, but the patient subsequently experiences opioid-induced constipation again, the interval between courses could be 4–14 days as per the naloxegol trial definition for confirmation of an inadequate response to laxative(s). However, if the patient is experiencing adequate laxation while receiving naloxegol, the patient should continue on naloxegol therapy for as long as they continue opioids
Anticipated number of repeat courses of treatments	For as long as the patient continues on opioid therapy, naloxegol would be continued
Dose adjustments	*Patients with renal impairment* The starting dose for patients with moderate or severe renal insufficiency is 12.5 mg. If side effects impacting tolerability occur, naloxegol should be discontinued. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient. No dosage adjustment is required for patients with mild renal impairment. *CYP3A4 inhibitors* The starting dose for patients taking moderate CYP3A4 inhibitors (e.g.

	diltiazem, verapamil) is 12.5 mg once daily. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient. *Gastrointestinal adverse events* For patients with severe/persistent or worsening gastrointestinal adverse events consideration may be given to reducing the dose to 12.5 mg, depending upon the response and tolerability of individual patients.

1.11 ***For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.***

N/A

1.12 ***Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?***

In patients with any condition which may result in increased potential for GI perforation (e.g. severe peptic ulcer disease, Crohn's disease, active or recurrent diverticulitis, infiltrative GI tract malignancies, or peritoneal metastases), caution with regards to the use of naloxegol should be exercised. In such instances, healthcare professionals may perform an abdominal x-ray (or similar) at their own discretion. The overall benefit-risk profile for each patient should therefore be taken into account.

Naloxegol should be prescribed with caution in patients with clinically important disruptions to the blood brain barrier (e.g. advanced Alzheimer's, active multiple sclerosis, CNS metastases, primary brain malignancies etc.). Such patients should be observed for potential CNS effects, such as opioid withdrawal symptoms and/or interference with opioid analgesia.

Other anticipated contraindications for the use of naloxegol do not require any additional tests or investigations.

1.13 ***Is there a need for monitoring of patients over and above usual clinical practice for this technology?***

There is no requirement to monitor patients receiving naloxegol over and above usual clinical practice.

1.14 ***What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?***

There is no stated requirement for routine pre-medication in the product SPC. However, as naloxegol is indicated for the treatment of OIC, it is intended that naloxegol will only be administered as add-on therapy to existing opioid therapy. When naloxegol therapy is initiated, it is recommended that all currently used laxative maintenance therapy should cease, until the clinical effects of naloxegol are determined. However, the multifactorial nature of OIC may mean that some patients continue to use laxatives in a PRN manner to address other contributing factors of their constipation not caused by opioids. For example, symptoms that result from inactivity due to patients' underlying conditions, or potential under-hydration and other medications such as anticholinergics.

2 Context

2.1 *Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.*

Opioid-induced constipation (OIC) is the most common, persistent and debilitating side-effect reported in patients receiving opioids to manage pain (12). The analgesic effects of opioids are primarily exerted through mu-opioid receptors in the central nervous system (CNS) (31). 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 (5). The result is an accumulation of hard, dry stools that are difficult to pass (38). Other GI-related opioid-induced symptoms include abdominal pain, nausea, overflow diarrhoea and incontinence and faecal impaction (39).

The NICE definition of constipation is unsatisfactory defecation due to infrequent bowel movements, difficult stool passage, or a feeling of incomplete evacuation (40). According to The British Society of Gastroenterology, doctors define constipation as opening the bowels less than three times per week (1) which also constitutes one of the Rome III criteria for a diagnosis of constipation (41). Longer term consequences of constipation include rectal pain and burning, the formation of haemorrhoids, bowel obstruction, potential bowel rupture and in rare cases, death (14).

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 (42):

- “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.”

When asked to give their thoughts on this statement at a recent AstraZeneca Advisory Board meeting on OIC, comments from the advisors[a] included the fact that the definition does not take overflow incontinence into account. Also, it does not include the subjective experience of patients, as patients sometimes deny that they are constipated, despite the presence of upper GI symptoms (29).

OIC occurs in approximately 45–80% of patients receiving opioids for non-cancer pain (7-9) and in at least 90% of patients receiving opioids for the management of cancer-related pain (10). Consequently, OIC has been demonstrated to have a negative impact on patient quality of life (QoL) and overall well-being (7). A survey of patients in the US

[redacted]

and Europe reported that the opioid-induced GI side-effects regarded as the most “bothersome” in order of rank were constipation (81% of patients), straining to pass a bowel movement (58% of patients) and bowel movements too hard or too small (50% of patients) (7). OIC can be disabling and troublesome to patients to the extent that some reduce the dose or even discontinue their opioid medication in order to have a bowel movement, thus compromising optimal pain management (7, 12, 13).

Many people will experience constipation at some time in their lives. In the majority of cases, this is classified as functional constipation and can be effectively treated with laxative(s) (43). However, while OIC is acknowledged as a common and significant side-effect of opioid treatment, there are few guidelines that offer specific protocols for the management or prevention of OIC and consequently there is currently [redacted] One reason for this may be the multifactorial nature of the condition which requires patients to be treated individually depending on their underlying condition and other confounding factors.

It is widely accepted that inactivity, inadequate hydration and opioids independently lead to constipation. In addition to the reduction in intestinal motility that results from the use of opioids, patients with OIC are often inactive as a result of their underlying condition (5). Patients with constipation are often encouraged to make dietary and lifestyle modifications, such as increasing their fluid and fibre intake and taking regular exercise (45). However, this is difficult for many OIC patients due to their underlying condition which is causing their pain.

As with functional constipation, laxative(s) are typically used as the first-line treatment for OIC in clinical practice, although bulking agents are not recommended as they may cause obstruction (45). However, due to differences in the mechanisms of functional constipation and OIC, patients with OIC may not respond adequately to laxative(s) (42). Laxative(s) are only effective in alleviating the symptoms of constipation that result from inactivity and poor hydration and do not specifically target the opioid-related mechanisms that additionally contribute to constipation in these patients. A recent global burden of illness study found that at least 89% of OIC patients reported inconsistent efficacy with their laxative use (11). A US survey of patients receiving opioid treatment for non-cancer related pain reported that only 46% of patients achieved the desired treatment result at least 50% of the time according to the study criteria (16). Another US population web-based survey found that 25% of respondents using opioids for the management of non-cancer pain reported dissatisfaction with available laxatives, while 45% reported experiencing diarrhoea or urgency while using laxatives (8). Unfortunately, many patients who fail to achieve an adequate response to one laxative then switch to an alternative laxative, without targeting the underlying cause of their OIC.

While it is evident from the literature that there are a substantial number of OIC patients with an inadequate response to laxative(s), there is currently no accepted method for defining this subpopulation in clinical practice. [redacted]. See section 10.14 for further details on this survey. The definition of a laxative inadequate response used in the pivotal trials for naloxegol (KODIAC 4 and 5, section 6.3) is therefore provided in the absence of any clinically accepted alternative. To be classified as a laxative inadequate responder in the trials,

patients had to have reported OIC symptoms of at least moderate severity (i.e. incomplete bowel movement, hard stools, straining, or false alarms) while taking at least one laxative class for a minimum of four days during the pre-study period (33). The baseline patient characteristics of this population in KODIAC 4 and 5 were representative of patients who would be treated in clinical practice in terms of reduced frequency of spontaneous bowel movements (SBMs), straining to pass a bowel movement (BM), passing hard stools etc.

When laxative(s) alone have provided inadequate pharmacological relief of constipation, patients may be treated with formulations containing opioid antagonists. Peripherally acting mu-opioid receptor antagonists (PAMORAs) are pharmacological agents that block the agonist effects of opioids on the gut with limited capacity to cross the blood brain barrier and hence have minimal effects on the central analgesic effects of the opioid medication. Methylnaltrexone is currently the only PAMORA available for the treatment of OIC in the UK. It is indicated for the treatment of OIC in adult patients with advanced illness receiving palliative care and in whom usual laxative therapy has been unsuccessful (18). In addition, it is a subcutaneous injection which is usually administered in a healthcare setting, [redacted] Methylnaltrexone's limited indication and issues around administration both mean that methylnaltrexone has very limited use in clinical practice.

Physicians may also consider prescribing naloxone-oxycodone (Targinact®), an oral combination therapy in which the opioid antagonist naloxone is added to the opioid oxycodone to competitively inhibit the action of oxycodone at opioid receptors in the GI tract, thus reducing the risk of OIC (19). The obvious drawback is that oxycodone will not be suitable for all patients requiring opioid medication and even for those in whom it is appropriate, the use of naloxone-oxycodone is limited to set doses to ensure the correct ratio of naloxone to oxycodone. The maximum daily dose of naloxone-oxycodone is 80 mg oxycodone and 40 mg naloxone. Administration of supplemental prolonged release oxycodone (up to a maximum daily dose of 400 mg) may be considered for patients requiring higher pain relief. However, in these circumstances, the beneficial effects of naloxone on bowel function may be impaired. This means that naloxone-oxycodone may not provide adequate relief from OIC for many patients requiring stronger pain management (19). In addition, cost-effectiveness of naloxone-oxycodone versus oxycodone monotherapy with concomitant laxatives has not been robustly proven according to local health authorities (22). In addition, naloxone-oxycodone has a different decision problem to naloxegol as in line with NICE CG 140 could see clinicians use it as a prophylactic option. In summary, based on the aforementioned limitations, naloxone-oxycodone may not be an appropriate choice for physicians to prescribe for patients requiring second-line treatment for OIC (i.e. patients who continued to have at least moderate symptoms of OIC while taking at least one laxative class for a minimum of 4 days).

If OIC persists and all treatment options have been exhausted, rectal interventions such as suppositories and enemas may be necessary and finally, manual evacuation of the impacted stool may be necessary. Besides being unpleasant, these procedures can increase patient anxiety and may have further negative impacts on health (23).

As OIC tends to persist for as long as the opioid therapy is administered, it can be associated with a considerable economic burden. Patients with OIC often have diminished quality of life and as a consequence may require the use of additional healthcare resources (25). A study conducted in Sweden reported that the biggest drivers of total healthcare costs in patients with OIC were indirect costs as a result of absenteeism from employment followed by costs for outpatient care (46).

In summary, evidence in the literature demonstrates that there is a substantial subpopulation of patients with OIC for whom the current treatment options do not provide the required relief from their symptoms, i.e. patients who have an inadequate response to laxative(s) therapy (see section 1.5). Consequently, patients with OIC who have an inadequate response to laxative(s) have a clear and substantial unmet medical need and would therefore benefit from a novel oral treatment option that directly targets the underlying pathophysiology of the disease in the GI tract with limited capacity to cross the blood brain barrier.

2.2 ***Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.***

The prevalence of OIC patients in England and Wales is not known, largely due to the lack of an ICD-10 code that prevents more reliable quantification. However, studies provide evidence that up to 80% of patients receiving opioid therapy for non-cancer pain and at least 90% of cancer pain patients report OIC as an unwanted side effect of their treatment (7-10). In addition, scientific literature suggests that 50-80% of patients taking laxatives for OIC report dissatisfaction with laxative treatment (8, 11), or that their treatment does not improve or alleviate their symptoms (16).

In the anticipated licensed population, it is expected that the total number of patients eligible for treatment with naloxegol will be [redacted] in year 1, rising to [redacted] in year 5. It is expected that the total number of patients in the anticipated licensed population eligible for treatment with naloxegol who are also receiving a Step 3 opioid will be [redacted] in year 1, rising to [redacted] in year 5.

2.3 ***Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.***

OIC is not associated with a reduction in life expectancy for the majority of patients. However, the potential consequences of long-term constipation or constipation if left untreated include bowel obstruction, bowel perforation and in rare cases, death (14). For cancer patients, the underlying condition is the life-limiting factor rather than OIC.

2.4 ***Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.***

In the context of the anticipated licensed indication for naloxegol, there are no current NICE guidelines specifically for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s). However, NICE has published the following related guidelines:

- NICE Clinical Guideline No. 140, May 2012, “Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults” (40). This guideline provides recommendations for the management of constipation in patients receiving strong opioid treatment for pain (see section 2.5).

The following Health Technology Appraisal which is of relevance to the treatment of OIC in patients with non-cancer pain is currently suspended following the MHRAs rejection of the OIC indication due to insufficient evidence of efficacy (47):

- “Lubiprostone for treating opioid-induced constipation in people with chronic, non-cancer pain”.

2.5 ***Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.***

The majority of patients with OIC are managed in primary care. The aims of management are to improve symptoms, achieve a complete bowel movement at least every 2–3 days without difficulty, and consequently to improve patient satisfaction and overall quality of life (45). NICE CG 140 states that laxatives should be prescribed for all patients initiating strong opioid treatment (40). It is recommended that the use of bulk-forming laxatives should be avoided in OIC as the effects of opioid treatment may result in painful colic and in rare cases, obstruction (4, 45). Instead, osmotic laxatives, stool softeners and stimulant laxatives should be used. In addition, patients are advised to increase their fluid and fibre intake and where possible, to increase their activity levels. Patients are also encouraged to develop regular toileting habits (4, 45).

There is currently no guidance around the use of methylnaltrexone or naloxone-oxycodone. The two palliative care formularies available for methylnaltrexone position this product as a potential second-line option after the use of a stimulant such as senna. [redacted]. The many limitations to their use (discussed previously in section 2.1) may mean that very few patients receive either medication.

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). This is a key group of patients with a clear unmet need for an effective oral therapy that can alleviate the symptoms of OIC. A recent burden of illness study reported that 93% of patients had an inadequate response to laxatives, despite taking sufficient laxative therapy (11).

There is currently a lack of guidance to enable physicians to identify patients in clinical practice who have had an inadequate response to laxative(s). [redacted] (44). Therefore, identification of suitable patients by physicians will be based on the definition of this population utilised in the pivotal clinical trials and which forms the basis of the anticipated licensed population for naloxegol. This is expected to include the following criteria:

- Receiving opioid therapy for pain relief
- taking ≥1 laxative class for ≥4 days during the last two weeks, and
- reporting moderate, severe, or very severe symptoms in at least one of the four stool symptom domains (i.e. incomplete bowel movement, hard stools, straining, or false alarms)

It is therefore anticipated that following the introduction of naloxegol, patients with OIC will continue to be initiated on laxative therapy. However, should the first or subsequent laxative(s) fail to relieve all of the symptoms of constipation within 4-14 days, naloxegol will provide an alternative treatment option to existing laxatives, which targets the underlying opioid-related cause of the constipation, in an oral formulation and allows flexible dosing of the opioid medication.

2.6 ***Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.***

There is currently no clear consensus on the treatment pathway for patients with OIC in England and Wales. This may be due to the multifactorial nature of OIC. First-line therapies for the treatment of OIC are laxative(s), but these do not target the underlying mechanisms of OIC, and approximately 25% of patients report that they are dissatisfied with their treatments (8) while 25–50% of patients report an inadequate response to laxative treatment (11, 16). Methylnaltrexone and naloxone-oxycodone are current treatment options when laxative(s) therapy proves inadequate. However, the combination therapy of naloxone-oxycodone is only indicated for the treatment of severe pain and may not be suitable for use in all patients (19). Also, due to lack of robust evidence demonstrating the cost-effectiveness of naloxone-oxycodone when prescribed as a fixed dose in combination versus oxycodone monotherapy plus concomitant laxative use, it has been prohibited from use by many local health authorities (20-22). Methylnaltrexone is currently only indicated in OIC patients with advanced illness receiving palliative care. In addition, it is only available as a subcutaneous injection (18). Thus, patients who fail to adequately respond to laxative treatment currently have very limited treatment options available to them.

In summary, there is a clear unmet need for an effective oral treatment option that is independent of opioid molecule or opioid dose and with a tolerable side-effect profile that specifically targets the underlying causes of OIC, thus maintaining patient quality of life.

2.7 ***Please identify the main comparator(s) and justify their selection.***

The final scope for this appraisal specifies the following comparator treatments in adults with opioid-induced constipation and their relevance as direct comparators to naloxegol is discussed:

Oral laxative treatment without naloxegol:

- While naloxegol is indicated for use in patients with an inadequate response to laxative(s) this does not preclude laxative(s) from being a suitable comparator as patients in the UK often switch to an alternative second-line laxative if treatment with a first line laxative results in inadequate response. Patients need only have had an inadequate response to one laxative class prior to initiating naloxegol therapy and so subsequent laxative therapy may also be considered. Although oral laxative(s) may

be considered the main comparator to naloxegol in the overall OIC population, they are also considered a relevant comparator to the anticipated licensed indication for naloxegol i.e. patients with an inadequate response to laxative(s). In the absence of RCT data demonstrating the head-to-head efficacy of naloxegol versus laxatives, trial data from KODIAC 4 and 5 comparing SBMs – those BMs that occurred without the need for rescue medication[b] (bisacodyl) in the last 24 hours – with total BMs in the placebo plus rescue bisacodyl arm – those BMs that occurred as a result of rescue bisacodyl – will be used as a proxy for stimulant laxative used PRN. An additional analysis comparing total BMs in the naloxegol plus rescue bisacodyl arm with total BMs in the placebo plus bisacodyl arm will demonstrate the effectiveness of naloxegol when used in combination with stimulant laxative used PRN.

- Given the multifactorial nature of constipation (see section 1.14) it is likely that rescue laxative(s) may be used as adjunctive therapy to baseline naloxegol use in clinical practice. In a recent survey conducted among 29 healthcare professionals (including GPs, palliative care specialists, and pain specialists), the majority of respondents agreed that rescue medication would be a suitable proxy for determining the efficacy of an investigational agent in the absence of any head-to-head data vs laxatives (28).

For adults in whom oral laxatives have provided inadequate relief:

- Peripheral mu-opioid receptor antagonist (methylnaltrexone): has a restricted ability to cross the blood brain barrier and therefore exerts it's pharmacological effects on peripheral mu-opioid receptors in tissues such as the GI tract without impacting opioid-mediated analgesic effects on the central nervous system (18). Like naloxegol, methylnaltrexone is a PAMORA. However, the use of methylnaltrexone is restricted by its licence to patients with advanced illness receiving palliative care. Given this limited use and its position in therapy, it is questionable whether methylnaltrexone is an appropriate comparator for naloxegol as it represents a small subgroup of OIC patients. However, for completeness and in line with the scope, a comparison of naloxegol with subcutaneous methylnaltrexone is presented in this submission.
- Opioid analgesic and opioid receptor antagonist combinations (naloxone-oxycodone): the opioid antagonist naloxone is added to the opioid analgesic oxycodone to counteract OIC by competitively blocking the action of oxycodone at opioid receptors in the GI tract (19). Like methylnaltrexone, use of naloxone-oxycodone is limited in the UK due to restrictions in the dose of oxycodone that can be prescribed as part of the fixed-dose combination. It has also been prohibited from use by many national and local health authorities due to a lack of robust evidence demonstrating cost-effectiveness when prescribed as a fixed dose in combination versus oxycodone monotherapy plus concomitant laxative use (20, 22). Oxycodone is a Step 3 opioid on the WHO analgesic ladder (i.e. prescribed for the relief of moderate to severe pain),

[b]Refers to laxative used as a rescue therapy when a patient is unable to have an adequate bowel movement within a pre-determined period of time.

the comparison with naloxegol is restricted to the sub-population of OIC patients with an inadequate response to laxative(s) receiving a strong opioid. In addition, the label for naloxone-oxycodone is different to that of naloxegol, as there is also the option to use as prophylaxis.

- 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.

2.8 ***Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.***

Naloxegol has an acceptable safety profile to both patients and clinicians and the drug has proven to be generally well-tolerated in OIC patients with non-cancer pain. The most commonly reported adverse reactions in clinical studies of naloxegol (≥5% of patients) were abdominal pain, diarrhoea, flatulence, nausea and headache. These adverse events were mainly mild to moderate in intensity, occurred early on in treatment and generally resolved with continued treatment. There is no requirement with naloxegol therapy for additional therapies to manage adverse events. For patients who experience severe/persistent/worsening GI adverse events, consideration may be given to reducing the dose of naloxegol to 12.5 mg.

2.9 ***Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.***

Naloxegol is likely to be prescribed in the following settings: general practitioners, gastroenterology clinics, pain clinics, provision of palliative care and hospice care. Overall, naloxegol has the potential to have a positive impact on NHS resource use. For example, patients will already be under the care of their GP for a chronic condition of which OIC is a side effect of treatment, thus naloxegol should not mean an increase in GP visits. Also, OIC is often a barrier to optimal pain management as some patients reduce or skip their dose of opioids to facilitate having a bowel movement (7, 12, 13). As naloxegol targets the cause of OIC without impacting on the analgesic effects of the opioid, there is the potential for better patient adherence to their opioid treatment so that subsequent pain management is improved. Thus, the addition of naloxegol to the patient's opioid treatment pathway has the potential to reduce the number of GP and nurse consultations in addition to GI clinic visits and Chronic Pain clinics. In addition, naloxegol has the potential to reduce the number of hospital admissions and district nurse visits for complications associated with OIC (e.g. faecal impaction (16)).

2.10 ***Does the technology require additional infrastructure to be put in place?***

It is not anticipated that any additional infrastructure will be required for the implementation of naloxegol treatment into clinical practice.

3 Equality

3.1 *Identification of equality issues*

3.1.1 *Please let us know if you think that this appraisal:*

- ***could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;***
- ***could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology***
- ***could lead to recommendations that have any adverse impact on people with a particular disability or disabilities***

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

There are no potential equality issues relating to naloxegol as a treatment for opioid-induced constipation.

3.1.2 *How has the analysis addressed these issues?*

N/A

4 Innovation

4.1.1 *Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.*

Naloxegol's innovation lies in the combination of it's mode of action (naloxegol is a pegylated derivative of naloxone and is a peripherally acting mu-opioid receptor antagonist [PAMORA]) and its formulation (being both oral and once daily). Unlike other PAMORAs, pegylation of the parent molecule renders it a substrate of the P-glycoprotein (P-gp) transporter. The P-gp transporter is located on the blood brain barrier where it transports substrates out of the central nervous system. Thus, the P-gp transporter reduces the ability of naloxegol to cross the blood brain barrier and disrupt the central analgesic effects of opioids while not interfering with its ability to bind to opioid receptors in the gastrointestinal (GI) tract. This allows naloxegol to alleviate OIC without reducing the central analgesic effects of the patient's opioid pain relief. Compared with conventional laxatives, naloxegol directly targets the cause of OIC in the GI tract. The benefits of naloxegol over methylnaltrexone and naloxone-oxycodone have been previously discussed in section 2.

In summary, naloxegol is a once daily, oral treatment that offers patients:

- a targeted mode of action, proven to work in LIR patients, by acting peripherally as a mu-opioid antagonist thereby reversing the constipating effects of opioids
- more convenient management of their OIC, unlike methylnaltrexone, which is a subcutaneous injection, and thus would normally be administered by a healthcare professional
- a convenient way to manage their OIC more effectively as naloxegol will not have a significant impact on a potentially already high pill burden associated with the treatment of their underlying condition. The single daily dose of naloxegol may also be less than high doses of the currently available laxatives.
- the potential to improve patient adherence to their opioid regimens. OIC may result in patients skipping or reducing the dose of their pain medication in order to have a bowel movement. As naloxegol directly targets the cause of OIC in the GI tract without impacting on the analgesic effects of the opioid, naloxegol is likely to improve patient adherence to their opioids and thus improve pain management

Compared with currently available treatments:

- naloxegol offers greater flexibility in dosing for both physicians and patients, as unlike naloxone-oxycodone, it can be used independently of the opioid prescribed
- unlike conventional laxatives, naloxegol requires no up-titration so is therefore simpler to manage for both physicians and patients

  Naloxegol offers a step-change approach to the management of OIC for physicians. 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

4.1.2 ***Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.***

N/A

4.1.3 ***Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.***

N/A

5 Statement of the decision problem

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) (33).
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 (i.e. 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 • HRQL	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	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
	technologies being compared. Costs will be considered from an NHS and Personal Social Services 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 (40). 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 (49) 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

Abbreviations: GI, gastrointestinal; HRQL, Health related quality of life; N/A, not applicable; OIC, opioid-induced constipation; SBM, spontaneous bowel movement; WHO, World Health Organisation.

Section B – Clinical and cost effectiveness

6 Clinical evidence

Summary

- The efficacy evidence for naloxegol from the pivotal RCTs KODIAC 4 and KODIAC 5 demonstrates that naloxegol is an effective treatment for OIC. Clinically relevant improvements in the frequency of spontaneous bowel movements (SBMs) and in the symptoms of OIC were demonstrated in patients receiving naloxegol compared with placebo over the 12 week treatment period. Such improvements are also meaningful and important to the patient with OIC. A key feature of KODIAC 4 and 5 was the inclusion of a pre-defined patient population with an inadequate response to laxatives (defined as the anticipated licensed population). Results are presented for this population and the ITT population.
  - The naloxegol 25 mg dose was consistently superior to placebo for the primary endpoint in the intent-to-treat population and in the anticipated licensed population
  - All individual symptoms of OIC assessed (i.e. straining, days per week, with at least one complete SBM, stool consistency) showed greater improvement over 12 weeks of treatment with naloxegol compared with placebo in the anticipated licensed population
  - Patients receiving naloxegol demonstrated symptomatic improvement and greater quality of life as measured across three patient reported outcome instruments
- Naloxegol is well-tolerated by patients with OIC and the majority of adverse events are mild to moderate in intensity.
- Safety evidence in the pivotal RCTs is further supported by the results of KODIAC 7, a 12 week extension study of KODIAC 4 that was specifically designed to assess safety.
- Longer-term safety evidence for naloxegol is provided from KODIAC 8, a 52 week open-label study, designed to demonstrate the safety and tolerability of naloxegol versus Usual Care, which demonstrated that naloxegol was well-tolerated for up to 52 weeks.
- A mixed treatment comparison comparing naloxegol data with two other mu-opioid receptor antagonists demonstrated that naloxegol 25 mg had a similar efficacy and adverse event profile to methylnaltrexone (Relistor®) and naloxone-oxycodone (Targinact®).

Introduction

The clinical efficacy evidence for naloxegol is primarily provided from two pivotal, Phase III randomised controlled trials (RCTs), KODIAC 4 and 5. Both studies were designed to demonstrate the efficacy and safety of naloxegol in OIC patients with non-cancer pain. AstraZeneca had also attempted to conduct a Phase III, multicentre, global study

designed to assess the efficacy and safety of naloxegol in patients with cancer related pain and OIC (KODIAC 6). However, due to inability to enrol sufficient patients as per the protocol, the study had to be terminated early.

The primary efficacy endpoint in KODIAC 4 and 5 was response to treatment (defined as ≥3 spontaneous bowel movements (SBMs) per week with a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 study weeks). The studies also included the following clinically important secondary endpoints: time (in hours) to first post-dose laxation without the use of rescue laxatives; and mean number of days per week with at least one spontaneous bowel movement during the treatment period.

A key feature of KODIAC 4 and 5 was the inclusion of a predefined patient population with an inadequate response to laxative(s) (the anticipated licensed population). While scientific publications demonstrate that there are a substantial number of patients who have an inadequate response to laxative(s), there is currently no accepted method for defining this population of patients [redacted] (28). [redacted] (44). In addition, there is currently no published guidance to enable physicians to identify patients who have had an inadequate response to laxative(s). After consultation with an advisory board of external experts, AstraZeneca devised a method to effectively classify OIC patients according to their response to laxative(s). The Baseline Laxative Response Status Questionnaire (BLRSQ) was subsequently developed. The BLRSQ was an investigator-administered questionnaire to assess the type of laxative used within the two weeks prior to enrolment into KODIAC 4/5, the frequency of the laxative use, and whether or not the patient had experienced any symptoms during laxative use. In KODIAC 4 and 5, patients were classified as laxative inadequate responders (LIR) provided they were taking ≥1 laxative class for ≥4 days prior to screening (see section 6.3). In addition, the LIR population maintained at least moderate symptoms of OIC defined as; reporting moderate, severe or very severe symptoms in at least one of the four stool symptom domains (incomplete bowel movement, hard stools, straining, or false alarms).

Patients with an inadequate response to laxative(s) represent an important subgroup of the OIC target population with an unmet need for a chronic oral treatment option. The EMA recognised this importance and granted a licence for naloxegol based on this patient population.

A brief summary of data collected from KODIAC 6 is also presented in this section. As discussed earlier this was a Phase III study designed to demonstrate the efficacy and safety of naloxegol in patients with cancer pain.

The safety evidence for naloxegol is provided from the two pivotal KODIAC 4 and 5 RCTs and also from KODIAC 7, a 12 week extension study of KODIAC 4. KODIAC 7 was primarily designed to assess the safety and tolerability of naloxegol versus placebo. In addition, longer-term safety evidence is provided from KODIAC 8. This was a 52 week open-label study designed to demonstrate the safety and tolerability of naloxegol versus Usual Care. Finally, additional safety data with respect to patients with renal impairment is provided in a brief summary of the KODIAC 9 trial while safety data in patients with

hepatic impairment is presented in a brief summary of the KODIAC 10 trial (section 6.9.4).

Given the importance of the anticipated licensed population, observational evidence for the relevance of this subpopulation to the target OIC patient population is presented in the burden of illness study in section 6.5.6.

6.1 *Identification of studies*

6.1.1 *Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.2, appendix 2.*

Two systematic reviews were conducted to identify relevant data from the published literature:

- Randomised controlled trial (RCT) evidence on the efficacy and safety of naloxegol and relevant comparators for the treatment of opioid-induced constipation (in patients with non-malignant pain), including, where possible, data for the LIR and LIR taking Step 3 opioids sub-populations
- Non-RCT evidence on the efficacy and safety of naloxegol for the treatment of opioid-induced constipation

To identify relevant RCT evidence, a systematic review was performed in October 2013 in part as an update to a review published by the Cochrane Collaboration in 2008, which included RCTs investigating the efficacy and safety of μ-opioid antagonists in opioid-induced bowel dysfunction. The current systematic review updated the search used in the Cochrane review to identify RCTs published between January 2006 and October 2013 and also included OIC trials identified in the Cochrane review that were published prior to January 2006. A broad search was carried out in October 2013 to capture interventions used in different markets (see section 10.2, appendix 2), including mu-receptor opioid antagonists, non-selective opioid antagonists, peripherally acting mu-opioid receptor antagonists (PAMORA), prokinetic 5HT4 receptor agonists, secretagogues, peptide agonists of guanylate cyclase-C receptors, laxatives, and other interventions such as ALKS 37 and bevenopran. Specific inclusion and exclusion criteria were then applied to the abstracts identified in order to include only interventions relevant to the UK and the scope of this appraisal (i.e. naloxegol, methylnaltrexone, naloxone-oxycodone and laxatives).

In addition, a UK specific update to the systematic review was conducted on August 21, 2014 to identify any recent studies relevant to the UK market and in line with the final scope for this appraisal. The interventions included in the update searches were methylnaltrexone and naloxone-oxycodone. Laxatives were not included in this update as there was a lack of recent data and head to head studies versus naloxegol identified in the initial searches. It was therefore considered unlikely that any new data for laxatives would be available. The searches carried out in October 2013 and August 2014 used

search strings to identify placebo and active-controlled Phase II and III RCTs, conducted in OIC populations regardless of age, gender and race, with at least one arm randomised to an intervention of interest (as outlined above) alone or in combination with any other pharmacological agent.

The following electronic databases were searched: Ovid MEDLINE, EMBASE (Ovid), and the Cochrane Library. In addition, the searches for relevant RCT data were supplemented by hand searching of the following relevant conference proceedings between 2010 and 2013, with updated searches carried out in August 2014 to include 2014 conference proceedings where possible: the American Academy of Pain Medicine (AAPM) Annual Meeting, the American Pain Society (APS) Annual Scientific Meeting, the International Association for the Study of Pain (IASP) World Congress on Pain, the American College of Gastroenterology Annual Scientific Meeting, United European Gastroenterology Week, and Digestive Disease Week (DDW).

To identify relevant non-RCT evidence, a systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of naloxegol for patients with OIC. The following electronic databases were searched: Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (Ovid), and Cochrane. Electronic searches were supplemented by hand searching the following sources:

- Clinicaltrials.gov;
- World Health Organisation international clinical trials registry platform;
- Conference abstracts from 2012, 2013, 2014 where available:
  - The American Academy of Pain Medicine (AAPM) Annual Meeting
  - American Pain Society (APS) Annual Scientific Meeting
  - American College of Gastroenterology Annual Scientific Meeting
  - United European Gastroenterology Week
  - Digestive Disease Week (DDW)

Full details of the search strategy for RCT evidence is provided in section 10.2 (Appendix 2) and the search strategy for non-RCT evidence is provided in section 10.6 (Appendix 6).

6.2 *Study selection*

6.2.1 *Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.*

For both the RCT and non-RCT systematic reviews, after removal of duplicates, studies identified were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded, and allocated a “reason code” to document the rationale for exclusion. Papers included after this stage were then assessed for eligibility based on the full text; further papers were excluded, yielding the final data sets for inclusion.

The final included data set for the RCT data consisted of clinical studies for naloxegol and those for comparator treatments. The full text of these comparator studies was screened and those suitable for MTC analysis were selected.

Inclusion and exclusion selection criteria for the RCT systematic review are shown in Table 3.

Table 3: Eligibility criteria used in search strategy for RCT evidence

	Description	Justification
Inclusion criteria		
Population	• OIC with Laxative inadequate responders (LIR) • OIC with 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. The subgroup of LIR patients taking a Step 3 opioid is considered to be clinically relevant (see section 5 for justification). 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
Interventions	• Naloxegol	Consistent with the final scope
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)
Outcomes	• Change in SBMs at 4 weeks • 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	Consistent with the final scope and for use in the economic model (see section 5)
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.
Language restrictions	English language only	To reduce the number of hits and to identify studies in patient populations relevant to the UK setting
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
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

	Description	Justification
Comparators	Studies that do not include a treatment arm with any of the selected comparators of interest	Not relevant to the final scope
Outcomes	Studies lacking relevant data on any clinical efficacy, safety, and tolerability outcomes of interest	Not relevant to the final scope
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.

Abbreviations: LIR, laxative inadequate responder; OIC, opioid-induced constipation; OTC, over the counter; PAMORA, peripherally acting mu-opioid receptor; RCT, randomised controlled trial; SBM, spontaneous bowel movement; TEAE, treatment emergent adverse event.

Inclusion and exclusion criteria for the non-RCT are shown in Table 4.

Table 4: Eligibility criteria used in search strategy for non-RCT evidence

	Description	Justification
Inclusion criteria		
Population	Patients with OIC, regardless of age, gender and race	Consistent with the final scope
Interventions	Naloxegol	Consistent with the final scope
Outcomes	Safety and efficacy	Consistent with the final scope
Study design	Non-RCT	RCT studies were identified in a separate review
Exclusion criteria		
Population	Patients without OIC or mixed populations in which outcomes for OIC patients are not reported separately	Consistent with the final scope

Abbreviations: OIC, opioid-induced constipation; RCT, randomised controlled trial.

6.2.2 ***A flow diagram of included and excluded studies at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses. Such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in Section 6.2.4.***

RCT systematic review

The RCT systematic review was conducted in October 2013 and updated in August 2014. After removal of duplicates, a total of 2,301 citations were screened on the basis of title and abstract. A further 2,228 citations were excluded according to the pre-specified exclusion criteria and 73 full text articles were assessed for eligibility. Following

assessment and exclusion of studies based on title, abstract and full text (where available), 74 publications (including 41 from the systematic search, 30 from conference abstracts and posters and 3 from a previous Cochrane review) of 34 RCTs met the inclusion criteria and were assessed for feasibility for meta-analysis. A further 26 RCTs were excluded at the feasibility assessment for reasons that included population differences, definition of certain outcomes, time points of evaluation and doses and schedules of comparator treatments. Five studies included patient populations with malignancy pain, three studies did not fully report sample size or time points of assessment, six studies did not report outcomes of interest, eleven studies did not include a comparator of interest, and one study was a naloxegol trial with no relevant subgroup analysis.

The updated systematic review conducted on 21 August, 2014 did not find any papers or abstracts providing relevant data for the planned analyses. However, one paper identified outside of the systematic review (50), provided additional naloxone-oxycodone data on a single outcome of interest (complete SBM response). This meeting abstract was presented at the Canadian Digestive Disease Week, a conference not included in the SLR protocol.

A total of 8 RCTs were identified for inclusion in the MTC (50-58). These 8 studies reported on comparator interventions that are of relevance to the decision problem, i.e. naloxegol, naloxone-oxycodone and methylnaltrexone. These studies are reported further in section 6.7.

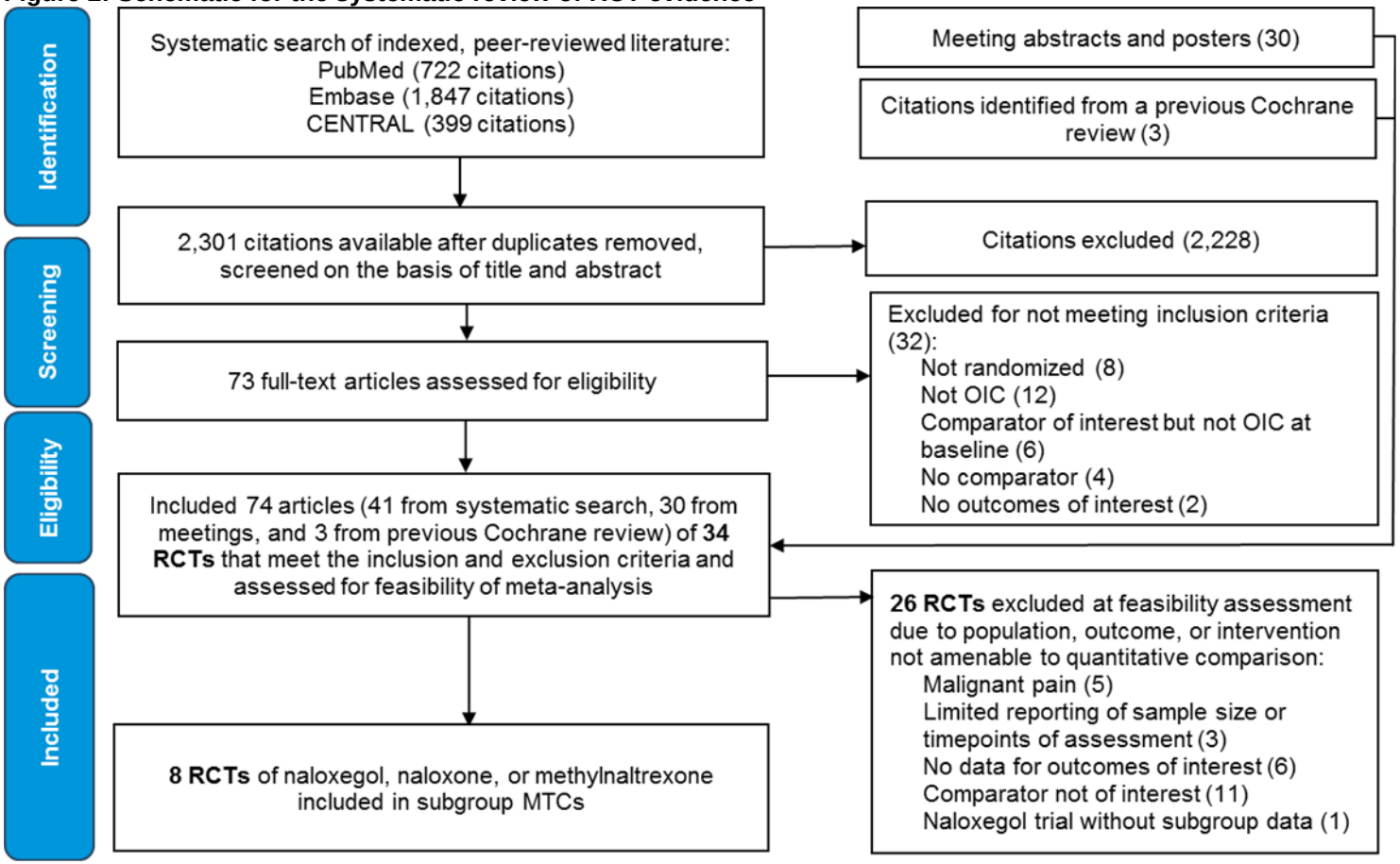
The RCT systematic review schematic is shown in Figure 2. Note that this diagram captures all searches conducted to date, including the systematic searches (conducted through October 2013) and the search update (conducted through August 2014) that included only key comparators of interest for these subgroup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

Non-RCT systematic review

The non-RCT systematic review was conducted on September 29, 2014. After removal of duplicates, a total of 54 citations were screened on the basis of title and abstract. A further 51 citations were excluded at first pass. Reasons for exclusion included duplicates, review articles, and disease area. Three full text articles were assessed for eligibility. Following assessment and exclusion of non-eligible studies, a single non-RCT met the inclusion criteria (59). The identified non-RCT (KODIAC 16) (59) is a Phase I study to characterise the pharmacokinetics (PK) of naloxegol following a single oral dose of naloxegol 12.5 mg or 25 mg. The study is currently open for recruitment.

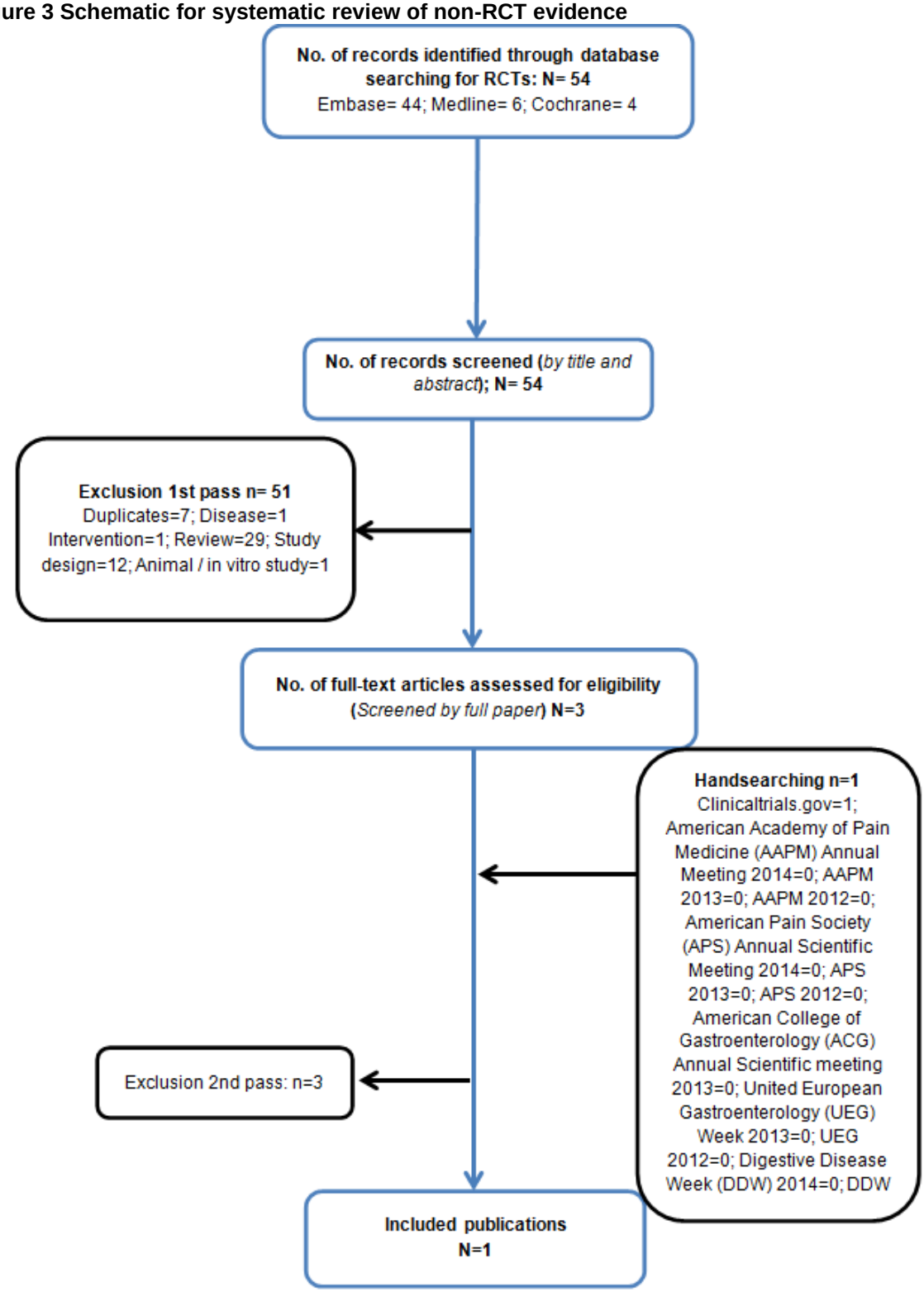
The schematic of the non-RCT systematic review procedure is shown in Figure 3.

Figure 2: Schematic for the systematic review of RCT evidence



Abbreviations: MTC, mixed treatment comparison; OIC, opioid-induced constipation; RCT, randomised controlled trial

Figure 3 Schematic for systematic review of non-RCT evidence



Abbreviations: RCT, randomised controlled trial.

6.2.3 *When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.*

The source of the data for KODIAC 4 and KODIAC 5 is the publication by Chey et al, 2014 (53) and the clinical study reports (CSRs) (51, 52). Data for an additional post-hoc subgroup analysis for the LIR + Step 3 opioids population and for some of the LIR population analyses was provided by AstraZeneca post-publication of the CSRs.

Complete list of relevant RCTs

6.2.4 *Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.*

The systematic review of clinical evidence identified 3 RCTs of naloxegol in the population of interest to this submission (Table 5). Placebo was the comparator in all three studies. Of these RCTs, KODIAC 4 and 5 were eligible for use in the MTC. The Phase II trial was not eligible for the MTC as it did not contain data for the LIR sub-population. A summary of the Phase II trial has been included in Section 6.5.5 for completeness. Details of other RCTs included in the systematic review and MTC for the comparator interventions are provided in Section 6.7.3.

Table 5: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
naloxegol Phase II	naloxegol 5 mg, 25 mg or 50 mg OD	placebo	Adult OIC patients with non-cancer or cancer-related pain	Webster et al, 2013 (60) and CSR (61)
KODIAC 4	naloxegol 12.5 mg or 25 mg OD	placebo	Adult OIC patients with non-cancer pain	Chey et al, 2014 (53) and CSR (51)
KODIAC 5	naloxegol 12.5 mg or 25 mg OD	placebo	Adult OIC patients with non-cancer pain	Chey et al, 2014 (53) (52)

Abbreviations: CSR, clinical study report; OD, once daily; OIC, opioid-induced constipation.

6.2.5 *Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.*

Although there is no direct comparison of naloxegol with laxatives, the use of rescue bisacodyl in KODIAC 4 and 5 has been analysed as a proxy comparison. Please see Section 2.7 for further details.

6.2.6 ***When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.***

No identified studies were excluded from further discussion.

List of relevant non-RCTs

6.2.7 ***Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in Section 6.8 and key details should be presented in a table; the following is a suggested format.***

The non-RCTs relevant to this submission are summarised in Table 6. Only one relevant non-RCT was identified. This study has not yet enrolled any patients. The estimated date for the final data collection for the primary outcome measure is January 2017.

Table 6: List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
KODIAC 16 NCT02099591	Naloxegol	Paediatric patients ages ≥6 months to <18 years receiving treatment with opioids	To characterise the pharmacokinetics (PK) of naloxegol after single oral dose and through population PK in paediatric patients with OIC	D3820C00016	Relevant population and intervention

Abbreviations: OIC, opioid-induced constipation; PK, pharmacokinetics

6.3 *Summary of methodology of relevant RCTs*

6.3.1 ***As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.***

Methods

6.3.2 ***Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following table provides a suggested format for when there is more than one RCT.***

While the clinical systematic review presented in section 6.1 identified 5 RCTs which were relevant for the comparator interventions, only the key naloxegol RCTs are presented in this section. The pivotal RCTs, KODIAC 4 and KODIAC 5, were studies to demonstrate the safety and efficacy of naloxegol in OIC patients with non-cancer pain. The methodology of the two trials was identical. However, patients were enrolled from non-overlapping study centres in order to demonstrate replication of the key study outcomes across two separate but identical studies. The KODIAC 5 study included three UK sites (total number of enrolled patients n=4). In addition to the intent-to-treat population which included all randomised patients and which was used for all analyses, a key feature of both studies was the inclusion of a pre-specified subgroup of patients with an inadequate response to laxative(s); the laxative inadequate response (LIR) subgroup (see section 6.3.7). The LIR subgroup is hereafter referred to as the anticipated licensed population in this section. The methodology of KODIAC 4 and 5 is summarised in Table 7.

Pivotal studies: KODIAC 4 and KODIAC 5

Table 7: Methodology of the pivotal RCTs (KODIAC 4 AND KODIAC 5)

Study	KODIAC 4	KODIAC 5
Study objective	To compare the efficacy and safety of naloxegol in patients with non-cancer related pain and OIC	
Location	International, multicentre RCT (98 sites) conducted in Australia (1), Germany (5), Slovakia (4) and the US (88)	International, multicentre RCT (167 sites) conducted in Belgium (1), Croatia (4), Czech Republic (4), Hungary (7), Spain (7), Sweden (2), the UK (3) and the US (88)
Design	Phase III, randomised, double-blind, placebo-controlled, parallel group study	
Duration of study	An initial screening period was followed by a 2 week OIC confirmation period followed by a 12 week treatment period	

Study	KODIAC 4	KODIAC 5
Method of randomisation	Patients were stratified on the basis of their response to laxative use (anticipated licensed population, laxative adequate responder [LAR], laxative unknown responder [LUR]), and randomly assigned in a 1:1:1 ratio to receive study drug at a dose of 12.5 mg or 25 mg OD or placebo. A minimum of 50% of patients were randomised into the anticipated licensed population group. Note that due to the small numbers of patients enrolled within the LAR baseline laxative response group, the LAR and LUR groups were combined and categorised as non-LIR.	
Method of blinding (care provider, patient and outcome assessor)	Naloxegol 12.5 mg and 25 mg tablets were identical in size and colour to their respective placebo tablets. Patients received two tablets per dose, either 12.5 mg active plus 25 mg placebo, 12.5 mg placebo plus 25 mg active or two placebo doses dependent upon which dose they were randomised to receive. To maintain blinding, the randomisation scheme was concealed from investigators and participants. In the case of a medical emergency, the treatment code could be broken via an interactive voice response system as described in the relevant user manual provided at each study centre.	
Intervention(s) (n =) and comparator(s) (n =)	12 weeks of either: • Naloxegol 12.5 mg OD (n=215) • Naloxegol 25 mg OD (n=218) • Placebo OD (n=216)	12 weeks of either: • Naloxegol 12.5 mg OD (n=231) • Naloxegol 25 mg OD (n=234) • Placebo OD (n=232)
Permitted and disallowed concomitant medications	Permitted medications: • Baseline opioid pain control regimen was to be maintained with dose adjustments according to clinical need • Medication considered necessary for the patient's safety and well-being was allowed at the discretion of the investigator Disallowed medications: • All laxatives and other bowel regimens • Opioid antagonists and mixed antagonists (e.g. buprenorphine, naloxone, methylnaltrexone) • Strong inhibitors of cytochrome P450 3A4 (CYP3A4) • P-glycoprotein (P-gp) inhibitors	
Rescue medication	Patients were permitted to use bisacodyl (10-15 mg dose) as rescue medication if a BM had not occurred within ≥72 hours of the last recorded BM. If the patient remained constipated, the dose could be repeated up to two additional times. A one-time enema could be administered if no BM was experienced following 3 doses of bisacodyl. If this intervention failed, the patient was discontinued from the study (or excluded from the study if the patient failed the rescue regimen prior to randomisation)	
Discontinuation of study therapy	In addition to standard reasons for discontinuation of study drug (e.g. AE, violation of protocol, lost to follow-up, patient decision), patients were to be discontinued for the following: • Inadequate pain control following unsuccessful attempts to control pain • Hepatotoxicity • Clinically significant or serious AE • Safety reasons as judged by the investigator • Significantly worsened OIC refractory to treatment as judged by the investigator	

Study	KODIAC 4	KODIAC 5
Assessments	Patients were required to complete a daily eDiary throughout the double-blind treatment period. The eDiary was used to record BMs, stool consistency, straining, complete/incomplete evacuation, pain level, use of rescue medication and use of opioid medication. Patient assessments were performed on Days 1, 8, 15, 29, 57 and 85 of the double-blind treatment period.	
Primary outcomes (including scoring methods and timings of assessments)	Response to study drug (ITT population) defined as: • % of patients with ≥3 SBMs per week with improvement from baseline of ≥1 SBM per week for ≥9 out of 12 study weeks and 3 out of the last 4 study weeks.	
Secondary outcomes (including scoring methods and timings of assessments)	**Key secondary outcomes** • Response to study drug (as defined for the primary outcome) in the anticipated licensed population. The anticipated licensed population was defined as: ○ Taking ≥1 laxative class for ≥4 days in the two weeks prior to screening and reporting moderate, severe or very severe symptoms in ≥1 of the four stool symptom domains (i.e. incomplete BM, hard stools, straining or false alarms) • Time to first post-dose SBM without the use of rescue medication in the last 24 hours • Mean number of days per week with ≥1 SBM **Other secondary outcomes** • Secondary assessment of response incorporating symptom data • Change from baseline in the mean degree of straining • Change from baseline in the mean stool consistency • % of days with a complete SBM (CSBM) • Mean weekly bisacodyl dose, Weeks 1–12 • Time to first post-dose SBM without the use of rescue medication within the last 24 hours in the anticipated licensed population • Change from baseline in PAC-SYM total score and each domain score for Weeks 2, 4, 8 and 12 • Change from baseline in PAC-QoL total score and each domain score for Weeks 4 and 12	
Duration of follow-up	Follow-up visit 2 weeks after the last dose of study drug	

Abbreviations: AE, adverse event; BM, bowel movement; CSBM, complete spontaneous bowel movement; eDiary, electronic diary; ITT, intent-to-treat; LAR, laxative adequate responder; LUR, laxative unknown responder; OD, once daily; OIC, opioid-induced constipation; PAC-QoL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms questionnaire; SBM, spontaneous bowel movement.

Participants

6.3.3 ***Provide details of the eligibility criteria (inclusion and exclusion) for the trial. Highlight any differences between the trials. The following table provides a suggested format for the presentation of inclusion and exclusion criteria for when there is more than one RCT.***

The inclusion and exclusion criteria for the pivotal RCTs are summarised in Table 8. Note that patients classified as the anticipated licensed population met all of the inclusion criteria in addition to the following:

- Taking ≥1 laxative class for ≥4 days prior to screening, and
- Reported moderate, severe, or very severe symptoms in at least one of the four stool symptom domains (i.e. incomplete BM, hard stools, straining, or false alarms).

Pivotal studies: KODIAC 4 and KODIAC 5

Table 8: Eligibility criteria in the pivotal RCTs (KODIAC 4 and KODIAC 5)

Study	Inclusion criteria	Exclusion criteria
KODIAC 4 KODIAC 5	• Male or female aged between ≥18 and <85 years • Self-reported active symptoms of OIC at screening† • Documented confirmed OIC‡ • During the OIC confirmation period, patients must have reported ≥1 of the following symptoms in ≥25% of the BMs recorded in the eDiary: BSS stool type 1 or 2; moderate, severe or very severe straining; incomplete BM • Receiving a stable maintenance opioid regimen (30 mg to 1000 mg morphine equivalents) for non-cancer related pain for a ≥4 weeks prior to screening	• Receiving opioids for treatment of cancer-related pain • History of cancer within 5 years of screening (excluding basal cell cancer and squamous cell skin cancer) • Any medical condition and treatment associated with diarrhoea or constipation • Previous diagnosis of IBS prior to first initiation of opioid therapy with: • No structural or biochemical explanation for pain symptoms • ≥12 weeks of abdominal discomfort/pain with ≥2 of the following in the last 12 months • Relieved with defecation • Onset associated with a change in stool frequency • Onset associated with a change in form of stool • Other medical conditions related to the GI tract including: IBD, intestinal obstruction, history of rectal prolapse, severe peptic ulcer • Acute GI conditions e.g. acute faecal impaction, complete obstipation (i.e. failure to pass stools or gas) • Any significant and/or progressive medical condition (e.g. poorly controlled seizures, inadequately controlled clinical depression)

		• Abnormal laboratory findings including elevated ALT or AST levels, reduced creatinine clearance • Symptoms of opioid withdrawal • Severe background pain refractory to opioid therapy • Any condition that may have affected the permeability of the BBB (e.g. multiple sclerosis) • Myocardial infarction within the last 6 months, symptomatic congestive heart failure or any other overt cardiovascular disease • Previous participation in any study with naloxegol

Abbreviations: ALT, alanine aminotransferase: AST, aspartate aminotransferase; BBB, blood brain barrier; BM, bowel movement; BSS, British Stool Scale; eDiary, electronic diary; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; OIC, opioid-induced constipation
†Defined as <3 SBMs/week and >1 symptom of hard/lumpy stools, straining or sensation of incomplete evacuation/anorectal obstruction in ≥25% of BMs over the previous 4 weeks; ‡Defined as <3 SBMs/week on average over the 2 week OIC confirmation period.

6.3.4 *Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.*

In this section, the patient characteristics for the following groups will be presented: anticipated licensed population (LIR), ITT population, and non-LIR population.

Pivotal studies: KODIAC 4 and KODIAC 5

Anticipated licensed population (LIR) vs non-LIR patients

In both studies, baseline demographic data were comparable across treatment groups by baseline laxative response status (i.e. anticipated licensed population [LIR] and non-LIR) (Table 9 and Table 10). The mean age of patients across treatment groups was 53.3 years for the anticipated licensed population and 51.2 years for the non-LIR group in KODIAC 4. In KODIAC 5, the mean age was 53.2 years in the anticipated licensed population and 50.7 years in the non-LIR group. The majority of patients in all subgroups in both studies were white (80.3% of the anticipated licensed population and 74.2% of the non-LIR groups in KODIAC 4 and 83.0% of the anticipated licensed population and 77.3% of the non-LIR groups in KODIAC 5). A higher proportion of patients in each subgroup were female in both studies. In KODIAC 4, >50% of patients had a BMI ≥30 kg/m^2 in both the anticipated licensed population and the non-LIR groups. In KODIAC 5, >45% patients had a BMI ≥30 kg/m2 in both the LIR and the non-LIR groups.

Back pain was reported as the most common reason for pain in both the anticipated licensed population and non-LIR groups in both studies: 55.1% and 57.0% of patients, respectively in KODIAC 4 and 55.9% and 57.7% of patients, respectively in KODIAC 5. In KODIAC 4, the median lifetime opioid use ranged from 60–96 months while the median time spent on current opioid treatment was 24–26 months across treatment groups. In KODIAC 5, patient median lifetime opioid use ranged from 78–84 months and

the median time spent on current opioid treatment ranged from 2–3 years across treatment groups.

Patient characteristics for the anticipated licensed population at baseline in KODIAC 4 and 5 are summarised in Table 9.

Table 9: Characteristics of the anticipated licensed population in the pivotal RCTs (KODIAC 4 and KODIAC 5) across randomised groups

KODIAC 4	**Naloxegol 12.5 mg (n=115)**	**Naloxegol 25 mg (n=117)**	**Placebo (n=118)**
Characteristic			
Age, mean (SD)	52.9 (10.3)	53.3 (10.72)	53.6 (9.96)
Female, n (%)	72 (62.6)	68 (58.1)	77 (65.3)
Race, n (%)			
White	88 (76.5)	101 (86.3)	92 (78.0)
Black or African American	21 (18.3)	14 (12.0)	20 (16.9)
Asian	5 (4.3)	1 (0.9)	2 (1.7)
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska native	0	0	1 (0.8)
Other	1 (0.9)	1 (0.9)	3 (2.5)
BMI (kg/m^2)			
<18.5	0	0	0
18.5 – <30	51 (44.3)	59 (50.4)	57 (48.3)
≥30	64 (55.7)	58 (49.6)	61 (51.7)
Primary reason for pain, n (%)			
Back pain	70 (60.9)	61 (52.1)	62 (52.5)
Joint pain	6 (5.2)	3 (2.6)	5 (4.2)
Fibromyalgia	2 (1.7)	7 (6.0)	9 (7.6)
Headache/migraine	0	2 (1.7)	2 (1.7)
Arthritis	10 (8.7)	12 (10.3)	12 (10.2)
Neuralgia	1 (0.9)	5 (4.3)	3 (2.5)
Pain syndrome	2 (1.7)	4 (3.4)	2 (1.7)
Other	24 (20.9)	23 (19.7)	23 (19.5)
Lifetime opioid use (months),median	96.0	72.0	60.0
Duration of current opioid use (months), median	26.0	24.0	24.0
KODIAC 5	**Naloxegol 12.5 mg (n=125)**	**Naloxegol 25 mg (n=124)**	**Placebo (n=121)**
Characteristic			
Age, mean (SD)	53.2 (11.02)	53.5 (11.36)	53.0 (11.99)
Female, n (%)	85 (68.0)	82 (66.1)	74 (61.2)

Race, n (%)			
White	102 (81.6)	107 (86.3)	98 (81.0)
Black or African American	22 (17.6)	16 (12.9)	21 (17.4)
Asian	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska native	0	0	0
Other	1 (0.8)	1 (0.8)	2 (1.7)
BMI (kg/m^2)			
<18.5	0	1 (0.8)	3 (2.5)
18.5 – <30	68 (54.4)	65 (52.4)	62 (51.2)
≥30	57 (45.6)	57 (46.0)	56 (46.3)
Primary reason for pain, n (%)			
Back pain	71 (56.8)	74 (59.7)	62 (51.2)
Joint pain	6 (4.8)	7 (5.6)	4 (3.3)
Fibromyalgia	10 (8.0)	3 (2.4)	9 (7.4)
Headache/migraine	0	2 (1.6)	1 (0.8)
Arthritis	8 (6.4)	14 (11.3)	9 (7.4)
Neuralgia	5 (4.0)	4 (3.2)	5 (4.1)
Pain syndrome	0	2 (1.6)	0
Other	25 (20.0)	18 (14.5)	31 (25.6)
Lifetime opioid use (months), median	78.0	84.0	84.0
Duration of current opioid use (months), median	36.0	24.0	24.0

ITT analysis set (mixed population including unlicensed non-LIR patients)

Patient characteristics at baseline in KODIAC 4 and KODIAC 5 are summarised in Table 10. Baseline demographic data across treatment groups in both studies were similar. The mean age of patients across treatment groups in KODIAC 4 was 52.3 years, while in KODIAC 5, the mean patient age was 52.1 years. The majority of patients in all treatment groups in KODIAC 4 and KODIAC 5 were white (77.5% and 80.3%, respectively). In both studies, a higher proportion of patients in all treatment groups were female (61.3% and 63.4% of patients in KODIAC 4 and KODIAC 5, respectively). The most common primary reasons for pain in both studies were back pain, “other” and arthritis which were reported by 56%, 19.7% and 10% of KODIAC 4 patients, respectively, and 56.8%, 17.1% and 9.8% of KODIAC 5 patients, respectively. In both studies, localised musculoskeletal pain was reported as the primary type of pain in the “other” category. In KODIAC 4, the median lifetime opioid use ranged from 60–84 months while the median time spent on current opioid treatment was 2 years for all treatment groups. In KODIAC 5, patient median opioid lifetime use ranged from 72–81.5 months and the median time spent on current opioid treatment ranged from 2–3 years across treatment groups.

Table 10: Characteristics of the ITT analysis set in the pivotal RCTs (KODIAC 4 and KODIAC 5) across randomised groups

KODIAC 4	Naloxegol 12.5 mg (n=213)	Naloxegol 25 mg (n=214)	Placebo (n=214)
Characteristic			
Age, mean (SD)	51.9 (10.43)	52.2 (10.29)	52.9 (9.99)
Female, n (%)	135 (63.4)	118 (55.1)	140 (65.4)
Race, n (%)			
White	164 (77.0)	173 (80.8)	160 (74.8)
Black or African American	42 (19.7)	38 (17.8)	44 (20.6)
Asian	5 (2.3)	1 (0.5)	4 (1.9)
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska native	1 (0.5)	0	2 (0.9)
Other	1 (0.5)	2 (0.9)	4 (1.9)
BMI (kg/m^2)			
<18.5	1 (0.5)	1 (0.5)	0
18.5 – <30	98 (46.0)	102 (47.7)	108 (50.5)
≥30	114 (53.5)	111 (51.9)	106 (49.5)
Primary reason for pain, n (%)			
Back pain	131 (65.1)	110 (51.4)	118 (55.1)
Joint pain	8 (3.8)	7 (3.3)	7 (3.3)
Fibromyalgia	6 (2.8)	9 (4.2)	15 (7.0)
Headache/migraine	1 (0.5)	4 (1.9)	3 (1.4)
Arthritis	20 (9.4)	22 (10.3)	22 (10.3)
Neuralgia	1 (0.5)	8 (3.7)	4 (1.9)
Pain syndrome	5 (2.3)	7 (3.3)	5 (2.3)
Other	41 (19.2)	46 (21.5)	39 (18.2)
Lifetime opioid use (months),median	84.0	72.0	60.0
Duration of current opioid use (months), median	24.0	24.0	24.0
KODIAC 5	**Naloxegol 12.5 mg (n=232)**	**Naloxegol 25 mg (n=232)**	**Placebo (n=232)**
Characteristic			
Age, mean (SD)	52.0 (11.02)	51.9 (12.11)	52.3 (11.62)
Female, n (%)	149 (64.2)	147 (63.4)	145 (62.5)
Race, n (%)			
White	187 (80.6)	189 (81.5)	183 (78.9)
Black or African American	41 (17.7)	40 (17.2)	44 (19.0)
Asian	1 (0.4)	0	0

Native Hawaiian or other Pacific Islander	0	1 (0.4)	0
American Indian or Alaska native	1 (0.4)	1 (0.4)	2 (0.9)
Other	2 (0.9)	1 (0.4)	3 (1.3)
BMI (kg/m^2)			
<18.5	3 (1.3)	2 (0.9)	3 (1.3)
18.5 – <30	123 (53.0)	112 (48.3)	118 (50.9)
≥30	106 (45.7)	115 (49.6)	111 (47.8)
Primary reason for pain, n (%)			
Back pain	136 (58.6)	130 (56.0)	129 (55.6)
Joint pain	11 (4.7)	16 (6.9)	10 (4.3)
Fibromyalgia	16 (6.9)	11 (4.7)	18 (7.8)
Headache/migraine	1 (0.4)	5 (2.2)	2 (0.9)
Arthritis	20 (8.6)	27 (11.6)	21 (9.1)
Neuralgia	6 (2.6)	7 (3.0)	5 (2.2)
Pain syndrome	0	3 (1.3)	2 (0.9)
Other	42 (18.1)	33 (14.2)	44 (19.0)
Lifetime opioid use (months), median	81.5	78.0	72.0
Duration of current opioid use (months), median	36	24	24

Abbreviations: BMI, body mass index; SD, standard deviation.

Outcomes

6.3.5 ***Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.***

The outcomes investigated in KODIAC 4 and 5 and their relevance to the decision problem are presented in Table 11. In particular, a defining and important feature of both studies was the analysis of the primary outcome of response to treatment in the anticipated licensed population which was assessed as a key secondary endpoint.

Pivotal studies: KODIAC 4 and KODIAC 5

Table 11: Primary and secondary outcomes of the pivotal RCTs (KODIAC 4 and KODIAC 5)

Study	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice
KODIAC 4 **KODIAC 5**	• Proportion of patients with ≥3 SBMs per week with improvement from baseline of ≥1 SBM per week (defined as a BM without the use of laxatives administered in the previous 24 hours) for ≥9 out of 12 study weeks and 3 out of the last 4 study weeks	• The assessment of constipation in the pivotal RCTs is based on the Rome III diagnostic criteria for functional constipation (41) and reflects standard practice. SBM frequency is a clinically meaningful measure commonly employed in clinical research to assess the efficacy of a treatment for chronic constipation. A multinational, survey study to assess the impact of opioid-induced bowel dysfunction in patients receiving opioids for chronic pain reported that the most bothersome symptoms for patients were constipation (81% of patients) and straining (58% of patients). A third of patients (33%) reported that they had reduced or stopped using opioids in order to have a bowel movement (7). In addition a recent cross-sectional online survey of patients with OIC found that having at least one more SBM/week was extremely important to 41% of patients (17)These findings suggest that the improvement in the frequency of BMs is very important to patients with OIC.
	Secondary outcome(s) and measures	**Reliability/validity/ current use in clinical practice**
	Key secondary outcomes • Responder rates for the anticipated licensed population defined as: ○ Taking ≥1 laxative class for ≥4 days prior to screening and reporting moderate, severe or very severe symptoms in ≥1 of the four stool symptom domains[†] • Time to first post-dose SBM without the use of rescue medication in the last 24 hours • Mean number of days per week with ≥1 SBM **Other secondary outcomes** • Supporting assessment of response incorporating symptom data • Change from baseline in the number of SBMs/week for Weeks 1–4 and Weeks 1–12 • Change from baseline in the mean degree of straining • Change from baseline in the mean stool consistency (BSS) • % of days with a complete SBM • Mean bisacodyl dose/week for Weeks 1–12 • Change from baseline in PAC-SYM total score and each domain score for Weeks 2, 4, 8 and 12 • Change from baseline in PAC-QoL total score and each domain score for Weeks 4 and 12	**Key secondary outcomes** • There is currently no accepted method in clinical practice for defining the subgroup of patients who have an inadequate response to laxative(s). In KODIAC 4 and 5, the anticipated licensed population represents conventional laxative users who continue to have moderate to very severe OIC symptoms at study entry. **Other secondary outcomes** • Improvement in the degree of straining is important to patients with OIC: a recent global burden of illness study found that 82% of patients reported straining or squeezing to pass a BM as their most bothersome symptom (11) • The PAC-SYM[‡] is constipation-specific, self-reported, 12-item questionnaire comprising three domains: abdominal symptoms (items 1–4); rectal symptoms (items 5–7) and stool symptoms (items 8–12). Patients score their symptoms on a 5-point Likert scale that ranges from: 0, absence of symptoms; 1, mild; 2, moderate; 3, severe; 4, very severe (62). • The PAC-QoL[‡] is a self-reported questionnaire which is designed to assess the burden of constipation on patients' QoL. The PAC-QoL comprises 28 items encompassing four domains: worries and concerns; physical discomfort; psychosocial discomfort; satisfaction. Patients' responses are recorded on a 5-point Likert scale: 1, not at all; 2, a little bit; 3, moderately; 4, quite a bit; 5, extremely (4). • The BSS is a self-reported instrument which classifies human faeces into seven categories as a measure of stool consistency: Type 1 & 2 indicate constipation; Type 3 & 4 indicate "ideal stools"; Type 5–7 represent diarrhoea or urgency (63)

Abbreviations: BM, bowel movement; BSS., Bristol Stool Scale; PAC-QoL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms questionnaire; QoL, quality of life; SBM, spontaneous bowel movement.

†Four stool symptom domains: incomplete BM, hard stools, straining and false alarms.
‡The PAC-SYM and the PAC-QoL are validated for use in chronic constipation but have not been validated for use in OIC.

Statistical analysis and definition of study groups

6.3.6 ***State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.***

Pivotal studies: KODIAC 4 and KODIAC 5

Population datasets analysed

anticipated ***licensed population (LIR patients)*****:** patients who were taking ≥1 laxative class for ≥4 days prior to screening, and reported moderate, severe, or very severe symptoms in at least one of the four stool symptom domains (i.e. incomplete BM, hard stools, straining, or false alarms).

Intent-to-treat (ITT) analysis set (mixed population including unlicensed non-LIR population): considered as the primary analysis set and used for all efficacy endpoints that were summarised by the response to laxatives at baseline. The ITT analysis set included all randomised patients with the exception of patients who had been randomised multiple times within the naloxegol program at different centres.

Modified intent-to-treat (mITT) analysis set: a subset of the ITT analysis set consisting of all randomised patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment. The primary analysis was repeated in the mITT analysis set as a sensitivity analysis.

Per-protocol (PP) analysis set: included only ITT patients with no important protocol deviations. Analysis of the primary efficacy endpoint was repeated on the PP analysis set.

Safety analysis set: all randomised patients who received at least one dose of study drug and excluded patients who were randomised multiple times within the naloxegol program. Selected summaries of adverse events (AEs) were presented by the response to laxatives at baseline.

The primary hypothesis in KODIAC 4 and KODIAC 5 is presented in Table 12 with a summary of the statistical analysis conducted.

Table 12: Summary of statistical analyses in the pivotal RCTs (KODIAC 4 and KODIAC 5)

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
KODIAC 4 **KODIAC 5**	To assess the proportion of responders to treatment over the 12 week study period defined as: % of patients with ≥3 SBMs per week with improvement from baseline of ≥1 SBM per week for ≥9 out of 12 study weeks and 3 out of the last 4 study weeks	Categorical data was summarised using frequency and percentages and descriptive statistics were used for continuous data. Longitudinal analyses of continuous endpoints were conducted using the mixed model repeated measures approach (MMRM). All MMRM models included the treatment group, the baseline value of the response variable, time (as a class variable for Weeks 1 to 12 as applicable), treatment-time interactions and baseline laxative response as fixed effects, and pooled centre as a random effect. Statistical significance of primary and key secondary outcomes is based on the Multiple testing procedure. All other statements of statistical significance are based on unadjusted/nominal p-values compared against alpha = 0.05 and should be interpreted with caution. **Primary efficacy outcome** For the primary analysis, differences in response rates between treatment groups were analysed using Cochran-Mantel-Haenszel tests stratified by the response to laxatives at baseline and further characterised by the relative risk (RR) with associated 95% CIs. The primary efficacy analysis was repeated on the mITT and PP analysis sets as sensitivity analyses. **Key Secondary outcomes** • Differences between the anticipated licensed population vs placebo were analysed using Chi-square tests. • Log-rank tests stratified by the response to laxatives at baseline were used to analyse treatment group differences for the time to first SBM. Kaplan Meier statistics were also presented. • Differences between treatment groups in the number of days with ≥1 SBM were analysed using MMRM **Other secondary outcomes** • MMRM was used to analyse differences between treatment groups in change from baseline in SBM/week, mean degree of straining, mean stool consistency and	To detect a difference of 25% in the response rate (60% on naloxegol and 35% on placebo), with 90% power and an alpha significance level of 0.025, a sample size of 105 patients per treatment group were required. Assuming the anticipated licensed population is 50% of the total study population, 210 patients per treatment group were required to provide adequate power to detect a treatment difference in the anticipated licensed population. Assumptions on the expected response rates were based on the naloxegol Phase II study and from other similar drugs based on response over 4 weeks.	To confirm that the patient was completing the eDiary, compliance with the eDiary was assessed remotely by the study centre at least every 48 hours. Patients were phoned if data was found to be missing. For patients with fewer than 4 days of diary data entered for a given week, the weekly SBM frequency was treated as missing for that week. For by-visit assessments, baseline was defined as the latest non-missing value collected prior to the first dose of study drug (screening, Visit 1 or Week 0, Visit 3). In general, baseline was based on data obtained during the OIC confirmation period. When calculating responder status, any weeks where the SBM frequency was missing were automatically classified as weeks where no improvement had been observed. Any patient with incomplete efficacy follow-up was automatically considered a non-responder, regardless of their SBM

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		number of days/week with a complete SBM. • PAC-SYM and PAC-QoL were assessed using descriptive statistics and MMRM. **Multiplicity adjustments for the primary and 3 key secondary outcomes** To control the overall type I error rate to be <0.05 for the multiple comparisons in the primary and the key secondary outcomes, a multiple testing procedure with Bonferroni-Holm over groups, and fixed-sequence within groups was applied. This resulted in an alpha significance level of 2.5% being applied for comparisons of the naloxegol 25 mg group vs placebo and 5% being applied for comparisons of the 12.5 mg group vs placebo.		data up to that point.

Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; MMRM, mixed model repeated measures; PAC-QoL, Patient Assessment of Constipation Quality of Life; PAQ-SYM, Patient Assessment of Constipation Symptoms questionnaire; PP, per-protocol; RR, relative risk; SBM, spontaneous bowel movement

6.3.7 *Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.*

KODIAC 4 and KODIAC 5: Pre-planned subgroup analyses

The primary efficacy outcome in the ITT population was analysed for the following subgroups:

- Demographic characteristics: age group, sex, race
- Location: region, country, centre
- Response to laxative(s) at baseline

Response to laxative(s) at baseline

Although there is scientific evidence that there are patients who have an inadequate response to laxative(s), there is no accepted method for defining this subpopulation. Therefore, following consultation with an advisory board of external experts, a method was devised to effectively classify OIC patients according to the adequacy of their response to the use of laxative(s). The Baseline Laxative Response Status Questionnaire (BLRSQ) was subsequently developed. This was an investigator-administered questionnaire to assess the type of laxative used by the patient within two weeks prior to enrolment in the study, the frequency of the laxative use, and any symptoms experienced while using the laxative. The analysis was pre-planned to assess the response to naloxegol in this specific subgroup of patients.

In KODIAC 4 and 5, for the analysis of response to laxatives at baseline, all patients were stratified by laxative responder status using the BLRSQ. Each patient's laxative response status was determined based on 4 questions. Patients were then classified based on their responses to the questions as follows:

- Anticipated licensed population (LIR): patients who were taking ≥1 laxative class for ≥4 days prior to screening and reported moderate, severe, or very severe symptoms in at least one of the four stool symptom domains (i.e. incomplete BM, hard stools, straining, or false alarms). Note that LIR patients represent an important subpopulation with a high unmet medical need for a chronic oral treatment option for OIC. Studies show that ≥ 45% of patients will have a laxative inadequate response to treatment (11, 16).
- Laxative adequate responder (LAR): patients who were taking ≥1 laxative class for ≥4 days prior to screening and had no symptoms or only mild symptoms
- Laxative unknown responder (LUR): patients who had not used laxative(s) over the previous two weeks or had taken ≥1 laxative classes on <4 days over the previous 2 weeks. These patients were not categorised as the anticipated licensed population because their laxative responder status could not be confirmed due to lack or infrequent use of laxatives in the 2 weeks before screening.

A schematic of the BLRSQ algorithm is presented in section 10.18 (Appendix 15)

Note that due to the small number of LAR patients enrolled in both KODIAC 4 and 5, the LAR and LUR groups were subsequently considered together as the non-LIR subgroup.

Thus all secondary efficacy outcomes were analysed for the anticipated licensed population and non-LIR subgroups.

An additional subgroup of patients was defined for analysis:

- 2xLIR: a subgroup of the anticipated licensed population 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 6 month OIC history prior to screening

Note that with the exception of the anticipated licensed population, KODIAC 4 and 5 were not designed or powered to assess the treatment effect of naloxegol versus placebo in any other subgroup of interest.

Post-hoc analysis: anticipated licensed population + Step 3 (strong) opioids (according to WHO analgesic ladder)

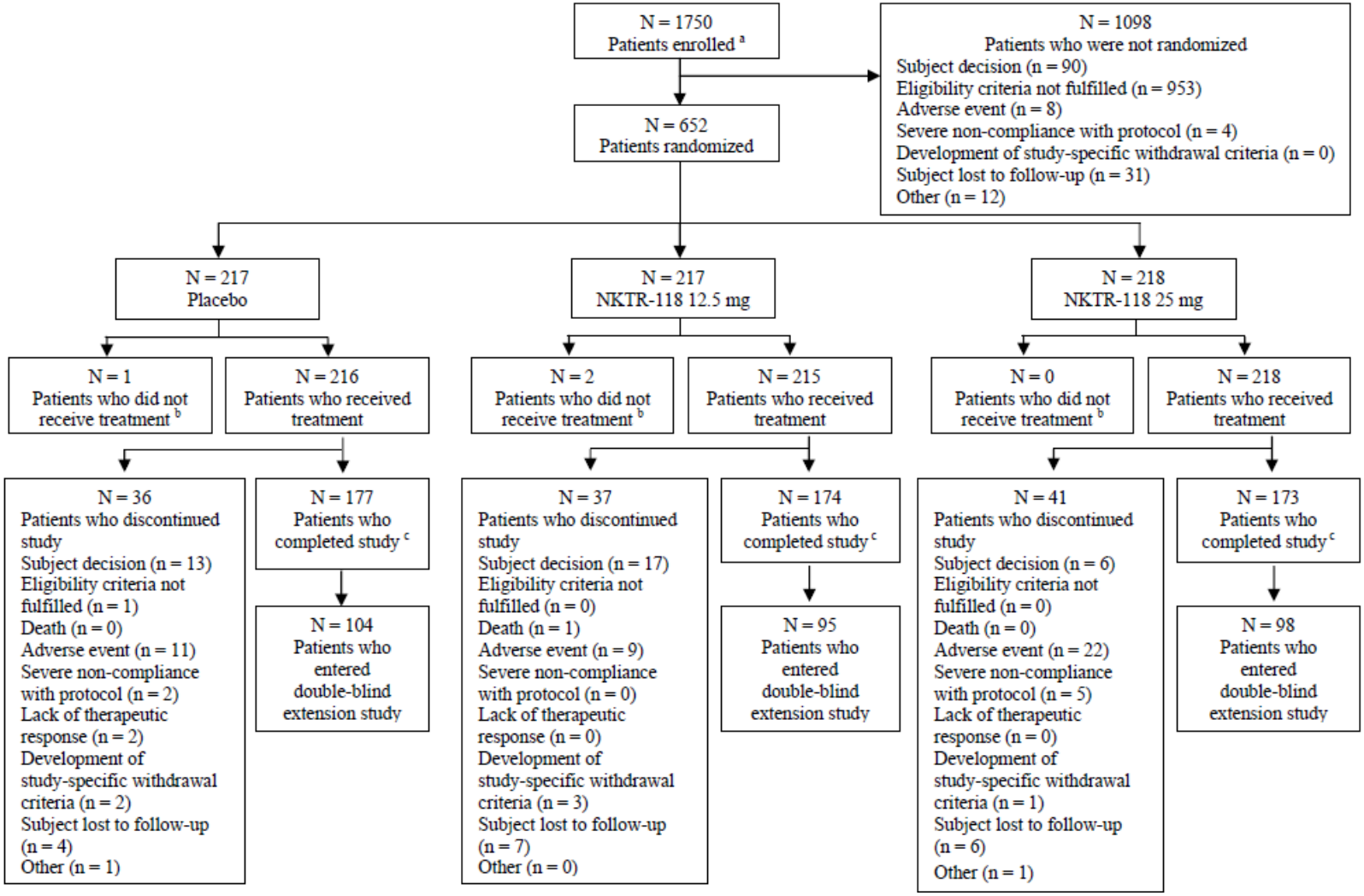
KODIAC 4 and 5 also included a post-hoc analysis of a subgroup of patients comprising the anticipated licensed population taking Step 3 opioids (classified according to World Health Organisation [WHO] analgesic ladder). This is a clinically valid subgroup of patients with OIC as the more severe forms of OIC are more likely to be related to the use of Step 3 opioids. A recent survey of 120 healthcare professionals found that >80% of cancer pain patients treated by palliative care specialists were likely to be receiving Step 3 opioids (64). Also, in palliative care patients with advanced disease, the higher doses of opioids that are typically prescribed to reduce severe pain subsequently result in more severe adverse effects (49). Although there are no specific guidelines in the UK for the treatment of OIC, NICE clinical guideline No. 140 provides recommendations for the management of constipation in patients in palliative care receiving strong opioids for pain (40). Current strategies for pain management are largely based on the World Health Organisation's (WHO) three-step "ladder" for the relief of cancer pain (65). This pain ladder was originally developed for the management of cancer pain in 1986, but the advice is now widely used for the management of patients with acute or chronic pain who require analgesics (66). The WHO three-step ladder is based on a stepwise approach to pain management; patients start on the lowest analgesic and "step up the ladder" if their pain persists or increases (65). The WHO pain ladder proposes that treatment should be initiated with a non-opioid (step 1: e.g. aspirin, paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs]). A weak opioid is introduced if pain relief is insufficient (step 2: e.g. codeine, dihydrocodeine, tramadol). Step 3 is for the management of moderate to severe pain and patients receive strong opioids (e.g. morphine, methadone, oxycodone, buprenorphine, hydromorphone, fentanyl) (65).

Participant flow

6.3.8 ***Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.***

CONSORT flow charts showing the numbers of patients who were eligible to enter KODIAC 4 and 5, and who were randomised and allocated to each treatment are presented in Figure 4 and Figure 5, respectively.

Figure 4: KODIAC 4 study flow chart



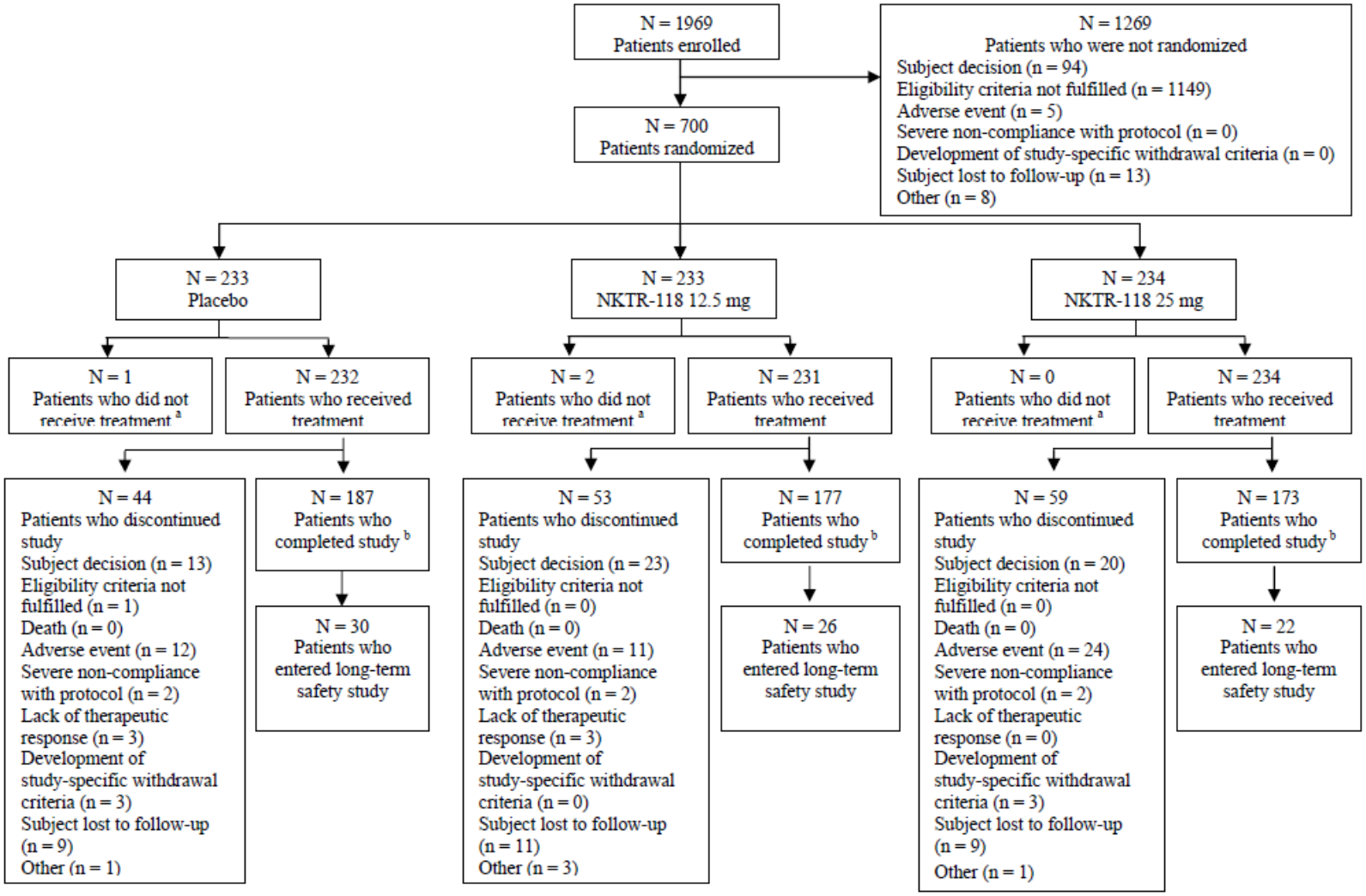
NKTR-118 = naloxegol

[a] After 22 March 2012, screening of non-LIR patients was stopped to ensure that a minimum of 50% of patients randomised would be LIR. Of the 652 patients randomised into the study, 553 patients were screened on or before 22 March 2012.

[b] Three patients did not receive treatment due to not fulfilling eligibility criteria (1 patient in the placebo group and 2 patients in the naloxegol 12.5 mg group)

[c] Eleven patients who completed the study (4 patients each in the naloxegol 12.5 mg and 25 mg groups and 1 patient in the placebo group) had been previously randomised at a different study centre and were therefore excluded from the ITT and Safety analysis sets.

Figure 5*: KODIAC 5 study flow chart*



NKTR-118 = naloxegol

[a] Patients did not receive treatment due to not fulfilling the eligibility criteria (1 patient each in the placebo and naloxegol 12.5 mg groups) and patient decision (1 patient in the naloxegol 12.5 mg group)

[b] Four patients had previously been randomised at a different study centre and were therefore excluded from the ITT and Safety analysis sets.

Patient disposition by baseline laxative status: KODIAC 4

Anticipated licensed population

In KODIAC 4, 350 patients (54.6%) were classified as the anticipated licensed population and 291 patients (45.4%) of patients were classified as non-LIR for the ITT analysis set.

In the anticipated licensed population, 18.6% of patients had taken more than one laxative class in the two weeks prior to baseline while 45.7% of patients reported severe straining.

Of the 355 randomised anticipated licensed population patients, 354 (99.7%) received treatment, and 294 (82.8%) completed the study in the ITT analysis set. In the anticipated licensed population, 55 patients (15.5%) who received treatment discontinued the study: 17 (14.7%), 19 (16.0%), and 19 (15.8%) patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. The most common reasons for discontinuation were as follows:

- Patient decision (7.8%, 2.5%, and 8.3% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 22 patients, 6.2%)
- Adverse events (5.3%, 9.2%, and 2.5% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 19 patients, 5.4%)
- Lost to follow-up (1.7%, 2.5% and 1.7% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 7 patients, 2.0%)

Discontinuations as a result of adverse events occurred in 5 (4.3%), 11 (9.2%), and 3 (2.5%) patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively.

Non-LIR population

Of the 297 randomised non-LIR patients, 295 (99.3%) received treatment, and 230 (77.4%) completed the study in the ITT analysis set. In the non-LIR group, 59 patients (19.9%) who received treatment discontinued the study: 20 (19.8%), 22 (22.2%), and 17 (17.5%) patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. The most common reasons for discontinuation were as follows:

- Adverse events (4.0%, 11.1%, and 8.2% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 23 patients, 7.7%)
- Patient decision (7.9%, 3.0%, and 3.1% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 14 patients, 4.7%)
- Lost to follow-up (5.0%, 3.0%, and 2.1% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 10 patients, 3.4%)

Discontinuations as a result of adverse events occurred in 4 (4.0%), 11 (11.1%), and 8 (8.2%) patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively.

Patient disposition by baseline laxative status: KODIAC 5

Anticipated licensed population

In KODIAC 5, 370 (53.2%) patients were classified as anticipated licensed population, and 326 (46.8%) patients were classified as non-LIR for the ITT analysis set.

In the anticipated licensed population, 22.7% of patients had taken more than one laxative class for at least 4 days in the two weeks prior to baseline, while 44.9% of patients reported severe straining.

Of the 371 randomised anticipated licensed population patients, 368 (99.2%) received treatment and 290 (78.2%) completed the study in the ITT analysis set. In the anticipated licensed population group, 77 patients (20.8%) who received treatment discontinued the study: 19 (15.2%), 34 (27.2%), and 24 (19.8%) patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. The most common reasons for discontinuation were as follows:

- Patient decision (8.0%, 8.0%, and 6.6% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 28 patients, 7.5%)
- Adverse events (2.4%, 10.4%, and 5.8% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 23 patients, 6.2%)
- Lost to follow-up (3.2%, 5.6%, and 2.5% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 14 patients, 3.8%)

Discontinuations as a result of adverse events occurred in 3 (2.4%), 13 (10.4%), and 7 (5.8%) patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively.

Non-LIR population

Of the 329 randomised non-LIR patients, 329 (100%) received treatment, and 247 (75.1%) completed the study in the ITT analysis set. In the non-LIR group, 79 patients (24.0%) who received treatment discontinued the study: 34 (31.5%), 25 (22.9%), and 20 (17.9%) patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. The most common reasons for discontinuation were as follows:

- Patient decision (12.0%, 9.2%, and 4.5% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 28 patients, 8.5%)
- Adverse events (7.4%, 10.1%, and 4.5% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 24 patients, 7.3%)
- Lost to follow-up (6.5%, 1.8%, and 5.4% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: Total 15 patients, 4.6%)

Discontinuations as a result of adverse events occurred in 8 (7.4%), 11 (10.1%), and 5 (4.5%) patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively.

6.4 *Critical appraisal of relevant RCTs*

6.4.1 ***The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.***

- ***Was the method used to generate random allocations adequate?***
- ***Was the allocation adequately concealed?***
- ***Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?***
- ***Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?***
- ***Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?***
- ***Is there any evidence to suggest that the authors measured more outcomes than they reported?***
- ***Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?***

6.4.2 ***Please provide as an appendix a complete quality assessment for each RCT. See Section 10.3, appendix 3 for a suggested format.***

A complete quality assessment for each RCT is provided in Section 10.3.

6.4.3 ***If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.***

A summary of the quality assessment results is presented in Table 13.

Table 13: Summary of the quality assessment results for the pivotal RCTs (KODIAC 4 and KODIAC 5)

	KODIAC 4	KODIAC 5
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
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	Yes

6.5 *Results of the relevant RCTs*

6.5.1 ***Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.***

6.5.2 ***The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.***

6.5.3 ***For each outcome for each included RCT, the following information should be provided.***

- ***The unit of measurement.***
- ***The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio in an equivalent statistic. Both absolute and relative data should be presented.***
- ***A 95% confidence interval.***
- ***Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.***
- ***When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.***
- ***Other relevant data that may assist in the interpretation of the results may be included, such as adherence to medication and/or study protocol.***
- ***Discuss and justify definitions of any clinically important differences.***
- ***Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.***

6.5.4 *Pivotal studies: KODIAC 4 and KODIAC 5*

KODIAC 4 and KODIAC 5: efficacy results

Naloxegol demonstrated significant improvements in the primary outcome of response to treatment defined as ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 study weeks. Similar response rates were observed in the ITT analysis set, the anticipated licensed population and the anticipated licensed population + Step 3 opioids group.

ITT population

Primary outcome

- In KODIAC 4 and 5, naloxegol 25 mg treatment was associated with significantly higher response rates compared with placebo over 12 weeks (KODIAC 4, 44.4% vs 29.4% patients; p=0.001: KODIAC 5, 39.7% and 29.3% patients, p=0.021, respectively)
    - In KODIAC 4, patients receiving 12.5 mg naloxegol demonstrated statistically significantly higher response rates compared with placebo patients (40.8% vs 29.4% patients, respectively; p=0.015)
    - In KODIAC 5, statistical significance was not demonstrated in the naloxegol 12.5 mg group vs placebo for the primary outcome (34.9% vs 29.3% patients, respectively; p=0.202)

Anticipated licensed population analysis

Response to treatment (defined as for the primary outcome)

- In KODIAC 4 and 5, statistically significantly higher response rates were achieved in the naloxegol 25 mg groups compared with placebo in the anticipated licensed population (KODIAC 4, 48.7% vs 28.8% patients, respectively; p=0.002: KODIAC 5, 46.8% vs 31.4% patients, respectively; p=0.014)
    - Response rates in the naloxegol 12.5 mg anticipated licensed population were statistically significantly higher vs placebo in KODIAC 4 (42.6% vs 28.8% patients, respectively; p=0.028) but not significant for the naloxegol 12.5 mg anticipated licensed population vs placebo in KODIAC 5 (42.4% vs 31.4% patients, respectively; p=0.074)

Secondary outcomes

- Patients in the naloxegol 12.5 mg and 25 mg groups had a shorter median time to first post-dose SBM compared with placebo:
    - KODIAC 4: 20.6 and 5.4 vs 43.4 hours in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively
    - KODIAC 5: 12.8 and 18.1 vs 38.2 hours in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively

- Naloxegol patients had an increase in the mean SBMs per week compared with placebo in both studies (Mean SBMs per week in KODIAC 4 were 3.9, 4.7, and 3.4 in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: and in KODIAC 5 were 4.3, 4.8, and 3.5 in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively)
- Naloxegol was associated with a greater increase in the mean number of days with ≥1SBM compared with placebo in both studies (mean number of days with ≥1SBM in KODIAC 4 were 3.5, 3.9, and 2.9 days in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively; and in KODIAC 5 were 3.7, 3.9, and 3.0 days naloxegol 12.5 mg, 25 mg and placebo groups, respectively)
- Use of rescue medication at least once over the treatment period was lower in the naloxegol groups compared with the placebo groups in both studies (KODIAC 4; 65.2%, 56.4%, and 76.3% of naloxegol 12.5 mg, 25 mg and placebo patients, respectively: KODIAC 5; 60.8%, 62.9% and 76.9% of naloxegol 12.5 mg, 25 mg and placebo patients, respectively)

Quality of life assessments

- Naloxegol treatment was associated with greater reductions across all domains in Patient Assessment of Constipation symptoms (PAC-SYM) compared with placebo, indicating improvement in symptoms
- Naloxegol demonstrated greater reductions across all domains in the Patient Assessment of Quality of Life (PAC-QoL) questionnaire compared with placebo, indicating improved quality of life
- The results for each domain of the EQ-5D in both KODIAC 4 and 5 demonstrated that a greater proportion of patients receiving naloxegol reported no problems from baseline to Week 12 compared with the placebo group

Anticipated licensed population + Step 3 opioids

Response to treatment

- In both KODIAC 4 and 5, patients in the naloxegol 25 mg group showed a greater response to treatment compared with the placebo group over Weeks 1–12 (49.4% vs 29.9% of patients, respectively; p=0.011 in KODIAC 4; 47.2% vs 28.9% of patients, respectively; p=0.014 in KODIAC 5)

Secondary outcomes

- Naloxegol resulted in shorter time to first post-dose SBM compared with placebo in both trials (KODIAC 4: 20.9, 4.4 and 32.7 hours in the naloxegol 12.5mg, 25 mg and placebo groups, respectively: KODIAC 5, 10.6, 7.4, and 47.9 hours in the naloxegol 12.5mg, 25 mg and placebo groups, respectively)
- Naloxegol patients had an increase in the mean SBMs per week compared with placebo in both studies (mean SBMs per week in KODIAC 4 were 4.1, 4.9, and 3.3 in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively: and in KODIAC 5

were 4.2, 5.3, and 3.5 in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively)

- Naloxegol was associated with a greater increase in the mean number of days with ≥1SBM compared with placebo in both studies (mean number of days with ≥1SBM in KODIAC 4 were 3.6, 3.9, and 2.8 days in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively; and in KODIAC 5 were 3.6, 4.0, and 3.0 days naloxegol 12.5 mg, 25 mg and placebo groups, respectively)
- Use of rescue medication at least once was lower in the naloxegol group compared with the placebo group in both studies (KODIAC 4; 51.7% and 77.9% of patients in the naloxegol 25 mg and placebo groups, respectively: KODIAC 5; 60.7% and 78.3% of patients in the naloxegol 25 mg and placebo groups, respectively)

Quality of life assessments

- Naloxegol was associated with an improvement in symptoms of constipation as observed across all domains of the PAC-SYM in both studies
- Naloxegol was associated with improvements in quality of life as indicated by greater reductions across all domains in the PAC-QoL in both studies
- Results from the EQ-5D demonstrated that a higher proportion patients in the naloxegol group reported no problems over the treatment period compared with placebo
- There was a greater reduction in the number of patients with severe problems compared with placebo, as measured by the EQ-5D

Datasets analysed

In the pivotal RCTs, KODIAC 4 and KODIAC 5, the primary efficacy outcome of response to study drug was based on the ITT analysis set, defined as all randomised patients. As the key focus of this submission is the anticipated licensed population (i.e. LIR group), only the primary outcome for the ITT analysis set is presented. All key secondary outcomes and additional outcomes for the ITT analysis set are presented in Appendix 14.

Primary Efficacy Results

Following regulatory advice the primary efficacy outcome definition ensured that improvement in SBMs had to be durable over the 12 week treatment period in order for a patient to be considered a responder. Note that this definition of responder was regulator defined. In KODIAC 4 and KODIAC 5, significantly higher response rates were achieved in patients treated with naloxegol 25 mg compared with placebo over 12 weeks (p=0.001 and p=0.021, respectively). A statistically significant higher response rate was achieved in patients treated with naloxegol 12.5 mg vs placebo in KODIAC 4 (p=0.015) (Table 14). In KODIAC 5, there was no statistically significant difference between the 12.5 mg group and placebo group (p=0.202) and as a result, statistical significance could not be claimed for key secondary variables regardless of effect. The primary efficacy outcomes for both studies are presented in Table 14.

In KODIAC 4, relative risk (RR) estimates indicated that patients randomised to the naloxegol 12.5 mg and 25 mg groups were 38.0% and 50.9%, respectively, more likely to respond than those patients randomised to placebo (Figure 6). RR estimates in KODIAC 5 indicated that patients randomised to naloxegol 12.5 mg and 25 mg were 18.8% and 34.5%, respectively more likely to respond than the placebo group (Figure 7).

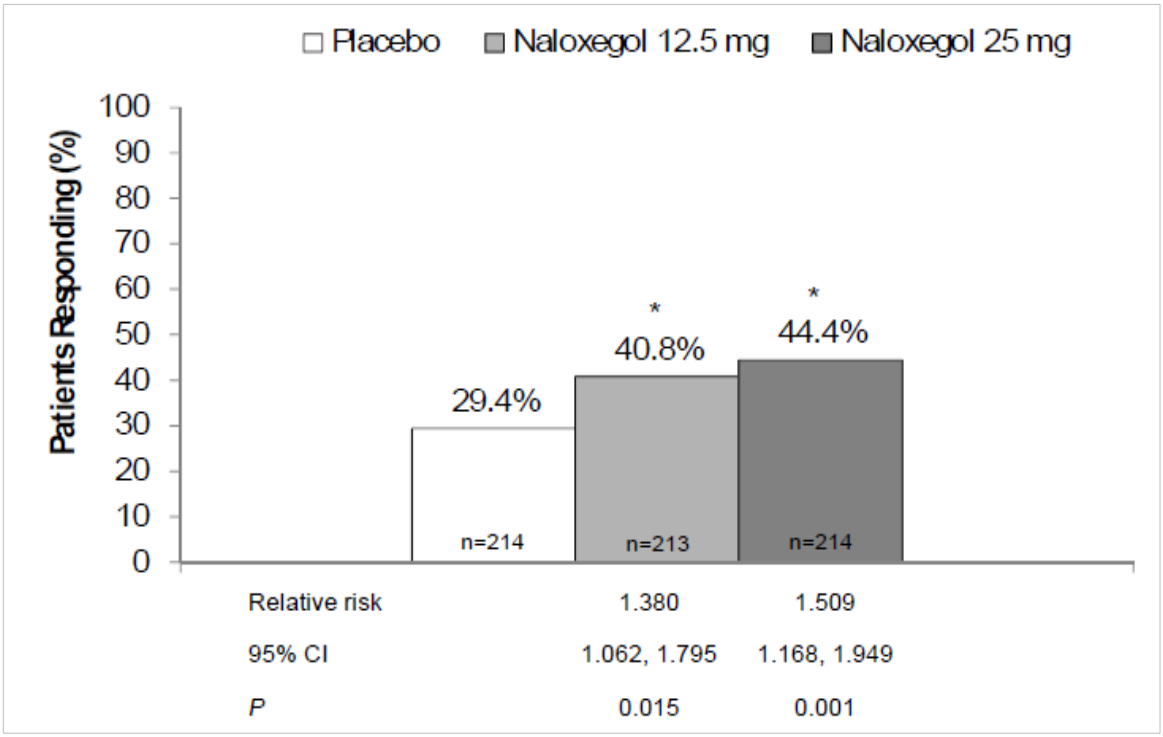
Sensitivity analyses of the primary efficacy outcomes were conducted in the mITT analysis set and the PP analysis set. Consistent with the results observed for the primary analysis in the ITT population, the results for each of the sensitivity analysis showed a statistically significant improvement for both the naloxegol 12.5 mg and 25 mg treatment groups compared with placebo.

Table 14: Summary of the primary efficacy outcome for Weeks 1–12 (ITT analysis set)

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

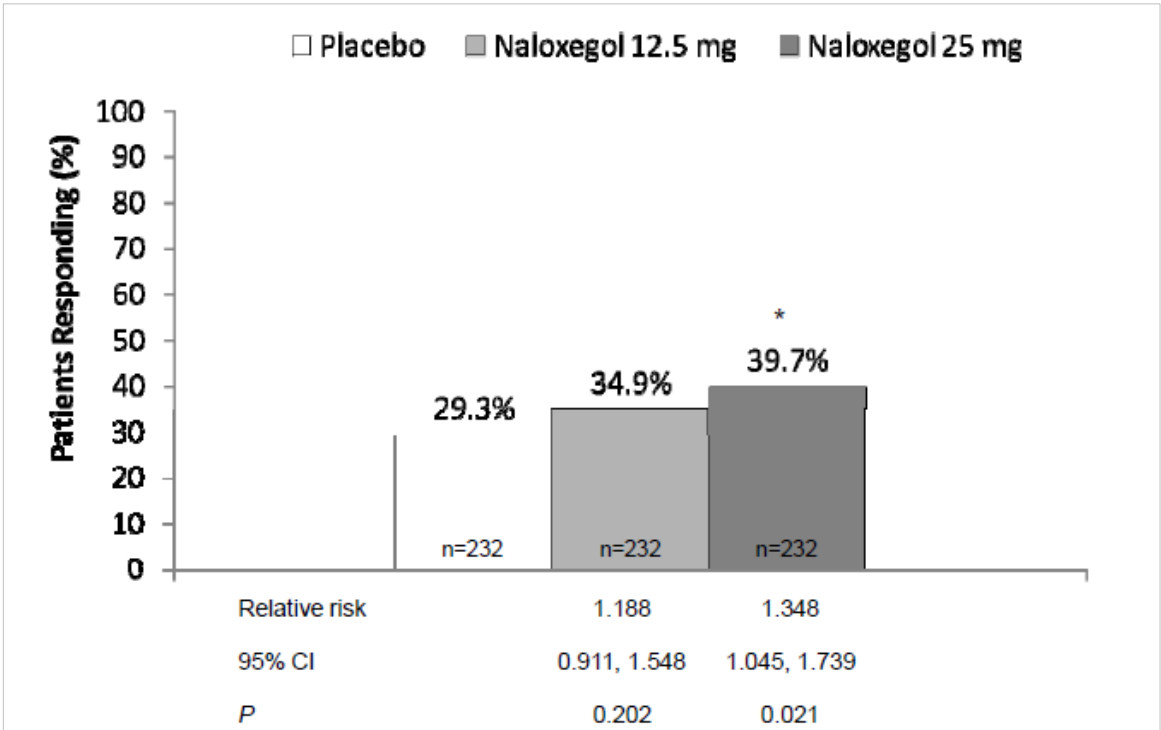
Abbreviations: CI, confidence interval; N/A, not applicable; RR, relative risk.
†Analysed using Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
Source: KODIAC 4 CSR (51) and KODIAC 5 CSR (52)

Figure 6: Analysis of response rate for Weeks 1–12 in KODIAC 4 (ITT analysis set)



Source: KODIAC 4 CSR (51)

Figure 7: Analysis of response rate for Weeks 1–12 in KODIAC 5 (ITT analysis set)



Source: KODIAC 5 CSR (52)

Anticipated licensed population results

Responder rates for the anticipated licensed population

In KODIAC 4 and KODIAC 5, in the anticipated licensed population, a statistically significantly higher response rate was achieved in the naloxegol 25 mg group vs placebo over the 12 week treatment period (p=0.002 and p=0.014, respectively). In the anticipated licensed population in KODIAC 4, a statistically significantly higher response rate was achieved in patients receiving naloxegol 12.5 mg vs placebo (p=0.028). However, the response rates for the naloxegol 12.5 mg anticipated licensed population in KODIAC 5 were not statistically significantly different (p=0.074) (Table 15 and Figure 8).

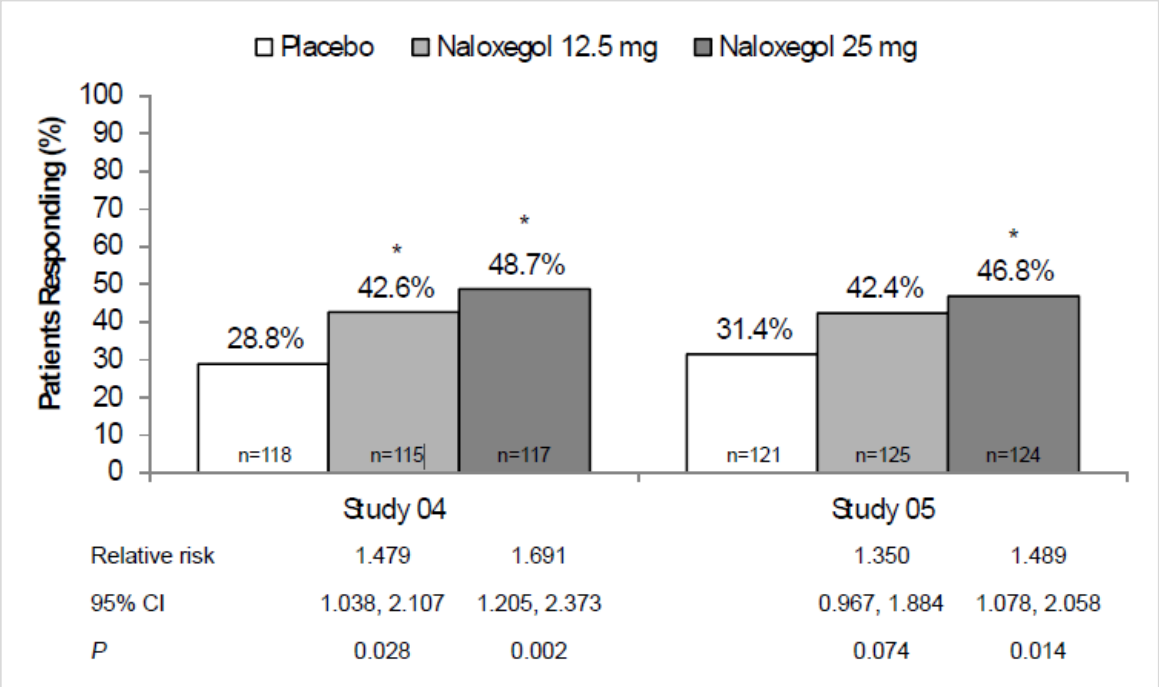
The results of this key secondary analysis provide evidence that naloxegol 25 mg is effective in the treatment of OIC in the anticipated licensed population; an absolute difference of more than 15% in response rate was observed over placebo in both studies.

Table 15: Response rates for Week 1–12 in the anticipated licensed population in KODIAC 4 and 5 (ITT analysis set)

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

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

Figure 8: Response rates for Weeks 1–12 in the anticipated licensed population in KODIAC 4 and 5 (ITT analysis set)



* Statistically significant under the multiple testing procedure.
Source: KODIAC 4 and 5 summary of clinical efficacy (67)

Time to first post-dose SBM without the use of rescue medication within the last 24 hours: anticipated licensed population

In KODIAC 4 and 5, in the anticipated licensed population, the naloxegol 12.5 mg and 25 mg groups had a shorter median time to first post-dose SBM compared with placebo which was reflected by the proportions of patients who had a SBM by 6 hours, 12 hours, or 24 hours in the three treatment groups (Table 16).

Table 16: Time to first post-dose SBM for the anticipated licensed population in KODIAC 4 and KODIAC 5 (ITT analysis set)

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

Abbreviations: SBM, spontaneous bowel movement.

Response to naloxegol during Weeks 1–12 by laxative response status: anticipated licensed population vs non-LIR subgroups

In KODIAC 4, greater 12 week response rates were observed for the naloxegol treatment groups compared with placebo for both the anticipated licensed population and non-LIR groups. A numerically larger treatment effect was observed in the anticipated licensed population (42.6%, 48.7%, and 28.8% in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively) compared with the non-LIR subgroup (38.8%, 39.2%, and 30.2% in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively) (Table 17). The improvement in SBM frequency observed in both treatment groups vs placebo was greater in the anticipated licensed population compared with the non-LIR subgroup. In the anticipated licensed population, the total SBMs/week were 3.9, 4.7, and 3.4 in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. In the non-LIR group, the total SBMs/week were 4.0, 4.3, and 3.4 in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. There were no differences in improvement in OIC symptoms compared with placebo, regardless of baseline laxative response group.

In KODIAC 5, although a formal analysis was not conducted for the non-LIR subgroup, patients in the anticipated licensed population had greater 12 week response rates in all treatment groups (42.4%, 46.8%, and 31.4% in the naloxegol 12.5 mg, 25 mg, and placebo groups, respectively) compared with non-LIR patients (26.2%, 31.5%, and 27.0% in the naloxegol 12.5 mg, 25 mg, and placebo groups, respectively) (Table 18). Similar results were also seen in comparisons of mean days per week with ≥1 SBM and mean SBMs per week between the anticipated licensed population and the non-LIR groups. In the anticipated licensed population, the total SBMs/week were 4.3, 4.8, and 3.5 in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. In the non-LIR group, the total SBMs/week were 3.9, 4.2, and 3.5 in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. Patients in the naloxegol 12.5 mg and 25 mg treatment groups had a shorter median time to first post dose SBM compared with placebo, regardless of baseline laxative response group. Similar differences were observed between naloxegol groups and placebo for change from baseline in the symptoms of OIC, regardless of baseline laxative response group (Table 18).

Table 17: Summary of efficacy endpoints by baseline laxative response in KODIAC 4 (anticipated licensed population and non-LIR group, ITT analysis set)

Outcome	Baseline laxative response	n	Naloxegol 12.5 mg (n=213)	n	Naloxegol 25 mg (n=214)	n	Placebo (n=214)
Response to treatment, n (%)	LP Non-LIR	115 98	49 (42.6) 38 (38.8)	117 97	57 (48.7) 38 (39.2)	118 96	34 (28.8) 29 (30.2)
Time (hours) to first SBM, median (95% CI)	LP Non-LIR	114 97	20.6 (8.1, 23.5) 20.3 (7.7, 24.2)	117 96	5.4 (3.9, 10.7) 6.9 (4.8, 21.3)	116 93	43.4 (25.2,48.2) 34.8 (25.2, 49.5)
Mean number of SBMs/week, (SD)	LP Non-LIR	114 97	3.9 (2.15) 4.0 (2.5)	117 95	4.7 (2.85) 4.3 (2.25)	118 93	3.4 (2.45) 3.4 (2.01)
Change from baseline, SBMs/week, mean (SD)†	LP Non-LIR	114 97	2.6 (2.27) 2.5 (2.10)	117 95	3.5 (2.84) 2.9 (2.22)	118 93	2.0 (2.36) 1.9 (1.90)
Days/week with ≥1 SBM, mean (SD)	LP Non-LIR	114 97	3.5 (1.64) 3.6 (1.56)	117 95	3.9 (1.8) 3.7 (1.63)	118 93	2.9 (1.75) 3.0 (1.59)
Change from baseline, Days/week with ≥1 SBM, mean (SD)†	LP Non-LIR	114 97	2.2 (1.76) 2.1 (1.65)	117 95	2.7 (1.76) 2.4 (1.68)	118 93	1.6 (1.63) 1.6 (1.57)
Change from baseline (Weeks 1-12)							
Mean degree of straining, mean (SD) ‡	LP Non-LIR	114 97	-0.7 (0.83) -0.6 (0.79)	117 95	-0.8 (0.85) -0.7 (0.91)	118 93	-0.6 (0.89) -0.6 (0.76)
Mean stool consistency, mean (SD)†	LP Non-LIR	114 97	0.6 (1.04) 0.5 (1.22)	117 95	0.8 (1.18) 0.6 (1.33)	118 93	0.5 (1.32) 0.6 (1.20)
% of days/week with ≥1 complete SBM, mean (SD)†	LP Non-LIR	114 97	24.5 (23.47) 19.5 (22.93)	117 95	28.8 (25.60) 26.0 (24.62)	118 93	17.5 (22.22) 18.2 (21.70)

Abbreviations: CI, confidence interval; LP, anticipated licensed population (LIR); SBM, spontaneous bowel movement; SD, standard deviation.
†Positive changes from baseline indicate improvement.
‡A negative change from baseline indicates improvement.

Table 18: Summary of efficacy endpoints by baseline laxative response in KODIAC 5 (anticipated licensed population and non-LIR group, ITT analysis set)

Outcome	Baseline laxative response	n	Naloxegol 12.5 mg (n=213)	n	Naloxegol 25 mg (n=214)	n	Placebo (n=214)
Response to treatment, n (%)	LP	125	53 (42.4)	124	58 (46.8)	121	38 (31.4))
	Non-LIR	107	28 (26.2)	108	34 (31.5)	111	30 (27.0)
Time (hours) to first SBM, median (95% CI)	LP	122	12.8 (6.4, 21.9)	120	18.1 (6.5, 22.8)	117	38.2 (28.9, 57.4)
	Non-LIR	106	21.8 (12.4, 25.4)	107	8.9 (6.0, 22.3)	111	33.9 (26.6, 47.1)
Mean number of SBMs/week, (SD)	LP	122	4.3 (2.07)	121	4.8 (3.19)	120	3.5 (2.37)
	Non-LIR	106	3.9 (2.70)	105	4.2 (2.71)	111	3.5 (1.92)
Change from baseline, total SBMs/week, mean (SD)†	LP	122	2.7 (2.08)	121	3.6 (3.31)	120	2.2 (2.31)
	Non-LIR	106	2.4 (2.63)	105	2.7 (2.64)	111	1.9 (1.97)
Days/week with ≥1 SBM, mean (SD)	LP	122	3.7 (1.65)	121	3.9 (1.79)	120	3.0 (1.77)
	Non-LIR	106	3.3 (1.6)	105	3.5 (1.64)	111	3.1 (1.52)
Change from baseline, Days/week with ≥1 SBM, mean (SD)†	LP	122	2.3 (1.65)	121	2.7 (1.90)	120	1.7 (1.74)
	Non-LIR	106	1.8 (1.58)	105	2.1 (1.57)	111	1.6 (1.58)
Change from baseline (Weeks 1-12)							
Mean degree of straining, mean (SD) ‡	LP	122	-0.7 (0.90)	121	-0.8 (0.99)	120	-0.5 (0.82)
	Non-LIR	106	-0.6 (0.83)	105	-0.8 (0.90)	111	-0.5 (0.77)
Mean stool consistency, mean (SD)†	LP	122	0.6 (1.20)	121	0.9 (1.35)	120	0.4 (1.24)
	Non-LIR	106	0.5 (1.23)	105	0.8 (1.28)	111	0.2 (1.25)
% of days/week with ≥1 complete SBM, mean (SD)†	LP	122	25.4 (24.93)	121	30.4 (28.89)	120	15.1 (20.83)
	Non-LIR	106	19.0 (21.16)	105	22.1 (23.70)	111	17.9 (20.75)

Abbreviations: CI, confidence interval; LIR, laxative inadequate responder; SBM, spontaneous bowel movement; SD, standard deviation.
†Positive changes from baseline indicate improvement.
‡A negative change from baseline indicates improvement.

Rescue medication and enema use: anticipated licensed population

In KODIAC 4, the mean bisacodyl dose per week over Weeks 1–12 was 6.8, 5.6, and 12.5 mg in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. A single rescue dose of bisacodyl was 10 to 15 mg. Bisacodyl was used at least once over the 12 week treatment period in 65.2%, 56.4%, and 76.3% of naloxegol 12.5 mg, 25 mg and placebo patients, respectively.

In KODIAC 5, the mean bisacodyl dose (mg) per week over Weeks 1–12 was 6.2, 6.8, and 9.6 in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. Over the treatment period, 60.8% and 62.9% of naloxegol 12.5 mg and 25 mg patients, respectively used bisacodyl at least once compared with 76.9% of placebo patients.

During the 12 week treatment period in KODIAC 4, the number of patients that used an enema was low in the anticipated licensed population group and similar across treatment groups. Three patients in each of the naloxegol dosing groups used an enema once during the treatment period compared with 5 patients in the placebo group (Table 19).

In KODIAC 5, 3 patients in the naloxegol 12.5 mg group and 1 patient in the 25 mg group used an enema once compared with 4 patients in the placebo group over the treatment period (Table 19).

Table 19: Summary of enema use in the anticipated licensed population

	KODIAC 4			KODIAC 5		
No. of times enema used during tx period	**Naloxegol 12.5 mg (n=115) n (%)**	**Naloxegol 25 mg (n=117) n (%)**	**Placebo (n=118) n (%)**	**Naloxegol 12.5 mg (n=125) n (%)**	**Naloxegol 25 mg (n=124) n (%)**	**Placebo (n=121) n (%)**
0	112 (97.4)	112 (95.7)	110 (93.2)	121 (96.8)	123 (99.2)	113 (93.4)
1	3 (2.6)	3 (2.6)	5 (4.2)	3 (2.4)	1 (0.8)	4 (3.3)
2	0	1 (0.9)	1 (0.8)	1 (0.8)	0	3 (2.5)
3	0	0	0	0	0	1 (0.8)
≥4	0	1 (0.9)	2 (1.7)	0	0	0

Abbreviations: tx, treatment.

Patient reported outcomes: PAC-SYM and PAC-QoL

Patient reported outcomes in KODIAC 4 and KODIAC 5 were determined using the patient assessment of constipation symptoms (PAC-SYM) and the patient assessment of constipation quality of life (PAC-QoL). Possible values for the PAC-SYM and PAC-QoL range from 0–4, with higher scores indicating worse outcomes and a reduction from baseline indicating an improvement in symptoms or quality of life, respectively.

Minimally important difference (MID) changes from baseline to Week 12 in total PAC-SYM and PAC-QoL scores and domain scores, based on clinical interpretation, for KODIAC 4 and KODIAC 5 are shown in Table 20 and Table 23. In both studies, patients treated with naloxegol, in the anticipated licensed population were less likely to report an increase of ≥0.8 from baseline to Week 12. Patients treated with naloxegol were also more likely to report a reduction of ≥0.8 in total PAC-SYM score from baseline to Week 12 compared with those treated with placebo, indicating that naloxegol treatment

improved patient symptoms compared with placebo over 12 weeks. Similarly, in both KODIAC 4 and KODIAC 5, patients treated with naloxegol in the anticipated licensed population were less likely to report an increase from baseline to Week 12 of ≥0.5 in terms of total PAC-QoL score compared with placebo. Patients treated with naloxegol were also more likely to report a reduction in total PAC-QoL score of ≥0.5 over 12 weeks compared with placebo, indicating that naloxegol improved patient quality of life compared with placebo over the treatment period. Changes in PAC-SYM scores from baseline to Week 12 in KODIAC 4 and KODIAC 5 are shown in Table 21 and Table 22, respectively. Compared with placebo, naloxegol treatment was associated with increased reductions in PAC-SYM scores across all domains in the anticipated licensed population, indicating improved symptoms. Changes in PAC-QoL scores from baseline to Week 12 in KODIAC 4 and KODIAC 5 are shown in Table 24 and Table 25, respectively. Compared with placebo, naloxegol treatment was associated with increased reductions in PAC-QoL scores across all domains in the anticipated licensed population, indicating improved quality of life.

Table 20: Summary of patients with MID changes from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population (ITT analysis set)

Domain	Change from baseline category	KODIAC 4		KODIAC 5	
		Naloxegol 25 mg (N=117)	Placebo (N=118)	Naloxegol 25 mg (N=124)	Placebo (N=121)
Total score	n	89	95	88	96
	Increase in ≥.08 from BL, n (%)	0 (0.0%)	5 (5.3%)	0 (0.0%)	2 (2.1%)
	OR (95%CI)	NA		NA	
	RR (95%CI)	NA		NA	
	ARR (95%CI)	−0.05 (−0.10, −0.01)		−0.02 (−0.05, 0.02)	
	Decrease in ≥0.8 from BL, (%)	50 (56.2%)	38 (40.0%)	44 (50.0%)	36 (37.5%)
	OR (95%CI)	1.92 (1.07, 3.46)		1.67 (0.93, 3.00)	
	RR (95%CI)	1.40 (1.03, 1.91)		1.33 (0.96, 1.86)	
	ARR (95%CI)	0.16 (0.02, 0.30)		0.13 (−0.02, 0.27)	
Abdominal Symptoms Score	n	89	95	88	96
	Increase in ≥.08 from BL, n (%)	3 (3.4%)	5 (5.3%)	3 (3.4%)	6 (6.3%)
	OR (95%CI)	0.63 (0.15, 2.71)		0.53 (0.13, 2.18)	
	RR (95%CI)	0.64 (0.16, 2.60)		0.55 (0.14, 2.12)	
	ARR (95%CI)	−0.02 (−0.08, 0.04)		−0.03 (−0.09, 0.03)	
	Decrease in ≥0.8 from BL, (%)	40 (44.9%)	37 (38.9%)	35 (39.8%)	38 (39.6%)
	OR (95%CI)	1.28 (0.71, 2.30)		1.01 (0.56, 1.82)	
	RR (95%CI)	1.15 (0.82, 1.62)		1.00 (0.70, 1.44)	
	ARR (95%CI)	0.06 (−0.08, 0.20)	95	0.00 (−0.14, 0.14)	
Rectal Symptoms Score	n	89	95	88	96
	Increase in ≥.08 from BL, n (%)	1 (1.1%)	7 (7.4%)	3 (3.4%)	4 (4.2%)
	OR (95%CI)	0.14 (0.02, 1.19)		0.81 (0.18, 3.73)	

	RR (95%CI)	0.15 (0.02, 1.21)		0.82 (0.19, 3.55)	
	ARR (95%CI)	−0.06 (−0.12, −0.01)		−0.01 (−0.06, 0.05)	
	Decrease in ≥0.8 from BL, (%)	41 (46.1%)	29 (30.5%)	39 (44.3%)	29 (30.2%)
	OR (95%CI)	1.94 (1.06, 3.56)		1.84 (1.00, 3.37)	
	RR (95%CI)	1.51 (1.03, 2.20)		1.47 (1.00, 2.15)	
	ARR (95%CI)	0.16 (0.02, 0.29)		0.14 (0.00, 0.28)	
Stool Symptoms Score	n	89	95	88	96
	Increase in ≥.08 from BL, n (%)	2 (2.2%)	1 (1.1%)	2 (2.3%)	8 (8.3%)
	OR (95%CI)	2.16 (0.19, 24.26)		0.26 (0.05, 1.24)	
	RR (95%CI)	2.13 (0.20, 23.14)		0.27 (0.06, 1.25)	
	ARR (95%CI)	0.01 (−0.03, 0.05)		−0.06 (−0.12, 0.00)	
	Decrease in ≥0.8 from BL, (%)	55 (61.8%)	43 (45.3%)	53 (60.2%)	46 (47.9%)
	OR (95%CI)	1.96 (1.09, 3.52)		1.65 (0.92, 2.96)	
	RR (95%CI)	1.37 (1.04, 1.80)		1.26 (0.96, 1.64)	
	ARR (95%CI)	0.18 (0.02, 0.31)		0.12 (−0.02, 0.27)	

Abbreviations: ARR, absolute risk reduction; BL, baseline; CI, confidence interval; MID, minimally important difference; NA, not applicable; OR, odds ratio; PAC-SYM, patient assessment of constipation symptoms; RR, relative risk.

Table 21: Summary of change from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population (KODIAC 4, ITT set)

Domain	Summary statistics	Placebo (N=118)		Naloxegol 25 mg (N=117)	
		PAC-SYM domain scores	CFB in PAC-SYM domain scores	PAC-SYM domain scores	CFB in PAC-SYM domain scores
Total score	n	97	95	92	89
	Mean, (SD)	1.2 (0.82)	−0.7 (0.87)	1.0 (0.62)	−0.9 (0.77)
	Median	1.0	−0.6	0.8	−0.8
Difference vs placebo					
	Adjusted mean (SE)				−0.2 (0.10)
	95% two sided CI				(−0.42, −0.04)
Abdominal symptoms score	n	97	95	92	89
	Mean, (SD)	1.1 (0.93)	−0.6 (0.96)	0.9 (0.71)	−0.8 (0.84)
	Median	1.0	−0.8	0.8	−0.8
Difference vs placebo					
	Adjusted mean (SE)				−0.2 (0.11)
	95% two sided CI				(−0.38, 0.06)
Rectal symptoms score	n	97	95	92	89
	Mean, (SD)	0.8 (0.87)	−0.5 (0.94)	0.5 (0.60)	−0.8 (0.82)
	Median	0.3	−0.3	0.3	−0.7
Difference vs placebo					
	Adjusted mean (SE)				−0.3 (0.10)
	95% two sided CI				(−0.46, −0.05)
Stool symptoms score	n	97	95	92	89
	Mean, (SD)	1.5 (0.97)	−0.8 (1.05)	1.3 (0.82)	−1.1 (0.97)
	Median	1.4	−0.6	1.2	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.2 (0.13)
	95% two sided CI				(−0.48, 0.02)

Abbreviations: CFB, change from baseline; CI, confidence interval; PAC-SYM, patient assessment of constipation symptoms; SD, standard deviation; SE, standard error.

Table 22: Summary of change from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population (KODIAC 5, ITT set)

Domain	Summary statistics	Placebo (N=121)		Naloxegol 25 mg (N=124)	
		PAC-SYM domain scores	CFB in PAC-SYM domain scores	PAC-SYM domain scores	CFB in PAC-SYM domain scores
Total score	n	96	96	90	88
	Mean, (SD)	1.4 (0.82)	−0.6 (0.81)	1.0 (0.75)	−0.9 (0.88)
	Median	1.3	−0.6	0.8	−0.8
Difference vs placebo					
	Adjusted mean (SE)				−0.4 (0.10)
	95% two sided CI				(−0.57, −0.15)
Abdominal symptoms score	n	96	96	90	88
	Mean, (SD)	1.1 (0.90)	−0.7 (0.99)	1.0 (0.87)	−0.7 (1.01)
	Median	1.0	−0.6	0.8	−0.8
Difference vs placebo					
	Adjusted mean (SE)				0.0 (0.11)
	95% two sided CI				(−0.18, 0.26)
Rectal symptoms score	n	96	96	90	88
	Mean, (SD)	1.0 (0.85)	−0.5 (0.79)	0.6 (0.71)	−0.8 (0.90)
	Median	0.7	−0.3	0.3	−0.7
Difference vs placebo					
	Adjusted mean (SE)				−0.4 (0.10)
	95% two sided CI				(−0.55, −0.16)
Stool symptoms score	n	96	96	90	88
	Mean, (SD)	1.8 (1.01)	−0.6 (0.97)	0.8 (0.97)	−1.0 (1.10)
	Median	1.8	−0.6	1.0	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.5 (0.12)
	95% two sided CI				(−0.73, −0.26)

Abbreviations: CFB, change from baseline; CI, confidence interval; PAC-SYM, patient assessment of constipation symptoms; SD, standard deviation; SE, standard error.

Table 23: Summary of patients with MID changes from baseline in PAC-QoL domain scores at Week 12 in the anticipated licensed population (KODIAC 4 and 5, ITT analysis set)

Domain	Change from baseline category	KODIAC 4		KODIAC 5	
		Anticipated licensed population		Anticipated Licensed population	
		Naloxegol 25mg (N=117)	Placebo (N=118)	Naloxegol 25mg (N=124)	Placebo (N=121)
Total score	n	91	95	89	98
	Increase in ≥.0.5 from BL, n (%)	1 (1.1%)	5 (5.3%)	4 (4.5%)	6 (6.1%)
	OR (95%CI)	0.20 (0.02, 1.75)		0.72 (0.20, 2.65)	
	RR (95%CI)	0.21 (0.02, 1.75)		0.73 (0.21, 2.52)	
	ARR (95%CI)	−0.04 (−0.09, 0.01)		−0.02 (−0.08, 0.05)	
	Decrease in ≥0.5 from BL, (%)	56 (61.5%)	57 (60.0%)	64 (71.9%)	55 (56.1%)
	OR (95%CI)	1.07 (0.59, 1.92)		2.00 (1.09, 3.69)	
	RR (95% CI)	1.03 (0.81, 1.29)		1.28 (1.03, 1.59)	
	ARR (95% CI)	0.02 (−0.12, 0.16)		0.16 (0.02, 0.29)	
Physical discomfort score	n	91	95	89	98
	Increase in ≥.0.5 from BL, n (%)	5 (5.5%)	9 (9.5%)	9 (10.1%)	5 (5.1%)
	OR (95%CI)	0.56 (0.18, 1.73)		2.09 (0.67, 6.50)	
	RR (95%CI)	0.58 (0.20, 1.67)		1.98 (0.69, 5.69)	
	ARR (95%CI)	−0.04 (−0.12, 0.04)		0.05 (−0.03, 0.13)	
	Decrease in ≥0.5 from BL, (%)	65 (71.4%)	62 (65.3%)	68 (76.4%)	67 (68.4%)
	OR (95%CI)	1.33 (0.72, 2.48)		1.50 (0.78, 2.87)	
	RR (95% CI)	1.09 (0.90, 1.33)		1.12 (0.94, 1.33)	
	ARR (95% CI)	0.06 (−0.07, 0.20)		0.08 (−0.05, 0.21)	
Psychosocial discomfort score	n	91	95	89	98
	Increase in ≥.0.5 from BL, n (%)	3 (3.3%)	11 (11.6%)	5 (5.6%)	11 (11.2%)

Domain	Change from baseline category	KODIAC 4		KODIAC 5	
		Anticipated licensed population		Anticipated Licensed population	
		Naloxegol 25mg (N=117)	Placebo (N=118)	Naloxegol 25mg (N=124)	Placebo (N=121)
	OR (95%CI)	0.26 (0.07, 0.97)		0.47 (0.16. 1.41)	
	RR (95%CI)	0.28 (0.08, 0.99)		0.50 (0.18, 1.38)	
	ARR (95%CI)	−0.08 (−0.16, −0.01)		−0.06 (−0.13, 0.02)	
	Decrease in ≥0.5 from BL, (%)	53 (58.2%)	53 (55.8%)	56 (62.9%)	48 (49.0%)
	OR (95%CI)	1.11 (0.62, 1.98)		1.77 (0.99, 3.17)	
	RR (95% CI)	1.04 (0.81, 1.34)		1.28 (0.99, 1.66)	
	ARR (95% CI)	0.02 (−0.12, 0.17)		0.14 (0.00, 0.28)	
Worries/concerns score	n	91	95	89	98
	Increase in ≥.0.5 from BL, n (%)	3 (3.3%)	7 (7.4%)	6 (6.7%)	10 (10.2%)
	OR (95%CI)	0.43 (0.11, 1.71)		0.64 (0.22, 1.83)	
	RR (95%CI)	0.45 (0.12, 1.68)		0.66 (0.25, 1.74)	
	ARR (95%CI)	−0.04 (−0.10, 0.02)		−0.03 (−0.11, 0.04)	
j	Decrease in ≥0.5 from BL, (%)	52 (57.1%)	54 (56.8%)	64 (71.9%)	53 (54.1%)
	OR (95%CI)	1.01 (0.57, 1.81)		2.17 (1.18, 4.00)	
	RR (95% CI)	1.01 (0.78, 1.29)		1.33 (1.06, 1.66)	
	ARR (95% CI)	0.00 (−0.14, 0.15)		0.18 (0.04, 0.31)	
Satisfaction score	n	91	95	89	98
	Increase in ≥.0.5 from BL, n (%)	1 (1.1%)	5 (5.3%)	5 (5.6%)	7 (7.1%)
	OR (95%CI)	0.20 (0.02, 1.75)		0.77 (0.24, 2.53)	
	RR (95%CI)	0.21 (0.02, 1.75)		0.79 (0.26, 2.39)	
	ARR (95%CI)	−0.04 (−0.09, 0.01)		−0.02 (−0.09, 0.05)	
	Decrease in ≥0.5 from BL, (%)	62 (68.1%)	49 (51.6%)	63 (70.8%)	45 (45.9%)

Domain	Change from baseline category	KODIAC 4		KODIAC 5	
		Anticipated licensed population		**Anticipated Licensed population**	
		Naloxegol 25mg (N=117)	**Placebo (N=118)**	**Naloxegol 25mg (N=124)**	**Placebo (N=121)**
	OR (95%CI)	2.01 (1.10, 3.65)		2.85 (1.56, 5.23)	
	RR (95% CI)	1.32 (1.04, 1.68)		1.54 (1.20, 1.99)	
	ARR (95% CI)	0.17 (0.03, 0.30)		0.25 (0.11, 0.39)	

Abbreviations: ARR, absolute risk reduction; BL, baseline; CI, confidence interval; MID, minimally important difference; NA, not applicable; OR, odds ratio; PAC-QoL, patient assessment of constipation quality of life; RR, relative risk.

Table 24: Summary of change from baseline in PAC-QoL domain scores at 12 weeks in the anticipated licensed population (KODIAC 4, ITT analysis set)

Domain	Summary statistics	Placebo (N=118)		Naloxegol 25 mg (N=117)	
		PAC-QOL domain scores	CFB in PAC-QOL domain scores	PAC-SYM domain scores	CFB in PAC-QOL domain scores
Total score	n	97	95	94	91
	Mean, (SD)	1.4 (0.84)	−0.8 (0.85)	1.1 (0.77)	−0.9 (0.79)
	Median	1.3	−0.7	0.9	−0.9
Difference vs placebo					
	Adjusted mean (SE)				−0.2 (0.11)
	95% two sided CI				(−0.40, 0.03)
Physical discomfort score	n	97	95	94	91
	Mean, (SD)	1.2 (0.93)	−0.9 (1.01)	1.1 (0.86)	−1.0 (0.90)
	Median	1.0	−0.8	1.0	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.1 (0.12)
	95% two sided CI				(−0.37, 0.11)
Psychosocial discomfort score	n	97	95	94	91
	Mean, (SD)	0.8 (0.83)	−0.6 (0.93)	0.6 (0.73)	−0.7 (0.81)
	Median	0.6	−0.6	0.4	−0.8
Difference vs placebo					
	Adjusted mean (SE)				−0.1 (0.10)
	95% two sided CI				(−0.35, 0.06)
Worries/ concerns score	n	97	95	94	91
	Mean, (SD)	1.3 (0.96)	−0.7 (0.92)	1.0 (0.89)	−0.8 (0.91)
	Median	1.2	−0.7	0.8	−0.7
Difference vs placebo					
	Adjusted mean (SE)				−0.2 (0.12)
	95% two sided CI				(−0.38, 0.08)
Satisfaction score	n	97	95	94	91
	Mean, (SD)	2.4 (1.08)	−0.9 (1.17)	2.1 (1.14)	−1.3 (1.17)
	Median	2.6	−0.6	2.0	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.4 (0.16)
	95% two sided CI				(−0.67, −0.03)

Abbreviations: CFB, change from baseline; CI, confidence interval; PAC-QoL, patient assessment of constipation quality of life; SD, standard deviation; SE, standard error.

Table 25: Summary of change from baseline in PAC-QoL domain scores at 12 weeks in the anticipated licensed population (KODIAC 5, ITT analysis set)

Domain	Summary statistics	Placebo (N=121)		Naloxegol 25 mg (N=124)	
		PAC-QOL domain scores	CFB in PAC-QOL domain scores	PAC-QOL domain scores	CFB in PAC-QOL domain scores
Total score	n	98	98	92	89
	Mean, (SD)	1.4 (0.94)	−0.6 (0.82)	1.1 (0.90)	−1.0 (0.91)
	Median	1.3	−0.6	0.9	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.4 (0.12)
	95% two sided CI				(−0.59, −0.13)
Physical discomfort score	n	98	98	92	89
	Mean, (SD)	1.4 (0.97)	−0.8 (0.72)	1.0 (0.93)	−1.0 (0.96)
	Median	1.3	−0.8	0.8	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.3 (0.12)
	95% two sided CI				(−0.52, −0.05)
Psychosocial discomfort score	n	98	98	92	89
	Mean, (SD)	0.9 (0.94)	−0.6 (0.97)	0.6 (0.89)	−0.8 (0.90)
	Median	0.5	−0.4	0.4	−0.6
Difference vs placebo					
	Adjusted mean (SE)				−0.1 (0.11)
	95% two sided CI				(−0.36, 0.06)
Worries/ concerns score	n	98	98	92	89
	Mean, (SD)	1.3 (1.03)	−0.6 (0.91)	1.1 (0.99)	−1.0 (0.99)
	Median	1.2	−0.6	0.7	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.4 (0.13)
	95% two sided CI				(−0.61, −0.11)
Satisfaction score	n	98	98	92	89
	Mean, (SD)	2.5 (1.23)	−0.8 (1.20)	1.8 (1.25)	−1.5 (1.36)
	Median	2.6	−0.4	1.7	−1.4
Difference vs placebo					
	Adjusted mean (SE)				−0.7 (0.18)
	95% two sided CI				(−1.02, −0.32)

Abbreviations: CFB, change from baseline; CI, confidence interval; PAC-QoL, patient assessment of constipation quality of life; SD, standard deviation; SE, standard error.

Subgroup analysis: anticipated licensed population + Step 3 opioids results

In addition to the analysis in the ITT population and the anticipated licensed population, a post-hoc analysis was conducted in a subgroup of the anticipated licensed population taking Step 3 opioids for pain management.

Response to treatment and degree of straining

The anticipated licensed population + Step 3 opioids group was a subset of the anticipated licensed population. In KODIAC 4, a greater response to treatment (as defined for the primary endpoint) was observed in the naloxegol 25 mg group compared with the placebo group at Weeks 1–12 (49.4% of naloxegol 25 mg patients showed a response to treatment compared with 29.9% of placebo patients (p=0.011). Although patients in the naloxegol 25 mg group showed an improvement in the degree of straining over the treatment period, a numerically greater improvement was observed in the placebo group (Table 26).

Table 26: Summary of efficacy endpoints in anticipated licensed population + Step 3 opioids (KODIAC 4, ITT analysis set)

Outcome	Naloxegol 25 mg (n=87)	Placebo (n=77)	Comparison vs placebo		
			RR	95% CI	p value
Response to treatment, n (%)					
Week 1–12	43 (49.4)	23 (29.9)	1.655	(1.106, 2.476)	0.011
Degree of straining, Weeks 1-12, mean (SD)	2.4 (0.81)	2.8 (0.81)	-	-	-
Change from baseline in degree of straining†, mean (SD)	-0.5 (0.86)	-0.9 (0.89)	-	-	-

Abbreviations: CI, confidence interval; LIR, laxative inadequate responder; SD, standard deviation.
† A negative change from baseline indicates improvement.

In KODIAC 5, over Weeks 1-4, the response to treatment was higher in the naloxegol 25 mg treatment group compared with placebo (56.2% vs 39.8% patients, respectively; p=0.032). From Weeks 1-12, 47.2% of naloxegol 25 mg patients showed a response to treatment compared with 28.9% of placebo patients (p=0.014). Patients in the naloxegol 25 mg group showed a greater improvement in the degree of straining compared with placebo patients over the treatment period (Table 27).

Table 27: Summary of efficacy endpoints in anticipated licensed population + Step 3 opioids (KODIAC 5, ITT analysis set)

Outcome	Naloxegol 25 mg (n=89)	Placebo (n=83)	Comparison vs placebo		
			RR	95% CI	p value
Response to treatment, n (%)					
Week 1–12	42 (47.2)	24 (28.9)	1.632	(1.091, 2.441)	0.014
Degree of straining, mean (SD)	2.3 (0.86)	2.9 (0.78)	-	-	-

Change from baseline in degree of straining†, mean (SD)	-0.9 (1.00)	-0.6 (0.82)	-	-	-

Abbreviations: CI, confidence interval; LIR, laxative inadequate responder; SD, standard deviation.
† A negative change from baseline indicates improvement.

Time to first post-dose SBM without the use of rescue medication in the last 24 hours

In KODIAC 4, the median time to first post-dose SBM was considerably shorter for both the naloxegol 12.5 mg and 25 mg groups compared with placebo (20.9 and 4.4 hours vs 32.7 hours, respectively). In both treatment groups, a higher proportion of naloxegol 12.5 mg and 25 mg patients had an SBM within <6 hours compared with placebo (35.2% and 58.6% vs 16.9%, respectively). (Table 28)

In KODIAC 5, a significantly shorter median time to first post-dose SBM was achieved in the naloxegol 12.5 mg and 25 mg groups vs placebo (10.6 and 7.4 hours, vs 47.9 hours, respectively). As observed in KODIAC 4, in both treatment groups a higher proportion of naloxegol patients had an SBM within <6 hours, compared with placebo (41.9% and 46.1% vs 15.7%, respectively). (Table 28)

Change from baseline in the mean number of SBMs per week

In both KODIAC 4 and KODIAC 5, an increase in the mean number of SBMs per week was observed in the naloxegol 12.5 mg and 25 mg groups compared with placebo, as measured by a higher positive change from baseline to Week 12 (KODIAC 4: 3.0 and 3.8 SBMs vs 2.0 SBMs, respectively; KODIAC 5: 2.6 and 4.1 SBMs vs 2.0 SBMs, respectively). In KODIAC 4, the mean number of SBMs per week in the naloxegol 12.5 mg and 25 mg groups were 4.1 and 4.9, respectively compared with 3.3 in the placebo group. In KODIAC 5, the mean number of SBMs per week in the naloxegol 12.5 mg and 25 mg groups were 4.2 and 5.3, respectively compared with 3.5 in the placebo group (Table 28).

Change from baseline in mean number of days/week with ≥1 SBM

From Weeks 1–12 in KODIAC 4 and 5, there was a significant increase in the mean number of days/week with ≥1 SBM in the naloxegol 12.5 mg and 25 mg groups compared with placebo, as measured by higher positive changes from baseline (KODIAC 4: 2.5 and 2.8 days/week vs 1.6 days/week, respectively; KODIAC 5: 2.2 and 2.9 days/week vs 1.6 days/week, respectively). (Table 28)

Change from baseline in mean stool consistency and mean percentage number of days/week with complete SBM

In KODIAC 4, an improvement in stool consistency and days/week with complete SBM (CSBM) was observed in both the naloxegol 12.5 mg and 25 mg treatment groups vs placebo from baseline to Week 12 (change from baseline: 0.7 and 0.9 vs 0.5, respectively; mean percentage of days/week with CSBM: 29.5% and 30.4% vs 15.9%, respectively) (Table 28).

Similar results were observed in KODIAC 5 for both the naloxegol 12.5 mg and 25 mg treatment groups vs placebo over the treatment period (change from baseline to Week 12 in stool consistency of 0.6 and 1.0 vs 0.3, respectively: change from baseline to Week

12 in mean percentage number of days/week with CSBM of 22.9% and 32.7% vs 13.3%, respectively). (Table 28)

Table 28: Key secondary outcomes and improvements in the symptoms of OIC in the anticipated licensed population + Step 3 opioids group (KODIAC 4 and 5, ITT analysis set)

Outcome	KODIAC 4			KODIAC 5		
	Naloxegol 12.5 mg (N=71)	Naloxegol 25 mg (N=87)	Placebo (N=77)	Naloxegol 12.5 mg (N=86)	Naloxegol 25 mg (N=89)	Placebo (N=83)
Time to first post-dose SBM (ITT analysis set)						
Number of patients with post-dose SBM (%)[‡]	71 (100.0)	87 (100.0)	77 (100.0)	84 (97.7)	86 (96.6)	80 (96.4)
Median time to first SBM, hours, (95% CI)[†]	20.9 (6.8, 24.3)	4.4 (3.5, 6.7)	32.7 (24.8, 48.2)	10.6 (5.6, 22.0)	7.4 (4.0, 21.3)	47.9 (31.2, 64.9)
Patient with SBM by ≤6 hours (%)	25 (35.2)	51 (58.6)	13 (16.9)	36 (41.9)	41 (46.1)	13 (15.7)
Patient with SBM by ≤12 hours (%)	32 (45.1)	54 (62.1)	20 (26.0)	43 (50.0)	47 (52.8)	17 (20.5)
Patient with SBM by ≤24 hours (%)	43 (60.6)	67 (77.0)	28 (36.4)	56 (65.1)	56 (62.9)	29 (34.9)
Mean number of SBMs per week (SD)	4.1 (2.30)	4.9 (3.01)	3.3 (2.22)	4.2 (2.05)	5.3 (3.41)	3.5 (2.32)
Change from baseline in mean number of SBMs per week for Weeks 1–12 (ITT analysis set)						
Number of patients (n)	71	87	77	84	87	83
Mean change from baseline (SD)[§]	3.0 (2.31)	3.8 (3.01)	2.0 (2.00)	2.6 (2.05)	4.1 (3.57)	2.0 (2.32)
Change from baseline in mean number of days/week with ≥1 SBM for Weeks 1–12 (ITT analysis set)						
Number of patients (n)	71	87	77	84	87	83
Observed days, mean (SD)	3.6 (1.66)	3.9 (1.80)	2.8 (1.66)	3.6 (1.60)	4.0 (1.72)	3.0 (1.70)
Mean change from baseline, days (SD)	2.5 (1.70)	2.8 (1.79)	1.6 (1.48)	2.2 (1.63)	2.9 (1.90)	1.6 (1.71)
Change from baseline in mean stool consistency for Weeks1–12 (ITT analysis set)						
Number of patients (n)	71	87	77	84	87	83
Mean consistency (SD)[¶]	3.4 (0.99)	3.6 (1.08)	3.3 (0.96)	3.6 (0.99)	3.7 (0.97)	3.0 (1.06)
Mean change from baseline [§]	0.7 (1.00)	0.9 (1.20)	0.5 (1.27)	0.6 (1.16)	1.0 (1.38)	0.3 (1.19)
Change from baseline in mean percentage number of days/week with ≥1 CSBM for Weeks 1–12 (ITT analysis set)						
Number of patients (n)	71	87	77	84	87	83
Mean CSBMs, % (SD)	34.3 (25.53)	35.3 (28.17)	21.6 (20.76)	30.3 (24.80)	37.0 (28.89)	19.0 (21.07)
Mean change from baseline, % days (SD) [§]	29.5 (24.58)	30.4 (27.55)	15.9 (18.95)	22.9 (23.52)	32.7 (29.90)	13.3 (18.56)

Abbreviations: CI, confidence interval; CSBM, complete spontaneous bowel movement; ITT, intent-to-treat; N/A, not applicable; RR, relative risk; SBM, spontaneous bowel movement; SD, standard deviation.

†Estimates calculated using the Kaplan-Meier technique; ‡The percentages are based on the number of intent-to-treat patients in each treatment group under corresponding subgroup; §A positive change from baseline represents an increase in this parameter per week; ¶Range of possible values are 1=Type 1 separate hard lumps; 2=Type 2 sausage-shaped but lumpy; 3=Type 3 like a sausage but with cracks on its surface; 4=Type 4 like a sausage, smooth and soft; 5=Type 5 soft blobs with clear-cut edges; 6=Type 6 fluffy pieces with ragged edges; 7=Type 7 watery, no solid pieces.

Rescue medication and enema use: anticipated licensed population + Step 3 opioids

In KODIAC 4, the mean bisacodyl dose per week over Weeks 1-12 was 5.6 and 12.7 mg in the naloxegol 25 mg and placebo groups, respectively. Bisacodyl was used at least once over the treatment period in 51.7% and 77.9% of patients in the naloxegol 25 mg and placebo groups, respectively.

In KODIAC 5, the mean bisacodyl dose per week over Weeks 1-12 was 6.1 and 9.1 mg in the naloxegol 25 mg and placebo groups, respectively. Over the treatment period, 60.7% of naloxegol 25 mg patients used bisacodyl at least once compared with 78.3% of placebo patients.

During the treatment period in KODIAC 4, the number of patients that used an enema was low and similar across treatment groups. One patient used an enema one time during the treatment period compared with 4 patients in the placebo group (Table 29).

In KODIAC 5, none of the naloxegol 25 mg patients used an enema during the treatment period (Table 29).

Table 29: Summary of enema use in anticipated licensed population + Step 3 opioids (KODIAC 4 and 5)

	KODIAC 4		KODIAC 5	
No. of times enema used during tx period	**Naloxegol 25 mg (n=87) n (%)**	**Placebo (n=77) n (%)**	**Naloxegol 25 mg (n=89) n (%)**	**Placebo (n=83) n (%)**
0	84 (96.6)	70 (90.9)	89 (100.0)	76 (91.6)
1	1 (1.1)	4 (5.2)	0	4 (4.8)
2	1 (1.1)	1 (1.3)	0	3 (3.6)
3	0	0	0	0
≥4	1 (1.1)	2 (2.6)	0	0

Abbreviations: tx, treatment.

Patient reported outcomes: PAC-SYM and PAC-QoL

Patient reported outcomes in KODIAC 4 and KODIAC 5 were determined using the patient assessment of constipation symptoms (PAC-SYM) and the patient assessment of constipation quality of life (PAC-QoL). Possible values for the PAC-SYM and PAC-QoL range from 0–4, with higher scores indicating worse outcomes and a reduction from baseline indicating an improvement in symptoms or quality of life, respectively.

Minimally important difference (MID) changes from baseline to Week 12 in total PAC-SYM and PAC-QoL scores and domain scores for KODIAC 4 and KODIAC 5 are shown in Table 30 and Table 33. In both studies, patients treated with naloxegol, in the anticipated licensed population + Step 3 opioids, were less likely to report an increase of ≥0.8 from baseline to Week 12. Patients treated with naloxegol were also more likely to report a reduction of ≥0.8 in total PAC-SYM score from baseline to Week 12 compared with those treated with placebo, indicating that naloxegol treatment improved patient symptoms compared with placebo over 12 weeks. Similarly, in both KODIAC 4 and KODIAC 5, patients treated with naloxegol in the anticipated licensed population + Step

3 opioids were less likely to report an increase from baseline to Week 12 of ≥0.5 in terms of total PAC-QoL score compared with placebo. Patients treated with naloxegol were also more likely to report a reduction in total PAC-QoL score of ≥0.5 over 12 weeks compared with placebo, indicating that naloxegol improved patient quality of life compared with placebo over the treatment period.

Changes in PAC-SYM scores from baseline to Week 12 in KODIAC 4 and KODIAC 5 are shown in Table 31 and Table 32, respectively. Compared with placebo, naloxegol treatment was associated with increased reductions in PAC-SYM scores across all domains in the anticipated licensed population + Step 3 opioids, indicating improved symptoms. Changes in PAC-QoL scores from baseline to Week 12 in KODIAC 4 and KODIAC 5 are shown in Table 34 and Table 35, respectively. Compared with placebo, naloxegol treatment was associated with increased reductions in PAC-QoL scores across all domains in the anticipated licensed population + Step 3 opioids, indicating improved quality of life.

Table 30: Summary of patients with MID changes from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population + Step 3 opioids (ITT analysis set)

Domain	Change from baseline category	KODIAC 4		KODIAC 5	
		Naloxegol 25 mg (N=87)	Placebo (N=77)	Naloxegol 25 mg (N=89)	Placebo (N=83)
Total score	n	63	64	61	65
	Increase in ≥.08 from BL, n (%)	0 (0.0%)	4 (6.3%)	0 (0.0%)	1 (1.5%)
	OR (95%CI)	NA		NA	
	RR (95%CI)	NA		NA	
	ARR (95%CI)	−0.06 (−0.12, −0.01)		−0.02 (−0.05, 0.03)	
	Decrease in ≥0.8 from BL, (%)	39 (61.9%)	24 (37.5%)	35 (57.4%)	19 (29.2%)
	OR (95%CI)	2.71 (1.32, 5.55)		3.26 (1.56, 6.81)	
	RR (95%CI)	1.65 (1.14, 2.39)		1.96 (1.27, 3.03)	
	ARR (95%CI)	0.24 (0.08, 0.41)		0.28 (0.12, 0.45)	
Abdominal Symptoms Score	n	63	64	61	65
	Increase in ≥.08 from BL, n (%)	3 (4.8%)	4 (6.3%)	2 (3.3%)	5 (7.7%)
	OR (95%CI)	0.75 (0.16, 3.50)		0.41 (0.08, 2.18)	
	RR (95%CI)	0.76 (0.18, 3.27)		0.43 (0.09, 2.12)	
	ARR (95%CI)	−0.01 (−0.09, 0.06)		−0.04 (−0.12, 0.03)	
	Decrease in ≥0.8 from BL, (%)	32 (50.8%)	23 (35.9%)	27 (44.3%)	22 (33.8%)
	OR (95%CI)	1.84 (0.90, 3.74)		1.55 (0.76, 3.19)	
	RR (95%CI)	1.41 (0.94, 2.12)		1.31 (0.84, 2.03)	
	ARR (95%CI)	0.15 (−0.02, 0.32)		0.10 (−0.07, 0.27)	
Rectal Symptoms Score	n	63	64	61	65
	Increase in ≥.08 from BL, n (%)	1 (1.6%)	5 (7.8%)	1 (1.6%)	3 (4.6%)

	OR (95%CI)	0.19 (0.02, 1.68)		0.34 (0.03, 3.40)	
	RR (95%CI)	0.20 (0.02, 1.69)		0.36 (0.04, 3.32)	
	ARR (95%CI)	−0.06 (−0.13, 0.01)		−0.03 (−0.09, 0.03)	
	Decrease in ≥0.8 from BL, (%)	36 (57.1%)	18 (28.1%)	32 (52.5%)	17 (26.2%)
	OR (95%CI)	3.41 (1.63, 7.13)		3.12 (1.48, 6.58)	
	RR (95%CI)	2.03 (1.30, 3.17)		2.01 (1.25, 3.22)	
	ARR (95%CI)	0.29 (0.13, 0.45)		0.26 (0.10, 0.43)	
Stool Symptoms Score	n	63	64	61	65
	Increase in ≥.08 from BL, n (%)	2 (3.2%)	1 (1.6%)	1 (1.6%)	6 (9.2%)
	OR (95%CI)	2.07 (0.18, 23.37)		0.16 (0.02, 1.40)	
	RR (95%CI)	2.03 (0.19, 21.85)		0.18 (0.02, 1.43)	
	ARR (95%CI)	0.02 (−0.04, 0.07)		−0.08 (−0.15, 0.00)	
	Decrease in ≥0.8 from BL, (%)	42 (66.7%)	29 (45.3%)	41 (67.2%)	28 (43.1%)
	OR (95%CI)	2.41 (1.18, 4.95)		2.71 (1.31, 5.60)	
	RR (95%CI)	1.47 (1.07, 2.03)		1.56 (1.12, 2.17)	
	ARR (95%CI)	0.21 (0.04, 0.38)		0.25 (0.07, 0.41)	

Abbreviations: ARR, absolute risk reduction; BL, baseline; CI, confidence interval; MID, minimally important difference; NA, not applicable; OR, odds ratio; PAC-SYM, patient assessment of constipation symptoms; RR, relative risk

Table 31: Summary of change from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population + Step 3 opioids (KODIAC 4 - ITT set)

Domain	Summary statistics	Placebo (N=77)		Naloxegol 25 mg (N=87)	
		PAC-SYM domain scores	CFB in PAC-SYM domain scores	PAC-SYM domain scores	CFB in PAC-SYM domain scores
Total score	n	65	64	65	63
	Mean, (SD)	1.3 (0.84)	−0.6 (0.81)	1.0 (0.67)	−1.0 (0.81)
	Median	1.1	−0.5	0.8	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.4 (0.13)
	95% two sided CI				(−0.61, −0.12)
Abdominal symptoms score	n	65	64	65	63
	Mean, (SD)	1.2 (0.94)	−0.5 (0.96)	1.0 (0.76)	−0.8 (0.90)
	Median	1.3	−0.5	1.0	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.2 (0.14)
	95% two sided CI				(−0.50, 0.05)
Rectal symptoms score	n	65	64	65	63
	Mean, (SD)	0.8 (0.94)	−0.4 (0.88)	0.5 (0.62)	−1.0 (0.85)
	Median	0.7	−0.3	0.3	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.4 (0.13)
	95% two sided CI				(−0.67, −0.16)
Stool symptoms score	n	65	64	65	63
	Mean, (SD)	1.7 (1.00)	−0.7 (0.99)	1.3 (0.89)	−1.1 (1.01)
	Median	1.4	−0.7	1.2	−1.2
Difference vs placebo					
	Adjusted mean (SE)				−0.4 (0.16)
	95% two sided CI				(−0.76, −0.13)

Abbreviations: CFB, change from baseline; CI, confidence interval; PAC-SYM, patient assessment of constipation symptoms; SD, standard deviation; SE, standard error.

Table 32: Summary of change from baseline in PAC-SYM domain scores at Week 12 in the anticipated licensed population + Step 3 opioids (KODIAC 5 - ITT set)

Domain	Summary statistics	Placebo (N=83)		Naloxegol 25 mg (N=89)	
		PAC-SYM domain scores	CFB in PAC-SYM domain scores	PAC-SYM domain scores	CFB in PAC-SYM domain scores
Total score	n	65	65	62	61
	Mean, (SD)	1.4 (0.82)	−0.5 (0.78)	0.9 (0.74)	−1.1 (0.93)
	Median	1.3	−0.5	0.7	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.5 (0.13)
	95% two sided CI				(−0.73, −0.23)
Abdominal symptoms score	n	65	65	62	61
	Mean, (SD)	1.2 (0.91)	−0.6 (1.02)	1.0 (0.84)	−0.8 (1.06)
	Median	1.0	−0.5	0.8	−0.8
Difference vs placebo					
	Adjusted mean (SE)				−0.2 (0.15)
	95% two sided CI				(−0.46, 0.12)
Rectal symptoms score	n	65	65	62	61
	Mean, (SD)	0.9 (0.81)	−0.4 (0.73)	0.5 (0.54)	−1.0 (0.91)
	Median	0.7	−0.3	0.3	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.5 (0.11)
	95% two sided CI				(−0.68, −0.25)
Stool symptoms score	n	65	65	62	61
	Mean, (SD)	1.8 (1.03)	−0.5 (0.93)	1.1 (1.01)	−1.3 (1.16)
	Median	2.0	−0.4	0.8	−1.2
Difference vs placebo					
	Adjusted mean (SE)				−0.7 (0.16)
	95% two sided CI				(−1.07, −0.42)

Abbreviations: CFB, change from baseline; CI, confidence interval; PAC-SYM, patient assessment of constipation symptoms; SD, standard deviation; SE, standard error.

Table 33: Summary of patients with MID changes from baseline in PAC-QoL domain scores at Week 12 in the anticipated licensed population + Step 3 opioids (ITT analysis set)

Domain	Change from baseline category	KODIAC 4		KODIAC 5	
		Anticipated licensed population + Step 3 opioids		Anticipated licensed population + Step 3 opioids	
		Naloxegol 25mg (N=87)	Placebo (N=77)	Naloxegol 25mg (N=89)	Placebo (N=83)
Total score	n	65	64	62	67
	Increase in ≥.0.5 from BL, n (%)	1 (1.5%)	3 (4.7%)	2 (3.2%)	6 (9.0%)
	OR (95%CI)	0.32 (0.03, 3.14)		0.34 (0.07, 1.75)	
	RR (95%CI)	0.33 (0.04, 3.07)		0.36 (0.08, 1.72)	
	ARR (95%CI)	−0.03 (−0.09, 0.03)		−0.06 (−0.14, 0.02)	
	Decrease in ≥0.5 from BL, (%)	43 (66.2%)	38 (59.4%)	46 (74.2%)	32 (47.8%)
	OR (95%CI)	1.34 (0.65, 2.74)		3.14 (1.49, 6.62)	
	RR (95% CI)	1.11 (0.85, 1.46)		1.55 (1.16, 2.08)	
	ARR (95% CI)	0.07 (−0.10, 0.23)		0.26 (0.10, 0.43)	
Physical discomfort score	n	65	64	62	67
	Increase in ≥.0.5 from BL, n (%)	3 (4.6%)	7 (10.9%)	6 (9.7%)	3 (4.5%)
	OR (95%CI)	0.39 (0.10, 1.60)		2.29 (0.55, 9.57)	
	RR (95%CI)	0.42 (0.11, 1.56)		2.16 (0.56, 8.27)	
	ARR (95%CI)	−0.06 (−0.16, 0.03)		0.05 (−0.04, 0.14)	
	Decrease in ≥0.5 from BL, (%)	50 (76.9%)	40 (62.5%)	48 (77.4%)	45 (67.2%)
	OR (95%CI)	2.00 (0.93, 4.31)		1.68 (0.77, 3.67)	
	RR (95% CI)	1.23 (0.98, 1.55)		1.15 (0.93, 1.43)	
	ARR (95% CI)	0.14 (−0.01, 0.30)		0.10 (−0.05, 0.26)	
Psychosocial discomfort score	n	65	64	62	67
	Increase in ≥.0.5 from BL, n (%)	3 (4.6%)	7 (10.9%)	2 (3.2%)	10 (14.9%)

Domain	Change from baseline category	KODIAC 4		KODIAC 5	
		Anticipated licensed population + Step 3 opioids		Anticipated licensed population + Step 3 opioids	
		Naloxegol 25mg (N=87)	Placebo (N=77)	Naloxegol 25mg (N=89)	Placebo (N=83)
	OR (95%CI)	0.39 (0.10, 1.60)		0.19 (0.04, 0.90)	
	RR (95%CI)	0.42 (0.11, 1.56)		0.22 (0.05, 0.95)	
	ARR (95%CI)	−0.06 (−0.16, 0.03)		−0.12 (−0.21, −0.02)	
	Decrease in ≥0.5 from BL, (%)	36 (55.4%)	34 (53.1%)	42 (67.7%)	27 (40.3%)
	OR (95%CI)	1.10 (0.55, 2.19)		3.11 (1.51, 6.41)	
	RR (95% CI)	1.04 (0.76, 1.43)		1.68 (1.20, 2.36)	
	ARR (95% CI)	0.02 (−0.15, 0.19)		0.27 (0.11, 0.44)	
Worries/concerns score	n	65	64	62	67
	Increase in ≥.0.5 from BL, n (%)	3 (4.6%)	5 (7.8%)	4 (6.5%)	10 (14.9%)
	OR (95%CI)	0.57 (0.13, 2.50)		0.39 (0.12, 1.33)	
	RR (95%CI)	0.59 (0.15, 2.37)		0.43 (0.14, 1.31)	
	ARR (95%CI)	−0.03 (−0.12, 0.05)		−0.08 (−0.19, 0.02)	
	Decrease in ≥0.5 from BL, (%)	41 (63.1%)	35 (54.7%)	47 (75.8%)	30 (44.8%)
	OR (95%CI)	1.42 (0.70, 2.86)		3.86 (1.82, 8.22)	
	RR (95% CI)	1.15 (0.86, 1.54)		1.69 (1.25, 2.29)	
	ARR (95% CI)	0.08 (−0.09, 0.25)		0.31 (0.15, 0.47)	
Satisfaction score	n	65	64	62	67
	Increase in ≥.0.5 from BL, n (%)	1 (1.5%)	3 (4.7%)	3 (4.8%)	6 (9.0%)
	OR (95%CI)	0.32 (0.03, 3.14)		0.52 (0.12, 2.16)	
	RR (95%CI)	0.33 (0.04, 3.07)		0.54 (0.14, 2.07)	
	ARR (95%CI)	−0.03 (−0.09, 0.03)		−0.04 (−0.13, 0.05)	
	Decrease in ≥0.5 from BL, (%)	47 (72.3%)	32 (50.0%)	48 (77.4%)	30 (44.8%)

Domain	Change from baseline category	KODIAC 4		KODIAC 5	
		Anticipated licensed population + Step 3 opioids		Anticipated licensed population + Step 3 opioids	
		Naloxegol 25mg (N=87)	Placebo (N=77)	Naloxegol 25mg (N=89)	Placebo (N=83)
	OR (95%CI)	2.61 (1.26, 5.43)		4.23 (1.97, 9.09)	
	RR (95% CI)	1.45 (1.08, 1.93)		1.73 (1.28, 2.33)	
	ARR (95% CI)	0.22 (0.06, 0.39)		0.33 (0.17, 0.48)	

Abbreviations: ARR, absolute risk reduction; BL, baseline; CI, confidence interval; MID, minimally important difference; NA, not applicable; OR, odds ratio; PAC-QoL, patient assessment of constipation quality of life; RR, relative risk.

Table 34: Summary of change from baseline in PAC-QoL domain scores at 12 weeks in the anticipated licensed population + Step 3 opioids (KODIAC 4, ITT analysis set)

Domain	Summary statistics	Placebo (N=77)		Naloxegol 25 mg (N=87)	
		PAC-QOL domain scores	CFB in PAC-QOL domain scores	PAC-QOL domain scores	CFB in PAC-QOL domain scores
Total score	n	65	64	67	65
	Mean, (SD)	1.4 (0.84)	−0.7 (0.78)	1.1 (0.82)	−1.0 (0.84)
	Median	1.3	−0.7	0.8	−0.9
Difference vs placebo					
	Adjusted mean (SE)				−0.3 (0.13)
	95% two sided CI				(−0.58, −0.06)
Physical discomfort score	n	65	64	67	65
	Mean, (SD)	1.3 (0.94)	−0.8 (0.99)	1.1 (0.87)	−1.1 (0.92)
	Median	1.0	−0.8	1.0	−1.0
Difference vs placebo					
	Adjusted mean (SE)				−0.3 (0.15)
	95% two sided CI				(−0.56, 0.03)
Psychosocial discomfort score	n	65	64	67	65
	Mean, (SD)	0.8 (0.87)	−0.6 (0.87)	0.6 (0.79)	−0.8 (0.90)
	Median	0.6	−0.6	0.4	−0.6
Difference vs placebo					
	Adjusted mean (SE)				−0.2 (0.13)
	95% two sided CI				(−0.45, 0.05)
Worries/ concerns score	n	65	64	67	65
	Mean, (SD)	1.4 (1.00)	−0.7 (0.87)	1.0 (0.92)	−0.9 (0.95)
	Median	1.2	−0.6	0.7	−0.9
Difference vs placebo					
	Adjusted mean (SE)				−0.3 (0.14)
	95% two sided CI				(−0.61, −0.04)
Satisfaction score	n	65	64	67	65
	Mean, (SD)	2.5 (0.99)	−0.8 (1.02)	2.0 (1.20)	−1.4 (1.23)
	Median	2.6	−0.5	2.0	−1.2
Difference vs placebo					
	Adjusted mean (SE)				−0.5 (0.19)
	95% two sided CI				(−0.93, −0.17)

Abbreviations: CFB, change from baseline; CI, confidence interval; PAC-QoL, patient assessment of constipation quality of life; SD, standard deviation; SE, standard error.

Table 35: Summary of change from baseline in PAC-QoL domain scores at 12 weeks in the anticipated licensed population + Step 3 opioids (KODIAC 5, ITT analysis set)

Domain	Summary statistics	Placebo (N=83)		Naloxegol 25 mg (N=89)	
		PAC-QOL domain scores	CFB in PAC-QOL domain scores	PAC-QOL domain scores	CFB in PAC-QOL domain scores
Total score	n	67	67	64	62
	Mean, (SD)	1.4 (0.94)	−0.5 (0.82)	1.0 (0.90)	−1.2 (0.95)
	Median	1.3	−0.4	0.8	−1.1
Difference vs placebo					
	Adjusted mean (SE)				−0.6 (0.15)
	95% two sided CI				(−0.85, −0.27)
Physical discomfort score	n	67	67	64	62
	Mean, (SD)	1.4 (0.97)	−0.7 (0.77)	1.0 (0.94)	−1.1 (1.03)
	Median	1.3	−0.5	0.8	−1.3
Difference vs placebo					
	Adjusted mean (SE)				−0.4 (0.14)
	95% two sided CI				(−0.69, −0.12)
Psychosocial discomfort score	n	67	67	64	62
	Mean, (SD)	0.9 (0.97)	−0.4 (0.92)	0.6 (0.82)	−0.9 (0.91)
	Median	0.6	−0.3	0.3	−0.8
Difference vs placebo					
	Adjusted mean (SE)				−0.4 (0.14)
	95% two sided CI				(−0.66, −0.11)
Worries/ concerns score	n	67	67	64	62
	Mean, (SD)	1.4 (1.04)	−0.4 (0.95)	1.0 (0.98)	−1.2 (1.06)
	Median	1.2	−0.4	0.7	−1.2
Difference vs placebo					
	Adjusted mean (SE)				−0.5 (0.16)
	95% two sided CI				(−0.86, −0.23)
Satisfaction score	n	67	67	64	62
	Mean, (SD)	2.5 (1.21)	−0.7 (1.18)	1.7 (1.28)	−1.7 (1.36)
	Median	2.6	−0.4	1.5	−1.8
Difference vs placebo					
	Adjusted mean (SE)				−0.9 (0.22)
	95% two sided CI				(−1.32, −0.47)

Abbreviations: CFB, change from baseline; CI, confidence interval; PAC-QoL, patient assessment of constipation quality of life; SD, standard deviation; SE, standard error.

EQ-5D data

A summary of the results for each domain of the EQ-5D in KODIAC 4 and KODIAC 5 for the anticipated licensed population and the anticipated licensed population +Step 3 opioids is presented in Table 36–Table 37 and Figure 9–Figure 10. At 12 weeks, naloxegol was associated with greater improvements in the anxiety and depression, and mobility domains. Overall, the increase in the proportion of patients with no problems from baseline to 12 weeks was greater with naloxegol than with placebo, while the reduction in the number of patients with moderate problems was greater for naloxegol than for placebo. The change in the proportion of patients with severe problems from baseline to Week 12 appeared similar between naloxegol and placebo in the LIR population; however, in the anticipated licensed population + Step 3 opioid groups there was a greater reduction in the number of patients with severe problems, compared with placebo.

Table 36: EQ-5D responses in KODIAC-4 and KODIAC-5 in the anticipated licensed population

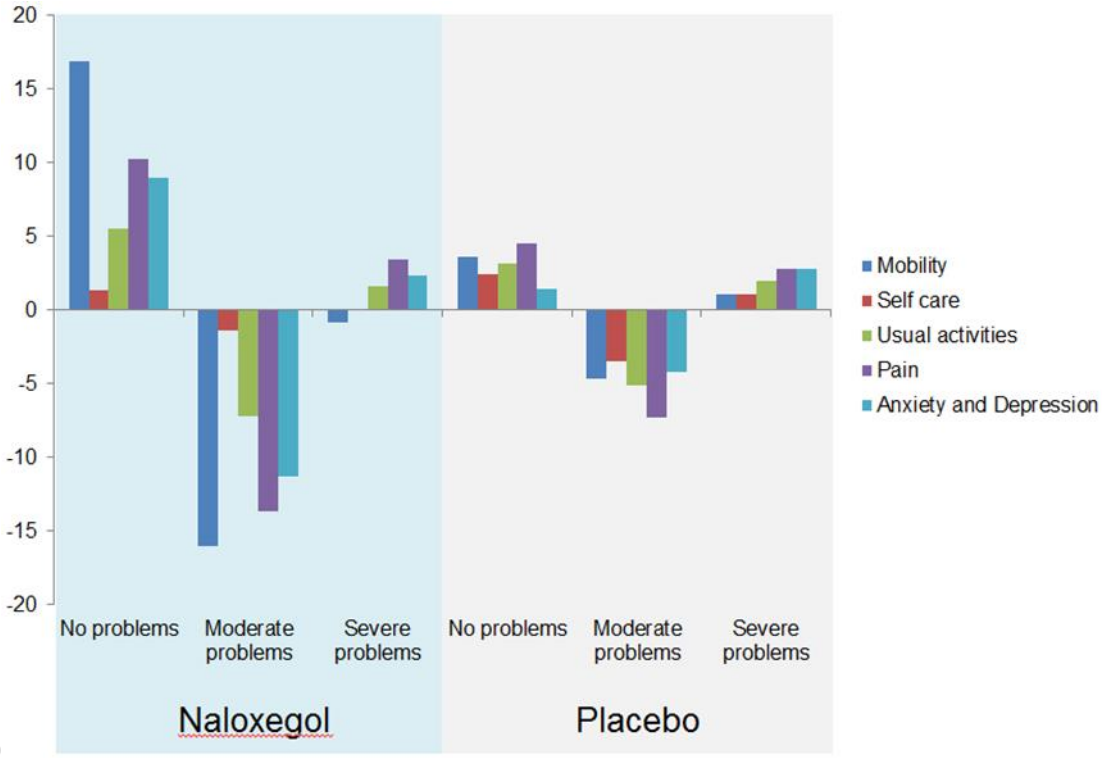
		Naloxegol			Placebo		
		No problems	Moderate problems	Severe problems	No problems	Moderate problems	Severe problems
KODIAC 4							
Mobility	Week 0	41.59	57.52	0.88	42.24	57.76	0
	Week 4	46.43	53.57	0	49.56	50.44	0
	Week 12	58.51	41.49	0	45.83	53.13	1.04
Self-care	Week 0	80.53	19.47	0	76.72	23.28	0
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

		Naloxegol			Placebo		
		No problems	Moderate problems	Severe problems	No problems	Moderate problems	Severe problems
and depress-ion	Week 4	60	33.04	6.96	60.34	38.79	0.86
	Week 12	76.09	20.65	3.26	57.14	38.78	4.08

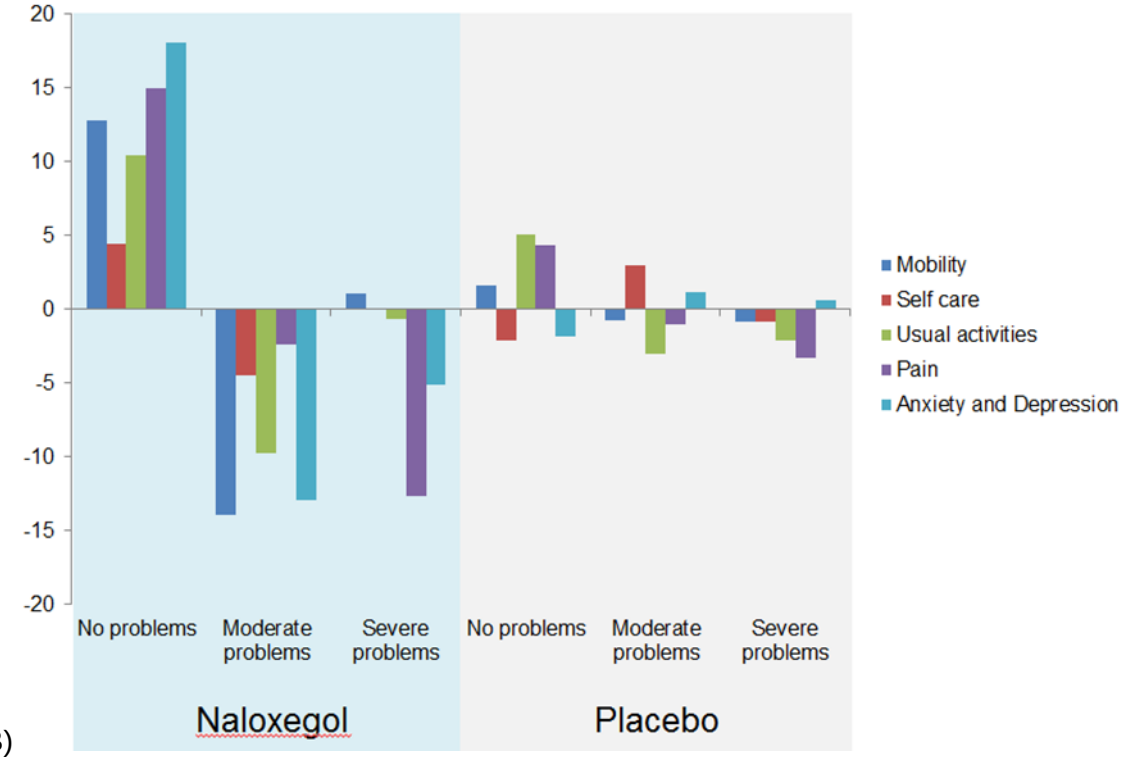
Table 37: EQ-5D responses in KODIAC 4 and KODIAC 5 in the anticipated licensed population +Step 3 opioid group

		Naloxegol			Placebo		
		No problems	Moderate problems	Severe problems	No problems	Moderate problems	Severe problems
KODIAC 4							
Mobility	Week 0	40.48	58.33	1.19	36.84	63.16	0
	Week 4	46.43	53.57	0	44	56	0
	Week 12	52.24	47.76	0	39.06	60.94	0
Self-care	Week 0	83.33	16.67	0	73.68	26.32	0
	Week 4	82.14	17.86	0	69.33	30.67	0
	Week 12	86.57	13.43	0	76.56	23.44	0
Usual activities	Week 0	41.67	54.76	3.57	26.32	67.11	6.58
	Week 4	44.05	52.38	3.57	32	57.33	10.67
	Week 12	41.79	55.22	2.99	29.79	62.5	7.81
Pain	Week 0	2.38	76.19	21.43	5.26	71.05	23.68
	Week 4	4.76	78.58	16.67	8	68	24
	Week 12	16.42	61.19	22.39	7.81	62.5	29.69
Anxiety and depress-ion	Week 0	70.24	29.76	0	55.26	39.47	5.26
	Week 4	67.86	32.14	0	54.67	37.33	8
	Week 12	73.13	23.88	2.99	51.56	43.75	4.69
KODIAC 5							
Mobility	Week 0	39.08	60.92	0	45.12	53.66	1.22
	Week 4	45.24	54.76	0	51.9	48.1	0
	Week 12	57.81	42.19	0	46.27	53.73	0
Self-care	Week 0	78.16	21.84	0	82.93	15.85	1.22
	Week 4	79.76	20.24	0	83.54	16.46	0
	Week 12	84.38	15.63	0	79.1	20.9	0
Usual activities	Week 0	41.38	51.72	6.9	36.59	57.32	6.1
	Week 4	46.43	47.62	5.95	40.51	53.16	6.33
	Week 12	51.56	42.19	6.25	38.81	58.21	2.99
Pain	Week 0	4.6	68.97	26.44	6.1	74.39	19.51
	Week 4	14.29	63.1	22.62	12.66	72.15	15.19
	Week 12	15.63	71.88	12.5	13.43	70.15	16.42
Anxiety and depress-ion	Week 0	62.07	31.03	6.9	59.76	37.8	2.44
	Week 4	65.48	27.38	7.14	59.49	40.51	0
	Week 12	79.69	17.19	3.13	53.73	44.78	1.49

Figure 9: Change from baseline to Week 12 in number of patients in each EQ-5D domain level in the anticipated licensed population in (A) KODIAC 4 and (B) KODIAC 5

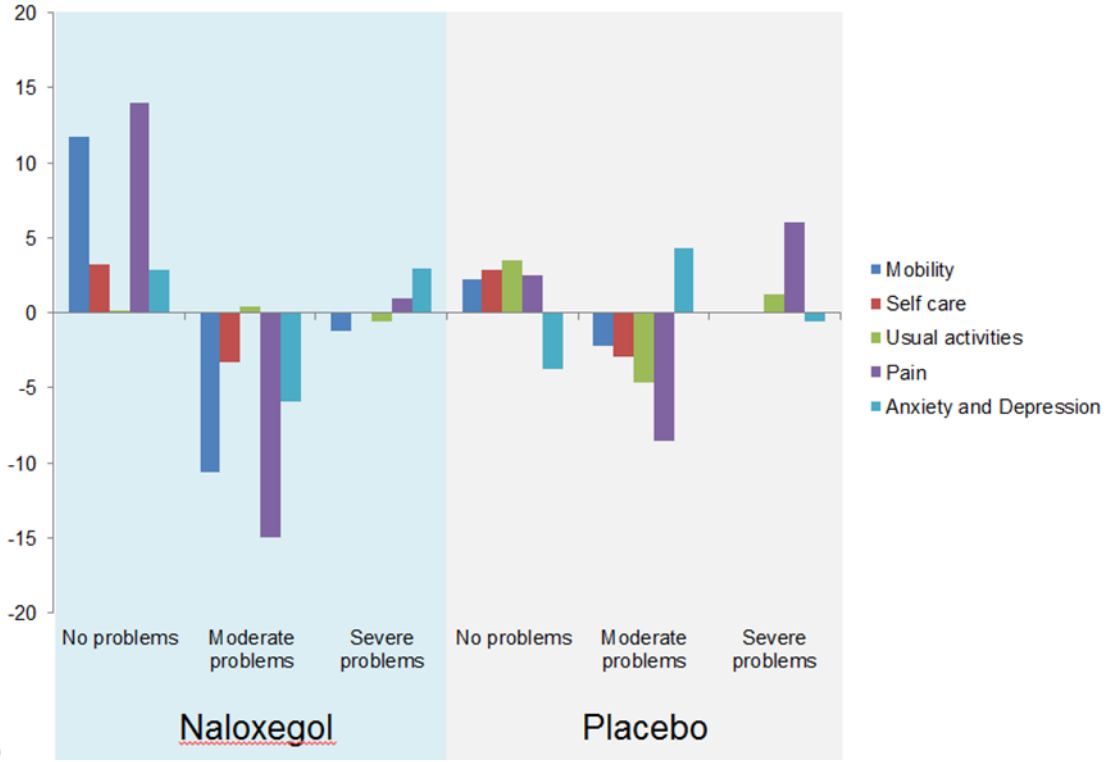


(A)

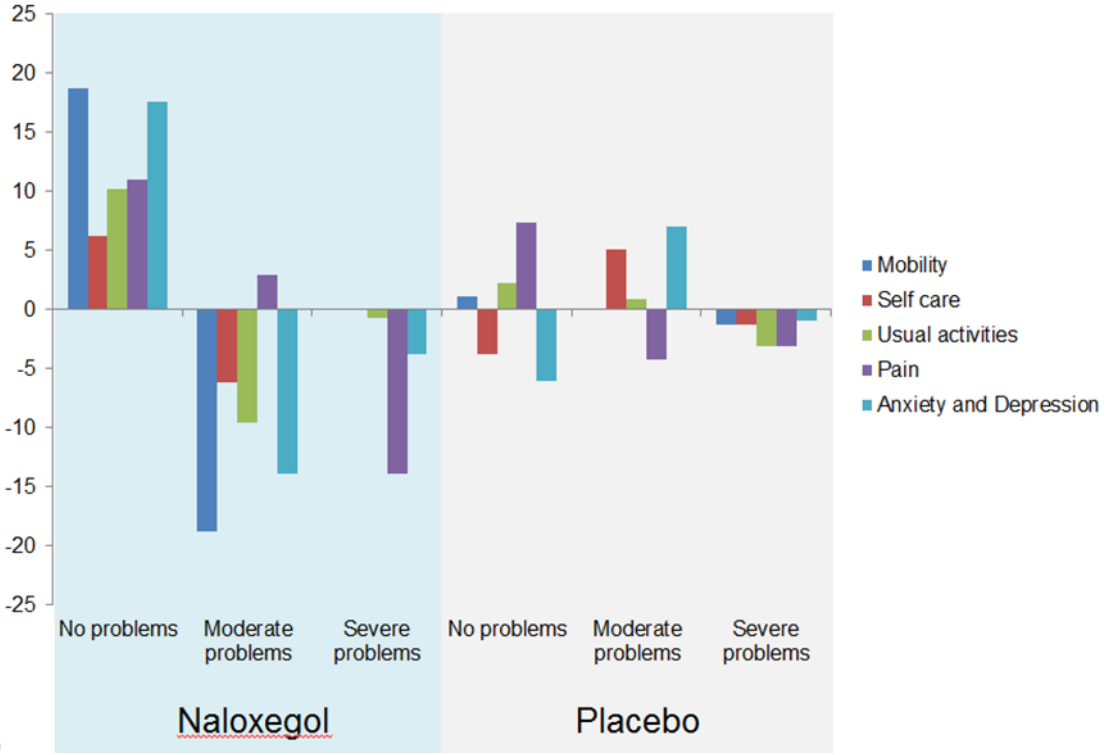


(B)

Figure 10: Change from baseline in number of patients in each EQ-5D domain level in the anticipated licensed population +Step 3 opioid group in (A) KODIAC 4 and (B) KODIAC 5



(A)



(B)

6.5.5 *Supporting evidence from other RCTs*

Phase IIb study (07-IN-NX003)

Study 07-IN-NX003 was a Phase II, dose-escalation study to assess the efficacy, safety and tolerability of naloxegol in patients with OIC. The methodology and efficacy outcomes of study 07-IN-NX003 is summarised in Table 38.

Table 38: Methodology and efficacy outcomes from study 07-IN-NX003

Study	Study 07-IN-NX003
Objectives	To assess the efficacy, safety and tolerability of naloxegol at various dose levels in patients with OIC.
Study location	A multicentre, international study conducted at 54 sites in the US (38 sites), Germany (7 sites), Romania (5 sites) and Canada (4 sites)
Design details	A Phase II, multicentre, randomised, double-blind, placebo-controlled, dose escalation study. A 10 day screening period was followed by a 2 week OIC confirmation period. Patients were required to discontinue laxative and other bowel regimens. Bisacodyl was permitted as a rescue medication if a BM had not occurred within 72 hours of the last recorded BM. Patients kept a daily eDiary to record the following: BMs, pain scores, unscheduled use of opioids for pain, and rescue medication use. Patients with confirmed OIC were randomised and entered a 1 week single-blind placebo run-in period followed by a 4 week, double-blind treatment period. Patients were randomised in a 1:1 ratio, stratified based on total opioid dose at baseline (low dose, 30–100 MEU/day, and high dose (>100–1000 MEU/day) using an IVRS system.
Interventions	Patients were randomised to receive the following: • Naloxegol 4% oral solution equivalent to a naloxegol dose of 5 mg (cohort 1), 25 mg (cohort 2), or 50 mg (cohort 3) once daily, or • Placebo Note that a 100 mg dose of naloxegol (cohort 4) was withdrawn upon review of safety data from the 50 mg cohort
Key inclusion criteria	• Aged ≥18 years • Receiving a stable oral opioid regimen (30–1000 mg/day) oral morphine equivalent doses for ≥2 weeks prior to screening for non-malignant pain or cancer-related pain • Documented OIC with ≤5 SBMs confirmed during the 2 week screening period (corresponding with ≤3 SBMs/week) • Self-reported OIC (<3 SBMs/week) with ≥1 associated symptom of hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction at initial screening
Key exclusion criteria	• Elevated serum creatinine, alanine transaminase, aspartate transaminase, serum bilirubin, or cirrhosis • Ischemic heart disease or any medical condition which would increase the risk to the patient • Life expectancy <6 months • History of GI haemorrhage related to ongoing GI pathology • Faecal incontinence, IBS, IBD, intestinal obstruction, or other GI condition associated with diarrhoea, intermittent loose stools or constipation
Efficacy endpoints	<u>Primary outcome</u> • Change from baseline to the end of Week 1 in the double-blind period in the number of SBMs/week (defined as a BM occurring without the use of rescue medication within the last 24 hours)

Study	Study 07-IN-NX003
	Secondary outcomes • Change from baseline in SBMs/week for Weeks 2, 3, and 4 • Mean number of SBMs/week across the double-blind treatment period • Time from first dose of study drug to first laxation • Patient symptom and QoL assessments (PAC-SYM, PAC-QoL and SF-36) • Subgroup analysis of change from baseline SBMs/week by baseline opioid stratum
Populations analysed	Efficacy analyses were based on the mITT population, defined as all randomised patients who received ≥1 dose of study drug during the double-blind period.
Statistical analysis	Assuming a SD of 3.5 SBMs/week with a 0.10 two-sided significance level using a Mann-Whitney test, 27 patients in each cohort would have 80% power to detect a difference of ≥2.5 SBMs/week between naloxegol vs placebo. Treatment groups within each cohort were compared using the Wilcoxon rank-sum test. A two-sided significance level of 5% was applied for all statistical Comparisons. Summary statistics were used for analysis of the PAC-SYM, PAC-QoL and SF-36
Population disposition	Of the 208 randomised patients, 207 received at least one dose of single-blind placebo run-in medication; 5 mg cohort, n=71; 25 mg cohort, n=60, 50 mg cohort, n=76). A total of 194 patients received at least one dose of study drug. A total of 32 patients (15.4%) discontinued the study. Reasons for discontinuation included: AEs (n=15), and withdrawal of consent (n=6).
Population demographics and baseline characteristics	The majority of patients were female (62.2%), white (86.5%) and the mean patient age was 49.7 years. The mean BMI across treatment groups ranged from 29.6–33.7 kg/m^2.

Efficacy outcomes	Primary endpoint
	• There was no statistical difference in the change from baseline SBMs/week in the naloxegol 5 mg group vs placebo
	• Patients in the naloxegol 25 mg group had a statistically significantly greater change from baseline in SBMs/week at Week 1 compared with placebo (2.9 vs 1.0; p=0.0020)
	• Naloxegol 50 mg was associated with a statistically significantly greater change from baseline in SBMs/week compared with placebo (3.3 vs 0.5; p=0.0001)
	Secondary outcomes
	• The increase in SBMs/week vs placebo in the naloxegol 25 mg and 50 mg groups was maintained over the 4 week treatment period (25 mg, 3.0 vs 0.8; p=0.0022: 50 mg, 3.5 vs 1.0; p<0.0001)
	• Median time to first post-dose laxation was statistically significantly shorter in the naloxegol 25 mg and 50 mg cohorts compared with placebo (25 mg, 6.6 vs 48.6 hours, respectively; p=0.0012: 50 mg, 2.9 vs 44.9 hours, respectively, p=0.0016)
	• Significant changes in baseline SBMs/week were observed for naloxegol 25 mg and 50 mg vs placebo in both the low and high-baseline opioid stratum groups:
	  ○ Low-baseline opioid stratum: naloxegol 25mg, p=0.0487; 50 mg, p=0.0024.
	  ○ High baseline opioid stratum: naloxegol 25mg, p=0.0320; naloxegol 50 mg, p=0.0002.
	• Mean PAC-SYM scores were <2 at most post-dose time points for all treatment groups indicating mild GI symptoms for both naloxegol and placebo groups
	• Naloxegol patients reported greater satisfaction as measured by the PAC-QoL compared with placebo patients

Study	Study 07-IN-NX003
	• Naloxegol 25 mg patients had statistically significant SF-36 scores vs placebo in the domains of physical functioning, mental health, social functioning, and vitality at various (but not all) post-dose time points.
Study conclusions	Naloxegol at doses of 25 mg and 50 mg was associated with a statistically significant and clinically meaningful increase in the frequency of weekly SBMs in patients with OIC. Naloxegol showed a dose-dependent increase in efficacy as measured by SBMS over the dose range of 5–50 mg. Both the 25 mg and 50 mg doses of naloxegol were associated with an improvement in patient QoL.

Abbreviations: BM, bowel movement; BMI, body mass index; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IVRS, interactive voice response system; OIC, opioid-induced constipation; PAC-QoL, Patient Assessment of Constipation Quality of life Questionnaire; PAC-SYM, Patient Assessment of Constipation Symptom Questionnaire; QoL, quality of life; SBM, spontaneous bowel movement; SD, standard deviation; SF-36, short form 36.

KODIAC 6

KODIAC 6 was a Phase III, multicentre study to assess the efficacy and safety of naloxegol in patients with cancer-related pain and OIC. The study consisted of two parts:

- Part A: a double-blind, randomised, placebo-controlled, parallel group study to evaluate the efficacy and safety of naloxegol 12.5 mg and 25 mg in the treatment of OIC in cancer patients with pain related to malignancy (i.e. pain directly related to a tumour or pain resulting from the direct treatment of a tumour) over a 4 week period.
- Part B: 12 week active treatment extension study. Patients could transition from Part A to Part B providing they met the relevant criteria.

Recruitment into KODIAC 6 was stopped early due to difficulty enrolling an adequate number of patients for Part A of the study (n=14 randomised patients of the 366 planned). Due to the early termination of this study, a brief summary of the efficacy and safety outcomes is provided in this section.

Results of KODIAC 6

Fourteen patients were randomised, received treatment and completed Part A of the study. Nine patients (64.3%) continued to the active treatment extension study (3 patients in the naloxegol 12.5 mg group, 3 in the naloxegol 25 mg group, and 3 in the placebo group). Of the 14 patients in the study, 9 patients demonstrated a response to treatment which was defined as experiencing an average of ≥3 BMs/week without the use of rescue medication and a ≥1 rescue medication free BM increase to Week 4 over baseline. Response to treatment was demonstrated in 4 out of 5 patients, in the naloxegol 12.5 mg group, 3 out of 5 patients in the naloxegol 25 mg group, and 2 out of 4 patients in the placebo group.

Naloxegol was generally safe and well-tolerated over 12 weeks of treatment for OIC:

- There were no serious adverse events, discontinuations due to AEs or deaths during the study
- During Part A, AEs were reported in 3 patients (60.0%) in the naloxegol 12.5 mg group, 2 patients (40.0%) in the naloxegol 25 mg group, and 2 patients (50%) in the placebo group

- Gastrointestinal (GI) events were the most common AEs during Part A (2 out of 5 patients and 1 out of 5 patients in the naloxegol 12.5 mg and 25 mg groups, respectively, and 0 patients in the placebo group)
- Treatment-emergent GI AEs included hematochezia and nausea in the naloxegol 12.5 mg group and nausea in the 25 mg group

- During Part B, AEs were reported in 1 patient in the naloxegol 12.5 mg group and 4 patients in the naloxegol 25 mg group. No AE was observed in more than a single patient during Part B.
- No AEs met the criteria to be sent for adjudication

Conclusions from KODIAC 6

Due to the small numbers of patients randomised, treatment comparisons for efficacy and safety could not be conducted. No new safety findings were detected in this study population.

6.5.6 *Other supporting evidence*

Burden of illness study

A prospective hybrid burden of illness (BOI) study was conducted to assess the burden of OIC among patients receiving opioid therapy for non-cancer pain using a combination of retrospective data from patient records, a prospective internet-based patient survey, and a physician survey. A key feature of this study was that it demonstrated that the LIR population represents a significant proportion of OIC patients who have an inadequate response to laxative(s). A summary of the methodology and key findings is presented in Table 39.

Table 39: Methodology and key findings from the BOI study

Study	BOI study
Objectives	[redacted]
Study location	[redacted]
Design details	[redacted]
Key inclusion criteria	[redacted]

Study	BOI study
	[redacted]
Key exclusion criteria	• History of chronic constipation • Received an investigational medication to treat constipation or participated in any investigational study involving naloxegol within ≤90 days prior to the baseline visit

Study objectives	<u>Primary objective</u>
	• To estimate the rate of LIR, defined as having either:
	  ○ Sufficient laxative use: using ≥1 laxatives ≥4 times per reference period, or
	  ○ Inadequate response: <3 BMs or ≥1 of the following symptoms on the PAC-SYM scored as moderate, severe or very severe: BMs too hard, BMs too small, straining, urge to pass a BM but unable to.
	<u>Key secondary objectives</u>
	• Estimate the rate of LIR for two subgroups:
	  ○ LIR: defined as the use of at least one laxative ≥4 times during the reference period
	• Drug utilisation and self-management of OIC
	• Patient assessment of constipation symptoms (PAC-SYM)
	• Patient-reported impact of OIC on HRQL (EQ-5D, PAC-QoL), and pain management

Populations analysed	The target population was comprised of two subgroups: • Patients with ≥4 weeks and ≤2 years of routine opioid use, and • Patients with ≥2 years of routine opioid use Unless otherwise specified, all analyses were performed using the analysable population, defined as: a subset of all of the patients recruited into the study that were on opioids per protocol, reported OIC and completed the baseline survey.
Statistical analysis	Descriptive statistics were used to analyse continuous variables and the number and percent distribution by category was calculated for categorical variables. Uncertainty in results was reflected using 95% CIs. Data reported for incomplete surveys were retained in the study data base. The data were analysed as observed and included all information reported during the course of follow-up. No imputations were performed for missing responses. Values identified as out of range and not able to be validated were set to missing.
Population disposition	Out of 489 eligible participants, 293 (59%) completed at least 7 out of 8 follow-up surveys. Chart reviews were completed for 486 patients (99%) at baseline, and 477 patients (95%) at Week 24.
Population demographics and baseline characteristics	[redacted]
Study outcomes	[redacted]

Study	BOI study
	[redacted]
Study conclusions	Data from this BOI study demonstrate the burden of OIC over time with many of the constipation symptoms being reported as highly prevalent, frequent in occurrence and highly bothersome. The burden of OIC symptoms was further reflected in a range of patient-reported outcomes.

Abbreviations: BM, bowel movement; BSW, Global Assessment of Treatment Benefit, Satisfaction, and Willingness to Continue; CI, confidence interval; EQ-5D, EuroQoL 5 dimension; HRQL, health-related quality of life; LIR, laxative inadequate responder; OIC, opioid-induced constipation; PAC-SYM, Patient Assessment of Constipation Symptoms;

6.6 *Meta- analysis*

6.6.1 *The following steps should be used as a minimum when presenting a meta-analysis.*

- ***Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.***
- ***Statistically combine (pool) the results for the both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).***
- ***Provide an adequate description of the methods of statistical combination and justify their choice.***
- ***Undertake sensitivity analysis when appropriate.***
- ***Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).***

Direct meta-analysis

A direct meta-analysis for active treatments versus placebo was conducted based on the same studies used in the mixed treatment comparison (MTC) that is presented in section 6.7. The direct meta-analysis examines the same comparisons as the MTC, without incorporating ancillary arms of the evidence network.

Methodology

Eight trials were identified by the systematic review and are presented in section 6.1.

The analysis was limited to comparisons of naloxegol and naloxone-oxycodone (fixed ratio combination) compared with placebo. Direct meta-analysis of the two included RCTs evaluating methylnaltrexone compared with placebo was not undertaken due to dosing differences (one study of subcutaneous methylnaltrexone and one study of oral methylnaltrexone). Two of the naloxone trials were also excluded due to reporting of results at different timepoints. These studies were evaluated separately. The studies included in the direct meta-analysis were:

Naloxegol

- KODIAC 4 (51, 53): a Phase III, 12 week study of naloxegol vs placebo (one of the pivotal naloxegol trials reported in detail in section 6.3)
- KODIAC 5 (52, 53): a Phase III, 12 week study of naloxegol vs placebo (one of the pivotal naloxegol trials reported in detail in section 6.3)

Naloxone-oxycodone

- Lowenstein et al, 2009 (54): a Phase III, 12 week study of naloxone-oxycodone vs placebo
- Simpson et al, 2008 (58): a Phase III, 12 week study of naloxone-oxycodone vs placebo

Please see section 6.7.2 to 6.7.4 for a detailed description of the included studies.

The direct meta-analysis employed a random-effects model in which the random-effects variance was estimated using empirical Bayes methods, and was conducted using the metafor package (version 1.6) in R 2.15.2. Random effects analyses were used in the base case, with fixed effects used only if there was a strong rationale for its use (please see section 6.7.5 for further discussion of the methods of the MTC and of the rationale for the use of a random effects model).

Statistical heterogeneity was assessed by examining a sequence of pairwise meta-analyses; high values of I^2 (an estimate of the percent of variability due to heterogeneity) indicate heterogeneity for that comparison.

Results of the heterogeneity assessment

The proportion of total variability explained by heterogeneity, calculated using the I^2 statistic is provided in Table 40. There was no evidence of heterogeneity with the exception of the oxycodone/naloxone trials. With respect to the naloxegol studies, the evidence of heterogeneity was weak from a statistical viewpoint.

The I^2 value of 74% for naloxone-oxycodone discontinuations due to adverse events (DAEs) represents heterogeneity between the Simpson 2009 (58) and Lowenstein 2009 (54) studies. Rates of DAEs were similar between the two trials but differed in the placebo arms and the ratio therefore varied (placebo vs naloxone = 11.3% vs 4,9% in the Simpson 2008 study and 3% vs 5.4% in the Lowenstein 2009 study). The difference in DAEs between the Simpson 2008 and Lowenstein 2009 studies may be explained by differences in the baseline characteristics of patients enrolled in the studies: Simpson 2008 enrolled 70–75% patients with osteoarthritis and 17% with neuropathic pain (58), whereas Lowenstein 2009 enrolled approximately 30% patients with osteoarthritis and 60% with back pain (54).

Table 40: Summary of I^2 statistic values

Treatments compared in direct meta-analysis:	Mean Change in SBMs per Week (MD)		SBM Response (OR)	CSBM Response (OR)	DAEs (OR)	TEAEs (OR)
	4 weeks	4–12 weeks				
Anticipated licensed population analyses						
Naloxegol (12.5 mg) vs Placebo	0%	0%	0%	--	0%	0%
Naloxegol (25 mg) vs Placebo	0%	0%	0%	18.80%	0%	0%
Naloxone PR (FRC OD) vs Placebo	--	--	--	0%	73.70%	--
Anticipated licensed population + Step 3 analyses						
Naloxegol (12.5 mg) vs Placebo	0%	0%	54.40%	--	0%	43.80%
Naloxegol (25 mg) vs Placebo	0%	0%	0%	0%	0%	66.50%
Naloxone PR (FRC OD) vs Placebo	--	--	--	0%	73.70%	--

Abbreviations: CSBM, complete spontaneous bowel movement; DAE, discontinuations due to adverse events; FRC, fixed ratio combination; LIR, laxative inadequate responder; MD, mean difference; mg,

milligram; OD, once daily; OR, odds ratio; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.

Results of the direct meta-analysis

The results of the direct meta-analyses for the anticipated licensed population and the anticipated licensed population + Step 3 opioids vs placebo are presented in Table 41 and Table 42. Estimates and their confidence intervals for absolute effects for each treatment are presented in section 10.21. These are derived from the MTC, which is based on relative differences.

Mean change in SBMs per week

Naloxegol (both doses) but not naloxone-oxycodone was available for this analysis. In both the anticipated licensed population and the anticipated licensed population + Step 3 opioids group, both doses of naloxegol were associated with an increase in the mean number of SBMs per week compared with placebo. Naloxegol 12.5 mg, but not naloxegol 25 mg, showed a statistically significant advantage over placebo in both populations (anticipated licensed population: mean difference [MD] 0.37–1.23 at 4 weeks; MD 0.14–0.95 at 4–12 weeks; anticipated licensed population + Step 3 opioids: MD 0.58–1.61 at 4 weeks; MD 0.31–1.27 at 4–12 weeks).

SBM response

Naloxegol (both doses) but not naloxone-oxycodone was available for this analysis. In both the anticipated licensed population and the anticipated licensed population + Step 3 opioids group, both doses of naloxegol were associated with a greater SBM response versus placebo. Statistical significance versus placebo was demonstrated in the naloxegol 12.5 mg group in the anticipated licensed population (OR 1.97, 95% CrI, 1.34–2.90). All other results were not statistically significant.

CSBM response

CSBM response data were only available for naloxegol 25 mg and the fixed ratio combination of naloxone-oxycodone. All treatments were associated with greater odds of CSBM versus placebo. In both the anticipated licensed population and the anticipated licensed population + Step 3 opioids group, naloxegol 25 mg was associated with a greater CSBM response versus placebo, although the results were not statistically significant (anticipated licensed population: OR 2.40, 95% CrI 1.52, 3.79: anticipated licensed population + Step 3 opioids group: OR 3.82, 95% CrI 2.28–6.40).

Proportion of patients with DAEs

Naloxegol (both doses) and naloxone-oxycodone were available for this analysis. All treatments were associated with an increased odds of DAEs compared with placebo. Naloxegol 25 mg showed large credible intervals in both the anticipated licensed population and in the anticipated licensed population + Step 3 opioids group. The only statistically significant result was observed in the naloxegol 25 mg dose for both populations (anticipated licensed population: OR 20.8, 95% CrI 1.01–4.26; anticipated licensed population + Step 3 opioids group: OR 2.87, 95% CrI 1.24–6.63).

Proportion of patients with TEAEs

Naloxegol (both doses) but not naloxone-oxycodone was available for this analysis. Both doses of naloxegol were associated with increased odds of TEAEs relative to placebo. The only significant results were observed in the naloxegol 25 mg group for the anticipated licensed population (OR, 1.95, 95% CrI 1.35–2.82).

Conclusion

Based on the results of the direct meta-analysis, both naloxegol and naloxone-oxycodone demonstrated greater improvement versus placebo in the outcomes assessed, reflecting the individual results of the respective trials. Specifically:

- In both the anticipated licensed population and the anticipated licensed population + Step 3 opioids group, naloxegol 12.5 mg demonstrated significantly greater increases in SBMs over 4 weeks and up to 12 weeks versus placebo
- Naloxegol 12.5 mg and 25 mg had statistically significantly increased odds of SBM response compared with placebo in the anticipated licensed population
- Naloxegol 25 mg had increased odds of CSBM compared with placebo in both the anticipated licensed population and the anticipated licensed population + Step 3 opioids group
- Naloxegol 25 mg was associated with an increased odds of DAEs compared with placebo in both populations
- Naloxegol 25 mg was associated with a statistically significantly increased odds of TEAEs compared with placebo in the anticipated licensed population

Table 41: Results from direct meta-analysis in the anticipated licensed population – treatment vs placebo

Treatment	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response† (OR [95%CrI])	CSBM Response‡ (OR [95%CrI])	DAEs (OR [95%CrI])	TEAEs (OR [95%CrI])
	4 weeks	4–12 weeks				
Naloxegol (12.5 mg)	0.8 [0.37, 1.23]**	0.55 [0.14, 0.95]**	1.97 [1.34, 2.90]**	--	0.67 [0.26, 1.71]	1.06 [0.73, 1.55]
Naloxegol (25 mg)	1.85 [1.35, 2.33]*	1.45 [0.96, 1.94]*	1.86 [1.26, 2.74]**	2.40 [1.52, 3.79]*	2.08 [1.01, 4.26]**	1.95 [1.35, 2.82]**
Naloxone PR (FRC OD)	--	--	--	2.79 [2.03, 3.85]*	0.81 [0.19, 3.57]	--

Abbreviations: CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; LIR, laxative inadequate responder; MD, mean difference; OR, odds ratio; OD, once daily; PR, prolonged release; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.

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

**Statistically conclusive result (i.e. 95% CrI excludes the null point of 1 or 0), which was not so in the corresponding MTC analysis.

†Defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.

‡Defined as the proportion of patients with ≥3 SBMs/week and ≥1 SBM per week increase from baseline for 75% of weeks.

Table 42: Results from direct meta-analysis in the anticipated licensed population with Step 3 opioids – treatment vs placebo

	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response† (OR [95%CrI])	CSBM Response‡ (OR [95%CrI])	DAEs (OR [95%CrI])	TEAEs (OR [95%CrI])
Treatment	**4 weeks**	**4–12 weeks**				
Naloxegol (12.5 mg)	1.09 [0.58, 1.61]**	0.79 [0.31, 1.27]**	2.59 [1.26, 5.34]*	--	0.62 [0.2, 1.95]	1.11 [0.61, 2.04]
Naloxegol (25 mg)	2.27 [1.68, 2.86]*	1.93 [1.34, 2.51]*	2.64 [1.64, 4.24]*	3.82 [2.28, 6.40]*	2.87 [1.24, 6.63]**	2.13 [0.999, 4.56]
Naloxone PR (FRC OD)	--	--	--	2.79 [2.03, 3.85]*	0.81 [0.19, 3.57]	--

Abbreviations: CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; LIR, laxative inadequate responder; MD, mean difference; OR, odds ratio; OD, once daily; PR, prolonged release; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.

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

**Statistically conclusive result (i.e. 95% CrI excludes the null point of 1 or 0), which was not so in the corresponding MTC analysis.

† Defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.

‡ Defined as the proportion of patients with ≥3 SBMs/week and ≥1 SBM per week increase from baseline for 75% of weeks.

6.6.2 ***If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.***

N/A

6.6.3 ***If any of the relevant RCTs listed in response to Section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.***

One of the RCTs listed in section 6.2.4 (the naloxegol Phase II study) was excluded from the direct meta-analysis because it did not report data for the population of interest, i.e. patients with an inadequate response to laxative(s) (the anticipated licensed population).

6.7 *Indirect and mixed treatment comparisons*

6.7.1 ***Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.4, appendix 4.***

Please see section 6.1 for the methods used to identify evidence on the efficacy and safety of comparator treatments of relevance to the decision problem.

6.7.2 ***Please follow the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in Section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.***

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, i.e. oral laxative treatment, methylnaltrexone, naloxone-oxycodone (see section 6.2.4. Table 3 for a description of the inclusion/exclusion criteria used to identify relevant studies). The objective of this analysis was to provide subgroup analyses specific to England and Wales. 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. 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).

Study selection

In total, 8 RCTs were considered for inclusion in the MTC analysis. Seven of these studies were identified in the systematic review and one was an abstract published at the Canadian Digestive Disease Week 2014, which was not identified as part of the systematic review. The included studies were:

Naloxegol

- KODIAC 4 (51, 53): a Phase III, 12 week study of naloxegol vs placebo (one of the pivotal naloxegol trials reported in detail in section 6.3)
- KODIAC 5 (52, 53): a Phase III, 12 week study of naloxegol vs placebo (one of the pivotal naloxegol trials reported in detail in section 6.3)

Methylnaltrexone

- Michna et al, 2011 (56): a Phase III, 4 week study of subcutaneous methylnaltrexone vs placebo
- Rauck et al, 2012 (57): a Phase III, 12 week study of oral methylnaltrexone vs placebo

Naloxone-oxycodone

- Meissner et al, 2009 (55): a Phase II, 4 week study of naloxone-oxycodone vs prolonged release (PR) oxycodone. The oxycodone prolonged release (PR) treatment in this study was considered to be equivalent to placebo arms.
- Lowenstein et al, 2009 (54): a Phase III, 12 week study of naloxone-oxycodone vs placebo
- Simpson et al, 2008 (58): a Phase III, 12 week study of naloxone-oxycodone vs placebo
- Arsenault et al, 2014 (50): a 5 week study of naloxone-oxycodone vs placebo

Summary of methodology of relevant RCTs

A summary of the methodology of the relevant RCTs included in the MTC subgroup analyses is presented in Table 43.

Table 43: Summary of the studies used to conduct the MTC

Study name (ref)	Trial design	Location	Duration	Patient population	Treatment/dose	Severity of OIC
Naloxegol						
KODIAC 4 (51, 53)	Phase III, double-blind RCT	Multicentre	12 weeks	OIC patients with non-malignant pain. Only data from the LIR and LIR + 3 step opioid subgroup is included in the MTC	• naloxegol 12.5 mg OD, n=213 • naloxegol 25 mg OD, n=214 • placebo OD, n=214	≤3 SBMs/week + additional dysfunction
KODIAC 5 (52, 53)	Phase III, double-blind RCT	Multicentre	12 weeks	OIC patients with non-malignant pain. Only data from the LIR and LIR + 3 step opioid subgroup is included in the MTC	• naloxegol 12.5 mg OD, n=232 • naloxegol 25 mg OD, n=232 • placebo OD, n=232	≤3 SBMs/week + additional dysfunction
Methylnaltrexone						
Michna 2011 (56)	Phase III, double-blind RCT	NR	4 weeks	OIC patients with non-malignant pain, n=469	• methylnaltrexone 12 mg OD, n=150 • methylnaltrexone 12 mg QAD, n=148 • placebo OD, n=162	<3 rescue free BMs/week + additional dysfunction
Rauck 2012 (57)	Phase III, double-blind RCT	NR	12 weeks	OIC patients with non-malignant pain, n=804	• methylnaltrexone 150 mg OD, n=201† • methylnaltrexone 300 mg OD, n=201† • methylnaltrexone OD, n=201† 450 mg • placebo OD, n=201†	Unclear
Naloxone						
Meissner et al, 2009 (55)	Phase II, double-blind RCT	Germany	4 weeks	OIC patients, 2.9% with malignant and 97.1% with non-malignant pain, n=202	• naloxone 10 mg OD, n=51 • naloxone 20 mg OD, n=51 • naloxone 40 mg OD, n=50 • placebo OD, n=50	Unclear
Lowenstein 2009 (54)	Phase III, double-blind RCT	Germany	12 weeks	OIC patients with lower back pain, n=278	• Naloxone-oxycodone OD, n=130 • Placebo OD, n=135	≤3 CSBMs/week + additional dysfunction
Simpson 2008 (58)	Phase III, double-blind RCT	Europe	12 weeks	OIC patients with non-malignant pain, n=322	• Naloxone-oxycodone, n=162 • placebo, n=160	Unclear
Arsenault 2014 (50)	Randomised, double-blind, cross-over study	NR	5 weeks	OIC patients with chronic non-malignant pain, n=59	• naloxone-oxycodone • placebo	Unclear

Abbreviations: BM, bowel movement; CSBM, complete spontaneous bowel movement; NR, not reported; OD, once daily; OIC, opioid-induced constipation; QAD, every other day; RCT, randomised controlled trial. † Sample size imputed on the basis of the total number randomised and the randomisation ratio

Critical appraisal of relevant RCTs

A summary of the quality assessments for the studies included in the MTC are provided in Table 44. Quality assessment summaries for KODIAC 4 and 5 have previously been provided in section 6.4 and section 10.3 (Appendix 3). A complete quality assessment of all the studies is provided in section 10.5 (Appendix 5).

Although the majority of included studies reported that participants and outcome assessors were blind to treatment allocations, it was unclear whether concealment of treatment allocations was adequate in many of the studies. Similarly, the majority of studies did not clearly report details of randomisation. Study quality was particularly unclear in the Rauck 2012 (57) and Arsenault 2014 (50) studies.

Table 44: Summary of the quality assessment results for the studies included in the MTC

	Methylnaltrexone		Naloxone			
	Michna 2011 (56)	**Rauck 2012 (57)**	**Meissner 2009 (55)**	**Lowenstein 2009 (54)**	**Simpson 2008 (58)**	**Arsenault 2014 (50)**
Was randomisation carried out appropriately?	Yes	Not clear	Yes	Not clear	Not clear	Not clear
Was the concealment of treatment allocation adequate?	Yes	Not clear	Not clear	Yes	Not clear	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes	Not clear
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Not clear	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	Not clear	No	No	No	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	Not clear
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	Not clear	Yes	Yes	Yes	Yes

Results of relevant RCTs

A summary of the results from the studies used to conduct the MTC are shown in Table 45. For a detailed discussion of the results of KODIAC 4 and 5, see section 6.5. KODIAC 4 and KODIAC 5 reported data for naloxegol vs placebo in LIR and LIR with Step 3 opioids populations, which were used in the MTC. All other studies reported data only for the main trial population.

Table 45: Summary of results from studies used to conduct the comparisons

Outcome	Naloxegol		Methylnaltrexone		Naloxone-oxycodone			
	KODIAC 4	KODIAC 5	Michna 2011 (36)	Rauck 2012 (40)	Meissner 2009 (37)	Lowenstein 2009 (38)	Simpson 2008 (39)	Arsenault 2014 (24)
Mean change from baseline in SBMs/week (4–12 weeks)	Naloxegol 12.5 mg, OD, n=213: 2.5 Naloxegol 25 mg OD, n=214: 3.3 Placebo, n=214: 1.8	Naloxegol 12.5 mg, OD, n=232: 2.5 Naloxegol 25 mg OD, n=232: 3.2 Placebo, n=232: 1.8	MNTX 12 mg OD, n=150: 3.1 MNTX 12 mg QAD, n=148: 2.1 Placebo, n=162: 1.5	MNTX 150 mg OD, n=201: 1.88 MNTX 300 mg OD, n=201: 2.39 MNTX 450 mg, n=200: 2.4	-	-	-	-
SBM response† over 4 weeks (%)	Naloxegol 12.5 mg, OD, n=213: 39.44% Naloxegol 25 mg OD, n=214,: 43.46% Placebo, n=214: 26.64%	Naloxegol 12.5 mg, OD, n=232: 33.19% Naloxegol 25 mg OD, n=232: 33.62% Placebo, n=232: 25.43%	MNTX 12 mg OD, n=150: 58.7% MNTX 12 mg QAD, n=148: 45.3% Placebo, n=162: 38.3%	-	-	-	-	-
CSBM response‡ at 4 weeks (%)	Naloxegol 12.5 mg, OD, n=213: 26.1% Naloxegol 25 mg OD, n=214,: 32% Placebo, n=214: 21.3%	Naloxegol 12.5 mg, OD, n=232: 27.7% Naloxegol 25 mg OD, n=232: 25.1% Placebo, n=232: 19.7%	-	-	-	Naloxone PR/Oxycodone PR FRC OD, n=130: 51% Placebo, n=135: 26%	Naloxone PR/Oxycodone PR FRC OD, n=162: 65% Placebo, n=160: 39%	Naloxone /Oxycodone PR 60 or 80 mg BD, 29.5% Placebo, 15.6%
DAEs, 4-12 weeks (%)	Naloxegol 12.5 mg, OD, n=211: 4.3% Naloxegol 25 mg OD, n=214,: 10.3% Placebo, n=213: 4.7%	Naloxegol 12.5 mg, OD, n=230: 4.8% Naloxegol 25 mg OD, n=232: 10.3% Placebo, n=231: 4.8%	MNTX 12 mg OD, n=150: 6.7% MNTX 12 mg QAD, n=148: 8.8% Placebo, n=162: 2.5%	-	Naloxone 10 mg BD, n=51: 9.8% Naloxone 20 mg BD, n=51: 11.8% Naloxone 40 mg BD, n=50: 18%	Naloxone PR/Oxycodone PR FRC OD, n=130: 5.4% Placebo, n=135: 3%	Naloxone PR/Oxycodone PR FRC OD, n=162: 4.9% Placebo, n=160: 11.3%	-
TEAEs, 4 weeks (%)	Naloxegol 25 mg, OD, n=204: 48% Placebo, n=195: 35%	Naloxegol 25 mg, OD, n=213: 58% Placebo, n=203: 36%	-	-	-	-	-	-

Abbreviations: BD, twice daily; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse event; FRC, fixed ratio combination; MNTX, methylnaltrexone; OD, once daily; PR, prolonged release; QAD, every other day; SBM, spontaneous bowel movement;
† Defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period. ‡ Defined as the proportion of patients with ≥3 CSBMs/week at four weeks

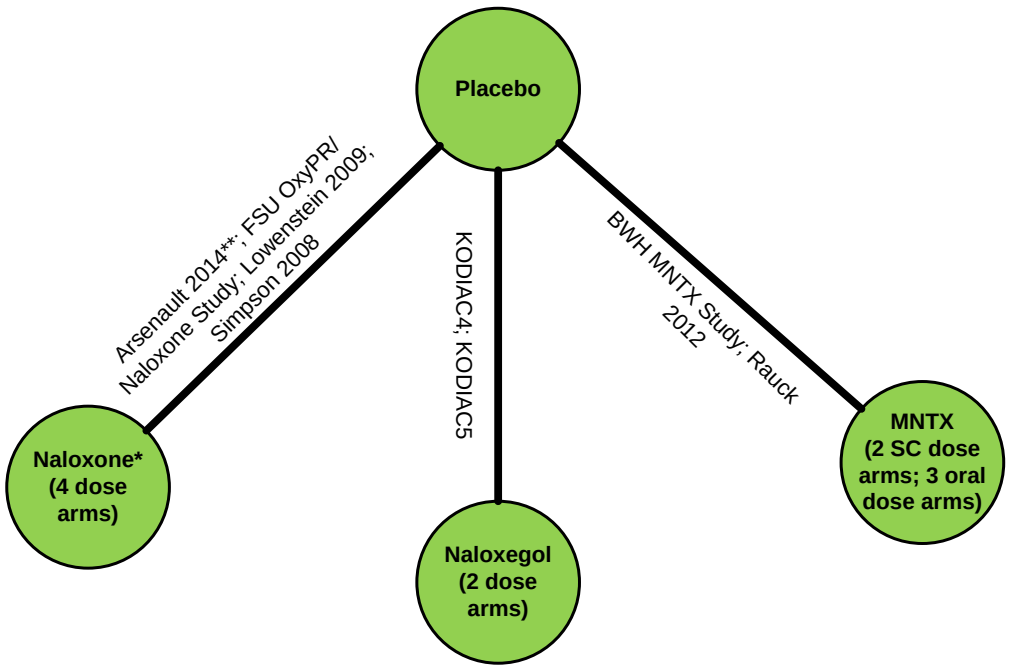
6.7.3 *Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.*

A summary of trials used to conduct the indirect comparison is provided in Table 46. The network diagram is presented in Figure 11.

Table 46: Summary of the trials used to conduct the comparisons

No. trials	References of trials	Intervention (naloxegol)	Comparator B (methylnaltrexone)	Comparator C (naloxone-oxycodone)	Comparator D (placebo)
2	• KODIAC 4 (51, 53) • KODIAC 5 (52, 53)	✓			✓
2	• Michna 2011 (56) • Rauck 2012 (57)		✓		✓
4	• Meissner 2009 (55) • Lowenstein 2009 (54) • Simpson 2008 (58) • Arsenault 2014 (50)			✓	✓

Figure 11: MTC subgroup analysis network diagram



Abbreviations: BWH MNTX, Michna et al, 2011; MNTX, methylnaltrexone; SC, subcutaneous.
*The oxycodone PR treatment in this trial was considered to be equivalent to placebo arms. Patients received naloxone/oxycodone or oxycodone alone.
**Arsenault 2014, published as an abstract at the Canadian Digestive Disease Week, was not identified as part of the Systematic review, as this conference was not searched as part of the prospectively designed protocol.

Inconsistency

An MTC brings together all available evidence from clinical trials to estimate treatment effects. As this involves combining direct and indirect measures of effect, it is important to examine whether or not these two ‘sources’ of evidence are consistent with one another. The evidence networks analysed in this report contained no closed loops of evidence and therefore no tests for inconsistency were necessary. Note that in cases where evidence networks do contain both direct and indirect evidence (closed loops) combining the direct and indirect evidence in an MTC will produce more precise estimates of direct comparisons and broaden inferences to the population samples because it links and maximises existing information within the network.

Feasibility assessment

Synthesising data across multiple studies in order to estimate effects for treatment comparisons that were not addressed directly in a head-to-head trial depends on several assumptions. Therefore, a limitation of an MTC is the extent to which these assumptions are valid. An important assumption is that the studies are all estimating the same relative effects. For this to be so, the trials must be identical both in terms of their various features; populations must be the same, clinical features must not differ, trial designs must be similar, etc. An initial feasibility analysis, during which trials are reviewed for clinical heterogeneity, can therefore help improve statistical properties.

A feasibility assessment was conducted to evaluate the evidence from the included RCTs to support a MTC analysis. This assessment evaluated the feasibility of conducting MTC analysis on an outcome-by-outcome basis for OIC. The feasibility of each analysis was dependent on a number of factors, including the similarity of the patient populations, number of trials identified, follow-up times for those trials, manner in which outcome data were reported, and shape of the evidence network.

The following factors could not be controlled for in the base case analysis:

1. Variation across patient populations due to the pain indication for opioid use
2. Variation across patient populations in definition and baseline severity of OIC
3. Variation across patient populations due to prior opioids and concomitant opioid treatments
4. Variation across patient populations in allowed concomitant and rescue treatments

This was due to either missing data across studies, the complexity of the above factors, or the small number of studies available for analysis. While these factors may impact absolute effects (e.g. a certain type of prior medication use may decrease the chance of either group having an event), the randomised nature of the data helps control for differing levels of these factors when relative effects are calculated. Only if a factor has an interaction effect with relative treatment efficacy will variation in that factor potentially lead to statistical heterogeneity within the results.

Steps taken to mitigate heterogeneity in the analyses included the exclusion of trials conducted in malignant pain populations, thus controlling for clinical heterogeneity resulting from different opiate requirements than other OIC patients. When statistical heterogeneity was found, the factors listed above were reviewed first to determine

whether they may be the cause for said heterogeneity. The most common sources of heterogeneity identified in the feasibility assessment were opioid indications among patient populations, doses and schedules of comparator treatments, time points of evaluation, and definitions of certain outcomes. Study characteristics potentially contributing to heterogeneity are provided in Table 47.

Table 47: Study characteristics potentially contributing to clinical heterogeneity

Study name	Most common pain indication for opioid use	Definition and baseline severity OIC	Prior opioids	Concomitant opioid treatments	Concomitant and rescue OIC treatments
Naloxegol					
KODIAC 4 (51, 53)	• Back pain (56–59%) • Arthritis (9–12%) • Other (18–22%)	• OIC (<3 SBMs/week on average over the 2 week OIC confirmation period and a report in the eDiary of ≥ 1 of the following symptoms: BSS stool type 1 or 2, moderate, severe or very severe straining; incomplete BM) • Mean baseline SBM/week: 1.3–1.4	≥ 4 weeks	• Mean MED: 30–1000 mg	Bisacodyl rescue; if no BM following bisacodyl rescue, the investigator could prescribe 1-time use of an osmotic laxative or an enema
KODIAC 5 (52, 53)	• Back pain (56–59%) • Arthritis (9–12%) • Other (18–22%)	• OIC (<3 SBMs/week on average over the 2 week OIC confirmation period and a report in the eDiary of ≥ 1 of the following symptoms: BSS stool type 1 or 2, moderate, severe or very severe straining; incomplete BM) • Mean baseline SBM/week: 1.3–1.6	≥ 4 weeks	• Mean MED: 30–1000 mg	Bisacodyl rescue; if no BM following bisacodyl rescue, the investigator could prescribe 1-time use of an osmotic laxative or an enema
Methylnaltrexone					
Michna 2011 (56)	• Back pain (55–65%)	• OIC (<3 rescue-free BMs occurring without the use of any laxative in the prior 24 hours per week that were associated with 1 or more of the following signs and symptoms: hard or lumpy stools, straining during bowel movements, or a sensation of incomplete evacuation after a bowel movement) • Mean baseline SBM/week: 0.9–1.1	NR	Median baseline MED: 155–161 mg	Rescue laxatives were permitted during the study if the patient had no BM for 3 consecutive days, at which point bisacodyl tablets (1 dose, up to 4 tablets orally) were permitted
Rauck 2012 (57)	NR	• History of OIC (<3 rescue-free BMs/week on average associated with at least one of: BSS type 1 or 2 for ≥ 25% of rescue-free BMs, straining during at least 25% of rescue-free BMs, or sensation of incomplete evacuation after ≥ 25% of rescue-free BMs) • Mean baseline SBM/week:1.4–1.5	NR	Mean MED: 200–262 mg	NR

Study name	Most common pain indication for opioid use	Definition and baseline severity OIC	Prior opioids	Concomitant opioid treatments	Concomitant and rescue OIC treatments
Naloxone-oxycodone					
Meissner 2009 (55)	• Back pain (24%) • Post-operative complications (15%)	• OIC (definition NR) • Mean baseline SBM/week: NR	NR	• Oxycodone 40–80 mg • Naloxone 10, 20, or 40 mg	No laxatives during double-blind phase, except previously-used laxative could be restarted if no bowel evacuations occurred within 3 days of the start of this phase
Lowenstein 2009 (54)	• Back pain (multiple indications could be reported) (61%) • OA (28–30%) • Osteoporosis (9–10%) • Neuralgia (10–11%)	• Constipation (<3 CSBMs/week) caused or aggravated by opioid therapy • BFI at randomisation: 64–67 • Mean baseline SBM/week: NR	Around the clock opioid therapy (60–80 mg/day OED)	• 1:2 FRC with oxycodone • Oxycodone immediate release permitted as rescue treatment	• Bisacodyl use (considered concomitant) not permitted within 72 hours of last BM • Within 72 hours of BM, oral bisacodyl as needed if discomfort • Maximum intake: 5 doses of 10 mg/day in 7 days • After first bisacodyl use, if no BM within 24 hours, bisacodyl could be repeated with enema if no BM after a further 24 hours
Simpson 2008 (58)	• OA (70–75%) • Neuropathic pain (17%)	• Constipation caused or aggravated by an opioid • BFI at randomisation: 61–62 • Mean baseline SBM/week: NR	Around the clock opioid therapy (20–50 mg/day OED)	• 1:2 FRC with oxycodone • Rescue analgesic allowed (type NR)	Bisacodyl (considered concomitant)
Arsenault 2014 (50)	• Chronic non-cancer pain of ≥3 months	• OIC (definition NR)	60 or 80 mg CR oxycodone every 12 hours	• Daily dose of oxycodone optimised to 60 or 80 mg every 12 hours	NR

Abbreviations: BFI, bowel function index; BM, bowel movement; BSS, Bristol Stool Scale; CSBM, complete spontaneous bowel movement; FRC, fixed ratio combination; MED, morphine equivalent dose; NR, not reported; OA, osteoarthritis; OED, oxycodone equivalent dose; OIC, opioid-induced constipation; PR, prolonged release; SBM, spontaneous bowel movement.

6.7.4 *For the selected trials, provide a summary of the 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 (i.e. LIR and LIR + Step 3 opioids subgroups). This was possible via custom analysis of the KODIAC 4 and KODIAC 5 Phase III trials, which were designed to provide data for each of the outcomes of interest for the LIR and LIR + Step 3 opioids subgroups. As none of the other trials reported data specifically for the LIR and LIR + Step 3 opioids subgroups, the MTC analysis uses the main enrolled trial populations to inform the analysis as per the pre-specified protocol (See Section 6.2.1).

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.

Data was available for comparison of all treatments included in the subgroup analysis for the following outcomes:

- Mean difference for change in SBMs per week, from baseline to average over 4 weeks
- Mean difference for change in SBMs per week, from baseline to average over 4–12 weeks (pooled)
- OR for SBM response, defined as the proportion of patients with ≥ 3 SBMs/week over a 4 week treatment period
- OR for discontinuation due to AEs, 4–12 weeks, pooled
- OR for treatment-emergent AEs over 4 weeks
- OR for complete SBM (CSBM) response at 4 weeks, defined as the proportion of patients with ≥ 3 complete SBMs/week at Week 4.

For the analysis of DAEs and TEAEs, while 4–12 week data was available for the analysis of DAEs, only 4 week data were available for the analysis of TEAEs in the populations of interest (i.e. the anticipated licensed population and the anticipated licensed population + Step 3 opioids group).

Six of the eight included trials reported outcomes at more than one time point. During the examination of the trials, the literature generally showed bowel outcomes to improve dramatically over the first week of treatment for OIC and then remain stable until treatment is discontinued. Therefore, time points were pooled between four and 12 weeks, choosing the latest time point available up to 12 weeks. In addition, the relative effects between the active treatments and placebo (rather than the absolute effects) drive MTC analysis; hence pooling the data from 4-12 weeks is appropriate

The analysed outcomes available in each trial are shown in Table 48.

Table 48: Summary of the data used in the MTC

Active Treatment	Study (Ref)	Phase	Duration (wks)	Mean change from baseline in SBMs/ week, over period		SBM Response† (%)	CSBM Response‡	DAEs (%)	TEAEs (%)
				4 weeks	4–12 weeks pooled§	Each week over 4 weeks	4 weeks	4–12 weeks pooled*	4 weeks
Naloxegol	KODIAC 4 (51, 53)	3	12	✓	✓	✓	✓	✓	✓
	KODIAC 5 (52, 53)	3	12	✓	✓	✓	✓	✓	✓
Methylnaltrexone	Michna 2011 (56)	3	4	☑	☑	✓		✓	✓
	Rauck 2012 (57)	3	12	✓	✓				
Naloxone-oxycodone	Meissner 2009 (55)	2	4					✓	
	Lowenstein 2009 (54)	3	12				✓	✓	
	Simpson 2008 (58)	3	12				✓	✓	
	Arsenault 2014¶ (50)	NR	5				✓		
Total Trials	**8**			**4**	**4**	**3**	**5**	**6**	**3**

Abbreviations: DAE, discontinuation due to adverse event; NR, not reported; SBM, spontaneous bowel movement; TEAE, treatment emergent adverse event.
Key: ✓Outcome available in study; ☑ Outcome extractable from a graph
§ Pooling over these time points refers to selecting the last time point with available data and utilising this in the analysis.
† This is defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
‡ This is defined as the proportion of patients with ≥3 CSBMs/week at 4 weeks.
§ Pooling over these time points refers to selecting the last time point with available data and utilising this in the analysis.
¶This trial, published as an abstract at the Canadian Digestive Disease Week, was not identified as part of the Systematic review, as this conference was not searched as part of the prospectively designed protocol.

6.7.5 *Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.*

MTC analysis

A Bayesian MTC meta-analysis was conducted as this enabled the incorporation of indirect comparisons from two or more trials that have one treatment in common, with a random-effects model selected as the base case for all analyses (please see below for further discussion).

The change in SBMs per week was meta-analysed as a mean difference. The relative proportions of patients with SBM within 4 and 12 hours after the first dose, response, TEAEs, and discontinuations due to adverse events (DAEs) were meta-analysed using odds ratios (ORs). Log-odds and mean differences were computed using the OpenBUGS software package. All analyses involved 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. The specific models employed are presented in section 10.19.

As per clinical recommendations, each treatment dose category was considered independently (i.e. each treatment/dose combination received its own treatment code in analysis).

In several studies, naloxone prolonged-release (PR) was given with oxycodone PR. Because patients receiving interventions and placebo in all other trials also received or continued opioid therapy, the oxycodone PR treatment was considered to be equivalent to placebo arms in the MTC analyses.

Each of the outcomes described in section 6.7.4, were analysed for the following relevant populations:

- Anticipated licensed population (LIR) data for the KODIAC 4 and 5 trials
- Anticipated licensed population plus Step 3 opioids subgroup data for the KODIAC 4 and 5 trials

As described in section 6.2.2, no published trials reported data for the subgroups of interest reported in the naloxegol trials (KODIAC 4 and 5). Therefore, the KODIAC subgroup data were compared with the main trial populations of the comparator studies. However, 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.

Comparator network and statistical approach

The following treatments were available for analysis as per the final scope:

Naloxegol

- Naloxegol (2 dose arms): 12.5 mg daily, 25 mg daily

Methylnaltrexone

- Subcutaneous methylnaltrexone (2 dose arms): 12 mg daily, 12 mg every other day
- Oral methylnaltrexone (3 dose arms) 150 mg daily, 300 mg daily, 450 mg daily

Naloxone-oxycodone

- Naloxone (4 dose arms): 10 mg daily, 20 mg daily, 40 mg daily, prolonged release (PR) fixed ratio combination (FRC) with oxycodone

The original systematic review initially identified a broader set of studies to capture interventions used in different markets. Therefore, to test the validity of conducting MTC analyses only in a network with comparators of interest for this appraisal (methylnaltrexone, naloxone, naloxegol, and placebo), analyses were compared with the results of a MTC including a wider network with additional treatments, which was initially carried out to meet the needs of several countries. Analyses were conducted in the main KODIAC 4 & 5 populations (i.e. the ITT population data included in the original MTC analyses, rather than subgroup data) in this limited network of comparators of interest for England and Wales for a single outcome (mean change in SBMs per week). These were compared with the results of the initial MTC analysis for this outcome, including a greater number of interventions, to determine the effect of removing the comparators not of interest from the network. The full (original) MTC network for mean change in SBMs per week included alvimopan, bevenopran, lubiprostone, prucalopride, and TD-1211. Because the network consisted of only indirect connections through placebo, the only substantive effect anticipated was changes to the credible intervals. Estimating the placebo effects will not change the relative effects estimates of the MTC. The MTC is driven by the relative data, not the absolute data, therefore any estimation of the absolute treatment effects would be subsequent and not impact the results of the MTC. A test of the limited network versus the full network supported the assumption that effect estimates would be minimally impacted by removing comparators from the full network. As random effects variance is partly estimated by having two or more trials evaluating the same two comparators, only alvimopan and lubiprostone, which were the only comparators removed from the full network that include more than one trial, which would produce any changes in the credible intervals between the full and limited networks.

The results of the test between the full network and the limited network are shown in Table 49. Note that only the relevant studies which reported the outcome of interest (SBMs per week) are reported. As expected, the point estimates are nearly identical (no more than differences of 0.02) and the credible intervals increased in width, from 0.27 to 0.57 in the smaller network. For the comparisons versus placebo, only naloxegol 12.5 mg lost its significant advantage as a result of reducing the size of the network.

Table 49: Results from MTC of mean change in SBMs per week from baseline to 4-12 weeks – treatment vs placebo

Treatment	Full Network†	Limited Network‡	Difference 95% CrI Width
Naloxegol (12.5 mg)	0.56 [0.08, 1.05]*	0.56 [-0.08, 1.26]	+0.37

Naloxegol (25 mg)	1.23 [0.77, 1.73]*	1.23 [0.65, 1.88]*	+0.27
Methylnaltrexone,SC (12 mg OD)	1.61 [0.83, 2.39]*	1.60 [0.56, 2.67]*	+0.55
Methylnaltrexone, SC (12 mg QAD)	0.62 [-0.18, 1.39]	0.60 [-0.4, 1.65]	+0.48
Methylnaltrexone, oral (150 mg OD)	0.18 [-0.52, 0.88]	0.17 [-0.77, 1.17]	+0.54
Methylnaltrexone, oral (300 mg OD)	0.68 [-0.07, 1.41]	0.69 [-0.3, 1.67]	+0.49
Methylnaltrexone, oral (450 mg OD)	0.68 [-0.02, 1.39]	0.70 [-0.28, 1.7]	+0.57

Abbreviations: CrI, credible interval; OD, once daily; QAD, every other day; SC, subcutaneous.
† Results from the original, base case, MTC analyses that additionally included alvimopan, bevenopran, lubiprostone, prucalopride, and TD-1211 as comparators.
‡This analysis uses the same data, patient population, and statistical methodology as the full network, but omits data from comparators not of interest for England and Wales. *Credible interval excludes the null point of 0.

Bucher indirect comparisons

In addition to these limited-network MTC analyses, Bucher indirect comparisons were additionally conducted for each of the analyses. This method examines the same comparisons as the MTC, without incorporating ancillary arms of the evidence network.

Bucher indirect comparisons adjust estimates according to the results of direct comparisons with a common comparator (e.g. placebo). For example, studies A vs C and B vs C can be used to obtain the adjusted indirect comparison of A vs B. with a common intervention C. If $\ln OR_{AC}$ denotes log-odds of A vs C and $\ln OR_{BC}$ denotes log-odds of B vs C, then $\ln OR_{AB} = \ln OR_{AC} - \ln OR_{BC}$. The standard error of this estimate is calculated by the following formula:

$$se(\ln OR_{AB}) = \sqrt{\{se(\ln OR_{AC})^2 + se(\ln OR_{BC})^2\}}$$

Bucher indirect comparison assumes that the relative effectiveness of a treatment is the same across all trials used in the comparison. It requires comparable populations where common treatment techniques (e.g. dosing, frequency) were applied. Empirical evidence suggests that results from the Bucher indirect comparisons, in general, are similar to those obtained from direct comparisons.

Unlike a MTC, Bucher indirect comparisons only incorporate data from individual trials comparing A vs B and B vs C; they do not incorporate random effects variance estimates from elsewhere in the evidence network (e.g. trials of C vs D or D vs A) do not contribute in any way.

Random effect vs fixed effects model choice

Random effects analyses are widely understood as appropriate when generalisations are to be made to a greater group of studies and patients and/or when where there is heterogeneity across studies' methods and researchers. Given the methodological

heterogeneity described in the feasibility assessment in section 6.7.3 (i.e. differences between studies in OIC definition), a random-effects model was especially appropriate. Statistical heterogeneity was assessed globally by considering the size of the sqrt(tau [τ]) from the random-effects MTC; high values of I^2 (an estimate of the percent of variability due to heterogeneity) indicate heterogeneity for that comparison. Random effects analyses were used in the base case, with fixed effects used only if there was a strong rationale for its use.

Model fit for each outcome was assessed using the deviance information criterion (DIC). The minimum DIC indicates that the model will make the best short-term predictions. Note that for this analysis, given the simplicity of the network and due to not having any nested models in the current analysis, an analysis of residual deviance was not considered necessary as it would not contribute any additional information.

6.7.6 *Please present the results of the analysis.*

Bayesian MTC results

Results from the Bayesian MTCs based on the random effects model are shown in Table 50 - Table 55. Results are presented by evaluated outcome. Comparisons with placebo are presented first followed by comparisons for naloxegol 12.5 or 25 mg with other treatments. For naloxegol, the anticipated licensed population and anticipated licensed population with Step 3 opioids were included in comparisons. As specific data was not available for these populations for other treatments, the main trial populations for naloxone and methylnaltrexone were included in comparisons. Additional supporting data in the form of square output tables for the results of the MTC is presented in section 10.21.

Mean change in SBMs per week, from baseline to average over 4 weeks

Methylnaltrexone (all subcutaneous and oral doses) and naloxegol (both doses), but not naloxone, were available for this analysis, with data for methylnaltrexone available only the main trial population and data for naloxegol available from the anticipated licensed population and anticipated licensed population + Step 3 opioids populations. All evaluated doses of both methylnaltrexone and naloxegol increased the number of SBMs per week relative to placebo (mean difference [MD] for anticipated licensed population: 0.16–1.85; MD for anticipated licensed population + Step 3 opioids: 0.17-2.29). Naloxegol 25 mg was the only comparator with a statistically conclusive advantage to placebo in these analyses (anticipated licensed population OR: 1.85 SBMs/week, 95%CrI: 0.34, 3.33; anticipated licensed population + Step 3 opioids OR: 2.29, 95%CrI: 0.43, 4.16). All other results were not statistically significant.

Mean change in SBMs per week, from baseline to average over 4 to 12 weeks

Methylnaltrexone (all subcutaneous and oral doses) and naloxegol (both doses), but not naloxone, were available for this analysis, with data for methylnaltrexone available only the main trial population and data for naloxegol available from the anticipated licensed population and anticipated licensed population with Step 3 opioids populations. All evaluated doses of both methylnaltrexone and naloxegol increased the number of SBMs per week relative to placebo (MD for anticipated licensed population: 0.17–1.6; MD for anticipated licensed population + Step 3 opioids: 0.17-1.93). Naloxegol 25 mg was the only comparator with a statistically conclusive advantage to placebo in these analyses (anticipated licensed population OR: 1.46 SBMs/week, 95%CrI: 0.02, 2.93; anticipated licensed population + Step 3 opioids OR: 1.93, 95%CrI: 0.06, 3.85). All other results were not statistically significant.

SBM response

Subcutaneous methylnaltrexone (both doses) and naloxegol (both doses), but not naloxone or oral methylnaltrexone, were available for this analysis, with data for methylnaltrexone available only the main trial population and data for naloxegol available from the anticipated licensed population and anticipated licensed population with Step 3 opioids populations. All evaluated treatments showed advantages to placebo for the proportion of patients achieving a response (anticipated licensed population ORs: 1.36–2.33; anticipated licensed population + Step 3 opioids ORs: 1.33–2.65). However, the

only estimates that were statistically significant were naloxegol 12.5 mg and 25 mg in the anticipated licensed population plus Step 3 opioids population. All other results were not statistically significant.

CSBM response

CSBM response data were only identified for the fixed ratio combination of naloxone with oxycodone, which was compared only with the 25 mg dose of naloxegol, with data for methylnaltrexone and naloxone available only the main trial population and data for naloxegol available from the anticipated licensed population and anticipated licensed population with Step 3 opioids populations. In both the anticipated licensed population and anticipated licensed population plus Step 3 opioids analyses, both naloxone (anticipated licensed population OR: 2.78, 95% CrI: 1.61, 4.83; anticipated licensed population + Step 3 opioids OR: 2.81, 95%CrI: 1.63, 4.73) and naloxegol (anticipated licensed population OR: 2.42, 95% CrI: 1.25, 4.74; anticipated licensed population + Step 3 opioids OR: 3.92, 95% CrI 1.94, 8.05) were conclusively superior to placebo. All other results were not statistically significant.

Proportion of patients with DAEs

Subcutaneous methylnaltrexone (both doses), naloxone (all doses) and naloxegol (both doses), but not oral methylnaltrexone, were available for this analysis, with data for methylnaltrexone and naloxone available only the main trial population and data for naloxegol available from the anticipated licensed population and anticipated licensed population with Step 3 opioids populations. Most treatments were associated with increased odds of DAEs compared with placebo. However, none of these relationships were statistically conclusive. Several comparisons showed extremely large credible intervals, which are common in the case of outcomes with few events. Several treatment arms demonstrated low numbers of events. For example, in the Meissner et al, 2009 study, the rate of DAEs in the placebo arm was only 2% (55). The extremely low rate in the placebo arm effectively widens the credible intervals around the estimates from this analysis.

Naloxegol 12.5 mg was associated with reduced odds of DAEs compared with all treatments (anticipated licensed population ORs: 0.04–0.9; anticipated licensed population + Step 3 opioids ORs: 0.04–0.82). The only statistically conclusive relationship was superiority of naloxegol 12.5 mg to naloxone 20 mg in the anticipated licensed population plus Step 3 opioids analysis (OR: 0.06, 95% CrI: 0, 0.98) and naloxone 40 mg (anticipated licensed population OR: 0.04, 95% CrI: 0, 0.62; anticipated licensed population + Step 3 opioids OR: 0.04, 95% CrI: 0, 0.57).

Proportion of patients with TEAEs

Subcutaneous methylnaltrexone (both doses) and naloxegol (both doses), but not naloxone or oral methylnaltrexone, were available for this analysis, with data for methylnaltrexone available only the main trial population and data for naloxegol available from the anticipated licensed population and anticipated licensed population with Step 3 opioids populations. Naloxegol 12.5 mg yielded similar rates to placebo (anticipated licensed population OR: 1.06; anticipated licensed population + Step 3 opioids OR: 1.11) and the other treatments showed increased odds of TEAEs relative to placebo (anticipated licensed population ORs: 1.33–1.98; anticipated licensed population + Step

3 opioids ORs: 1.33–2.16). However, no differences were statistically conclusive. No comparisons between treatments were statistically significant.

Table 50: Results from MTC in the anticipated licensed population – treatment vs placebo†

		Mean Change in SBMs per Week (MD [95%CrI])		SBM Response‡ (OR [95%CrI])	CSBM Response§ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
Treatment	**Number of studies**	**4 weeks**	**4-12 weeks**				
Naloxegol (12.5 mg)	2	0.79 [-0.67, 2.23]	0.55 [-0.81, 1.96]	1.98 [0.98, 4.06]	--	0.66 [0.18, 2.21]	1.06 [0.53, 2.13]
Naloxegol (25 mg)	2	1.85 [0.34, 3.33]*	1.46 [0.02, 2.93]*	1.88 [0.93, 3.78]	2.42 [1.25, 4.74]*	2.13 [0.71, 6.57]	1.98 [0.99, 3.99]
Methylnaltrexone, SC (12 mg OD)	1	1.6 [-0.48, 3.6]	1.6 [-0.41, 3.54]	2.33 [0.91, 5.95]	--	2.93 [0.59, 16.49]	1.56 [0.6, 4.03]
Methylnaltrexone, SC (12 mg QAD)	1	0.59 [-1.43, 2.62]	0.61 [-1.36, 2.58]	1.36 [0.51, 3.46]	--	3.93 [0.84, 21.74]	1.33 [0.52, 3.4]
Methylnaltrexone, oral (150 mg OD)	1	0.16 [-1.82, 2.17]	0.17 [-1.77, 2.15]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	1	0.67 [-1.38, 2.75]	0.69 [-1.31, 2.71]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	1	0.68 [-1.34, 2.72]	0.68 [-1.32, 2.67]	--	--	--	--
Naloxone PR (FRC)	CSBM: 3 DAEs: 2	--	--	--	2.78 [1.61, 4.83]*	0.72 [0.26, 2.38]	--
Naloxone (10 mg BD)	1	--	--	--	--	6.86 [0.68, 205.82]	--
Naloxone (20 mg BD)	1	--	--	--	--	8.75 [0.87, 246.41]	--
Naloxone (40 mg BD)	1	--	--	--	--	14.44 [1.56, 407.08]*	--

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; SC, subcutaneous; TEAE, treatment-emergent adverse event.
* Credible interval excludes the null point of 1 (for ORs) or 0 (for MDs).
† Populations included in comparisons were main trial populations for methylnaltrexone and naloxone and the LIR population for naloxegol.
‡This is defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
§ This is defined as the proportion of patients with ≥3 CSBMs/week at four weeks.

Table 51: Results from MTC in the anticipated licensed population – naloxegol 12.5 mg vs comparators†

	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response‡ (OR [95%CrI])	CSBM Response§ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
Treatment	**4 weeks**	**4-12 weeks**				
Methylnaltrexone, SC (12 mg OD)	-0.8 [-3.33, 1.74]	-1.05 [-3.48, 1.39]	0.85 [0.26, 2.84]	--	0.23 [0.03, 1.63]	0.68 [0.21, 2.18]
Methylnaltrexone, SC (12 mg QAD)	0.2 [-2.33, 2.7]	-0.05 [-2.48, 2.4]	1.45 [0.45, 4.88]	--	0.17 [0.02, 1.23]	0.79 [0.25, 2.55]
Methylnaltrexone, oral (150 mg OD)	0.63 [-1.9, 3.07]	0.37 [-2.08, 2.8]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	0.12 [-2.4, 2.62]	-0.14 [-2.56, 2.25]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	0.11 [-2.37, 2.55]	-0.14 [-2.54, 2.26]	--	--	--	--
Naloxone PR (FRC)	--	--	--	--	0.9 [0.15, 4.36]	--
Naloxone (10 mg BD)	--	--	--	--	0.09 [0, 1.37]	--
Naloxone (20 mg BD)	--	--	--	--	0.07 [0, 1.09]	--
Naloxone (40 mg BD)	--	--	--	--	0.04 [0, 0.62]*	--

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; SC, subcutaneous; TEAE, treatment-emergent adverse event.
* Credible interval excludes the null point of 1 (for odds ratios) or 0 (for mean differences).
† Comparator populations were main trial populations, whereas naloxegol populations were LIR populations.
‡ This is defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
§ This is defined as the proportion of patients with ≥3 CSBMs/week at four weeks.

Table 52: Results from MTC in the anticipated licensed population – naloxegol 25 mg vs comparators†

	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response‡ (OR [95%CrI])	CSBM Response§ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
Treatment	**4 weeks**	**4-12 weeks**				
Methylnaltrexone, SC (12 mg OD)	0.25 [-2.29, 2.84]	-0.13 [-2.59, 2.29]	0.81 [0.26, 2.63]	--	0.74 [0.09, 5.18]	1.27 [0.4, 4.19]
Methylnaltrexone, SC (12 mg QAD)	1.26 [-1.32, 3.76]	0.85 [-1.61, 3.35]	1.38 [0.43, 4.64]	--	0.54 [0.07, 3.65]	1.48 [0.46, 4.82]
Methylnaltrexone, oral (150 mg OD)	1.68 [-0.87, 4.13]	1.28 [-1.16, 3.77]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	1.17 [-1.37, 3.63]	0.76 [-1.7, 3.27]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	1.17 [-1.36, 3.63]	0.77 [-1.64, 3.22]	--	--	--	--
Naloxone PR (FRC)	--	--	--	0.87 [0.38, 2.11]	2.97 [0.59, 13.14]	--
Naloxone (10 mg BD)	--	--	--	--	0.31 [0.01, 4.07]	--
Naloxone (20 mg BD)	--	--	--	--	0.24 [0.01, 3.25]	--
Naloxone (40 mg BD)	--	--	--	--	0.15 [0, 1.87]	--

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; SC, subcutaneous; TEAE, treatment-emergent adverse event.
* Credible interval excludes the null point of 1 (for odds ratios) or 0 (for mean differences).
† Comparator populations were main trial populations, whereas naloxegol populations were LIR populations.
‡ This is defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
§ This is defined as the proportion of patients with ≥3 CSBMs/week at four weeks.

Table 53: Results from MTC in the anticipated licensed population + Step 3 opioids subpopulation – treatment vs placebo†

		Mean Change in SBMs per Week (MD [95%CrI])		Response SBMs‡ (OR [95%CrI])	Response CSBMs§ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
Treatment	**Number of studies**	**4 weeks**	**4-12 weeks**				
Naloxegol (12.5 mg)	2	1.08 [-0.78, 2.92]	0.78 [-1.06, 2.7]	2.62 [1.13, 6.13]*	--	0.6 [0.13, 2.58]	1.11 [0.46, 2.67]
Naloxegol (25 mg)	2	2.29 [0.43, 4.16]*	1.93 [0.06, 3.85]*	2.65 [1.15, 6.19]*	3.92 [1.94, 8.05]*	3.01 [0.96, 10.33]	2.16 [0.91, 5.11]
Methylnaltrexone, SC (12 mg OD)	1	1.6 [-1.02, 4.17]	1.6 [-1.06, 4.23]	2.3 [0.76, 6.97]	--	3.01 [0.6, 17.81]	1.58 [0.5, 5.11]
Methylnaltrexone, SC (12 mg QAD)	1	0.6 [-2.05, 3.14]	0.6 [-2.05, 3.29]	1.33 [0.44, 4.06]	--	4.07 [0.83, 23.45]	1.33 [0.42, 4.3]
Methylnaltrexone, oral (150 mg OD)	1	0.17 [-2.35, 2.78]	0.17 [-2.45, 2.79]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	1	0.69 [-1.82, 3.3]	0.68 [-2, 3.34]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	1	0.68 [-1.88, 3.33]	0.68 [-1.97, 3.31]	--	--	--	--
Naloxone PR (FRC)	CSBM: 3 DAEs: 2	--	--	--	2.81 [1.63, 4.73]*	0.73 [0.26, 2.36]	--
Naloxone (10 mg BD)	1	--	--	--	--	7.65 [0.71, 270.43]	--
Naloxone (20 mg BD)	1	--	--	--	--	9.62 [0.9, 309.51]	--
Naloxone (40 mg BD)	1	--	--	--	--	16.2 [1.66, 535.39]*	--

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

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

† Populations included in comparisons were main trial populations for methylnaltrexone and naloxone and the LIR with Step 3 opioids population for naloxegol.

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

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

Table 54: Results from MTC in the anticipated licensed population+ Step 3 opioids subpopulation – naloxegol 12.5 mg vs comparators†

	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response‡ (OR [95%CrI])	CSBM Response§ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
Treatment	**4 weeks**	**4-12 weeks**				
Methylnaltrexone, SC (12 mg OD)	-0.51 [-3.75, 2.7]	-0.82 [-4.02, 2.49]	1.14 [0.29, 4.51]	--	0.19 [0.02, 1.76]	0.7 [0.16, 3.01]
Methylnaltrexone, SC (12 mg QAD)	0.5 [-2.65, 3.7]	0.19 [-3.1, 3.47]	1.98 [0.49, 7.78]	--	0.14 [0.01, 1.29]	0.83 [0.19, 3.5]
Methylnaltrexone, oral (150 mg OD)	0.91 [-2.31, 4]	0.62 [-2.54, 3.85]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	0.4 [-2.78, 3.5]	0.1 [-3.07, 3.38]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	0.4 [-2.82, 3.52]	0.1 [-3.1, 3.33]	--	--	--	--
Naloxone PR (FRC)	--	--	--	--	0.82 [0.12, 4.8]	--
Naloxone (10 mg BD)	--	--	--	--	0.08 [0, 1.24]	--
Naloxone (20 mg BD)	--	--	--	--	0.06 [0, 0.98]*	--
Naloxone (40 mg BD)	--	--	--	--	0.04 [0, 0.57]*	--

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; SC, subcutaneous; TEAE, treatment-emergent adverse event.
* Credible interval excludes the null point of 1 (for odds ratios) or 0 (for mean differences).
† Comparator populations were main trial populations, whereas naloxegol populations were LIR with Step 3 opioids populations.
‡This is defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
§ This is defined as the proportion of patients with ≥3 CSBMs/week at four weeks.

Table 55: Results from MTC in the anticipated licensed population + Step 3 opioids subpopulation – naloxegol 25 mg vs comparators

	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response† (OR [95%CrI])	CSBM Response‡ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
Treatment	**4 weeks**	**4-12 weeks**				
Methylnaltrexone, SC (12 mg OD)	0.68 [-2.52, 3.89]	0.33 [-2.93, 3.61]	1.16 [0.29, 4.7]	--	1 [0.12, 7.5]	1.37 [0.32, 5.86]
Methylnaltrexone, SC (12 mg QAD)	1.69 [-1.51, 4.91]	1.33 [-2, 4.67]	2 [0.5, 8.11]	--	0.74 [0.09, 5.52]	1.63 [0.38, 6.77]
Methylnaltrexone, oral (150 mg OD)	2.12 [-1.12, 5.29]	1.76 [-1.48, 5.09]	--	--	--	--
Methylnaltrexone, oral (300 mg OD)	1.6 [-1.64, 4.77]	1.25 [-2.03, 4.52]	--	--	--	--
Methylnaltrexone, oral (450 mg OD)	1.6 [-1.62, 4.75]	1.25 [-1.98, 4.52]	--	--	--	--
Naloxone PR (FRC)	--	--	--	1.39 [0.59, 3.5]	4.17 [0.79, 19.69]	--
Naloxone (10 mg BD)	--	--	--	--	0.4 [0.01, 5.49]	--
Naloxone (20 mg BD)	--	--	--	--	0.32 [0.01, 4.57]	--
Naloxone (40 mg BD)	--	--	--	--	0.19 [0, 2.51]	--

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; SC, subcutaneous; TEAE, treatment-emergent adverse event.
* Credible interval excludes the null point of 1 (for odds ratios) or 0 (for mean differences).
† Comparator populations were main trial populations, whereas naloxegol populations were LIR with Step 3 opioids populations.
‡ This is defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
§ This is defined as the proportion of patients with ≥3 CSBMs/week at four weeks

DIC results

Values of DIC for random and fixed effects models are provided in Table 56. The values for each of the outcomes of interest were generally similar for both the anticipated licensed population and the anticipated licensed population + Step 3 opioids.

Table 56: DIC values for random vs fixed effects models

Random effects / Fixed effects	Mean change in SBMs per week (MD)		SBM response (OR)	CSBM response (OR)	DAEs (OR)	TEAEs (OR)
Subpopulation Analysis:	**4 weeks**	**4-12 weeks**				
Anticipated licensed population	6.29 / 4.452	5.628 / 3.945	63.14 / 61.62	66.66 / 65.01	94.82 / 95.13	63.47 / 61.74
Anticipated licensed population + Step 3 opioids	9.211 / 7.631	8.893 / 7.608	61.71 / 60.9	64.23 / 62.45	92.27 / 92.4	62.8 / 62.51

Abbreviations: DAE, discontinuations due to adverse events; DIC, difference information criterion; LIR, laxative inadequate responders; MD, mean difference; OR, odds ratio; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.

Random and fixed effects model results

Based on the results of the DIC analysis, a random effects model was chosen over a fixed effects model. However, the results for both the random and fixed effects are presented for completeness. A summary of the Bayesian MTC results for the random and fixed-effects model analysis in the anticipated licensed population and the anticipated licensed population + Step 3 opioids is presented in Table 57 and Table 58. For both the anticipated licensed population and the anticipated licensed population + Step 3 opioids, point estimates for all outcomes assessed were similar for the random and fixed-effects models. However, the credible intervals were slightly wider for the random-effects model compared with the fixed effects model. Given that there were no differences in the results for the random and fixed effects models, a random effects model was deemed to be appropriate in this case.

The complete Bayesian MTC results for the random and fixed-effects model are presented in section 10.21. Results are presented by evaluated outcome. Comparisons with placebo are presented first followed by comparisons for naloxegol 12.5 or 25 mg with other treatments. Forest plots were generated for the MTC analysis of the anticipated licensed population and the anticipated licensed population + Step 3 opioids subgroup and are presented in section 10.22.

Table 57: Summary of Bayesian MTC results for the random and fixed-effects model in the anticipated licensed population –comparators vs placebo

Treatment	Mean change in SBMs per week (MD [95%CrI])		SBM response[†] (OR [95%CrI])	CSBM response[‡] (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
	4 weeks	4-12 weeks				
Naloxegol (12.5 mg)						
Random-effects	0.79 [-0.67, 2.24]	0.55 [-0.81, 1.96]	1.98 [0.98, 4.06]	-	0.66 [0.18, 2.21]	1.06 [0.53, 2.13]
Fixed-effects	0.79 [0.37, 1.22]	0.55 [0.14, 0.95]	1.98 [1.35, 2.93]	-	0.65 [0.25, 1.64]	1.06 [0.73, 1.55]
Naloxegol (25 mg)						
Random-effects	1.85 [0.34, 3.33]	1.46 [0.02, 2.93]	1.88 [0.93, 3.78]	2.42 [1.25, 4.74]	2.13 [0.71, 6.57]	1.98 [0.99, 3.99]
Fixed-effects	1.85 [1.35, 2.33]	1.45 [0.95, 1.94]	1.87 [1.27, 2.76]	2.43 [1.61, 3.68]	2.12 [1.05, 4.5]	1.96 [1.35, 2.83]
Methylnaltrexone (12 mg OD)						
Random-effects	1.60 [-0.48, 3.60]	1.60 [-0.48, 3.60]	2.33 [0.91, 5.95]	-	2.93 [0.59, 16.49]	1.56 [0.6, 4.03]
Fixed-effects	1.60 [1.06, 2.14]	1.60 [1.06, 2.14]	2.3 [1.47, 3.62]	-	2.97 [0.95, 11.18]	1.58 [1.01, 2.48]
Methylnaltrexone (12 mg QAD)						
Random-effects	0.59 [-1.43, 2.62]	0.59 [-1.43, 2.62]	1.36 [0.51, 3.46]	-	3.93 [0.84, 21.74]	1.33 [0.52, 3.4]
Fixed-effects	0.60 [0.04, 1.14]	0.60 [0.04, 1.14]	1.34 [0.85, 2.1]	-	4.04 [1.37, 14.64]	1.34 [0.85, 2.11]
Methylnaltrexone (150 mg OD)						
Random-effects	0.16 [-1.82, 2.17]	0.16 [-1.82, 2.17]	-	-	-	-
Fixed-effects	0.17 [-0.23, 0.57]	0.17 [-0.23, 0.57]	-	-	-	-
Methylnaltrexone (300 mg OD)						
Random-effects	0.67 [-1.38, 2.75]	0.67 [-1.38, 2.75]	-	-	-	-
Fixed-effects	0.68 [0.22, 1.14]	0.68 [0.22, 1.14]	-	-	-	-
Methylnaltrexone (450 mg OD)						

Random-effects	0.68 [-1.34, 2.72]	0.68 [-1.34, 2.72]	-	-	-	-
Fixed-effects	0.69 [0.26, 1.12]	0.69 [0.26, 1.12]	-	-	-	-
Naloxone PR (FRC)						
Random-effects	-	-	-	2.78 [1.61, 4.83]	0.72 [0.26, 2.38]	-
Fixed-effects	-	-	-	2.81 [2.05, 3.9]	0.66 [0.33, 1.29]	-
Naloxone (10 mg BD)						
Random-effects	-	-	-	-	6.86 [0.68, 205.82]	-
Fixed-effects	-	-	-	-	6.92 [0.95, 248.1]	-
Naloxone (20 mg BD)						
Random-effects	-	-	-	-	8.75 [0.87, 246.41]	-
Fixed-effects	-	-	-	-	8.63 [1.22, 308.6]	-
Naloxone (40 mg BD)						
Random-effects	-	-	-	-	14.44 [1.56, 407.08]	-
Fixed-effects	-	-	-	-	14.54 [2.28, 500.8]	

Abbreviations: BD, twice daily; Crl., credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse event; MD, mean difference; OD, once daily; OR, odds ratio; QAD, every other day; PR, prolonged release; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.
† Defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
‡ Defined as the proportion of patients with ≥3 CSBMs/week at four weeks

Table 58: Summary of Bayesian MTC results for the random and fixed-effects model in the anticipated licensed population + Step 3 opioids – comparator vs placebo

	Mean change in SBMs per week (MD [95%CrI])		SBM Response† (OR [95%CrI])	CSBM Response‡ (OR [95%CrI])	DAEs (OR [95%CrI]) (4–12 weeks)	TEAEs (OR [95%CrI]) (4 weeks)
Treatment	**4 weeks**	**4-12 weeks**				
Naloxegol (12.5 mg)						
Random-effects	1.08 [-0.78, 2.92]	0.78 [-1.06, 2.7]	2.62 [1.13, 6.13]	-	0.6 [0.13, 2.58]	1.11 [0.46, 2.67]
Fixed-effects	1.08 [0.56, 1.59]	0.77 [0.29, 1.25]	2.61 [1.62, 4.29]	-	0.61 [0.18, 1.93]	1.12 [0.71, 1.76]
Naloxegol (25 mg)						
Random-effects	2.29 [0.43, 4.16]	1.93 [0.06, 3.85]	2.65 [1.15, 6.19]	3.92 [1.94, 8.05]	3.01 [0.96, 10.33]	2.16 [0.91, 5.11]
Fixed-effects	2.27 [1.67, 2.85]	1.93 [1.33, 2.51]	2.68 [1.68, 4.33]	3.89 [2.33, 6.65]	3 [1.32, 7.4]	2.17 [1.4, 3.36]
Methylnaltrexone (12 mg OD)						
Random-effects	1.6 [-1.02, 4.17]	1.6 [-1.06, 4.23]	2.3 [0.76, 6.97]	-	3.01 [0.6, 17.81]	1.58 [0.5, 5.11]
Fixed-effects	1.6 [1.06, 2.14]	1.6 [1.06, 2.14]	2.29 [1.46, 3.63]	-	2.98 [0.93, 11.47]	1.58 [1, 2.47]
Methylnaltrexone (12 mg QAD)						
Random-effects	0.6 [-2.05, 3.14]	0.6 [-2.05, 3.29]	1.33 [0.44, 4.06]	-	4.07 [0.83, 23.45]	1.33 [0.42, 4.3]
Fixed-effects	0.6 [0.04, 1.14]	0.6 [0.04, 1.14]	1.34 [0.85, 2.1]	-	4.03 [1.34, 15]	1.33 [0.85, 2.1]
Methylnaltrexone (150 mg OD)						
Random-effects	0.17 [-2.35, 2.78]	0.17 [-2.45, 2.79]	-	-	-	-
Fixed-effects	0.17 [-0.23, 0.57]	0.17 [-0.23, 0.57]	-	-	-	-
Methylnaltrexone (300 mg OD)						
Random-effects	0.69 [-1.82, 3.3]	0.68 [-2, 3.34]	-	-	-	-
Fixed-effects	0.68 [0.22, 1.14]	0.68 [0.22, 1.14]	-	-	-	-
Methylnaltrexone (450 mg OD)						

Random-effects	0.69 [-1.88, 3.33]	0.68 [-1.97, 3.34]	-	-	-	-
Fixed-effects	0.69 [0.26, 1.12]	0.69 [0.26, 1.12]	-	-		-
Naloxone PR (FRC)						
Random-effects	-	-	-	2.81 [1.63, 4.73]	0.73 [0.26, 2.36]	-
Fixed-effects	-	-	-	2.81 [2.05, 3.9]	0.66 [0.33, 1.29]	-
Naloxone (10 mg BD)						
Random-effects	-	-	-	-	7.65 [0.71, 270.43]	-
Fixed-effects	-	-	-	-	6.75 [0.9, 171]	-
Naloxone (20 mg BD)						
Random-effects	-	-	-	-	9.62 [0.9, 309.51]	-
Fixed-effects	-	-	-	-	8.34 [1.19, 203.6]	-
Naloxone (40 mg BD)						
Random-effects	-	-	-	-	16.2 [1.66, 535.39]	-
Fixed-effects	-	-	-	-	13.99 [2.19, 338.1]	-

Abbreviations: BD, twice daily; CrI., credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse event; MD, mean difference; OD, once daily; OR, odds ratio; QAD, every other day; PR, prolonged release; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.
† Defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
‡ Defined as the proportion of patients with ≥3 CSBMs/week at four weeks

6.7.7 *Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible*

These analyses were characterised by a moderate-to-high level of heterogeneity. The estimate of random-effects variance (sqrt(τ)) were higher overall in the focused network including treatments relevant to the final scope than the estimates in the MTC analyses with a broader network including additional treatments. This increase in statistical heterogeneity is driven by the limited MTC network used for these analyses. That is, the removal of some of the comparators that had two or more trials estimating the same comparison (alvimopan and lubiprostone), contributed to the estimate of random effects variance. In these analyses, the estimate of the random effects variance almost exclusively relies on the KODIAC trials.

Table 59: Estimates of random effects variance from Bayesian MTC

Outcome	Sqrt(τ) [median]*		Number of studies of the same comparison [n]
	Anticipated licensed population	Anticipated licensed population + Step 3 opioids	
Mean change in SBMs per week, from baseline to average over 4 weeks	0.3127	0.4677	Naloxegol 12.5 mg vs placebo [2] Naloxegol 25 mg vs placebo [2] Naloxegol 25 mg vs naloxegol 12.5 mg [2]
Mean change in SBMs per week, from baseline to average over 4–12 weeks	0.3106	0.475	Naloxegol 12.5 mg vs placebo [2] Naloxegol 25 mg vs placebo [2] Naloxegol 25 mg vs. naloxegol 12.5 mg [2]
SBM Response†	0.2372	0.3379	Naloxegol 12.5 mg vs placebo [2] Naloxegol 25 mg vs placebo [2] Naloxegol 25 mg vs naloxegol 12.5 mg [2]
CSBM Response‡	0.219	0.1987	Naloxegol 25 mg vs placebo [2] Naloxone PR FRC vs placebo [3]
TEAEs at 4 weeks	0.2298	0.482	Naloxegol 12.5 mg vs placebo [2] Naloxegol 25 mg vs placebo [2] Naloxegol 25 mg vs naloxegol 12.5 mg [2]
DAEs 4–12 wks pooled	0.4957	0.3929	Naloxone PR FRC vs placebo [2] Naloxegol 12.5 mg vs placebo [2] Naloxegol 25 mg vs placebo [2] Naloxegol 25 mg vs naloxegol 12.5 mg [2]

Abbreviations: CSBM, complete spontaneous bowel movement; DAE, discontinuations due to adverse events; FRC, fixed ratio combination; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse events.
* This value is from base case analysis, which used a random-effects model.
† Defined as the proportion of patients with ≥3 SBMs/week (%) over a four-week treatment period.
‡ Defined as the proportion of patients with ≥3 CSBMs/week at four weeks.

Overall, the direct meta-analysis results more often yielded statistically conclusive results than the MTC (see section 6.6) . This is likely due to the heterogeneity seen between the

KODIAC 4 and KODIAC 5 trial data, as fixed-effects sensitivity analyses of the MTC also showed similarly narrow credible intervals. The heterogeneity in the anticipated licensed population + Step 3 opioids results stems from counterintuitive differences between the results from the former and the overall anticipated licensed population. There was no heterogeneity for any of the outcomes of interest for the anticipated licensed population. With respect to the naloxegol studies, the evidence of heterogeneity was weak from a statistical viewpoint.

6.7.8 *If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.*

Due to the small number of trials in the network, sensitivity analyses were not considered to be of value. However, Bucher indirect comparisons have been carried out in addition to the MTCs due to the small number of trials (see Section 6.7.9).

6.7.9 *Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.*

Bucher indirect comparison

In addition to MTC analyses, each of these comparisons were also examined via Bucher indirect comparison methods. This method examines the same comparisons as the MTC, without incorporating ancillary arms of the evidence network. Overall, Bucher indirect comparison results more often yielded statistically conclusive results than the MTC. With the Bucher indirect comparison, there was no evidence of heterogeneity with the exception of the naloxegol trials. With respect to the naloxegol studies, the evidence of heterogeneity was weak from a statistical viewpoint (see section 6.6, Table 40).

The Bucher indirect comparisons yielded new statistically conclusive results for naloxegol versus select doses of methylnaltrexone on the mean change in SBMs per week and DAE analyses. Naloxegol 25 mg was associated with statistically significant increased mean changes in SBMs per week at 4 weeks and 4–12 weeks compared with subcutaneous methylnaltrexone (12 mg QAD) and all oral doses of methylnaltrexone in the anticipated licensed population and the anticipated licensed population with Step 3 opioids. Naloxegol 12.5 mg was also associated with statistically significant increases in mean changes in SBMs per week at 4 weeks compared with oral methylnaltrexone (150 mg OD) in both populations. In addition, naloxegol 12.5 mg was associated with statistically significant reductions in ORs for DAEs compared with subcutaneous methylnaltrexone (12 mg QAD) in both the anticipated licensed population and the anticipated licensed population with Step 3 opioids. These differences are presented in Table 60-Table 63.

Table 60: Results from Bucher indirect comparisons in the anticipated licensed population – naloxegol 12.5 mg vs comparators

Treatment	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response† (OR [95%CrI])	CSBM Response‡ (OR [95%CrI])	DAEs (OR [95%CrI])	TEAEs (OR [95%CrI])
	4 weeks	4–12 weeks				
Methylnaltrexone (12 mg OD)	-0.8 [-1.49, -0.11]	-1.05 [-1.73, -0.38]	0.86 [0.47, 1.56]	--	0.24 [0.05, 1.07]	0.67 [0.37, 1.22]
Methylnaltrexone (12 mg QAD)	0.2 [-0.49, 0.89]	-0.05 [-0.73, 0.63]	1.48 [0.81, 2.68]	--	0.18 [0.04, 0.77]**	0.79 [0.44, 1.43]
Methylnaltrexone (150 mg OD)	0.63 [0.05, 1.21]**	0.38 [-0.19, 0.94]	--	--	--	--
Methylnaltrexone (300 mg OD)	0.12 [-0.51, 0.75]	-0.13 [-0.75, 0.48]	--	--	--	--
Methylnaltrexone (450 mg OD)	0.11 [-0.50, 0.72]	-0.14 [-0.74, 0.45]	--	--	--	--
Naloxone PR (FRC OD)	--	--	--	--	0.83 [0.14, 4.74]	--
Naloxone (10 mg BD)	--	--	--	--	0.13 [0.01, 1.36]	--
Naloxone (20 mg BD)	--	--	--	--	0.1 [0.01, 1.08]	--
Naloxone (40 mg BD)	--	--	--	--	0.06 [0.01, 0.63]*	--

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; LIR, laxative inadequate responder; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.
* Credible interval excludes the null point of 1 (for ORs) or 0 (for mean differences).
**Statistically conclusive result (i.e. 95% CrI excludes the null point of 1 or 0), which was not so in the corresponding MTC analysis.
† Defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
‡ Defined as the proportion of patients with ≥3 SBMs/week and ≥1 SBM per week increase from baseline for 75% of weeks.

Table 61: Results from Bucher indirect comparisons in the anticipated licensed population – naloxegol 25 mg vs. comparators

	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response† (OR [95%CrI])	CSBM Response‡ (OR [95%CrI])	DAEs (OR [95%CrI])	TEAEs (OR [95%CrI])
Treatment	**4 weeks**	**4–12 weeks**				
Methylnaltrexone (12 mg OD)	0.25 [-0.49, 0.98]	-0.15 [-0.88, 0.59]	0.81 [0.45, 1.47]	--	0.74 [0.18, 2.93]	1.24 [0.69, 2.22]
Methylnaltrexone (12 mg QAD)	1.25 [0.51, 1.98]**	0.85 [0.12, 1.59]**	1.39 [0.77, 2.53]	--	0.55 [0.14, 2.11]	1.46 [0.81, 2.62]
Methylnaltrexone (150 mg OD)	1.68 [1.04, 2.31]**	1.28 [0.65, 1.92]**	--	--	--	--
Methylnaltrexone (300 mg OD)	1.17 [0.49, 1.84]**	0.77 [0.10, 1.45]**	--	--	--	--
Methylnaltrexone (450 mg OD)	1.16 [0.50, 1.81]**	0.763 [0.12, 1.42]**	--	--	--	--
Naloxone PR (FRC OD)	--	--	--	0.86 [0.49, 1.50]	2.55 [0.49, 13.19]	--
Naloxone (10 mg BD)	--	--	--	--	0.39 [0.04, 3.89]	--
Naloxone (20 mg BD)	--	--	--	--	0.32 [0.03, 3.09]	--
Naloxone (40 mg BD)	--	--	--	--	0.19 [0.02, 1.79]	--

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; LIR, laxative inadequate responder; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.
* Credible interval excludes the null point of 1 (for ORs) or 0 (for mean differences).
**Statistically conclusive result (i.e. 95% CrI excludes the null point of 1 or 0), which was not so in the corresponding MTC analysis.
† Defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
‡ Defined as the proportion of patients with ≥3 SBMs/week and ≥1 SBM per week increase from baseline for 75% of weeks.

Table 62: Results from Bucher indirect comparisons in the anticipated licensed population with Step 3 opioids – naloxegol 12.5 mg vs. comparators

	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response† (OR [95%CrI])	CSBM Response‡ (OR [95%CrI])	DAEs (OR [95%CrI])	TEAEs (OR [95%CrI])
Treatment	**4 weeks**	**4–12 weeks**				
Methylnaltrexone (12 mg OD)	-0.51 [-1.26, 0.25]	-0.81 [-1.54, -0.09]	1.13 [0.48, 2.66]	--	0.22 [0.04, 1.14]	0.71 [0.33, 1.51]
Methylnaltrexone (12 mg QAD)	0.50 [-0.26, 1.25]	0.19 [-0.54, 0.92]	1.94 [0.83, 4.57]	--	0.16 [0.03, 0.83]**	0.83 [0.39, 1.78]
Methylnaltrexone (150 mg OD)	0.93 [0.27, 1.58]**	0.62 [-0.01, 1.24]	--	--	--	--
Methylnaltrexone (300 mg OD)	0.42 [-0.28, 1.11]	0.11 [-0.56, 0.78]	--	--	--	--
Methylnaltrexone (450 mg OD)	0.41 [-0.27, 1.08]	0.10 [-0.55, 0.75]	--	--	--	--
Naloxone PR (FRC OD)	--	--	--	--	0.77 [0.19, 4.95]	--
Naloxone (10 mg BD)	--	--	--	--	0.12 [0.01, 1.38]	--
Naloxone (20 mg BD)	--	--	--	--	0.1 [0.01, 1.09]	--
Naloxone (40 mg BD)	--	--	--	--	0.06 [0.01, 0.64]*	--

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; LIR, laxative inadequate responder; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.
* Credible interval excludes the null point of 1 (for ORs) or 0 (for mean differences).
**Statistically conclusive result (i.e. 95% CrI excludes the null point of 1 or 0), which was not so in the corresponding MTC analysis.
† Defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
‡ Defined as the proportion of patients with ≥3 SBMs/week and ≥1 SBM per week increase from baseline for 75% of weeks.

Table 63: Results from Bucher indirect comparisons in the anticipated licensed population with Step 3 opioids – naloxegol 25 mg vs comparators

	Mean Change in SBMs per Week (MD [95%CrI])		SBM Response† (OR [95%CrI])	CSBM Response‡ (OR [95%CrI])	DAEs (OR [95%CrI])	TEAEs (OR [95%CrI])
Treatment	**4 weeks**	**4–12 weeks**				
Methylnaltrexone (12 mg OD)	0.67 [-0.13, 1.47]	0.33 [-0.47, 1.13]	1.15 [0.6, 2.22]	--	1.02 [0.24, 4.33]	1.36 [0.56, 3.29]
Methylnaltrexone (12 mg QAD)	1.67 [0.87, 2.47]**	1.33 [0.53, 2.13]**	1.98 [1.03, 3.8]**	--	0.75 [0.18, 3.12]	1.6 [0.66, 3.88]
Methylnaltrexone (150 mg OD)	2.10 [1.4, 2.81]**	1.76 [1.05, 2.47]**	--	--	--	--
Methylnaltrexone (300 mg OD)	1.59 [0.84, 2.34]**	1.25 [0.50, 2.00]**	--	--	--	--
Methylnaltrexone (450 mg OD)	1.58 [0.85, 2.31]**	1.24 [0.51, 1.97]**	--	--	--	--
Naloxone PR (FRC OD)	--	--	--	1.37 [0.75, 2.51]	3.52 [0.64, 19.26]	--
Naloxone (10 mg BD)	--	--	--	--	0.54 [0.05, 5.59]	--
Naloxone (20 mg BD)	--	--	--	--	0.44 [0.04, 4.44]	--
Naloxone (40 mg BD)	--	--	--	--	0.27 [0.03, 2.58]	--

Abbreviations: BD, twice daily; CrI, credible interval; CSBM, complete spontaneous bowel movement; DAE, discontinuation due to adverse events; FRC, fixed ratio combination; LIR, laxative inadequate responder; MD, mean difference; OR, odds ratio; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.
* Credible interval excludes the null point of 1 (for ORs) or 0 (for mean differences).
**Statistically conclusive result (i.e. 95% CrI excludes the null point of 1 or 0), which was not so in the corresponding MTC analysis.
† Defined as the proportion of patients with ≥3 SBMs/week (%) over 4-week treatment period.
‡ Defined as the proportion of patients with ≥3 SBMs/week and ≥1 SBM per week increase from baseline for 75% of weeks.

Limitations of the analysis

The results from the MTC subgroup analyses should be interpreted in the context of the following limitations:

- Subgroup data for the anticipated licensed population and anticipated licensed population + Step 3 opioids were available only for the KODIAC 4 and 5 trials, and data included from the comparator trials are based on the enrolled, or intention-to-treat, populations. However, as described in section 6.7.2, 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.
- The analysis of CSBM response includes one trial identified outside the scope of the systematic review, having been published in a conference not prospectively included in the review protocol.
- Because a limited MTC network (only including trials of methylnaltrexone, naloxone, and naloxegol) was utilised for these analyses, most of the random effect variance is based on the estimate of heterogeneity between the KODIAC trials (as there existed fewer trials in the analysis able to contribute to the estimate of heterogeneity). As these subgroups included smaller numbers of patients, these estimates are inherently less precise. As it was not possible to estimate heterogeneity for comparisons in which only one study was available, KODIAC 4 and KODIAC 5 contributed to more statistical heterogeneity in the analyses and thus wider credible intervals, especially for the anticipated licensed population + Step 3 opioids analysis (the smaller of the two subgroups) for some outcomes. While it is possible that other treatments that are only investigated in one trial may have led to statistical heterogeneity if investigated more than once, it is not possible to determine whether that is the case, and treatment comparisons that are only investigated once cannot lead to an increase in statistical heterogeneity.
- There was a general lack of data similar to the naloxegol (KODIAC 4 and 5) trials, and many of the included trials were of poorer or unclear quality, particularly with regard to randomisation and concealment of treatment allocation methods. Available data to be used in comparisons between naloxone and other treatments were particularly limited. Studies duration varied from 4 weeks to 12 weeks. There were also considerable differences between studies in terms of patient baseline characteristics, definitions of OIC and permitted concomitant medications, as detailed in Section 6.7.5. Differences in the available data for naloxegol compared to methylnaltrexone and oxycodone/naloxone partly relate to the differences between the treatments eg. naloxegol is an oral treatment vs SC methylnaltrexone and naloxegol can be used with any opioid and any dose unlike oxycodone/naloxone.
- link to the fact that, as the first oral treatment licensed for OIC, naloxegol is confers several advantages over the other available treatments:

Conclusion

- 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. As described in section 6.7.5, reducing the size of the evidence network from the full network – including a greater number of treatment interventions – to the England and Wales specific network, including only comparators of interest in the England and Wales – did not affect point estimates. However, credible intervals were increased when the size of the network was reduced, thereby making it less likely that statistical significance would be achieved. A number of newly statistically significant results were obtained using Bucher indirect comparisons, which were not subject to large credible intervals. Generally, naloxegol was not statistically superior to methylnaltrexone or naloxone-oxycodone in any anticipated licensed population or anticipated licensed population + Step 3 opioids analysis, but demonstrated non-statistically significant favourable trends in some cases, as summarised below:

- 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

6.8 *Non-RCT evidence*

6.8.1 ***If non-RCT evidence is considered (see Section 6.2.7), please repeat the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in Sections 10.6 and 10.7, appendices 6 and 7.***

Study selection

The identification of non-RCT evidence is described in Sections 6.1 and 6.2. Following assessment and exclusion of studies based on title, abstract and full text, one record for a non-RCT was identified; study KODIAC 16 (D3820C00016) (59).

However, as this particular study is only relevant to a paediatric population with OIC and not adults, it was not considered relevant for this submission. A critical appraisal and results of KODIAC 16 are presented in section 10.23.

6.9 *Adverse events*

Summary of safety data

- Safety data from the two pivotal 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
  - The majority of GI-related AEs occurred within the first 7 days of treatment and with the exception of AEs of abdominal pain and flatulence , the majority of GI events typically were resolved within 1 week
- There were no notable differences in the type or frequency of serious adverse events (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
- Long-term treatment with naloxegol (52 weeks) was generally well tolerated with an AE profile that was largely consistent with that observed in the confirmatory pivotal 12 week RCTs
- There were no clinically meaningful differences between the naloxegol and placebo/Usual Care groups with respect to vital signs, ECG, physical examination and laboratory analyses
- There were no clinically important differences across treatment groups with respect to cardiovascular AEs
  - Naloxegol treatment was not associated with an increased frequency of major adverse cardiac events compared with placebo and Usual Care treatment groups
  - There were no notable differences between treatment groups in any of the studies with respect to AEs related to changes in blood pressure
- No GI events in any of the safety evaluations of naloxegol were adjudicated as bowel perforations

- There were no clinically important differences in centrally mediated opioid withdrawal signs in patients receiving naloxegol compared with placebo treatment groups
  - Longer exposure to naloxegol (52 weeks) was not associated with clinically relevant differences in opioid withdrawal compared with Usual Care
- Post-hoc analysis of the anticipated licensed population and anticipated licensed population + Step 3 opioids in KODIAC 4 and KODIAC 5 demonstrated that there were no clinically meaningful increases in average pain score in patients receiving naloxegol as measured by the NRS

The identification of clinical evidence is described in Sections 6.1 and 6.2. All trials relevant to this submission are listed in Table 5 in section 6.2.4 and Table 6 in section 6.2.7. Details of other RCTs included in the systematic review and the MTC for the comparator interventions are provided in section 6.7. The methodology, critical appraisal and results of relevant trials that are designed primarily to assess safety outcomes are presented in Section 6.9.1. Safety results from other studies, primarily designed to assess efficacy are described in Section 6.9.2.

6.9.1 ***If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.***

Summary of methodology of trials designed to primarily assess safety

In addition to KODIAC 4 and KODIAC 5, two studies were primarily designed to assess the safety and tolerability of naloxegol in OIC patients with non-cancer pain. KODIAC 7 was a 12 week extension study of KODIAC 4 while KODIAC 8 was a 52 week open label study. Neither of these studies were powered to assess a specific safety endpoint, but rather general safety and tolerability. The methodology of the relevant trials is summarised in Table 64 and Table 65.

Safety extension study: KODIAC 7

Table 64: Methodology of KODIAC 7

Study	KODIAC 7
Study objective	To assess the safety and tolerability of naloxegol in patients with non-cancer related pain and OIC
Location	The study was conducted in 52 centres in the US
Design	A 12 week extension study of KODIAC 4
Method of randomisation	Patients who successfully completed KODIAC 4 were to continue on their randomised doses of study drug without

	unblinding
Method of blinding (care provider, patient and outcome assessor)	Naloxegol 12.5 mg and 25 mg tablets were identical in size and colour to their respective placebo tablets. Patients received two tablets per dose (i.e. either 12.5 mg active plus 25 mg placebo, 12.5 mg placebo plus 25 mg active or two placebo doses). To maintain blinding, the randomisation scheme was concealed from investigators and participants. In the case of a medical emergency, the treatment code could be broken via an interactive voice response system, as instructed in the relevant user manual provided at each study centre.
Intervention(s) (n =) and comparator(s) (n =)	12 additional weeks of either: • Naloxegol 12.5 mg OD (n=96) • Naloxegol 25 mg OD (n=98) • Placebo OD (n=103)
Permitted and disallowed concomitant medications	As per KODIAC 4 study (Table 7)
Rescue medication	As per KODIAC 4 study (Table 7)
Discontinuation of study therapy	As per KODIAC 4 study (Table 7)
Assessments	Assessments were conducted at Weeks 4, 8 and 12
Primary safety outcomes	Incidence, nature and intensity of AEs, treatment-related AEs, SAEs, AEs resulting in discontinuation and AEs of special interest
Other safety outcomes	• Change from baseline† in the mean daily opioid dose for Weeks 1–4 and Weeks 1–12 • Change from baseline† in the mean NRS pain score for Weeks 4, 8 and 12 • Observed values and change from baseline† in composite score in mHS • Change in ECGs • Laboratory assessments and physical examinations • Suicidal behaviour/suicidal ideation based on the C-SSRS
Other outcomes	• Change from baseline in PAC-SYM total score and each domain score for Weeks 4, 12 and 14 • Data on the EQ-5D questionnaire at enrolment, Weeks 4, 12, and 14.
Duration of follow-up	Follow-up visit 2 weeks after the last dose of study drug

Abbreviations: AE, adverse events; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; EQ-5D, EuroQoL 5 Dimension; mHS, Modified Himmelsbach scale; NRS, numeric rating scale; OD, once daily; OIC, opioid-induced constipation; PAC-SYM, Patient Assessment of Constipation Symptoms questionnaire; SAE, serious adverse event.
†For all parameters, baseline was defined as the latest non-missing value collected prior to the first dose of study drug in KODIAC 4, screening, Visit 1 or Week 0, Visit 3 as appropriate.

Long-term safety study: KODIAC 8

Table 65: Methodology of KODIAC 8

Study	KODIAC 8
Study objective	To assess the long-term safety and tolerability of naloxegol versus Usual Care in patients with non-cancer

	related pain and OIC
Location	United States
Design	A Phase III, open-label, randomised, parallel group study
Duration of study	A 2 week initial screening period was followed by a 2 week OIC confirmation period and a 52 week treatment period
Method of randomisation	Patients were recruited in one of three ways: • Patients were enrolled directly from the KODIAC 5 RCT, or • Patients were enrolled from the KODIAC 7 extension study of KODIAC 4, or • Patients had not previously participated in any naloxegol study Patients were randomised in a 2:1 ratio to receive either naloxegol or Usual Care. Patients from KODIAC 4 or 5 could be randomised to a different treatment in KODIAC 8 than received previously. Patients enrolling from a previous study had no break in treatment.
Method of blinding (care provider, patient and outcome assessor)	N/A
Intervention(s) (n =) and comparator(s) (n =)	52 weeks of either • Naloxegol 25 mg (n=563) • Usual Care (n=281)
Permitted and disallowed concomitant medications	<u>New patients</u> New patients were required to stop all laxatives/bowel regimens during the OIC confirmation period and followed the guidelines for bisacodyl rescue medication as described for KODIAC 4/5 (Table 7). Guidelines differed during the treatment period according to the assigned treatment arm. <u>Naloxegol treatment arm</u> With the exception of bisacodyl rescue medication, patients were not allowed to take any additional constipation medications unless there was a need for urgent intervention. <u>Usual Care treatment arm</u> Constipation was managed using laxatives prescribed by the investigator. Peripheral μ-opioid antagonists (e.g. methylnaltrexone) were not permitted. Patients were not assigned any specific rescue medication. <u>Permitted medications</u> As described for KODIAC 4/5 (Table 7) <u>Other disallowed medications</u> As described for KODIAC 4/5 (Table 7)
Discontinuation of study therapy	• As described for KODIAC 4/5 (Table 7)
Assessments	Patient visits were conducted on Weeks 0, 1 and 2, and at monthly intervals up until Month 12.
Primary safety outcomes	• Incidence, nature and intensity of AEs, treatment-related AEs, SAEs • Changes in laboratory assessments, weight, physical examination • Change in ECG

	• Change from baseline in the mean NRS pain score for Weeks 1 and 2, and Months 1, 2, 3, 6, 9, and 12 • Change from baseline in the mean daily opioid dose for randomisation to Month 1, Months 1–3, 3–6, 6–9 and 9–12 • Change from baseline in composite score in mHS at Week 1, and Months 1, 3, 6, 9, and 12 • Suicidal behaviour/ideation based on the C-SSRS
Secondary safety outcomes	• As reported for the primary outcomes with the addition of mean bisacodyl dose/week for naloxegol patients from randomisation to Month 1, and Months 1–3, 3–6, 6–9 and 9–12
Duration of follow-up	2 weeks after Month 12

Abbreviations: AE, adverse event; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; mHS, Modified Himmelsbach scale; N/A, not applicable; NRS, numeric rating scale; OIC, opioid-induced constipation; SAE, serious adverse event.

Participants

The inclusion and exclusion criteria for the relevant safety studies are summarised in Table 66 and Table 67.

Safety extension study: KODIAC 7

Table 66: Eligibility criteria in KODIAC 7

Study	Inclusion criteria	Exclusion criteria
KODIAC 7	• Completion of KODIAC 4 • Males and females between the ages of ≥18 and ≤85 years • Continued to receive a stable maintenance opioid regimen (30 mg to 1000 mg of oral morphine or morphine equivalents daily)	• As per KODIAC 4 (Table 8) • Previous participation in any study with naloxegol with the exception of KODIAC 4

Long-term safety study: KODIAC 8

Table 67: Eligibility criteria in KODIAC 8

Study	Inclusion criteria	Exclusion criteria
KODIAC 8	• Males and females between the ages of ≥18 and ≤85 years New patients only • As described for KODIAC 4 and 5 (Table 8) Patients enrolling from KODIAC 5 or 7 • Receiving a stable maintenance opioid regimen (30 to 1000 mg oral morphine or morphine equivalents daily) Patients randomised to usual care • Willingness to adhere to using approved laxatives throughout the 52 week treatment period	• As described for KODIAC 4 and 5 (Table 8), and • Increased risk for ventricular arrhythmia, family history of sudden cardiac death, family history of long QT syndrome, myocardial infarction within the last 6 months, overt cardiovascular disease

Patient characteristics at baseline

Safety extension study: KODIAC 7

Patient characteristics at baseline in KODIAC 7 are summarised in Table 68. In general, baseline characteristics were similar across patient groups. The majority of patients were white (74.7%), the mean age was 52.3 years and a higher proportion of patients were female (60.8%). Back pain (53.4% of patients), “other” (19.3% of patients) and arthritis (11.5% of patients) were the most common primary reasons for pain reported. The median time that patients had been on their current opioid regimen was 2 years for all treatment groups.

Table 68: Characteristics of the ITT population in KODIAC 7

KODIAC 7	Naloxegol 12.5 mg (n=95)	Naloxegol 25 mg (n=98)	Placebo (n=103)
Characteristic			
Age, mean (SD)	51.8 (9.51)	52.6 (10.19)	52.6 (10.0)
Female, n (%)	62 (65.3)	57 (58.2)	61 (59.2)
Race, n (%)			
White	71 (74.7)	74 (75.5)	76 (73.8)
Black or African American	24 (25.3)	22 (22.4)	23 (22.3)
Asian	0	0	1 (1.0)
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska native	0	0	1 (1.0)
Other	0	2 (2.0)	2 (1.9)
BMI (kg/m^2)			
<18.5	1 (1.1)	0	0

18.5 – <30	48 (50.5)	36 (36.7)	51 (49.5)
≥30	46 (48.4)	62 (63.3)	52 (50.5)
Primary reason for pain, n (%)			
Back pain	54 (56.8)	51 (52.0)	53 (51.5)
Joint pain	2 (2.1)	4 (4.1)	3 (2.9)
Fibromyalgia	3 (3.2)	6 (6.1)	9 (8.7)
Headache/migraine	1 (1.1)	1 (1.0)	2 (1.9)
Arthritis	8 (8.4)	11 (11.2)	15 (14.6)
Neuralgia	1 (1.1)	3 (3.1)	0
Pain syndrome	5 (5.3)	4 (4.1)	2 (1.9)
Other	21 (22.1)	18 (18.4)	18 (17.5)
Lifetime opioid use (months),median	77.0	70.0	60.0
Duration of current opioid use (months), median	24.0	24.0	24.0

Abbreviations: BMI, body mass index; SD, standard deviation.

Long-term safety study: KODIAC 8

Patient characteristics at baseline in KODIAC 8 are summarised in Table 69. In general, baseline demographic data across both treatment groups were similar. The majority of patients were white (78%), a higher proportion of patients were female (66.2%), and the mean age of patients was 52.7 years. The most common primary reasons for pain in new patients and rollover patients were back pain (55.9% and 59%, respectively), arthritis (21.1% and 10.8%, respectively) and “other” (8.5% and 15.7%, respectively). Localised musculoskeletal pain was reported as the primary type of pain in the “other” category. The median duration of current opioid use ranged from 2.2–3 years in new patients and 2–3 years in rollover patients.

Table 69: Characteristics of the safety analysis population in KODIAC 8

KODIAC 8	Naloxegol 25 mg (n=534)	Usual Care (n=270)
Age, mean (SD)	52.8 (10.09)	52.7 (10.24)
Female, n (%)	353 (66.1)	179 (66.3)
Race, n (%)		
White	423 (79.2)	204 (75.6)
Black or African American	98 (18.4)	60 (22.2)
Asian	4 (0.7)	3 (1.1)
Native Hawaiian or other Pacific Islander	0	0
American Indian or Alaska native	4 (0.7)	1 (0.4)
Other	5 (0.9)	2 (0.7)
BMI (kg/m^2)		
<18.5	3 (0.6)	1 (0.4)
18.5 – <30	262 (49.2)	120 (44.4)

≥30	267 (50.2)	149 (55.2)
Pain history – new patients	**Naloxegol 25 mg (n=481)**	**Usual Care (n=240)**
Primary reason for pain, n (%)		
Back pain	272 (56.5)	131 (54.6)
Joint pain	20 (4.2)	15 (6.3)
Fibromyalgia	33 (6.9)	14 (5.8)
Headache/migraine	1 (0.2)	2 (0.8)
Arthritis	39 (8.1)	22 (9.2)
Neuralgia	5 (1.0)	3 (1.3)
Pain syndrome	8 (1.7)	3 (1.3)
Other	103 (21.4)	49 (20.4)
Lifetime opioid use (months),median	72.0	78.0
Duration of current opioid use (months), median	36.0	26.5
Pain history – rollover patients	**Naloxegol 25 mg (n=53)**	**Usual Care (n=30)**
Primary reason for pain, n (%)		
Back pain	30 (56.6)	19 (63.3)
Joint pain	3 (5.7)	1 (3.3)
Fibromyalgia	5 (9.4)	2 (6.7)
Headache/migraine	0	0
Arthritis	7 (13.2)	2 (6.7)
Neuralgia	1 (1.9)	0
Pain syndrome	0	0
Other	7 (13.2)	6 (20.0)
Lifetime opioid use (months),median	60.0	108.0
Duration of current opioid use (months), median	24.0	36.0

Abbreviations: BMI, body mass index; SD, standard deviation.

Outcomes

The outcomes investigated in the identified safety studies and their relevance to the decision problem are presented in Table 70 and Table 71.

Safety extension study: KODIAC 7

Table 70: Primary and secondary outcomes of KODIAC 7

Trial no. (acronym)	Primary outcome(s) and measures	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
KODIAC 7	Incidence, nature and intensity of AEs, treatment-related AEs, SAEs, AEs resulting in discontinuation and AEs of special interest	• Change from baseline in the mean daily opioid dose for Weeks 1–4 and Weeks 1–12 • Change from baseline in the mean NRS pain score for Weeks 4, 8 and 12 • Observed values and change from baseline in composite score in mHS • Change in ECGs • Laboratory assessments and physical examinations • Change from baseline in PAC-SYM total score and each domain score for Weeks 4, 12 and 14 • Suicidal behaviour/suicidal ideation based on the C-SSRS	• The NRS is a self-reported scale in which patients rate their pain from 0 (no pain) to 10 (worst pain imaginable) (68) • The mHS scale is used to rate patients by examination for symptoms of opioid withdrawal (69). Patients are scored with respect to the following symptoms at the time of assessment: yawning, lacrimation, rhinorrhea, perspiration, tremor, mydriasis, piloerection, and restlessness. Symptoms are scored on a scale of 0–3, where 0=none, 1=mild, 2=moderate and 3=severe. • For discussion of PAC-SYM, see Table 11 • The C-SSRS is a method used to assess behaviour and ideation related to suicidal events and provides a summary of suicidality (70)

Abbreviations: AE, adverse events; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; mHS, Modified Himmelsbach scale; NRS, Numeric Rating Scale; PAC-SYM, Patient Assessment of Constipation Symptoms questionnaire; SAE, serious adverse event.

Long-term safety study: KODIAC 8

Table 71: Primary and secondary outcomes of KODIAC 8

Trial no. (acronym)	Primary outcome(s) and measures	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
KODIAC 8	• Incidence, nature and intensity of AEs, treatment-related AEs, SAEs • Changes in laboratory assessments, weight, physical examination • Change in ECG • Change from baseline in the mean NRS pain score for Weeks 1 and 2, and Months 1, 2, 3, 6, 9, and 12 • Change from baseline in the mean daily opioid dose for randomisation to Month 1, Months 1–3, 3–6, 6–9 and 9–12 • Change from baseline in composite score in mHS at Week 1, and Months 1, 3, 6, 9, and 12 • Suicidal behaviour/ideation based on the C-SSRS	• As reported for the primary outcomes with the addition of mean bisacodyl dose/week for naloxegol patients from randomisation to Month 1, and Months 1–3, 3–6, 6–9 and 9–12	• For discussion of NRS, mHS and C-SSRS see Table 70

Abbreviations: AE, adverse event; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; mHS, Modified Himmelsbach scale NRS, Numeric Rating Scale; SAE, serious adverse event.

Statistical analysis and definition of study groups

Safety extension study: KODIAC 7

Population datasets analysed

ITT analysis set: all randomised patients, with the exception of patients who had been randomised multiple times within the study program at different centres and who had signed informed consent to roll-over from KODIAC 4.

Safety analysis set: all patients who participated in KODIAC 4 and received at least one dose of study drug in the current study with the exception of patients who had been randomised multiple times within the study program at different centres.

mITT analysis set: a subset of the ITT analysis set that included patients in the safety analysis set who had at least 1 assessment for PAC-SYM or PAC-QoL beyond Day 1 of the current study.

The primary hypothesis in KODIAC 7 is presented in Table 72 with a summary of the statistical analysis conducted.

Table 72: Summary of statistical analyses in KODIAC 7

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
KODIAC 7	To compare the long-term safety and tolerability of naloxegol 12.5 mg and 25 mg vs placebo in patients continuing from KODIAC 4	No formal statistical analysis was conducted for this study. Categorical data was summarised using frequency and percentages and descriptive statistics were used for continuous data. The 25th and 75th percentiles were presented for the mHS, NRS, and mean daily opioid dose. Baseline was defined as the latest non-missing value collected prior to the first dose of study drug in KODIAC 4, screening, Visit 1 or Week 0, Visit 3 as appropriate for all parameters. An average over the OIC period was used as the baseline score for any parameters collected in the eDiary in KODIAC 4. Safety outcomes, NRS pain score, mHS score and EQ-5D were summarised using descriptive statistics.	N/A	The primary baseline for all outcome variables was defined as the latest non-missing value collected prior to the first dose of study drug in KODIAC 4. Patients withdrawing from treatment were not replaced in the study.

Abbreviations: EQ-5D, EuroQoL 5 dimension; mHS, Modified Himmelsbach scale; NRS, numeric rating scale

Long-term safety study: KODIAC 8

Population datasets analysed

Safety analysis set: all randomised patients who received at least one dose of study drug and patients who received Usual Care with the exception of with the exception of patients who had been randomised multiple times within the study program at different centres

No formal statistical analyses were conducted for any of the endpoints in KODIAC 8. Differences between open-label naloxegol and Usual Care were assessed using descriptive statistics. Data were presented separately for new and roll-over patients to avoid potential complication of interpretation of results. For new patients, baseline was defined as the latest non-missing value collected prior to the first dose of study drug in KODIAC 8. For patients entering the study from KODIAC 5 or KODIAC 7, the primary baseline was defined as the latest non-missing value collected prior to the first dose of study drug in the previous pivotal RCT (KODIAC 4 or 5). In addition, a supportive baseline was defined as the data collected at the final visit from the previous study.

Subgroup analyses

KODIAC 7

There were no subgroup analyses, either pre-planned or post-hoc, conducted in the KODIAC 7 study.

KODIAC 8: Pre-planned subgroup analyses

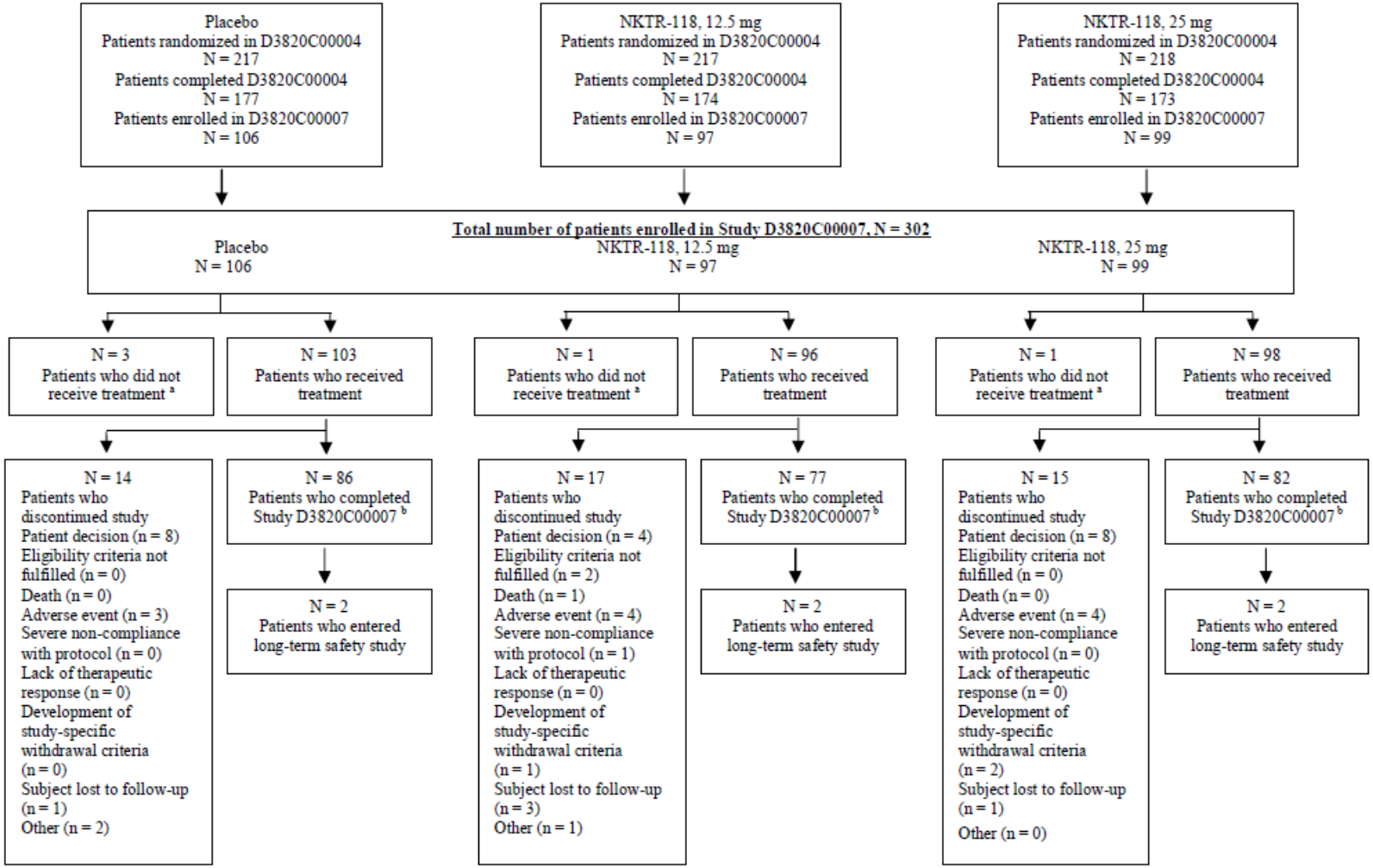
For new patients only, adverse events (AEs), serious adverse events (SAEs) and discontinuations were summarised for the following subgroups:

- Demographic characteristics: age group, sex, race, body mass index
- Response to laxatives: LIR, non/LIR
- Baseline opioid morphine equivalent dose units (<200 MEU/day, ≥200 MEU/day).

Participant flow

Consort flow charts showing the number of patients who were eligible to enter the relevant safety studies, and who were randomised and allocated to each treatment are presented in Figure 12 and Figure 13.

Figure 12: KODIAC 7 flow chart

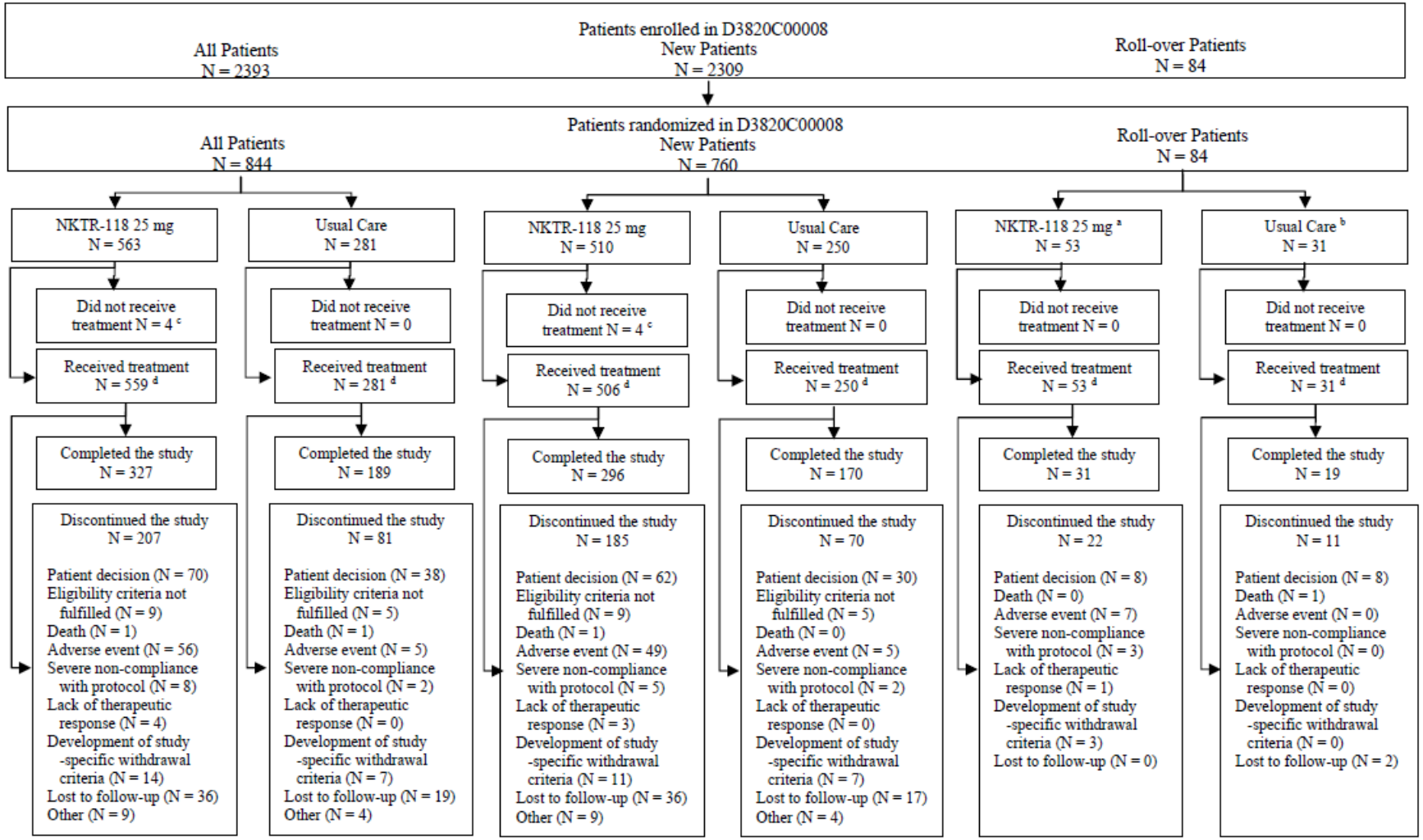


NKTR-118 = naloxegol

[a] Enrolled patients did not receive treatment due to: patient decision (1 placebo patient); eligibility criteria not fulfilled (1 patient each in the placebo and naloxegol 12.5 mg groups); lost to follow-up (1 patient each in the placebo and naloxegol 25 mg groups).

[b] Six patients had previously been randomised within the study program at a different centre so were excluded from the ITT and Safety analysis sets.

Figure 13: KODIAC 8 flow chart



NKTR-118 = naloxegol
[a] Forty nine patients from KODIAC 5 (previous naloxegol treatment: 12.5 mg, n=15; 25 mg, n=17; placebo, n=17). Four patients from KODIAC 7 (previous naloxegol treatment: 12.5 mg, n=1; 25 mg, n=2; placebo, n=1).

[b] Twenty eight patients from KODIAC 5 (previous naloxegol treatment: 12.5 mg, n=11; 25 mg, n=4; placebo, n=13). Two patients from KODIAC 7 (previous naloxegol treatment: 12.5 mg, n=1; 25 mg, n=0; placebo, n=1).
[c] Patients did not receive treatment due to: Patient decision (2 new patients in the naloxegol 25 mg group); and eligibility criteria not met (2 new patients in the naloxegol 25 mg group).
[d] Thirty six patients who received treatment (1 roll-over patient in the Usual Care group, 10 new patients in the Usual Care group, and 25 new patients in the naloxegol 25 mg group) had either: a) previously or concurrently participated in the programme at another centre; or b) been randomised at sites where data integrity issues were identified. These patients were therefore excluded from the Safety analysis set.

Critical appraisal of trials designed to primarily assess safety

A complete quality assessment for KODIAC 7 and 8 is provided in section 10.3.

A summary of the quality assessment results for KODIAC 7 and 8 are presented in Table 73

Table 73: Quality assessment results for KODIAC 7 and KODIAC 8

	KODIAC 7	KODIAC 8
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	No
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	No
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	N/A	N/A

6.9.2 ***Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.***

Safety Results: KODIAC 7

Datasets analysed

The safety analysis set in KODIAC 7 was used to assess all safety and tolerability variables and included all patients who participated in KODIAC 4 and received ≥1 dose of study drug in KODIAC 7. Since patients enrolled in KODIAC 7 continued to receive the same randomised treatment as received in KODIAC 4, any AEs recorded from Day 1 of KODIAC 7, up to and including the last day of study drug administration, were considered to be on-treatment events.

No formal statistical comparisons were carried out for any of the safety data in KODIAC 7. Unless specified, AE refers to treatment-emergent AE (TEAE) throughout this section.

Adverse events

The majority of AEs reported during KODIAC 7 were mild or moderate in intensity in all treatment groups. The number and percentage of patients who had ≥1 AE in any category during the treatment and follow-up periods are summarised in Table 74. One or more AEs were reported by 32 (34.0%) of patients treated with naloxegol 12.5 mg, 40 (41.2%) of patients treated with naloxegol 25 mg, and 33 (33.0%) of patients in the placebo group. The frequency of serious adverse events (SAEs) was low and similar across the naloxegol 12.5 mg, 25 mg and placebo groups (6.4%, 6.2% and 5.0%, respectively). One patient in the naloxegol 12.5 mg group died due to myocardial ischaemia. The death was not considered by the principal investigator to be related to study treatment. The number of patients discontinuing the study due to AEs was low and similar across all treatment groups.

Table 74: Summary of adverse events in KODIAC 7 (Safety analysis set)

Adverse events	Naloxegol 12.5 mg (n=94)	Naloxegol 25 mg (n=97)	Placebo (n=100)
Any AE, n (%)	32 (34.0)	40 (41.2)	33 (33.0)
Any AE leading to death, n (%)	1 (1.1)	0	0
Any SAE (including events leading to death), n (%)	6 (6.4)	6 (6.2)	5 (5.0)
Discontinuation due to AEs, n (%)	4 (4.3)	4 (4.1)	3 (3.0)

Abbreviations: AE, adverse event; SAE, serious adverse event.
Note: Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
Note: KODIAC 7 may have included a bias towards recruiting patients who had been observed to tolerate naloxegol well during the first 12 weeks in KODIAC 4. This may have been reflected in the lower incidence of new AEs observed overall in KODIAC 7 during weeks 12–24.

Upon entry into KODIAC 7, 79 (26.7%) of patients had an ongoing AE from the 12 week KODIAC 4 study. The most common ongoing AEs in the naloxegol treatment groups at entry into KODIAC 7 were gastrointestinal (GI) disorders (8.4% of naloxegol 12.5 mg patients and 13.3% of naloxegol 25 mg patients). Of the ongoing GI events, the most common event was abdominal pain, which was reported more frequently in the naloxegol 25 mg group. In the placebo group, the most common ongoing AEs were musculoskeletal and connective tissue disorders (7.8% of patients).

AEs occurring in ≥2% of patients in all treatment groups over the KODIAC 7 study period are presented in Table 75. For the naloxegol 12.5 mg treatment group, the most frequently reported AEs were diarrhoea and sinusitis, (5.3% and 3.2% of patients, respectively). In the naloxegol 25 mg group, the most frequently reported AEs were arthralgia (5.2% of patients), nausea , abdominal pain, gastroenteritis viral, and back pain (3.1% of patients each). In the placebo group, the most commonly reported AE was urinary tract infection (3.0% of patients). The predominance of GI AEs events which were observed in the confirmatory KODIAC 4 RCT (summarised in section 6.9.3) were not evident in the incidence of new AEs reported in this KODIAC 7 extension study.

Four patients had ongoing arthralgia at the start of KODIAC 7 (3.1% of patients in the naloxegol 25 mg group and 1% of patients in the placebo group). During KODIAC 7, 5.2% of patients in the naloxegol 25 mg group had an AE of arthralgia, one of whom had an event of arthralgia reported in KODIAC 4. Two of the 5 AEs of arthralgia were considered mild and three were considered severe in intensity. None of these events were considered to be related to study drug by the investigator and none of the 5 patients were withdrawn from the study due to arthralgia.

AEs by relationship to study drug

The majority of AEs reported in KODIAC 7 were not considered by the investigator to be related to study drug. During the study, AEs related to study treatment were reported in 3/29 patients with AEs in the naloxegol 12.5 mg treatment group, 2/36 patients in the naloxegol 25 mg group, and 2/30 patients in the placebo group.

Table 75: Adverse events occurring in ≥2% of patients in any treatment group, by preferred term, in KODIAC 7 (Safety analysis set)

Adverse event (MedDRA preferred term)	Number (%) patients†		
	Naloxegol 12.5 mg (n=94)	Naloxegol 25 mg (n=97)	Placebo (n=100)
Total no. of patients with any AE	29 (30.9)	36 (37.1)	30 (30.0)
Arthralgia	0	5 (5.2)	0
Nausea	1 (1.1)	3 (3.1)	1 (1.0)
Abdominal pain	1 (1.1)	3 (3.1)	0
Gastroenteritis viral	1 (1.1)	3 (3.1)	0
Back pain	0	3 (3.1)	1 (1.0)
Fall	0	3 (3.1)	0
Diarrhoea	5 (5.3)	2 (2.1)	1 (1.0)
Urinary tract infection	2 (2.1)	2 (2.1)	3 (3.0)
Upper respiratory tract infection	2 (2.1)	2 (2.1)	1 (1.0)
Muscle spasms	0	2 (2.1)	2 (2.0)
Vomiting	0	2 (2.1)	1 (1.0)
Cough	0	2 (2.1)	0
Sinusitis	3 (3.2)	1 (1.0)	1 (1.0)
Bronchitis	2 (2.1)	1 (1.0)	0
Pain in extremity	0	1 (1.0)	2 (2.0)
Depression	2 (2.1)	0	0
Fibromyalgia	0	0	2 (2.0)
Hypoaesthesia	0	0	2 (2.0)

Abbreviations: AE, adverse event.
†Patients are counted no more than once for incidence of AE by MeDRA preferred term.

Deaths

One patient in the naloxegol 12.5 mg group died due to a cardiovascular (CV) event (myocardial ischaemia) which was considered by the investigator as not related to study treatment.

Serious adverse events

In the naloxegol 12.5 mg, 25 mg and placebo groups, SAEs were reported in 5.3%, 5.2%, and 4.0% of patients respectively. No individual SAE was reported for more than one patient in any treatment group during the study.

Discontinuation due to AEs

The incidence of discontinuation due to study drug was low and similar across all three treatment groups in KODIAC 7. No individual discontinuation due to AE was reported for more than one patient in any treatment group during the treatment period. In the

naloxegol 12.5 mg and 25 mg groups and the placebo group, the number of patients discontinuing due to AEs was 4.3%, 4.1%, and 3.0%, respectively.

AEs of special interest

In KODIAC 7, AEs of special interest included selected CV events (i.e. major adverse CV events [MACE], congestive heart failure), serious GI adjudicated as bowel perforation events, AEs potentially related to abuse liability and AEs potentially related to opioid withdrawal.

One patient in the naloxegol 25 mg had a CV event of interest which was adjudicated as “heart failure requiring hospitalisation”. There were no GI events adjudicated as bowel perforation during the study. Two patients in the naloxegol treatment groups (one from each dosing group) had an AE related to opioid withdrawal. Neither event was considered by the investigator to be related to study drug. The proportion of patients with AEs of abuse potential was low and similar across the naloxegol 12.5 mg, 25 mg and the placebo group (2.1%, 2.1%, and 1.0% of patients, respectively).

Clinical laboratory parameters

No clinically important differences were observed in the analyses of mean changes in clinical chemistry, haematology or urinalysis parameters across the naloxegol and placebo groups during the study. One patient in the naloxegol 12.5 mg group had elevated alanine aminotransferase (ALT) during treatment but completed the study. No relevant differences in any vital sign parameters were observed across the treatment groups during the study.

Eight patients had a ≥7% decrease in weight during the study period: 1.1%, 4.1% and 3.0% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively.

Cardiovascular safety

There were no notable differences in analyses of mean changes in any ECG parameter across the naloxegol and placebo groups during the study. There were no clinically relevant differences between the naloxegol treatment groups compared with placebo with regard to systolic and diastolic blood pressure, heart rate or Fridericia corrected QT interval (QTcF) at any time point during the course of the study.

Additional safety observations

The following additional safety observations were also observed:

- There were no clinically important increases or decreases in the mean daily opioid dose observed in any of the treatment groups
- Throughout the study, average NRS pain scores were similar across the treatment groups
- From baseline to Week 24, mean opioid doses (mg/day) were similar across the three treatment groups
- Naloxegol treatment was not associated with clinically relevant changes in centrally mediated opioid withdrawal signs as assessed by the mHS
- There were no notable differences across the treatment groups with respect to suicidal behaviour or ideation as assessed by C-SSRS and AEs

Safety results: KODIAC 8

Datasets analysed

Safety and tolerability outcomes in KODIAC 8 were based on the Safety analysis set which included all randomised patients who received ≥1dose of naloxegol 25 mg and patients who received Usual Care.

A TEAE was defined as any AE that started on or after the first dose of study drug in KODIAC 8 through the end of the follow-up period. Unless specified, AE refers to TEAE throughout this section. For roll-over patients, any AEs that were ongoing at the end of the previous naloxegol study (i.e. KODIAC 5 or KODIAC 7) were not considered as TEAEs for the current study.

Adverse events

A summary of AEs in KODIAC 8 is presented in Table 76. The majority of AEs during KODIAC 8 were mild or moderate in intensity. There were no notable differences in the intensity of AEs between patients in the naloxegol and Usual Care groups. A higher proportion of patients in the naloxegol group were reported to have at least one AE compared with the Usual Care group (81.8% and 72.2% of patients, respectively). The frequency of serious adverse events (SAEs) was similar across the naloxegol and Usual Care groups (9.6%, and 11.1%, respectively). Two patients died during the study: one patient in each study group was reported to have a fatal AE. Neither death was considered by the principal investigator to be related to study drug. In the naloxegol group, 10.5% of patients discontinued the study due to an AE. Patients in the Usual Care group were not taking any study drug and could therefore not be categorised for this parameter.

Table 76: Summary of adverse events in KODIAC 8 (Safety analysis set)

Adverse events	Naloxegol 25 mg (n=534)	Usual Care (n=270)
Any AE, n (%)	437 (81.8)	195 (72.2)
Any AE leading to death, n (%)	1 (0.2)	1 (0.4)
Any SAE (including events leading to death), n (%)	51 (9.6)	30 (11.1)
Discontinuation due to AEs, n (%)	56 (10.5)	NA†

Abbreviations: AE, adverse event; SAE, serious adverse event.
†Patients in the Usual Care group were not taking any study drug and thus could not be categorised for this parameter.
Note: Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

AEs occurring in ≥2% of patients in all treatment groups over the KODIAC 7 study period are presented in Table 77. Five GI AEs which were reported in >5% of patients in the naloxegol group occurred in at least twice as many patients compared with the Usual Care group. These were: abdominal pain, diarrhoea, nausea, flatulence and upper abdominal pain. For the majority of GI events, onset of the event occurred within the first week of treatment. Most GI AEs reported were mild or moderate in intensity. Note that the predominance of GI-related AEs was not unexpected in this study given the nature of

the disease under investigation and the pharmacological mechanism of action of naloxegol.

A greater proportion of patients in the naloxegol group had AEs of headache compared with the Usual Care group (9.0% vs 4.8% of patients, respectively) and one moderate event of headache in the naloxegol group resulted in discontinuation of the study.

There was a higher incidence of hyperhidrosis in the naloxegol group compared with the Usual Care group (3.2% vs 0.4% of patients, respectively), although this event frequency did not meet the specified criteria for common AEs with a notable difference vs the Usual Care group. Five hyperhidrosis events were severe in intensity and two of these resulted in study discontinuation. One mild event of hyperhidrosis also resulted in study discontinuation.

AEs by relationship to study drug

During the study, 181 patients (33.9%) in the naloxegol group had AEs considered to be related to study drug by the investigator. The most common drug related AEs were: abdominal pain (14.8% of patients), diarrhoea (7.9% of patients), flatulence (5.6% of patients) and nausea (4.7% of patients).

AEs by time to first onset

In general, more AEs were reported for the first time during the first 12 weeks of treatment among new patients in the naloxegol group compared with the Usual Care group (63.8% vs 47.1% of patients, respectively). After 12 weeks of study drug exposure, the overall rates of new AEs between the naloxegol and Usual Care groups were similar (41.9% vs 38.9% during >12 to ≤24 weeks and 57.3% vs 53.0% after 24 weeks, respectively).

Table 77: Adverse events occurring in ≥2% of patients in any treatment group, by preferred term, in KODIAC 8 (Safety analysis set)

Adverse event (MedDRA preferred term)	Number (%) of patients†	
	Naloxegol 25 mg (n=534)	Usual Care (n=270)
Total no. of patients with any AE	428 (80.1)	194 (71.9)
Abdominal pain	95 (17.8)	9 (3.3)
Diarrhoea	69 (12.9)	16 (5.9)
Nausea	50 (9.4)	11 (4.1)
Back pain	48 (9.0)	24 (8.9)
Headache	48 (9.0)	13 (4.8)
Flatulence	37 (6.9)	3 (1.1)
Arthralgia	33 (6.2)	16 (5.9)
Nasopharyngitis	33 (6.2)	15 (5.6)
Upper respiratory tract infection	31 (5.8)	23 (8.5)
Bronchitis	30 (5.6)	12 (4.4)
Vomiting	27 (5.1)	15 (5.6)
Abdominal pain upper	27 (5.1)	3 (1.1)
Sinusitis	23 (4.3)	19 (7.0)
Urinary tract infection	22 (4.1)	22 (8.1)

Abbreviations: AE, adverse event.
†Patients are counted no more than once for incidence of AE by MeDRA preferred term.

Deaths

Two patients died during the study: one patient in the Usual Care group and one patient in the naloxegol 25 mg group. Both deaths were adjudicated as CV deaths and were not considered to be related to study drug by the investigator.

Serious adverse events

At least one SAE was reported in 9.6% of patients in the naloxegol 25 mg group and 11.1% of patients in the Usual Care group. A total of 28 patients had more than one SAE.

Discontinuation due to AEs

Only patients receiving naloxegol 25 mg could have an AE leading to discontinuation of study drug. Discontinuation due to study drug was reported in 10.5% of naloxegol patients. The most common AEs leading to discontinuation were: diarrhoea (11 [2.1%] patients; abdominal pain (9 [1.7%] patients), and vomiting (5 [0.9%] patients). Twenty patients had more than one AE leading to discontinuation, including 9 patients who discontinued treatment for more than one GI event.

AEs of special interest

AEs of special interest in KODIAC 8 included selected cardiovascular (CV) events (i.e. MACE events, congestive heart failure), serious GI adjudicated as bowel perforation events, AEs potentially related to abuse liability and AEs potentially related to opioid withdrawal.

Two CV events in each treatment group were adjudicated as MACE: one event in the naloxegol group and one event in the Usual Care group were adjudicated as CV deaths; one event was adjudicated as acute myocardial infarction in the naloxegol 25 mg group; and one event was adjudicated as stroke in the Usual Care group.

No AEs were adjudicated as bowel perforation events. The proportion of patients with ≥1 abuse potential AE was similar between the naloxegol 25 mg group and the Usual Care group.

Clinical laboratory parameters

Over the 52 week treatment period, there were no differences observed in the analyses of clinical chemistry, urinalysis or vital signs parameters between the naloxegol 25 mg and Usual Care groups.

There were no notable differences in physical examination findings between patients in the naloxegol 25 mg and Usual Care treatment groups during the study.

Cardiovascular safety

There were no notable differences in analyses of mean changes in any ECG parameter between new patients in the naloxegol 25 mg and Usual Care treatment groups during the study.

Additional safety observations

The following additional safety observations were also observed:

- There were no differences in mean change from baseline in mean daily opioid dose over the 52 week study period between the naloxegol 25 mg and Usual Care groups
- There were no differences in average pain intensity scores as assessed by the NRS between naloxegol 25 mg and Usual Care treatment groups
- Over the 52 week treatment period, there were no clinically important differences in centrally mediated opioid withdrawal signs as assessed by the mHS between the naloxegol 25 mg and Usual Care groups
- There were no differences between treatment groups with respect to suicidal behaviour or ideation as assessed by C-SSRS
- Use of rescue medication was low and stable over the 52 week study period in the naloxegol 25 mg group

6.9.3 *Safety results from the pivotal RCTs*

KODIAC 4 and KODIAC 5

AEs were recorded in the KODIAC 4 and KODIAC 5 pivotal RCTs which were designed to primarily assess the efficacy of naloxegol. The safety results from KODIAC 4 and 5 are discussed in this section. The methodology for these studies is presented in section 6.3. The safety evaluations in both studies was based on the Safety analysis set, defined as all randomised patients who received at least one dose of study drug.

Unless otherwise specified, AE refers to treatment-emergent AE throughout this section.

AES, SAEs and discontinuations due to AEs

A summary of AEs observed in KODIAC 4 and KODIAC 5 is presented in Table 78. In KODIAC 4 and 5, the majority of reported AEs were mild or moderate in intensity in all treatment groups. In both studies, a greater proportion of naloxegol 25 mg patients were reported to have at least one AE compared with the naloxegol 12.5 mg and placebo groups.

In KODIAC 4, two patients in the naloxegol 12.5 mg group died during the follow-up period (non-small cell lung cancer and cardiac valve replacement complication). Neither death was considered by the principal investigator to be related to study drug. SAEs were reported in 5.2%, 3.3% and 5.2% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. A higher proportion of patients in the naloxegol 25 mg group discontinued the study due to an AE compared with the naloxegol 12.5 mg and placebo groups (4.3%, 10.3% and 5.6% of patients, respectively).

In KODIAC 5, there were no deaths during the study. SAEs were reported in 6.1%, 3.4% and 5.2% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. A higher proportion of patients in the naloxegol 25 mg group discontinued the study due to an AE compared with the naloxegol 12.5 mg and placebo groups (5.2%, 10.3% and 5.2% of patients, respectively).

In the anticipated licensed population + Step 3 opioids in both KODIAC 4 and KODIAC 5 (Table 78), there were no deaths during the study. SAEs were reported in 2.6%, 4.0% of patients in the naloxegol 25 mg and placebo groups, respectively. A higher proportion of patients in the naloxegol 25 mg group discontinued the study due to an AE compared with the placebo groups (3.8% and 2.6% of patients, respectively).

Table 78: Summary of adverse events in KODIAC 4 and KODIAC 5 (Safety analysis set)

	KODIAC 4†			KODIAC 5†			KODIAC 4 and 5: anticipated licensed population + Step 3 opioids (Weeks 5-12)	
Adverse events	**Naloxegol 12.5 mg (n=211)**	**Naloxegol 25 mg (n=214)**	**Placebo (n=213)**	**Naloxegol 12.5 mg (n=230)**	**Naloxegol 25 mg (n=232)**	**Placebo (n=231)**	**Naloxegol 25 mg (n=156)**	**Placebo (n=151)**
Any AE, n (%)	104 (49.3)	131 (61.2)	100 (46.9)	137 (59.6)	160 (69.0)	136 (58.9)	50 (32.1)	55 (36.4)
Any AE leading to death, n (%)	2 (0.9)	0	0	0	0	0	0	0
Any SAE (including events leading to death), n (%)	11 (5.2)	7 (3.3)	11 (5.2)	14 (6.1)	8 (3.4)	12 (5.2)	4 (2.6)	6 (4.0)
Discontinuation due to AEs, n (%)	9 (4.3)	22 (10.3)	12 (5.6)	12 (5.2)	24 (10.3)	12 (5.2)	6 (3.8)	4 (2.6)

Abbreviations: AE, adverse event; SAE, serious adverse event.
†Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

A summary of AEs observed in KODIAC 4 over the treatment period by baseline laxative response group is shown in Table 79. In both populations, a greater proportion of naloxegol 25 mg patients had at least one AE compared with the naloxegol 12.5 mg and placebo groups. A higher proportion of patients in the naloxegol 25 mg group in both populations discontinued due to an AE compared with the naloxegol 12.5 mg and placebo groups.

Table 79: Summary of adverse events in KODIAC 4 by baseline laxative response

	Anticipated licensed population			**Non-LIR population**		
Adverse events	**Naloxegol 12.5 mg (n=114)**	**Naloxegol 25 mg (n=117)**	**Placebo (n=118)**	**Naloxegol 12.5 mg (n=97)**	**Naloxegol 25 mg (n=97)**	**Placebo (n=95)**
Any AE, n (%)	49 (43.0)	68 (58.1)	53 (44.9)	52 (53.6)	61 (62.9)	44 (46.3)
Any AE leading to death, n (%)	0	0	0	0	0	0
Any SAE (including events leading to death), n (%)	3 (2.6)	5 (4.3)	7 (5.9)	6 (6.2)	2 (2.1)	3 (3.2)
Discontinuation due to AEs, n (%)	5 (4.4)	11 (9.4)	4 (3.4)	4 (4.1)	11 (11.3)	6 (6.3)

Abbreviations: AE, adverse event; LIR, laxative adequate responder; SAE, serious adverse event.

Table 80 shows a summary of AEs observed in KODIAC 5 by baseline laxative response group over the treatment period. As observed in KODIAC 4, a higher proportion of patients in the naloxegol 25 mg group had at least one AE compared with the naloxegol 12.5 mg and placebo groups (Table 80).

Table 80: Summary of adverse events in KODIAC 5 by baseline laxative response

	Anticipated licensed population			**Non-LIR population**		
Adverse events	**Naloxegol 12.5 mg (n=123)**	**Naloxegol 25 mg (n=124)**	**Placebo (n=120)**	**Naloxegol 12.5 mg (n=107)**	**Naloxegol 25 mg (n=108)**	**Placebo (n=111)**
Any AE, n (%)	71 (57.7)	84 (67.7)	66 (55.0)	59 (55.1)	70 (64.8)	64 (57.7)
Any AE leading to death, n (%)	0	0	0	0	0	0
Any SAE (including events leading to death), n (%)	4 (3.3)	3 (2.4)	6 (5.0)	7 (6.5)	4 (3.7)	4 (3.6)
Discontinuation due to AEs, n (%)	3 (2.4)	13 (10.5)	7 (5.8)	8 (7.5)	11 (10.2)	4 (3.6)

A summary of AEs occurring in ≥2% of patients in all treatment groups in KODIAC 4 is presented in Table 81.

In KODIAC 4, the AEs which were reported in >5% of patients in either of the naloxegol treatment groups were abdominal pain, diarrhoea, nausea, flatulence and abdominal pain upper. In the naloxegol 25 mg treatment group, the most frequently reported AEs were abdominal pain (12.6% of patients), diarrhoea (9.3% of patients) and nausea (7.5% of patients). In the naloxegol 12.5 mg treatment group, the most commonly reported AEs were abdominal pain (8.5% of patients), and nausea (7.1% of patients). Two hyperhidrosis events in the naloxegol 25 mg group resulted in study discontinuation. A higher proportion of naloxegol 25 mg patients (30.8%) had AEs considered to be related to study drug compared with the naloxegol 12.5 mg (18.0% of patients) and placebo groups (11.3% of patients).

In KODIAC 4, there were no notable differences in the proportion of SAEs reported in any system organ class across the three treatment groups. Non-cardiac chest pain was the only SAE reported by more than one patient in the naloxegol 25 mg group (2 patients), while pneumonia was the only SAE reported by more than one patient in the naloxegol 12.5 mg group.

The proportion of patients discontinuing the study due to an AE was 4.3%, 10.3% and 5.6% in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively in KODIAC 4. A higher incidence of study discontinuations due to AEs was reported in the naloxegol 25 mg group compared with the naloxegol 12.5 mg and placebo groups. This was predominantly due to a greater incidence of GI events in this treatment group. Note that the prevalence of GI events in this study was not unexpected, due to the nature of the disease under investigation and the pharmacological action of naloxegol.

Table 81: Adverse events occurring in ≥2% of patients in any treatment group, by preferred term, in KODIAC 4 (Safety analysis set)

Adverse event (MedDRA preferred term)	Number (%) of patients†		
	Naloxegol 12.5 mg (n=211)	Naloxegol 25 mg (n=214)	Placebo (n=213)
Total no. of patients with any AE	101 (47.9)	129 (60.3)	97 (45.5)
Abdominal pain	18 (8.5)	27 (12.6)	7 (3.3)
Diarrhoea	7 (3.3)	20 (9.3)	9 (4.2)
Nausea	15 (7.1)	16 (7.5)	10 (4.7)
Flatulence	9 (4.3)	12 (5.6)	4 (1.9)
Abdominal pain upper	3 (1.4)	11 (5.1)	4 (1.9)
Hyperhidrosis	0	9 (4.2)	1 (0.5)
Headache	5 (2.4)	8 (3.7)	4 (1.9)
Back pain	0	7 (3.3)	5 (2.3)
Upper respiratory tract infection	6 (2.8)	6 (2.8)	6 (2.8)
Vomiting	3 (1.4)	6 (2.8)	7 (3.3)
Abdominal distension	7 (3.3)	5 (2.3)	4 (1.9)
Fall	3 (1.4)	3 (1.4)	5 (2.3)

Abbreviations: AE, adverse event.
† Patients are counted no more than once for incidence of AE by MeDRA preferred term.

A summary of AEs occurring in ≥2% of patients in all treatment groups in KODIAC 5 is presented in Table 82.

In KODIAC 5, the AEs which were reported in >5% of patients in either naloxegol treatment group were abdominal pain, diarrhoea, nausea, vomiting, flatulence, headache and back pain. The most frequently reported AEs in the naloxegol 25 mg group were abdominal pain (19.0% of patients), diarrhoea (9.1% of patients) and nausea (8.6% of patients). Abdominal pain, diarrhoea and nausea were the most frequently reported AEs in the naloxegol 12.5 mg treatment group (10.9%, 7.8%, and 6.1% of patients, respectively). The majority of GI events in the naloxegol 25 mg group began within the first week of study treatment. Most GI AEs were mild or moderate in intensity. Given the nature of the disease under investigation and the pharmacological mechanism of action of naloxegol, the increased prevalence of GI-related AEs in this study was not unexpected.

Two moderate events of hyperhidrosis in the naloxegol treatment groups resulted in study discontinuation. A higher proportion of patients in the naloxegol 25 mg group (34.1% of patients) had AEs considered to be related to study drug compared with the naloxegol 12.5 mg (23.0% of patients) and placebo groups (20.8% of patients).

In KODIAC 5, the frequency and types of SAEs reported during the study were similar across treatment groups. At least one SAE was reported in 6.1%, 3.4% and 5.2% of patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. The proportion of patients discontinuing the study due to an AE was 5.2%, 10.3% and 5.2% in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively in KODIAC 5. The higher incidence of discontinuation due to an AE in the naloxegol 25 mg groups was predominantly due to a higher incidence of GI-related discontinuations in this treatment group.

Table 82: Adverse events occurring in ≥2% of patients in any treatment group, by preferred term, in KODIAC 5 (Safety analysis set)

Adverse event (MedDRA preferred term)	Number (%) of patients†		
	Naloxegol 12.5 mg (n=230)	Naloxegol 25 mg (n=232)	Placebo (n=231)
Total no. of patients with any AE	130 (56.5)	154 (66.4)	130 (56.3)
Abdominal pain	25 (10.9)	44 (19.0)	18 (7.8)
Diarrhoea	18 (7.8)	21 (9.1)	10 (4.3)
Nausea	14 (6.1)	20 (8.6)	10 (4.3)
Vomiting	7 (3.0)	14 (6.0)	6 (2.6)
Flatulence	4 (1.7)	14 (6.0)	7 (3.0)
Headache	12 (5.2)	12 (5.2)	8 (3.5)
Back pain	12 (5.2)	12 (5.2)	4 (1.7)
Pain in extremity	5 (2.2)	7 (3.0)	1 (0.4)
Sinusitis	3 (1.3)	7 (3.0)	2 (0.9)
Nasopharyngitis	2 (0.9)	7 (3.0)	1 (0.4)
Abdominal pain upper	5 (2.2)	6 (2.6)	3 (1.3)
Abdominal distension	4 (1.7)	6 (2.6)	5 (2.2)
Fatigue	3 (1.3)	6 (2.6)	3 (1.3)
Hypertension	2 (0.9)	6 (2.6)	2 (0.9)
Upper respiratory tract infection	3 (1.3)	5 (2.2)	6 (2.6)
Anxiety	5 (2.2)	4 (1.7)	4 (1.7)
Dizziness	8 (3.5)	3 (1.3)	5 (2.2)
Fall	6 (2.6)	1 (0.4)	3 (1.3)
Blood thyroid stimulating hormone increased	5 (2.2)	0	0

Abbreviations: AE, adverse event.
† Patients are counted no more than once for incidence of AE by MeDRA preferred term.

AEs of special interest

AEs of special interest in KODIAC 4 and 5 included selected CV events (i.e. MACE events, congestive heart failure), AEs potentially related to blood pressure changes, serious GI events adjudicated for bowel perforation, AEs potentially related to abuse liability and AEs potentially related to opioid withdrawal.

In KODIAC 4, three CV events were adjudicated as MACE; one patient with acute myocardial infarction in the naloxegol 25 mg group, and one patient with acute myocardial infarction and CV death in the naloxegol 12.5 mg group. None of these events were considered related to study drug. In KODIAC 5, two CV events were adjudicated as MACE in the placebo group. There were no notable differences in AEs related to changes in blood pressure and no AEs adjudicated as bowel perforation events in either study.

In both KODIAC 4 and 5, the frequency of AEs potentially related to abuse liability was low and comparable between the naloxegol and placebo groups. In KODIAC 4, naloxegol treatment was not associated with a higher frequency of AEs identified as drug withdrawal compared with placebo. In KODIAC 5, a higher proportion of patients in the naloxegol 25 mg group had AEs of drug withdrawal compared with patients in the naloxegol 12.5 mg and placebo groups (4, 1 and 0 patients, respectively).

Cardiovascular safety

In both studies, naloxegol treatment was not associated with clinically important changes in ECG parameters across treatment groups. In addition, there were no clinically important differences in outlier analysis for systolic and diastolic blood pressure, heart rate or QTcF at any time point throughout the study, including the immediate 1–2 hours post first dose observation period between the naloxegol and placebo groups.

Additional safety observations

The following additional safety observations were also observed:

- The AE profile of patients with baseline LIR status was comparable to that of the overall Safety analysis set in both KODIAC 4 and KODIAC 5
- There were no differences in mean daily average or worst pain intensity scores as measured by the NRS between the treatment groups in both studies
- There were no clinically important increases or decreases in mean daily opioid dose between any of the treatment groups in KODIAC 4 and 5
- In both studies, there were no clinically important differences in centrally mediated opioid withdrawal signs as assessed by the mHS
- There were no clinically important changes in laboratory, vital signs, or physical examination parameters in patients receiving naloxegol in KODIAC 4 and 5
- In both studies there were no notable differences across treatment groups with respect to suicidal behaviour or ideation as assessed by C-SSRS and AEs

Post-hoc analyses: KODIAC 4 and KODIAC 5

A post-hoc analysis performed in the anticipated licensed population and anticipated licensed population + Step 3 opioids in KODIAC 4 and KODIAC 5 showed that the respective doses of naloxegol do not interfere with the analgesic effects of opioids. Consistent with the results from the ITT population, there were no clinically meaningful increases from baseline in pain intensity scores in as measured by the NRS in patients receiving naloxegol (Table 83).

Table 83: Analysis of MID change from baseline to NRS pain Week 1-12 in KODIAC 4 and KODIAC 5 (Safety analysis set)

	KODIAC 4				KODIAC 5			
	Anticipated licensed population		Anticipated licensed population + 3 step opioids		Anticipated licensed population		Anticipated licensed population + 3 step opioids	
Change from baseline category	**Naloxegol 25 mg (N=117)**	**Placebo (N=118)**	**Naloxegol 25 mg (N=87)**	**Placebo (N=77)**	**Naloxegol 25 mg (N=122)**	**Placebo (N=120)**	**Naloxegol 25 mg (N=88)**	**Placebo (N=83)**
Increase in ≥2 from baseline, n (%)	0	4 (3.4)	0	4 (5.2)	4 (3.3%)	1 (0.8%)	3 (3.4)	0
OR† (95%CI)	NA		NA		4.034 (0.444, 36.627)		NA	
RR† (95%CI)	NA		NA		3.934 (0.446, 34.963)		NA	
ARR† (95%CI)	-0.034 (-0.067, -0.001)		-0.052 (-0.102, -0.002)		0.024 (-0.011, 0.060)		0.034 (-0.004, 0.072)	
Decrease in ≥2 from baseline	9 (7.7)	6 (5.1)	7 (8.0)	4 (5.2)	3 (2.5)	2 (1.7)	3 (3.4)	2 (2.4)
OR (95%CI)	1.556 (0.536, 4.518)		1.597 (0.449, 5.679)		1.487 (0.244, 9.063)		1.429 (0.233, 8.777)	
RR (95%CI)	1.513 (0.556, 4.116)		1.549 (0.471, 5.089)		1.475 (0.251, 8.674)		1.415 (0.242, 8.255)	
ARR (95%CI)	0.226 (-0.036, 0.089)		0.029 (-0.047, 0.104)		0.008 (-0.028, 0.044)		0.010 (-0.040, 0.060)	

Abbreviations: ARR, absolute risk reduction MID, minimally important difference; NRS, numeric rating scale; OR, odds ratio; RR, relative risk.
†RR, OR, and ARR are based on an unstratified analysis.
Note: NRS pain score consists of an integer scale from 0 (no pain) to 10 (worst imaginable pain). Negative changes indicate improvement (i.e. less pain).
Note: Percentages are based on the number of patients (N) with non-missing baseline and post-baseline NRS scores in each treatment group at each assessment.
Note: OR, RR and ARR: placebo is the reference treatment group; Note: RR, OR, and ARR are based on an unstratified analysis.

Patient willingness to take naloxegol again

A post-hoc analysis carried out in the anticipated licensed population and anticipated licensed population + Step 3 opioids groups in KODIAC 4 and KODIAC 5 (Table 84), showed a patient willingness to take naloxegol again in a higher percentage of patients in the naloxegol group compared with placebo (KODIAC 4: 74.4% vs.69.5% respectively, in the anticipated licensed population; 71.3% vs 68.8% respectively in the anticipated licensed population + Step 3 opioids; KODIAC 5: 67.7 vs 63.3% in the anticipated licensed population; 65.2% vs. 60.2% in the anticipated licensed population + Step 3 opioids). Thus suggesting that any adverse events resulting from the use of naloxegol are not considered severe enough by the patient to outweigh the benefit of using naloxegol.

Table 84: Summary of patient willingness to take drug again in KODIAC 4 and KODIAC 5 (Safety analysis set)

		KODIAC 4				KODIAC 5			
		Anticipated licensed population		Anticipated licensed population + 3 step opioids		Anticipated licensed population		Anticipated licensed population + 3 step opioids	
Category	**Willingness to take drug again**	**Naloxegol 25 mg**	**Placebo**	**Naloxegol 25 mg**	**Placebo**	**Naloxegol 25 mg**	**Placebo**	**Naloxegol 25 mg**	**Placebo**
All patients	n	117	118	87	77	124	120	89	83
	Yes	87 (74.4)	82 (69.5)	62 (71.3)	53 (68.8)	84 (67.7)	76 (63.3)	58 (65.2)	50 (60.2)
	No	21 (17.9)	26 (22.0)	18 (20.7)	18 (23.4)	27 (21.8)	38 (31.7)	23 (25.8)	28 (33.7)
	Unknown	9 (7.7)	10 (8.5)	7 (8.0)	6 (7.8)	13 (10.5)	6 (5.0)	8 (9.0)	5 (6.0)
Patient completing	n	98	99	72	67	90	96	89	66
	Yes	82 (83.7)	78 (78.8)	58 (80.6)	50 (74.6)	77 (85.6)	69 (71.9)	58 (65.2)	46 (69.7)
	No	12 (12.2)	19 (19.2)	15 (22.4)	10 (13.9)	12 (13.3)	26 (27.1)	23 (25.8)	19 (28.8)
	Unknown	4 (4.1)	2 (2.0)	2 (3.0)	4 (5.6)	1 (1.1)	1 (1.0)	8 (9.0)	1 (1.5)
Patients prematurely discontinued	n	19	19	15	10	34	24	26	17
	Yes	5 (26.3)	4 (21.1)	4 (26.7)	3 (30.0)	(7 (20.6)	7 (29.2)	4 (15.4)	4 (23.5)
	No	9 (47.42)	7 (36.8)	8 (53.3)	3 (30.0)	15 (44.1)	12 (50.0)	15 (57.7)	9 (52.9)
	Unknown	5 (26.31)	8 (42.1)	3 (20.0)	4 (40.0)	12 (35.3)	5 (20.8)	7 (26.9)	4 (23.5)

6.9.4 *Other relevant safety data*

KODIAC 9

KODIAC 9 was a study designed to examine the impact of renal impairment on the pharmacokinetics of naloxegol 25 mg in patients with renal impairment classified as moderate, severe, or end-stage renal disease (ESRD) (71).

In patients with moderate or severe renal impairment, geometric mean area under the plasma concentration-time curve (AUC) was increased 1.7-fold and 2.2-fold, respectively compared with healthy controls. Maximum plasma concentrations (C_{max}) were also increased in patients with moderate (1.1-fold) or severe (1.8-fold) impairment. Both of these results were driven by higher exposures in two patients in each of the moderate and severe impairment groups; all other patients had similar exposures to the control group. ESRD patients had similar exposures overall. Patients with ESRD had 29% lower C_{max} compared with control patients. Other plasma pharmacokinetic parameters were minimally affected by renal impairment. Exposure to naloxegol was unaffected by the extent of renal impairment; no correlation was observed between either AUC or C_{max} and estimated glomerular filtration rate. Haemodialysis was an ineffective means of naloxegol clearance. Overall, naloxegol was well-tolerated in all treatment groups.

The study concluded that renal impairment had the potential to adversely affect clearance by hepatic and gut metabolism resulting in the increased exposures that were seen in outliers of the patients with moderate and severe renal impairment.

KODIAC 10

The aim of KODIAC 10 was to assess the pharmacokinetics of naloxegol 25 mg in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment versus healthy controls (72). Study patients were matched for age, sex and BMI.

Despite having similar maximum plasma concentrations (C_{max}), patients with hepatic impairment demonstrated a 17–18% reduction in the area under the plasma concentration versus time curve (AUC). These findings were unexpected based on the fact that naloxegol clearance is primarily via the hepatic route. Patients with moderate hepatic impairment demonstrated shorter time to C_{max} compared with patients with mild impairment and controls (0.6 hours vs 2.3 hours and 2.0 hours, respectively). The mean apparent terminal half-life was shorter in patients with mild and moderate hepatic impairment compared with healthy controls (9.6, 7.5 and 11.3 hours, respectively).

The study concluded that the observed reductions in AUC and terminal half-life in patients with hepatic impairment may be due to reductions in enterohepatic recycling of naloxegol. Overall, in KODIAC 10, naloxegol was generally well tolerated. In addition, the effects of mild or moderate hepatic impairment on the pharmacokinetics and safety of naloxegol were minimal.

6.9.5 *Give a brief overview of the safety of the technology in relation to the decision problem*

Please refer to the summary box at the beginning of Section 6.9 for further details.

6.10 *Interpretation of clinical evidence*

6.10.1 *Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.*

The clinical evidence is discussed in section 6.

Clinical benefit

Patients who develop opioid-induced constipation that is not adequately relieved by currently available laxative(s) have a clear unmet clinical need. Naloxegol is the first product to have demonstrated efficacy in LIR patients who were a pre-specified sub group in a well-designed robust phase 3 clinical program.

Naloxegol in the management of opioid-induced constipation offers patients and healthcare professionals a number of clinical benefits that currently available treatments, including laxative(s), do not provide:

- Targeted mode of action by acting peripherally as a mu-opioid antagonist, thereby reversing the constipating effects of opioids (33)
- Designed not to cross the blood brain barrier, thereby preserving analgesia with no requirement for alteration of the opioid dose (33)
- Offers a simple oral, once daily mechanistic approach to addressing OIC (unlike methylnaltrexone)
  - A single daily dose may be less than the volume of currently available laxatives required to achieve highest tolerated effective dose.
  - Does not require additional fluid intake (unlike e.g. macrogols where the daily dose should be dissolved in 375 ml of water) (73)
  - Palatable tablet unlike lactulose oral solution or docusate sodium oral suspension (74, 75)
- Single 25 mg dose independent of underlying opioid molecule or opioid dose offering a simple and flexible management for patients and healthcare professionals (33)
  - Dose titration not necessary (a half dose tablet is available if down-titration due to adverse events is necessary).
- Durable, sustained and predictable efficacy increasing median spontaneous bowel movements (SBMs) per week from 1.1 to 4.9 in KODIAC 4 and from 1.1 to 4.4 in KODIAC 5 across Weeks 1 to 12 (51-53) (Corresponding values for the placebo arm are 1.2 to 3.2 for KODIAC 4 and 1.5 to 3.2 for KODIAC 5)
  - This increase over baseline is meaningful to patients who report that even an increase of 1 SBM per week has a positive impact on their lives (17)
- Offers symptomatic improvement and enhanced QoL to already burdened patients, including reducing straining, one of the most bothersome symptoms of constipation (51, 52)
- Data in OIC patients with up to 52 weeks usage demonstrated no safety concerns compared to standard of care (76).

- Has the potential to improve pain management as OIC can cause patients to skip or reduce their opioid therapy in order to have a bowel movement (7, 12, 13).

Clinical harm

Naloxegol has been studied in OIC patients for up to 52 weeks of therapy. Treatment emergent adverse events (AEs), mainly GI in origin, were experienced more in naloxegol patients compared to placebo patients. However, these AEs were transient and in KODIAC 7 (roll over from KODIAC 4) the difference between active and placebo arms was negligible (77).

6.10.2 *Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.*

Strengths of the evidence base

The naloxegol clinical trial programme

The naloxegol clinical trial programme was the first to have pre-specified efficacy outcomes in laxative inadequate responders (LIR patients), targeting a patient sub-group with an unmet clinical need. Two (KODIAC 4 and 5) replicate, robustly designed, double blind, randomised Phase III studies recruited 720 LIR patients across 3 treatment arms: 25 mg naloxegol, 12.5 mg naloxegol and placebo from non over lapping sites. Patients enrolled in KODIAC 4 were able to roll over into KODIAC 7, a safety extension study that also recruited de-novo patients. This study was also double blinded. KODIAC 8 was a 52 week open label safety study recruiting about 90% de-novo patients with the remaining 10% rolling over from KODIAC 7. The robust study designs and long term safety data included in this submission provide a strong evidence base to support the use of naloxegol.

Study patient population

Patients recruited into the Phase III study programme were opioid users who either were not using laxative(s) for a variety of reasons or whom were using laxative(s) but without full relief of their constipation symptoms (laxative inadequate responders [LIR]). The latter patient group forms the anticipated licensed population in terms of the naloxegol marketing authorisation. A key strength of the Phase III programme was the inclusion of this pre-specified sub-group of laxative inadequate responders (the anticipated licensed population) in both KODIAC 4 and KODIAC 5, which were powered to detect statistically significant differences in response to study drug. The randomisation procedure in KODIAC 4 and 5 was designed to ensure that a minimum of 50% of patients in each treatment arm in both studies were classified as LIR at baseline. This enabled robust comparisons of naloxegol versus placebo to be made in the anticipated licensed indication.

Study endpoints

Treatment- responders

SBM is recognised as a robust and clinically meaningful measure commonly employed in clinical studies to assess the efficacy of a treatment for both OIC and chronic constipation resulting from other causes (78-80). In the naloxegol trials this endpoint was defined as the percentage of patients with ≥3 SBMs per week with improvement from

baseline of ≥1 SBM per week for ≥9 out of 12 study weeks and 3 out of the last 4 study weeks. This meant that efficacy had to be maintained throughout the 12 week treatment period for patients to be classified as responders. The definition of responder is discussed in more detail in section 6.3.7.

Improvement in days per week with a SBM

The definition of treatment responders does not fully describe the potential benefits that naloxegol 25 mg may offer to OIC patients as it only requires ≥3 SBMs per week and ≥1 SBM over baseline per week. The measurement of the actual number of SBMs per week helps to define the true level of improvement in bowel function and also reassures the patient as their bowel function returns to a frequency more closely aligned with their pre-opioid usage bowel function.

Symptom control as evidenced by patient reported outcomes

Health-related quality of life was assessed using two constipation specific, patient-reported questionnaires, the PAC-SYM and the PAC-QoL, both have been used previously in clinical trials of patients with OIC (80, 81). The PAC-SYM was selected as it has been used in previous trials of constipation and in patients taking opioids for pain (7) and has undergone some validation in OIC patients in The Netherlands (62). The PAC-QoL is the most frequently used instrument for the assessment of quality of life in patients with constipation (13). In addition, and most importantly, EQ-5D data were collected at randomisation and at Weeks 4 and 12 enabling in-trial estimates of health utility to be obtained.

Other end points were related to changes in constipation symptoms including degree of straining and stool consistency. These were relevant endpoints given that infrequent BMs and straining are reported by patients as the most “bothersome” of their opioid induced GI side-effects (7, 11). In addition, a recent study to identify the symptoms for investigation in clinical studies that are most important to patients with chronic constipation reported that the frequency and consistency of BMs were considered by patients as their most important symptoms (82), further demonstrating the importance of these endpoints and the relevance of their inclusion in KODIAC 4 and 5.

The British National Formulary provides a useful definition of constipation from a patients perspective; defined as the passage of hard stools less frequently than the patient's own normal pattern. The patient reported outcomes used in the naloxegol Phase III clinical program align to this definition (83).

Rescue medication

Naloxegol patients in the Phase III clinical studies required less rescue medication than the placebo arm supporting the efficacious nature of the investigational drug. Chronic pain patients may have a heavy pill burden related to their pain and to other co-morbidities, so reducing as required medications in this patient group is a benefit.

Pain control

Opioids relieve pain by acting centrally on mu-opioid receptors while the side effect of constipation is a result of peripheral agonism along the GI tract. Any medication with a mu-opioid antagonist action designed for the relief of constipation should work only at peripheral mu-opioid receptors with no central activity which could compromise pain

control. The naloxegol clinical trial program measured pain control for the duration of KODIAC 4 and 5 and demonstrated that pain scores as measured by a VAS did not change when patients received the active therapy.

Safety

The Phase III program across KODIAC 4, 5, 7 and 8 with treatment up to 52 weeks has demonstrated no safety issues with the use of naloxegol. Early onset GI tract side effects were generally mild and transient in nature.

Limitations of the evidence base

LIR definition: The rationale for the LIR definition used in the naloxegol Phase III program is discussed in section 6.3.7. While this definition aligns with the ROME criteria for defining constipation,

[redacted]

Cancer pain patients: The KODIAC 6 Phase III study which was designed to recruit only cancer pain patients is discussed in section 6.5.5. While it may be perceived as a limitation of the evidence base, it is AstraZeneca's position, and the position that the CHMP ultimately endorsed by granting naloxegol's positive opinion, which included cancer pain patients, that there is no scientific rationale to expect the pharmacodynamic properties of naloxegol to differ in this patient population. Hence, the extrapolation of the available safety and efficacy data to the treatment of OIC in cancer pain patients is justified.

Comparator: The use of a placebo comparator arm in a Phase III clinical study is not considered ideal. However, the prescription of laxatives is influenced by fashion availability and cost, and there is wide variation in their use between clinicians and countries (84, 85). Additionally, there is very little robust clinical evidence comparing one laxative against another that helps to inform on the best laxative to choose as a comparator in Phase III studies. The evidence base for most commonly used laxatives is largely empirical in nature. Choosing a laxative that would subsequently be acceptable to all study sites in a global Phase III program was therefore challenging and following consultation with the regulatory agencies placebo was agreed as the comparator arm in the pivotal Phase III studies.

6.10.3 *Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.*

Study patient population

The World Health Organisation (WHO) 3-step analgesic ladder forms the basis of managing moderate to severe pain in the western world in both cancer and non-cancer pain patients (65). Steps 2 and 3 of this ladder introduce the use of weak and strong opioids, respectively. The patient population in the naloxegol clinical trial program

represents pain patients being treated according to Steps 2 and 3 of the WHO analgesic ladder (65).

The two pivotal studies presented in this submission include an adequately powered subgroup of patients who are classified as having had an inadequate response to laxative(s). Therefore, in keeping with NICE's remit to assess new technologies in line with their licensed indication, the evidence base presented is relevant to the decision problem.

Evidence for an additional subgroup of the licensed population who were receiving a Step 3 opioid at baseline for the management of pain has been included in the submission. The relevance of this subgroup is highlighted in NICE CG 140 which recommends laxative treatment to be taken regularly at an effective dose for all patients strong opioids are initiated (40). Additionally, this NICE guidance states that the risk of the development of constipation in nearly all patients initiated on Step 3 opioids should be discussed by the clinician when prescribing the opioid. Moreover, the resource use questionnaire that informs the health economic model demonstrated that the majority of resource utilisation is driven by this group of opioids users (see section 10.28), and this [redacted]

Comparators

NICE requested that the main comparator in the overall OIC population should be oral laxative treatment. However, in light of the following:-

- The anticipated LIR indication where patients would be suitable for naloxegol following an inadequate response to one laxative class (please see section 6.3.7 for further detail)
- The absence of national guidelines and sub-national protocols resulting in the typical 2nd line approach for OIC patients of switching laxative class or using a combination of classes based on individual patient profile (please see section 2.1 for further detail)
- The potentially multifactorial nature of the patient's constipation (please see section 2.1 for further detail)

- the main comparison presented in this submission is the comparison of naloxegol versus placebo or naloxegol in combination with bisacodyl versus placebo in combination with bisacodyl (where bisacodyl is used as a proxy for stimulant laxatives used as required). These comparisons have been made in order to demonstrate that (1) naloxegol is both a clinically effective and cost-effective option from 2nd line, enabling physician choice and flexibility over where to introduce naloxegol, for example based on the individual patient need, and that (2) naloxegol is an effective approach when used in combination with additional laxative therapy as required when the opioid is one of several contributors to the patient's constipation.

The evidence base for both of these comparisons comes from in-trial data from the naloxegol clinical trial programme. While the KODIAC trials did not include a head-to-head comparison of naloxegol versus oral laxative(s) they did allow for the use of bisacodyl as rescue therapy in both the naloxegol and placebo arms. Therefore, in the absence of direct head-to-head data and a lack of published data pertaining to the efficacy of oral laxatives precluding a comparison by indirect means a comparison of SBMs in the naloxegol arm with all BMs in the placebo plus bisacodyl arm has been

presented. It is assumed that a comparison with “as required” laxatives may be appropriate for some patients within the licensed population of laxative inadequate responders as these patients need only have received one prior laxative to qualify as LIR and physicians may, therefore, consider the use of “as required” laxatives, or the use of naloxegol, as a suitable treatment option.

An additional comparison of all BMs in the naloxegol plus bisacodyl arm versus all BMs in the placebo plus bisacodyl arm has also been included. This latter scenario is intended to show the efficacy of naloxegol when used in combination with an as required stimulant laxative versus the use of an as required stimulant laxative alone; a scenario that is very plausible in clinical practice given the multifactorial nature of constipation discussed in section 2 of this submission and the likely self-medication by patients with over the counter laxative(s).

NICE requested additional comparisons with methylnaltrexone, naloxone-oxycodone and rectal interventions for the population defined as “adults in whom oral laxatives have provided inadequate relief”. Given naloxegol’s anticipated licensed indication in patients who have experienced an inadequate response to laxative(s), this subgroup is no longer felt to be appropriate as it could be interpreted as laxative refractory patients, i.e. those patients who have exhausted all treatment options with laxatives, rather than naloxegol’s indication in patients who have experienced an inadequate response to one or more laxatives.

Despite this, methylnaltrexone, naloxone-oxycodone and rectal interventions may be suitable comparators for a proportion of naloxegol’s licence and so a comparison with each has been presented. However, there are several limitations to these comparisons including their place in current therapy and limited use in clinical practice. Methylnaltrexone for example, is restricted for use in patients with advanced illness in palliative care, needs to be administered by subcutaneous injection and is consequently reserved or restricted on many formularies for last-line rescue therapy meaning very few patients actually receive it in UK clinical practice (86, 87). Indeed, according to the HSCIC data in the year to June 2014, only 781 methylnaltrexone injections have been prescribed in primary care (24). Naloxone-oxycodone similarly has very restricted use due to its formulation as a combination product in a fixed dose ratio that limits the dose of oxycodone that can be administered; many patients require a higher dose than the 40 mg it is possible to give in combination with naloxone. In addition, it has been shown to be not cost-effective versus the free combination of oxycodone and laxative(s) when prescribed separately (22, 25) and has consequently been “black-listed”, that is to say prohibited from being used, by a number of authorities (20-22). Rectal interventions include suppositories and enemas, which besides from being unpleasant to administer (23) and having unpleasant consequences when they take effect, need to be administered either in hospital or by a community nurse. In contrast, naloxegol is a once daily, oral therapy that offers the flexibility to be used independently of the opioid prescribed, does not require dose titration and does not involve any additional healthcare utilisation. Due to its mechanism of action and oral dosing it can be administered as maintenance therapy for the duration of opioid use and so alleviates the symptoms of OIC before the need for the rescue therapies described above.

The importance of BMs to patients

Patients report infrequent BMs to be one of the most “bothersome” of their OIC symptoms (7, 11).

[redacted]. The KODIAC trial definition of response to treatment, which included the requirement for an improvement in the number of SBMs from baseline that was sustained for the study period, can be regarded as clinically meaningful. The importance patients place on having a BM can be further verified by the finding that up to 49% of patients either miss, reduce or stop using their opioid medication in order to have a BM (7, 12, 13), resulting in suboptimal analgesia. Additional benefits of naloxegol, may therefore, include improvements in pain management as patients become more compliant to their opioid medication once this barrier to optimal use has been removed.

Treatment- responders

The definition of responder is discussed in section 6.3.

Constipation, whatever the underlying mechanistic cause, is a distressing condition that impacts on patients QoL. The continual need to strain to pass a bowel movement can also lead to other lower GI problems such as haemorrhoids and rectal bleeding. Relief of constipation is therefore a clinically important outcome that should have a positive impact on QoL. In the KODIAC studies, approaching 50% of LIR patients have at least 3 SBMs per week (responder) compared to approx. 30% in the placebo arm which for individual patients is a meaningful improvement over baseline (see section 6.5 for full information).

Improvement in SBM (in LIR population)

A key outcome in treating constipation is to return the patients bowels movements to a frequency consistent with the pre-constipation state. A study of 1055 factory workers in the UK in 1965 found that 99% of the working population maintained a bowel frequency of between three bowel movements per day and three per week (88).

The mean weekly SBMs with naloxegol 25 mg for weeks 1 to 12 of the Phase III studies was 4.4 and 4.9 which fits within the findings of Connell et al, 1965 (88) and is suggestive of a return to a normal but individualised weekly bowel movement pattern for patients.

Patient reported outcomes (in LIR population)

The KODIAC studies demonstrated improvements in patient reported outcomes for naloxegol compared to placebo across a spectrum of symptom domains (abdominal, bowel and stools) and in QoL instruments. Naloxegol 25 mg compared with placebo was shown to improve across all domains. Results from the EQ-5D demonstrated that a higher proportion of patients in the naloxegol group reported no problems over the treatment period compared with placebo. At 12 weeks, naloxegol was associated with greater improvements in the anxiety and depression, and mobility domains.

Other endpoints were related to changes in constipation symptoms, including degree of straining and stool consistency. These were relevant endpoints given that infrequent BMs and straining are reported by patients as the most “bothersome” of their opioid induced GI side-effects (7, 11). In addition, a recent study to identify the symptoms for

investigation in clinical studies that are most important to patients with chronic constipation reported that the frequency and consistency of BMs were considered by patients as their most important symptoms (82), further demonstrating the importance of these endpoints and the relevance of their inclusion in KODIAC 4 and 5.

It should be noted that patients with OIC have an underlying pain condition that will be little impacted by relief of their constipation and this co-morbidity will itself have a negative impact on overall QoL. Any improvement in QoL as a result of relief from constipation, a secondary condition, is therefore clinically meaningful in these patients.

Improvement in symptoms (in LIR population)

Based on scientific advice from the CHMP that it is not just an improvement in the number of BMs but also an improvement in OIC symptoms that are important to patients when assessing the overall efficacy of a treatment for OIC, an additional efficacy response endpoint was added that took accompanying constipation symptoms into account. Straining when passing stools, the consistency of the stools passed and feelings of incomplete evacuation can all be uncomfortable for patients and contribute to the burden of their disease. Considering not just SBMs, an objective endpoint, but patient reported symptoms, a subjective endpoint, treatment with naloxegol continued to show improved efficacy over the placebo arm.

Use of rescue medication (in LIR population)

In a clinical setting it is highly likely that patients will either self-medicate with as required laxative(s) or be prescribed them by their clinician when they show symptom deterioration or inadequate symptom relief despite use of a chronic daily maintenance laxative therapy.

The addition of a stimulant laxative such as bisacodyl to naloxegol 25 mg when a patient has not experienced a SBM for 72 hours is likely to be consistent with a patient's own self-management of their condition. The use of as required medication in the naloxegol 25 mg study arm was on average equivalent to less than two (i.e. 10 mg) doses per week per patient. The increased response observed with naloxegol 25 mg plus as required bisacodyl supports that in addition to constipation occurring as a direct result of mu-opioid receptor agonism, there are other multifactorial elements to patients' constipation.

Impact of naloxegol treatment on pain relief

OIC can cause patients to adjust their daily opioid dose (either by reducing or omitting doses) impacting pain management (17). By relieving constipation and removing the tendency to reduce opioid medication, adherence to pain treatment would be expected to improve and therefore overall pain management will be stabilised.

Any decrease in analgesia as a result of naloxegol administration is clearly undesirable. Given naloxegol's mechanism of action as an opioid receptor antagonist it may be hypothesised that in addition to relieving the unwanted side-effects of opioids, namely constipation, naloxegol may also interfere with their analgesic effects. However, analgesia is mediated through centrally located opioid receptors, unlike constipation, which is a result of the activation of peripheral mu-opioid receptors in the GI tract. Unlike other PAMORAs, naloxegol's chemical structure includes a pegylated entity which

increases its molecular weight and reduces its ability to cross the blood-brain barrier, thereby preventing it from interfering with a patient's pain management. The inclusion of this endpoint provides clinical evidence to support this theory.

6.10.4 ***Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?***

Cancer pain patients

AstraZeneca do not consider the external validity of the naloxegol clinical studies is affected by the absence of cancer pain patients in the studies. However, for completeness this subject has been included in this section. The major factor influencing the external validity of the study results to patients in routine clinical practice is the lack of clinical trial data in cancer pain patients and the reasons for this are discussed previously in section 1.4 and section 2. Historically there has been a dichotomy between cancer- and non-cancer-related pain but in reality these two categories of pain are often not distinct entities. The underlying physiology of pain is the same regardless of the underlying cause of that pain and therefore pain medications act on the same target receptors regardless of whether the trigger for the pain is cancer or non-cancer. Indeed, while the WHO analgesic ladder was developed in 1986 for the management of cancer pain, it is today used across all pain aetiologies. Likewise, the side effects of opioid use, including OIC, are independent of the cause of the underlying pain and there is no rationale to treat these side effects differently based on an arbitrary differentiation of cancer and non-cancer pain.

Study sites and baseline characteristics

Patient demographics and baseline disease characteristics in the pivotal RCTs (KODIAC 4 and 5) were considered to be representative of UK patients receiving long-term opioid treatment for non-cancer pain that would be observed in UK clinical practice in terms of age and duration of opioid treatment. This is supported by CPRD data that showed that opioid persistence was comparable to the Phase III studies (the mean duration of opioid use in patients, with at least 182 days of continuous exposure, receiving opioids for non-cancer pain and cancer pain management is approximately 18 months and 15 months, respectively) irrespective of underlying condition (89). Demographics of patients with cancer pain who may receive naloxegol may differ slightly in terms of patients being older and having a relatively shorter duration of opioid use.

[redacted]

– please see Section 7.9.5.

Choice of rescue laxative

Bisacodyl was chosen as the rescue laxative for use in the clinical trial programme as it was the only laxative that was licensed for constipation at standard doses in each of the study countries. Senna is the most commonly used stimulant laxative in the UK, however

market research confirmed that bisacodyl is a suitable proxy for stimulant laxatives used as rescue therapy (28).

Definition of laxative inadequate responder

In order to be classified as a laxative inadequate responder in KODIAC 4 and 5, patients were required to meet the following criteria:

- Receiving opioid therapy for pain relief
- Demonstrate ≥4 days of laxative use during the last two weeks, and
- report moderate, severe, or very severe symptoms in at least one of the four stool symptom domains (i.e. incomplete bowel movement, hard stools, straining, or false alarms)

This was the definition of laxative inadequate responder that formed the anticipated licensed indication for naloxegol. However, as discussed in detail in section 2.1, there is currently a lack of guidance to enable physicians to identify patients who have had an inadequate response to laxative(s) as highlighted by research conducted on behalf of AstraZeneca; the survey found no consensus on the definition of “laxative inadequate responder” among 29 healthcare professionals (44). Consequently, in the absence of guidance or consensus opinion, identification of the target population by physicians will be based on the pivotal clinical trial data (KODIAC 4 and 5) that formed the basis for the licensed indication for naloxegol. Irrespective of the definition of laxative inadequate responder used, the baseline characteristics of patients in KODIAC 4 and 5 are considered representative of the characteristics of OIC patients who would be treated in clinical practice, i.e. they are having a BM every 3 days (1.4 SBM per week), thus the clinical data from the pivotal trials is relevant to expected clinical practice.

Anticipated licensed dose

The anticipated licensed dose of naloxegol, as stated in the SPC is 25 mg, with 12.5 mg listed as the starting dose for patients with moderate or severe renal impairment or taking concomitant inhibitors of CYP3A4 (33). In both cases the dose can be increased to 25 mg if the 12.5 mg dose is well tolerated. Evidence from the pivotal trials (KODIAC 4 and 5), and the 12 week extension study (KODIAC 7) includes efficacy and safety data for both the 25 mg and 12.5 mg dose. In the longer-term KODIAC 8 study, safety evidence is presented for the naloxegol 25 mg dose versus usual care. The evidence base is therefore, entirely relevant to the dosing of naloxegol listed in the SPC.

7 Cost-effectiveness

Summary of cost-effectiveness

A de novo model was constructed to compare the cost-effectiveness of naloxegol based on the patients enrolled in KODIAC 4 and 5 for the treatment of adult patients with OIC who have had an inadequate response to laxative(s).

- The model was comprised of a decision-tree structure for the first 4 weeks of treatment, followed by a Markov structure over a time horizon of a maximum of 5 years.
- The base case analysis considered naloxegol compared with placebo based on the results of the pivotal clinical trials, KODIAC 4 and KODIAC 5.
- Additional analyses were undertaken for the following clinically relevant comparisons:
  - Naloxegol 25 mg vs placebo in combination with bisacodyl (to represent PRN stimulant laxative use as 2nd line therapy)
  - Naloxegol 25 mg plus bisacodyl versus placebo in combination with bisacodyl (a comparison using a common end-point of BMs)
- Results were also presented for naloxegol compared with methylnaltrexone and naloxone-oxycodone.
- In the absence of robust data enabling an indirect comparison with rectal interventions, a cost minimisation analysis was completed to compare naloxegol with rectal intervention.

Results of the model showed that:

- In the base case analysis (the inputs of which are based on the KODIAC 4 and 5 data) the ICER for naloxegol vs placebo is £10,849 per QALY gained for a 5 year time horizon.
- The additional analysis undertaken showed that:
  - the ICER for naloxegol 25 mg vs placebo in combination with bisacodyl is £12,639 per QALY gained
  - the ICER for naloxegol 25 mg plus bisacodyl vs placebo in combination with bisacodyl is £11,175 per QALY gained
- A large number of sensitivity and scenario analyses were completed in order to demonstrate the robustness of the model to changes in the model parameters and assumptions. In nearly all of the sensitivity analyses naloxegol was found to be cost-effective at a willingness to pay threshold of <£20,000.
- Naloxegol was found to be dominant vs methylnaltrexone and naloxone-oxycodone, when naloxegol is used with oral morphine.
- Compared with rectal interventions, naloxegol can be provided for 0.68 months for the same cost as a rectal intervention given at the patient's home and for 43.02 months if the rectal intervention is given in an inpatient care hospital setting.

7.1 *Published cost-effectiveness evaluations*

Identification of studies

7.1.1 ***Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in Section 10.10, appendix 10.***

A systematic review was conducted to identify cost-utility analysis studies from the published literature for naloxegol and comparator treatments for the treatment of opioid-induced constipation.

The following electronic databases were searched to identify the relevant economic evaluations:

- Ovid MEDLINE In-Process and Other Non-Indexed Citations
- EMBASE (Ovid)
- The Cochrane Library (Ovid), searching the following databases:
  - NHS Economic Evaluation Database (NHS EED)
  - Health Technology Assessment (HTA) Database
- Econlit (Ovid)

Electronic searches were supplemented by hand searching the following sources:

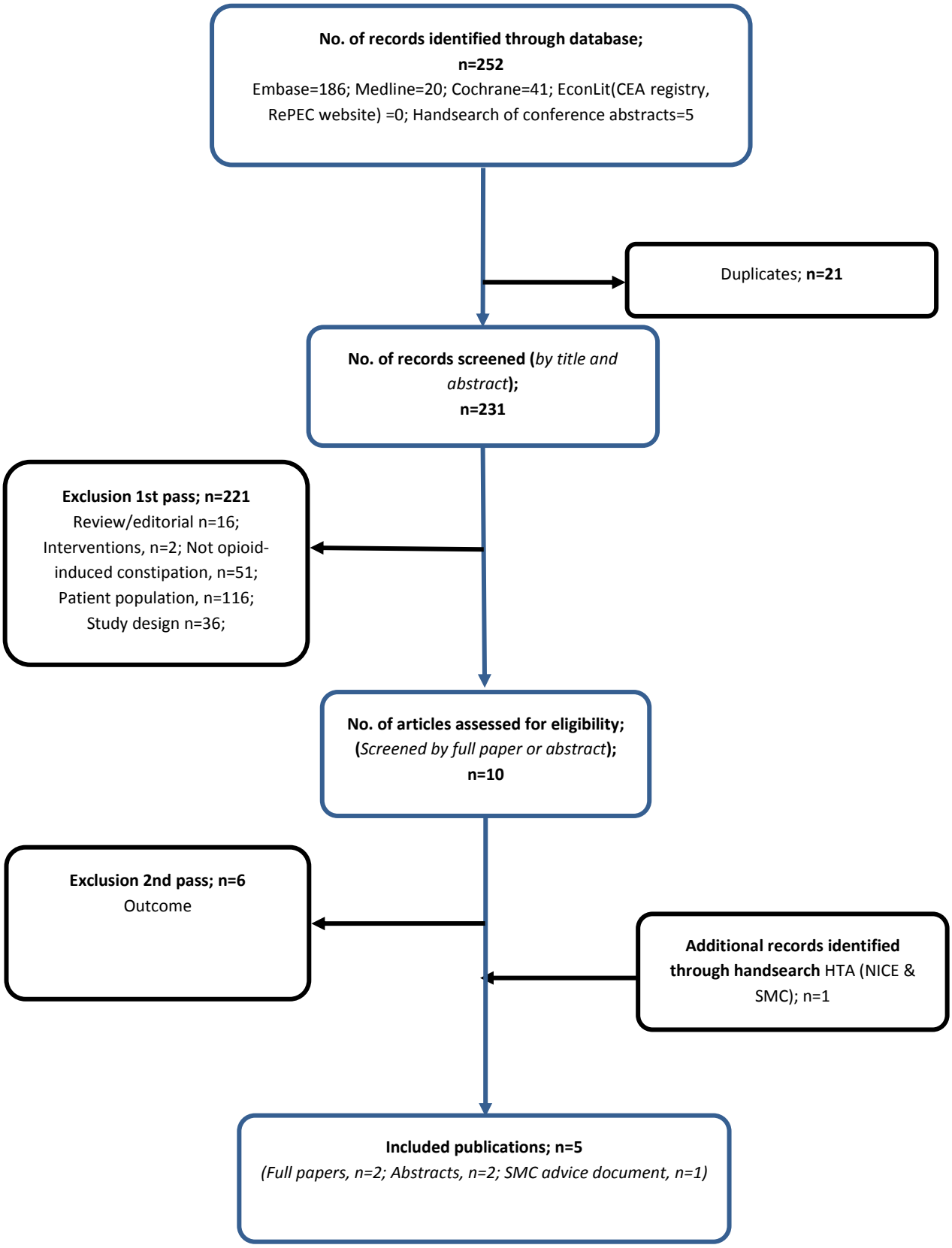
- Cost-effectiveness analysis (CEA) registry (90)
- Research Papers in Economics (RePEc) website (91)
- To identify any recent economic evaluations for which there are currently no full publications, the following conference proceedings between 2012 and 2014 were examined for relevant abstracts:
  - International Society for Pharmacoeconomics and Outcomes Research (ISPOR) database (92).
- To identify relevant HTA submissions, hand-searching was performed on the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) websites (93, 94) to identify previous relevant economic evaluations. The following HTA documentation was reviewed:
  - NICE TA211: Prucalopride for the treatment of chronic constipation in women (95)
  - NICE TA318: Lubiprostone for treating chronic idiopathic constipation (96)
  - NICE Clinical Guideline No. 140, May 2012, Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults (40)
  - SMC Advice 977/14: Lubiprostone (Amitiza) - the treatment of chronic idiopathic constipation and associated symptoms in adults, when response to diet and other non-pharmacological measures (e.g. educational measures, physical activity) are inappropriate (97)
  - SMC Advice 653/10: Prucalopride (Resolor) – chronic constipation (98).

Full details of the search are provided in section 10.11.

Results

The electronic database search and the conference abstract hand-search identified 252 publications in total. Upon the removal of duplicate papers, 231 titles and abstracts were reviewed, and 221 publications were excluded on review of title and abstract. Ten were ordered for full paper review, of which six were excluded, resulting in four relevant papers for final inclusion (Figure 14). In addition, one relevant SMC Advice document (99) identified from the SMC website hand-search was included.

Figure 14: Schematic for the systematic review of cost-effectiveness evidence



Description of identified studies

7.1.2 ***Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.***

Of the 11 studies identified for full paper review via electronic search, conference abstract search and HTA hand search, only five studies reported cost-effectiveness results for OIC treatments. They comprised four cost-utility analyses (25, 99-101), and one cost-effectiveness analysis (26). 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 (25, 26) , two were conference abstracts (100, 101) and one was a SMC advice document (99) obtained from the SMC website. A summary of all five studies is provided in Table 85.

None of the included studies evaluated the cost-effectiveness of naloxegol. Four studies evaluated the cost-effectiveness of naloxone-oxycodone (OXN) vs. oxycodone alone (OXY)(25, 99-101) and a single study (26) evaluated the cost-effectiveness of methylnaltrexone bromide (MNTX) plus standard care (SOC) vs. SOC alone. All studies used a time horizon of ≤1 year.

Two studies, Gerlier 2009 (101) and Dunlop 2013 (100) 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 around the modelling methods and inputs used, they were excluded from further consideration in the in-depth review, and are not discussed further. Earnshaw 2010 (26) evaluated the cost-effectiveness of MNTX versus SOC in OIC patients in the Netherlands. Since the review had identified full-text economic evaluation studies conducted from the perspective of the UK NHS, the present publication based on the healthcare system in the Netherlands was deemed to be of less relevance to decision making in England and Wales, and was excluded from the in-depth review for this reason.

Of the two remaining UK studies, one utilised a cohort model (details of the type of model applied are unclear) (25) and another used a decision analytical model (99). The two models took a UK NHS payer perspective, and both evaluated the cost-effectiveness of naloxone-oxycodone compared with oxycodone alone (11, 12). The clinical data used in the models were sourced from RCTs. In the model used in the cost-effectiveness analysis submitted to the SMC for naloxone-oxycodone (Targinact®) (99), 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* (25) 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 manufacturer was not, in the SMC's assessment, robust enough. Dunlop et al 2012 (25) 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. A brief overview of these two relevant studies (25, 99) is provided in section 10.11.

This SR was conducted to assess the available cost-effectiveness data for naloxegol for treatment in OIC patients. Reviewing the overall evidence, no economic evaluation has been identified for naloxegol. To address the lack of any published evidence for the cost-effectiveness of naloxegol, a de novo analysis has therefore been carried out.

Table 85: Summary list of other cost-effectiveness evaluations

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 (101), Netherlands , Belgium (Abstract)	• Decision analytical model • Societal perspective Netherlands and Belgium • Time horizon: three and 12 months • No discounting applied • Clinical data from OXN3001 trial • Utilities: SF-36 • Deterministic and probabilistic sensitivity analysis conducted	Naloxone-oxycodone vs oxycodone alone	• Patients with moderate/severe non-cancer pain. • Age NR	QALY gain • Netherlands 0.0026 • Belgium 0.0026	Incremental drug cost: • Netherlands €115 • Belgium €153	Incremental cost-effectiveness ratio at 12 months • Belgium €25,421/QALY • Netherlands €12,786/QALY Incremental cost-effectiveness ratio at three months • OXN dominant vs OXY in the Netherlands (data not shown) • Belgium €16,389/QALY	• 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. • 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.
Earnshaw SR 2010 (26), Netherlands (full paper)	• Decision analytical model • Payer perspective of Netherlands • Time horizon <12months • No discounting • Clinical data from (NCT00402038) • Utilities: EQ-5D • One way sensitivity analyses and PSA conducted	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

Dunlop W 2013 (100), 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 (25), UK (full paper)	• Cohort model (type of model is not clearly stated) • UK NHS perspective • 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 • 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	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 • OXY: £713.39	• 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, 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%

SMC submission Targinact® 2009 (99)	• 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 comparable with one another	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.

Abbreviations: ICER, incremental cost-effectiveness ratio, OIC, opioid-induced constipation; QALY(s), quality-adjusted life year(s); NR, not reported; SF-36, Short- form-36; SOC, standard of care; OXN, naloxone-oxycodone; OXY, oxycodone alone; MNTX, methylnaltrexone bromide; PSA, probabilistic sensitivity analysis; EQ-5D, EuroQol-5 dimensions; BFI, Bowel Function Index; SMC, Scottish Medicines consortium.

7.1.3 ***Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996 BMJ 313 (7052): 275–83), or Philips Z, et al. (2004 Health Technology Assessment 8: 36). For a suggested format based on Drummond and Jefferson (1996), please see Section 10.11, appendix 11.***

Quality assessments are provided in section 10.11. Quality assessment was performed only for full-text publications. Based on the quality assessment, the Dunlop et al, 2012 (25) and Earnshaw et al, 2010 (26) studies were considered to be of good quality.

7.2 *De novo analysis*

Patients

7.2.1 ***What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in Sections 1.4 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU***

The patients considered in the base case de novo economic analysis were as outlined in section 1.5, these being in line with the anticipated licence: treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s). In the pivotal RCTs for naloxegol (presented in section 6.3), to qualify as a laxative inadequate responder, patients had to have reported concurrent OIC symptoms of at least moderate severity (i.e. 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 (51, 52). Thus, naloxegol is indicated for any patient with OIC after inadequate response of one laxative class.

In addition, scenarios have been analysed using the subpopulation described in section 6.3.7; those patients within the anticipated licensed population using Step 3 opioids (classified according to World Health Organisation [WHO] analgesic ladder). Please see section 6.3.7 for a justification of the clinical relevance of this sub-population.

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 considers the generalisability to cancer patients of the results of the economic analysis for non-cancer patients.

Model structure

7.2.2 ***Please provide a diagrammatical representation of the model you have chosen.***

Comparison with previous economic models

The model was designed to incorporate the lessons learnt from earlier models of OIC:

- **Timeline**: Previous models have been criticised for adopting short timeframes, such as 1 year for non-malignant pain (27). The naloxegol model has a time horizon of up to 5 years.
- **Extrapolating beyond trial data**: Previous models have been criticised for assuming that short-term response is maintained over time (25, 26). The naloxegol model employs standard extrapolation techniques to estimate long-term response.
- **Health states**: Previous models have been criticised for defining health states in terms of laxative use, rather than by constipation status(22). The naloxegol model defines health states in terms of constipation status.
- **Chronic nature of OIC**: Previous models have been criticised for assuming that OIC is a stable condition, when in reality patients' experience with OIC varies over time (22). The naloxegol model allows constipation status to change over time.

The naloxegol model employs a simple Markov model structure (see later in this section), similar to that recently submitted to NICE for the evaluation of lubiprostone for chronic idiopathic constipation. The lubiprostone model also adopted a simple Markov structure, with health states defined by constipation status, with treatment discontinuation due to non-response based on a discontinuation curve derived from parametric analyses. While the ERG considered the economic submission met the requirements of the NICE reference case, a number of uncertainties with the model were noted, including:

- The utility values were criticised for being based on a different treatment population and definition of response. The naloxegol model avoids this concern by deriving utility from the EQ-5D data collected in the KODIAC 4 and 5 clinical trials
- The 1 year time horizon was considered too short as some patients still remained in the treatment state at the end of the year. The naloxegol model avoids this concern by adopting a 5 year time horizon, and running a number of time horizon scenarios
- The generalisability of US prescription data employed to model discontinuation was queried. The naloxegol model avoids this concern by deriving discontinuation functions from the clinical trial data

To these critiques AstraZeneca would add the fact that, in the lubiprostone model, non-responders move to an 'unresolved' state, where they stay for the remainder of the model time horizon. Our clinical advisors during an advisory board (section

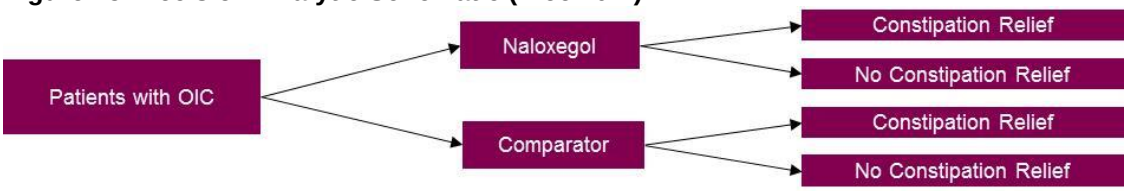
10.25) described constipation as a non-stable condition. As a result, the naloxegol model accounts for possible changes in non-OIC/OIC status over time.

Description of the economic model

A decision-analytic model was constructed to compare the cost-effectiveness of relevant treatment options (which are detailed in Section 7.2.7). This comprised a decision-tree structure for the first 4 weeks of treatment, followed by a Markov structure, with a cycle length of 4 weeks, and time horizon up to a maximum of 5 years.

All patients begin the model with OIC and start taking the assigned treatment – naloxegol or a selected comparator drug (Figure 15). Response to treatment is assessed after 4 weeks, with patients being classified as responders if they have achieved constipation relief and as non-responders if they have not.

Figure 15: Decision Analytic Schematic (Week 0-4)



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

Definition of OIC

Unless stated otherwise, OIC and non-OIC are defined as followed in the model:

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

This divergence from the clinical definition of effect was adopted as:

i) It corresponds with an internationally accepted definition of constipation (1-3)

ii) 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.

The base case comparison is naloxegol 25 mg (the recommended dose) compared with placebo as this is the comparator in the pivotal clinical trials. However, the most clinically relevant comparisons are:

- Naloxegol 25 mg vs placebo in combination with bisacodyl (to represent PRN stimulant laxative use as 2nd line therapy)
- Naloxegol 25 mg plus bisacodyl versus placebo in combination with bisacodyl (a comparison using a common end-point of total bowel movements [BMs]).

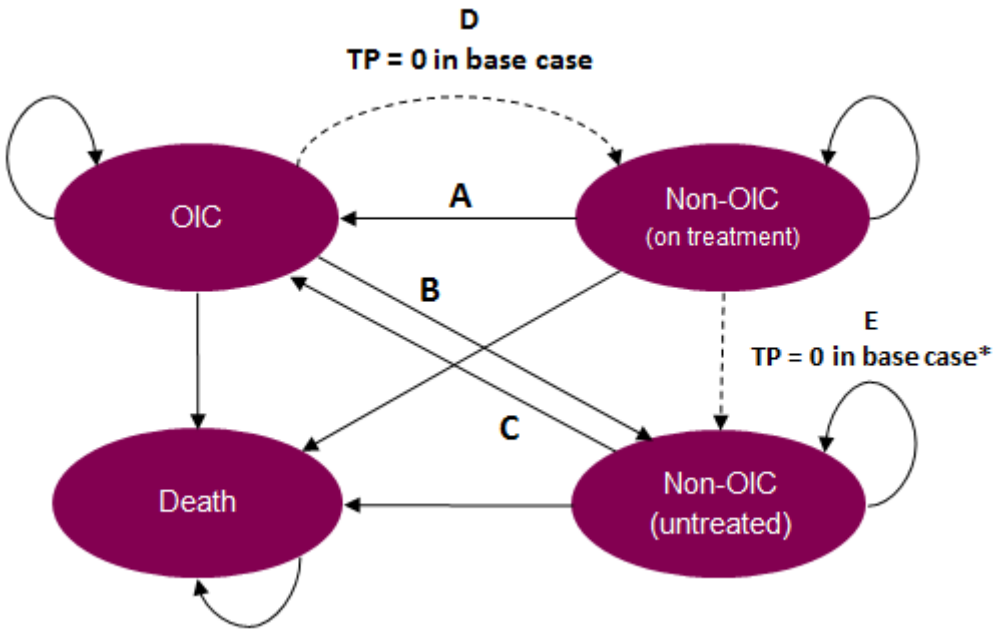
The comparators included in the de novo model are summarised in Table 86.

Table 86: Comparators used in the model

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 population + Step 3 Opioids

Abbreviations: BMs, Total Bowel Movements = Defined as all bowel movements, CSBMs, Complete Spontaneous Bowel Movements = Defined as spontaneous bowel movements with completeness of evacuation; OXN, naloxone-oxycodone; SBMs, Spontaneous Bowel Movements. Defined as a BM without the use of rescue medication administered in the last 24 hours; SC MNTX, subcutaneous methylnaltrexone.
Anticipated licensed population: Treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s). In the pivotal RCTs for naloxegol (presented in section 6.3), to qualify as a laxative inadequate responder, patients had to have reported concurrent OIC symptoms of at least moderate severity (i.e. 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 weeks prior to the screening period of the study (102). Thus, naloxegol is indicated for any patient with OIC after inadequate response to one laxative class.
Step 3 Opioids: Step 3 opioids are for the management of moderate to severe pain and patients receive strong opioids (e.g. morphine, methadone, oxycodone, buprenorphine, hydromorphone, fentanyl) based on the WHO pain ladder (65).

Figure 16: 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.
Abbreviations: OIC, opioid-induced constipation; TP, transition probability.

Response, according to the model definition outlined in section 7.2.2, at 4 weeks determines the health state in which patients enter the Markov model. Those who have responded to treatment by Week 4 will begin the Markov model in 'non-OIC (on treatment)' state. Non-responders at Week 4 will start the Markov phase in the 'OIC' health state.

Transitions

The model is designed to take into account the variable nature of OIC, ie. the fact that patients may move between the OIC and non-OIC state, even in the absence of effective treatment.

Constipation in patients with chronic pain may result from a combination of factors, including not only opioid use, but also influences such as mobility and diet. As a consequence, as these factors vary, so does the likelihood of being OIC. This description of OIC was supported by clinical experts at an Advisory Board held in July, 2013 (section 10.25). They described how a patient's experience of constipation is not stable, including movement from the 'OIC' to the 'non-OIC' state over time. This characterisation of the variable nature of OIC is also supported by the analysis of the trial data that suggested that patients in the placebo arm move between the 'OIC' and 'non-OIC' states (see transitions B and C in section 7.3.7). Previous models of OIC have been criticised for not allowing patients' experience of OIC to vary over time (103).

The base case model included the transitions in Table 87 and Table 88 that occur every 4 weeks.

Table 87: Transition Probabilities Summary

Transition probability	Definition	Source	Comments

A	Treatment failure rates: non-OIC (on treatment) to OIC for subsequent cycles (after week 4)	KODIAC 4 and 5 trial data	Type of curves used for extrapolation:
			• proportional hazard model:
			  ○ exponential functions
			  ○ Weibull functions
			• non-proportional hazard model
			  ○ lognormal,
			  ○ log logistic
			  ○ 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	Proportion of patients who move from OIC to non-OIC (untreated) per cycle Patients who had entered the 'OIC' state either at Week 4 or via transition A were followed until the time when they next became non-OIC	Analysis of the 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.
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

Abbreviations: LIR, laxative inadequate responder; OIC, opioid-induced constipation.

Table 88: Further Model Transitions Description

Initial health state	States patients can transition to	Comments
Patients entering the Markov model	Remain constipation-free and stay in the 'non-OIC (on treatment)' health state	Patients on 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 7.2.3). 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
	Treatment failure and relapse to the 'OIC' state (transition A)	
	Death	
Patients in the 'OIC' health state	Continue to experience OIC;	In the base case, patients are assumed to not move from the 'OIC' state to the 'non-OIC (on treatment)' state. That is, once patients have stopped responding to treatment and discontinued, they cannot go back onto the treatment.
	'Non-OIC (untreated)' state (transition B)	
	Death	
Patients in the 'non-OIC (untreated)' state	Relapse and move back to 'OIC state' (transition C)	
	Death	
Scenario		
Patients who are in the 'OIC' state	May go back onto treatment and transition to the 'non-OIC (on treatment)' state (transition D).	
Patients in the 'non-OIC (on treatment)' state	Can stop taking treatment with no impact on their OIC status, moving to 'non-OIC (untreated)' (transition E).	

Abbreviations: MNTX, methylnaltrexone; OIC, opioid-induced constipation; SC, subcutaneous.

Resource use

Patients receive the following treatments for constipation in the different states of the Markov model (see section 7.2.3 for further justification)

- Patients in the 'non-OIC (on treatment)' state receive the assigned constipation treatment (as detailed in section 7.2.7).
- Patients in the 'OIC' and 'non-OIC (untreated) health states are not assigned active treatment. Thus, patients for whom treatment does not work or for whom treatment stops working and become OIC are assumed to discontinue treatment (see section 7.2.3 for further justification of the discontinuation rule).
- Patients in the 'OIC' and 'non-OIC (untreated)' states use rescue therapy (e.g. laxatives) as required, with the laxative use in the 'non-OIC (untreated)' state being prophylactic. Patients in the 'non-OIC (on treatment)' state do not take rescue medication unless this is part of the treatment regimen being evaluated.

Beyond treatment costs, the following constipation-associated Health Care Resource Use (HCRU) is captured in the model:

- HCRU to manage OIC are incurred in the 'OIC' state, including: inpatient hospitalisations, outpatient and emergency department visits; primary care consultations, with both general practitioners and nurses; rescue interventions, including laxatives, enemas and manual evacuation; haemorrhoid stapling; imaging, including endoscopy and colonoscopy; and laboratory tests, including abdominal plain film x-ray. The frequency of HCRU varies with OIC status.
- The cost of treatment-related grade 3 or 4 adverse events (AEs), which are only incurred in the 'non-OIC (on treatment)' state.
- Opioid use: With the exception of the comparison to OXN, opioid cost has not been included in the estimation of OIC costs in either the base case or any scenarios. As an opioid (oxycodone) is intrinsic to OXN's unit cost, the cost of an opioid has been added for patients using naloxegol to ensure a "like for like" comparison between naloxegol and OXN. As oxycodone is classified as a Step 3 opioid according to the WHO analgesic ladder (65) the base case adds the cost of the most commonly prescribed Step 3 opioid (determined using IMS Disease Analyzer data (48)) and a scenario analysis has been presented with naloxegol patients using the same oxycodone dose as per the cited naloxone-oxycodone trials (54, 58)

7.2.3 *Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.*

As discussed in section 2.1 there is currently no clear consensus among UK physicians on the treatment pathway for patients with OIC (44). NICE CG 140 advises that laxatives should be prescribed for all patients initiating treatment with strong opioids (i.e. Step 3), but does not specify the laxative class or number of

classes (40).

[redacted]

Naloxegol as per its anticipated licensed population is positioned as a treatment option for patients with OIC for whom laxative(s) have not been able to provide adequate relief. As a result, clinicians would be able to prescribe naloxegol as a second line option, and beyond, in patients post their first inadequate response to a laxative class.

As the model is defined by health state rather than treatment, both the lack of treatment guidelines and naloxegol's anticipated licence are taken into account. Patients enter the model in an OIC state, irrespective of their treatment history. As such, it is considered suitable for modelling any line of therapy post-first line as per the anticipated licensed indication for naloxegol. In addition, the health state model structure selected also enables patients to use multiple therapies (e.g. naloxegol and a stimulant laxative used as required) to accommodate the potentially multifactorial nature of their condition.

7.2.4 *Please define what the health states in the model are meant to capture.*

The health states are primarily designed to capture the impact of OIC on health related quality of life (HRQL), which in turn has consequences for health care resource use (HCRU):

This approach was based on the following rationale:

- The literature on the impact of OIC on HRQL (see sections 7.4.1 and 7.4.2 for a summary of this literature)
- An analysis of the KODIAC 4 and 5 trial data, which demonstrated that OIC status is a key driver of patient utility (as described in section 7.4.3)
- Critiques of an earlier model of OIC treatment, which adopted "an unusual model structure" by defining health states in terms of laxative use rather than the degree of constipation (103)
- An analysis of the KODIAC 4 and 5 trial data, which demonstrated that OIC status is a key driver of patient utility (as described in section 7.4.3)

See section 7.2.2 for HCRU associated with OIC.

7.2.5 *How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.*

See Section 7.2.2 and 7.2.4.

Laxative(s) are typically used as the first-line treatment for OIC in clinical practice. However, due to differences in the mechanisms of functional constipation and OIC, patients with OIC may not respond adequately to laxative(s) (42). Laxative(s) are only effective in alleviating the symptoms of constipation that result from inactivity and poor hydration and do not specifically target the opioid-related mechanisms that additionally contribute to constipation in these patients. Unfortunately, many patients who fail to achieve an adequate response to one laxative then switch to an alternative laxative, without targeting the underlying cause of their OIC (see section 2.1).

7.2.6 *Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.*

A summary of the key features of the analysis is presented in Table 89.

Table 89: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Base case: 5 years Scenarios: 3 months, 1 year, 3 years	1. Previous models of OIC that adopted a 1 year timeframe were criticised for adopting too short a timeframe (27). For example, NICE's ERG critiqued the manufacturer's economic analysis of lubiprostone as treatment for chronic idiopathic constipation for only adopting a 1 year time horizon. The ERG explored the sensitivity of model results over different timeframes up to 20 years (104). 2. A time horizon of 5 years is longer than the average period of opioid persistence in the population of interest, but was selected to reflect the likely variance in persistence, with some patients being on opioids longer than the average period. However, a number of time horizon scenarios were run to test the impact of time horizon on the incremental cost-effectiveness ratio given: [redacted] b. Data from an analysis of the Clinical Practice Research Database (CPRD) database showed that, for patients with at least 182 days of continuous opioid exposure[3], 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 (89).	
Cycle length	4 weeks	4 weeks corresponds to the first time point at which estimates of treatment response were available for most treatments and has been adopted for other models (95)	N/A

[3] Additional screening criteria were applied including ensuring patients had at least one year of data prior to index date (and posterior to practice "up-to-standard" date), were naive to opioid prior to index date, older than 18 and excluding patients with less than 5 year of follow-up and still on index treatment at the end of follow-up

Factor	Chosen values	Justification	Reference
Half-cycle correction	Yes	To allow for the fact that transitions will happen within cycles	N/A
Were health effects measured in QALYs; if not, what was used?	Yes	NICE Reference Case. EQ-5D data collected from the KODIAC clinical studies has been used.	NICE Guide to Methods of Technology Appraisal 2013 (105)
Discount of 3.5% for utilities and costs	Yes	NICE Reference Case	NICE Guide to Methods of Technology Appraisal 2013 (105)
Perspective (NHS/PSS)	NHS and PSS	NICE Reference Case	NICE Guide to Methods of Technology Appraisal 2013 (105)

Abbreviations: ERG, Evidence Review Group; EQ-5D, European Quality of Life 5 Dimensions; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; OIC, opioid-induced constipation; PSS, personal social services; QALYs, quality-adjusted life years.

Technology

7.2.7 ***Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?***

The intervention and comparator(s) are implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5.

7.2.8 ***Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.***

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Patients are assumed to discontinue treatment if they do not respond to it. In addition, individuals on subcutaneous methylnaltrexone, a drug given for a maximum of 16 weeks (i.e. the maximum duration of treatment with subcutaneous methylnaltrexone is 16 weeks [4 cycles], irrespective of treatment response status at Week 16).

The basis for these stopping rules is as follows:

- The assumption that treatment is discontinued if there is no response was based on clinical advisors' view (described in section 10.25) that patients would immediately stop taking any treatment they perceived to be not working.
  [redacted]
- The SPC for subcutaneous methylnaltrexone states that the drug has not been studied in clinical trials lasting longer than 4 months, and should,

therefore, only be used for a limited period (106). Therefore the use of a '16 weeks' stopping rule was implemented in the model according to the SPC.

Various scenarios (as detailed in section 7.3.7) were examined to explore the impact of these discontinuation rules on model outcomes.

7.3 *Clinical parameters and variables*

7.3.1 *Please demonstrate how the clinical data were implemented into the model.*

A number of data were used to estimate response in the economic analysis, including:

- Sources of data: depending on the comparator selected (Table 86), estimates of response were taken from either an analysis of the trial data or an MTC (see below).
- Definition of response: where treatment included rescue bisacodyl, treatments were compared based on likelihood of any bowel movements (BMs), otherwise, response was defined based on SBMs.
- Denominator: 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, as a scenario analysis, the number of patients at risk (for whom observations were available at Week 4) was used as the denominator to generate the response rate[d].

[d] Of the patients in the KODIAC 4 and 5 trials, 22.1% did not complete the study. Almost half of these discontinuations (10.2%) were due to adverse events. Other important reasons recorded for discontinuation included subject decision (5.8%); lost to follow up (3.3%); and non-compliance with the trial protocol (1.6%). None of the discontinuations was recorded as being due to loss of therapeutic effect

Table 90, Table 91 and Table 92 summarise the response rate at Week 4 calculated using the methods described above. The response rates estimated with the MTC were lower (e.g. naloxegol 25 mg: 45.9%) than those taken directly from the trial (naloxegol 25 mg: 58.5%). This is because the definition of response adopted in the MTC was more stringent than that in the trial (see above).

Table 90: Proportion of patients in 'non-OIC (on treatment)' state at Week 4, trial-based (all anticipated licensed population patients)

Technology	ITT		Patient at risk	
	Mean	SE	Mean	SE
Naloxegol 25 mg†	58.51%	3.17%	65.58%	3.24%
Naloxegol 25 mg + rescue bisacodyl‡	72.20%	2.89%	79.09%	2.74%
Placebo†	39.75%	3.17%	42.41%	3.30%
Placebo + rescue bisacodyl‡	60.25%	3.17%	61.80%	3.18%

Abbreviations: ITT, intent-to-treat; SE, standard error.
†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

Table 91: Proportion of patients in 'non-OIC (on treatment)' state at week 4, trial-based (anticipated licensed population + step 3 opioids)

Technology	ITT		Patient at risk	
	Mean	SE	Mean	SE
Naloxegol 25 mg†	62.50%	3.65%	70.51%	3.65%
Naloxegol 25 mg + rescue bisacodyl‡	73.86%	3.31%	82.80%	3.01%
Placebo†	38.75%	3.85%	41.33%	4.02%
Placebo + rescue bisacodyl‡	61.25%	3.85%	62.42%	3.87%

Abbreviations: ITT, intent-to-treat; SE, standard error.
†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

Table 92: Proportion of patients in 'non-OIC (on treatment)' state at Week 4, MTC analysis

	LIR		LIR on 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%

Abbreviations: LIR, laxative inadequate responder; MNTX, methylnaltrexone; OXN, naloxone-oxycodone; QAD, every other day; SC, subcutaneous; SE, standard error.

The clinical data employed to estimate response differed from that employed in the analysis of clinical efficacy (section 6).The clinical efficacy analysis included a multifactor definition of response, including 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 intentionally focuses on absolute constipation status alone, without a measure of change in bowel

movements from baseline. This divergence from the clinical definition of effect was adopted as:

- it corresponds with an internationally accepted definition of constipation
- 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.

7.3.2 ***Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.***

See section 7.3.1 for a summary of the transition probabilities up to 4 weeks.

7.3.3 ***Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.***

See section 7.3.7 for a summary of the transition probabilities beyond 4 weeks, including longer term extrapolation.

7.3.4 ***Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?***

No surrogate markers were used in this model.

7.3.5 ***If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[e]:***

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***

[e] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).***

An Advisory Board was convened to inform the development of the model. See section 10.25 for further details. Key insights that were provided by the Advisory Board for the development of the model have been reported in section 7.2.3.

Summary of selected values

7.3.6 ***Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission.***

A summary of all variables used in the model is provided in Table 93 and Table 94.

Table 93: Summary of variables applied in the economic model (anticipated licensed population) (costs in 2014 £)

Variable	Value	Distribution	SE	Reference to section in submission
General Settings				
Population age†	52.2 years	-	-	N/A
Probability of response by 4 weeks – Trial-based (ITT)				
Naloxegol 25 mg‡	58.51%	Beta	3.17%	7.3.1
Naloxegol 25 mg + bisacodyl§	72.20%	Beta	2.89%	7.3.1
Placebo‡	39.75%	Beta	3.17%	7.3.1
Placebo + bisacodyl§	60.25%	Beta	3.17%	7.3.1
Probability of response by 4 weeks – MTC analysis				
Naloxegol 25 mg¶	45.87%	Beta	7.66%	7.3.1
SC MNTX QAD¶	38.40%	Beta	9.74%	7.3.1
Transition probabilities (from week 4)				
Transition A	See Section 7.3.2			
Transition B	28.98%	Beta	4.27%	7.3.7

Variable	Value	Distribution	SE	Reference to section in submission
Transition C	20.94%	Beta	5.44%	7.3.7
Mortality (per cycle)	0.027%	Beta	0.001%	7.3.7
Treatment and administration costs per cycle				
Naloxegol 25 mg	£ 51.52	-	-	7.5.5
Naloxegol 25 mg + bisacodyl	£ 51.81	-	-	7.5.5
SC MNTX QAD	£ 609.45	-	-	7.5.5
Placebo	£ 0	-	-	7.5.5
Placebo + bisacodyl	£ 0.29	-	-	7.5.5
Cost of adverse events (grade 3-4), Cycle 1				
Naloxegol 25 mg	£ 17.85	-	-	section 10.26
Naloxegol 25 mg + bisacodyl	£ 17.85	-	-	section 10.26
SC MNTX QAD	£ 16.83	-	-	section 10.26
Placebo	£ 10.83	-	-	section 10.26
Placebo + bisacodyl	£ 10.83	-	-	section 10.26
Cost of health states				
Non-OIC (on treatment	£ 0	Gamma	£ 1.59	7.5.6
OIC	£ 35.82	Gamma	£ 1.79	7.5.6
Non-OIC (untreated)	£ 3.14	Gamma	£ 0.16	7.5.6
Utility in health states – Naloxegol 25 mg vs placebo				
Non-OIC (on treatment) – Naloxegol 25 mg (cycles 1-2) -	0.620	Gamma	0.025	7.4.3

Variable	Value	Distribution	SE	Reference to section in submission
Non-OIC (on treatment) – Naloxegol 25 mg (cycles 3+)	0.665	Gamma	0.026	7.4.3
Non-OIC (on treatment) – placebo	0.613	Gamma	0.021	7.4.3
OIC	0.553	Gamma	0.022	7.4.3
Non-OIC (untreated)	0.613	Gamma	0.021	7.4.3
Utility in health states – Naloxegol 25 mg vs MNTX				
OIC	0.564	Gamma	0.017	7.4.3
Non-OIC	0.630	Gamma	0.014	7.4.3

Abbreviations: ITT, intent-to-treat; MTC, mixed treatment comparison; MNTX, methylnaltrexone; OIC, opioid-induced constipation; QAD, every other day; SC, subcutaneous; SE, standard error.
[†]The population age was based on the average age of participants in the KODIAC 4 and 5 trials.
[‡]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.
[¶]Response data: patients with ≥3 SBMs/week (%) over 4-week treatment period.

Table 94: Summary of variables applied in the economic model (anticipated licensed population + Step 3 opioids) (costs in 2014 £)

Variable	Value	Distribution	SE	Reference to section in submission
General Settings				
Population age	52.2 years	-	-	N/A
Probability of response by 4 weeks – Trial-based (ITT)				
Naloxegol 25 mg[†]	62.50%	Beta	3.65%	7.3.1
Naloxegol 25 mg + bisacodyl[‡]	73.86%	Beta	3.31%	7.3.1
Placebo[†]	38.75%	Beta	3.85%	7.3.1
Placebo + bisacodyl[‡]	61.25%	Beta	3.85%	7.3.1
Probability of response by 4 weeks – MTC analysis				
Naloxegol 25 mg[§]	53.99%	Beta	9.18%	7.3.1

SC MNTX QAD[§]	37.82%	Beta	10.97%	7.3.1
OXN[¶]	46.01%	Beta	6.59%	7.3.1
Transition probabilities				
Transition A	See Section 7.3.2			
Transition B	28.98%	Beta	4.27%	7.3.7
Transition C	20.94%	Beta	5.44%	7.3.7
Mortality (per cycle)	0.027%	Beta	0.001%	7.3.7
Treatment and administration costs per cycle (4 weeks)				
Naloxegol 25 mg	£ 51.52	-	-	7.5.5
Naloxegol 25 mg + bisacodyl	£ 51.79	-	-	7.5.5
SC MNTX QAD	£ 609.45	-	-	7.5.5
OXN	£ 125.54	-	-	7.5.5
Placebo	£ 0	-	-	7.5.5
Placebo + bisacodyl	£ 0.27	-	-	7.5.5
Cost of adverse events (grade 3-4), Cycle 1				
Naloxegol 25 mg	£ 19.31	-	-	section 10.26
Naloxegol 25 mg + bisacodyl	£ 19.31	-	-	section 10.26
SC MNTX QAD	£ 17.75	-	-	section 10.26
OXN	£ 13.92	-	-	section 10.26
Placebo	£ 11.50	-	-	section 10.26
Placebo + bisacodyl	£ 11.50	-	-	section 10.26
Cost of health states				
Non-OIC (on treatment	£ 0	Gamma	£ 1.85	7.5.6
OIC	£ 40.99	Gamma	£ 2.05	7.5.6
Non-OIC (untreated)	£ 3.12	Gamma	£ 0.16	7.5.6

Utility in health states: Naloxegol 25 mg vs placebo				
Non-OIC (on treatment) – Naloxegol 25 mg (cycles 1-2) -	0.594	Gamma	0.030	7.4.3
Non-OIC (on treatment) – Naloxegol 25 mg (cycles 3+)	0.679	Gamma	0.030	7.4.3
Non-OIC (on treatment) – placebo	0.572	Gamma	0.027	7.4.3
OIC	0.537	Gamma	0.027	7.4.3
Non-OIC (untreated)	0.572	Gamma	0.027	7.4.3
Utility in health states: naloxegol 25 mg vs MNTX and naloxegol 25 mg (exclusive use of morphine) vs OXN				
OIC	0.546	Gamma	0.021	7.4.3
Non-OIC	0.610	Gamma	0.017	7.4.3

Abbreviations: ITT, intent-to-treat; MTC, mixed treatment comparison; MNTX, methylnaltrexone; OIC, opioid-induced constipation; OXN, naloxone-oxycodone; QAD, every other day; SC, subcutaneous; SE, standard error.
[†]The population age was based on the average age of participants in the KODIAC 5 and 5 trials.
[‡]Response is defined as patients with ≥3 SBMs/week (%) over at least 3 out of past 4 weeks.
[§]Response data: patients with ≥3 SBMs/week (%) over 4-week treatment period
[¶]Response data: relative risk of patients with ≥3 CSBMs/week (%) at 4 weeks versus naloxegol 25 mg, applied to the probability of ≥3 SBMs/week (%) over 4-week treatment period with naloxegol

7.3.7 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.*

Transition A ('non-OIC [on treatment]' state to 'OIC' state)

A number of methods were used to generate estimates of transition A. These are summarised in Table 95 and described in more detail below.

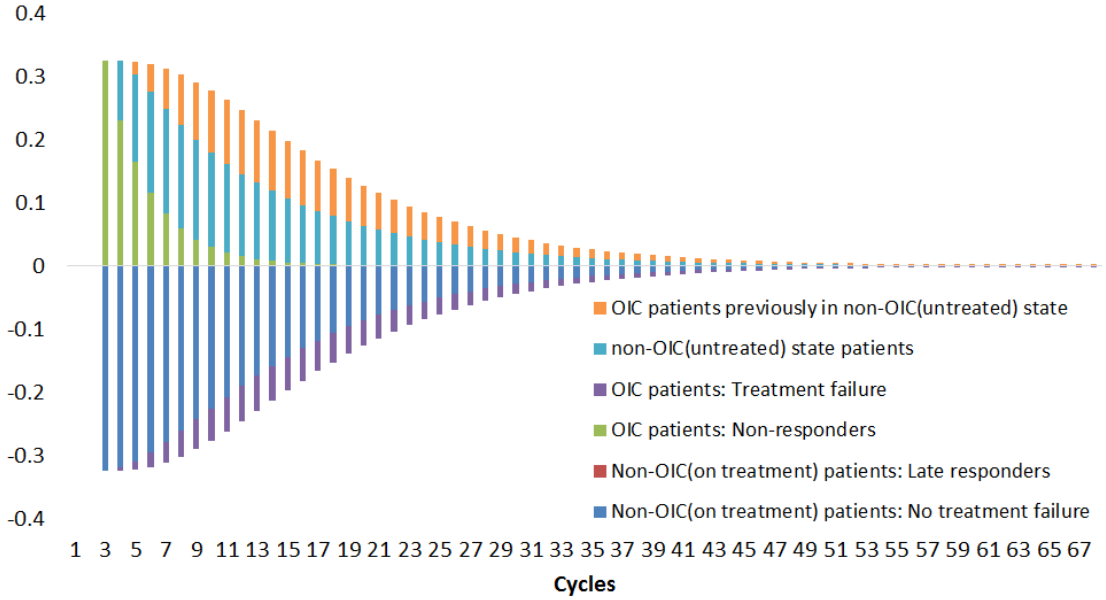
The base case model used the exponential function to extrapolate response over a period of 5 years. The model was generated based on weekly observations (between Weeks 4 and 12) in the KODIAC 4 and 5 data, and the corresponding transition probability applied from Week 4, per the Markov model described in section 7.2.2.

This approach was adopted in the base case as:

- A 5 year time horizon was selected as this was thought to reflect the upper end of the period of persistence of opioid use (Table 89). Also, running the

model suggests that it reaches a steady state within this period, as demonstrated in Figure 17.

Figure 17: Difference over time of patient transition between health states between naloxegol 25 mg and placebo



- The exponential function was selected as the most parsimonious of the functions tested in the absence of external validation and strong evidence in favour of any particular function. See later in this section for further detail.

Table 95: Summary of approaches used to measure transition A (X indicates where the extrapolation scenario was applied)

Scenario		Timeframe	Naloxegol 25 mg vs			
			Placebo	Placebo + bisacodyl	SC MNTX QAD	OXN
Fitting statistical functions to KODIAC 4 and 5	Exponential	1 year	X	X	X	-
		3 years	X	X	X	-
		5 years†	X	X	X	X
	Weibull	1 year	X	X	X	-
		3 years	X	X	X	-
		5 years	X	X	X	-
	Log logistic	1 year	X	X	-	-
		3 years	X	X	-	-
		5 years	X	X	-	-

Scenario		Timeframe	Naloxegol 25 mg vs			
			Placebo	Placebo + bisacodyl	SC MNTX QAD	OXN
	Log normal	1 year	X	X	-	-
		3 years	X	X	-	-
		5 years	X	X	-	-
A constant transition probability based on discontinuation data from K8		1 year	X	X	X	-
		3 years	X	X	X	-
		5 years	X	X	X	-
12 week response maintained		1 year	X	X	-	-
		3 years	X	X	-	-
		5 years	X	X	-	-
No extrapolation		12 weeks	X	X	-	-

Abbreviations: MNTX, methylnaltrexone; OXN, naloxone-oxycodone; QAD, every other day; SC, subcutaneous.
†Base case scenario

Fitting statistical functions

The Kaplan-Meier (KM) curve of the number of patients in 'non-OIC (on treatment)' state was derived from the KODIAC 4 and 5 studies. The KM curve was specified for each treatment separately (naloxegol 25 mg and placebo), based on the anticipated licensed population who were responders at 4 weeks.

Parametric survival analyses were performed on KODIAC 4 and 5 to predict the proportion of patients remaining in the non-OIC (treated) health state over time, based on weekly estimates of OIC status in the previous 4 weeks for Weeks 4–12.

To maximise the data available, but also to avoid capturing mortality in the transition probability (as this was a separate transition in the model), the data were censored for those patients with treatment exposure of less than 12 weeks. Specifically, the data was censored at the closest week following the last day of exposure to treatment.

The following curves were fitted to the data: exponential, Weibull, gamma, Gompertz, log-normal and log-logistic. Curves were fitted separately for naloxegol 25 mg and placebo, to allow for the possibility that changes in constipation status followed a different distribution in the two arms. Though, in accordance with best practice guidelines(107), the selection process resulted in the same function being used for naloxegol 25 mg and placebo.

Equations were fitted to the data using the LIFEREG procedure in SAS, and a specialised macro designed to fit a Gompertz model, as this is not a standard option in SAS. These procedures produce estimates of the scale and shape parameters of the distributions and allow the scale parameter to be regressed on predictors.

Table 96 shows the parameters of these fitting functions.

Table 96: Functions used to estimates transition A, anticipated licensed population (Weeks 4–12)

Function	Exponential	Weibull	Log-logistic	Log-normal	Gamma	Gompertz
Naloxegol 25 mg						
Intercept	5.474	5.634	5.388	5.556	5.628	4.948
Scale		1.106	1.033	1.909	0.497	
Shape		0.905			2.379	
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						
Intercept	4.897	4.763	4.508	4.567	3.557	4.931
Scale		0.863	0.776	1.382	1.618	
Shape		1.159			-2.030	
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

Abbreviations: AIC, Akaike's Information Criteria; BIC, Bayesian Information Criterion.

Figure 18 shows the predicted curves, under each distribution fit, versus the observed data, for proportions of patients remaining in the non-OIC (treated) health state over time in the naloxegol 25 mg arm (transition A). Figure 19 shows the extrapolation of this data out to 300 days, applying the curve fitted on Weeks 4–12 data from Week 4.

Figure 18: Predicted versus observed responders, naloxegol 25 mg, anticipated licensed population

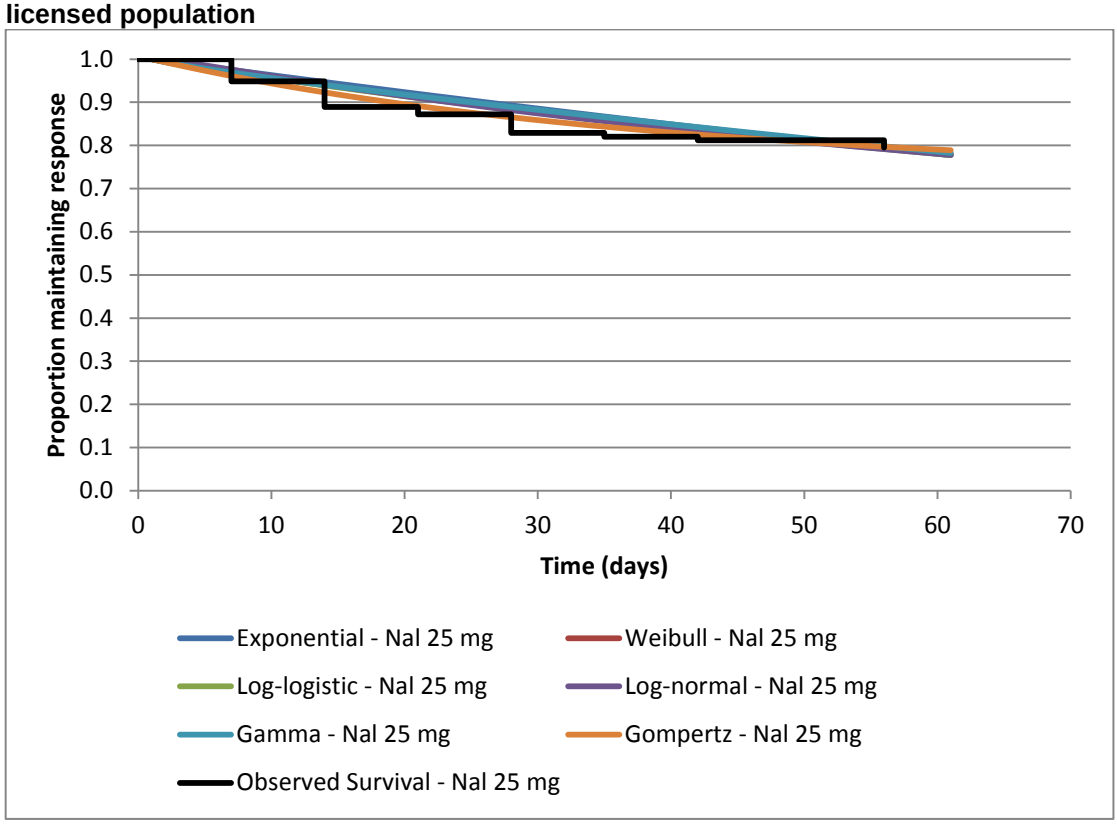


Figure 19: Extrapolation of response predictions (up to 300 days), naloxegol 25 mg, anticipated licensed population

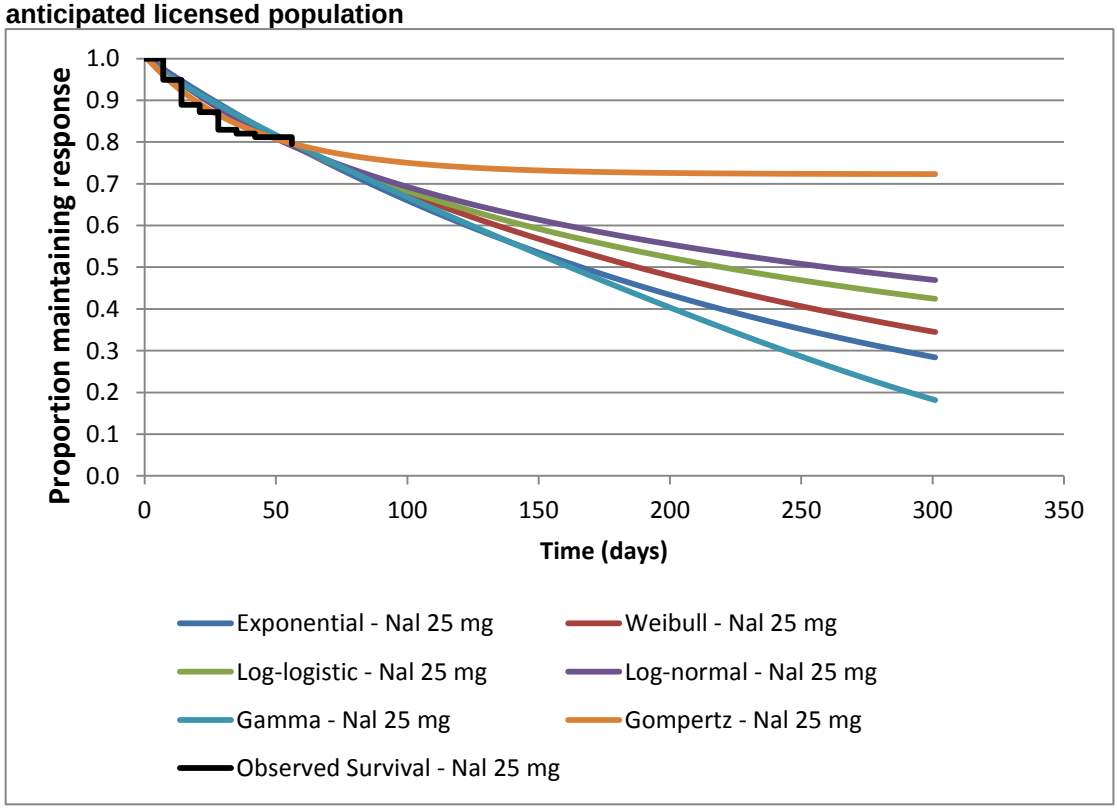


Figure 20 shows the predicted curves, under each distribution fit, versus the observed data, for the proportion of patients remaining in the non-OIC (treated) health state over time in the placebo arm (transition A). Figure 21 shows the extrapolation of this data out to 300 days.

Figure 20: Predicted versus observed responders, placebo, anticipated licensed population

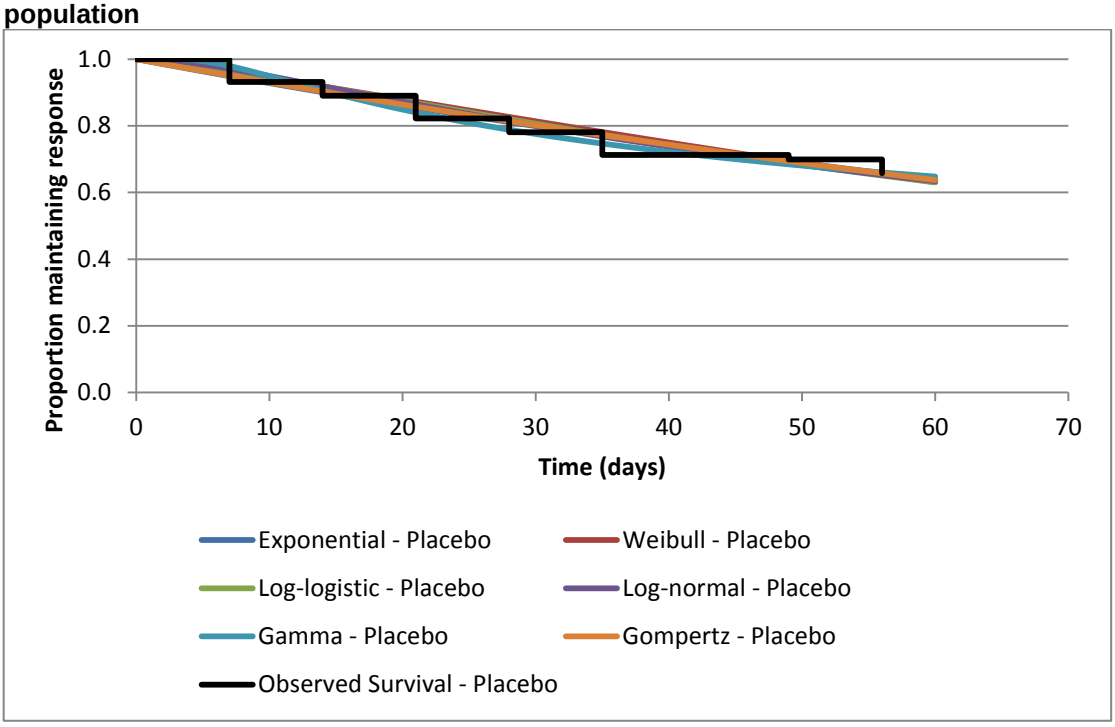
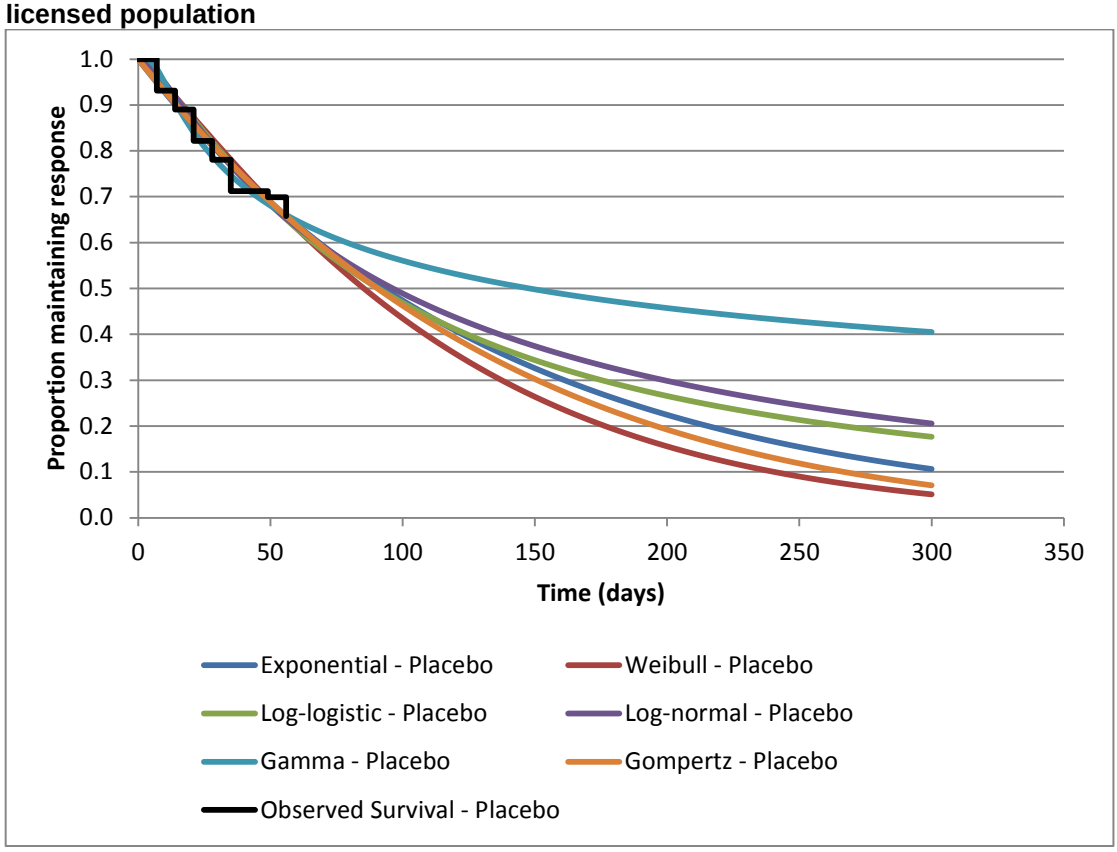


Figure 21: Extrapolation of response predictions (up to 300 days), placebo, anticipated licensed population



In line with best practice guidelines (107-109), the best-fitting distribution was identified and tested using the following information:

- Diagnostic plots associated with each of the distributions being considered (described in section 10.27) suggest that a log normal function may best reflect the distribution underlying the observed data.
- The Akaike's Information Criteria (AIC) and Bayesian Information Criterion (BIC) were compared (with lower values indicating better fit, see Table 96) suggesting that either the log normal or the exponential function may best fit the observed data, though all the functions demonstrated similar fit.
- Clinical experts' opinion on the clinical plausibility of the extrapolations (described in section 10.25) suggested that [redacted]
- No alternative data were available against which to externally validate the extrapolations.

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. On the basis that non-response after 4 weeks is likely to be related to the response rate at 4 weeks, functions for other treatments were estimated based on the naloxegol 25 mg curve, assuming proportional hazards to naloxegol, and using the following hazard ratios (HRs) values estimated from the MTC (see section 6.7). In the base case, the HR was estimated as the ratio of the 4 week response rate of the comparator relative to that of naloxegol 25 mg (Table 97). In a scenario analysis, the HR was set to 1.

Table 97: Hazard ratios used to estimate transition A (source: MTC)

Comparator	Anticipated licensed population	Anticipated licensed population + Step 3 opioids
SC MNTX QAD	0.84	0.70
OXN	1.07	0.85

Abbreviations: LIR, laxative inadequate response; MNTX, methylnaltrexone; OXN, naloxone-oxycodone; QAD, every other day; SC, subcutaneous.

KODIAC 8 discontinuation data

An extrapolation scenario was run using KODIAC 8 discontinuation data. KODIAC 8 was a 52-week open-label, long-term safety study that reported no efficacy data, and so was not used to inform the base case. The inculsion/exclusion criteria was broadly in line with KODIAC 4 and 5 and included the LIR licensed population. However, this trial did include data on discontinuation. Discontinuation data was used to estimate

the probability of transitioning from ‘non-OIC (on treatment)’ to ‘OIC’ for naloxegol 25 mg. 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.

KODIAC 8 included patients rolled over from KODIAC 5 (n=84) and new patients (n=760). The transition A estimates were generated on the new patients, as roll over patients had been receiving naloxegol for 12 weeks on KODIAC 5 during which time discontinuation was restricted by the trial protocol. 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.

The KODIAC 8 data were used to derive a constant probability for transition A (3.43% per cycle). On the basis that discontinuation after 4 weeks is likely to be related to the response rate at 4 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.

No extrapolation

A scenario was run that used 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 KODIAC 5 trials, and did not extrapolate beyond this trial period. This was intended to represent a worst case response scenario. The analysis used the number of patients in the relevant group in the trial at baseline as the denominator (i.e. an intent-to-treat approach). Table 98 and Table 99 summarise 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 98: Proportion of patients remaining in ‘non-OIC (on treatment)’ state at Week 4, 8, 12 (anticipated licensed population)

Treatment	Week 4	Week 8	Week 12
Naloxegol 25 mg[†]	58.51%	55.60%	55.19%
Naloxegol 25 mg + bisacodyl[‡]	72.20%	64.32%	61.83%
Placebo[†]	39.75%	43.93%	41.42%
Placebo + bisacodyl[‡]	60.25%	55.65%	53.97%

[†]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.

Table 99: Proportion of patients remaining in 'non-OIC (on treatment)' state at Week 4, 8, 12 (anticipated licensed population + Step 3 opioids)

Treatment	Week 4	Week 8	Week 12
Naloxegol 25 mg†	62.50%	56.25%	55.11%
Naloxegol 25 mg + bisacodyl‡	73.86%	65.34%	61.93%
Placebo†	38.75%	44.38%	43.75%
Placebo + bisacodyl‡	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.

Response maintained

A scenario was considered that used estimates of the proportion of patients in the 'non-OIC (on treatment)' state from the KODIAC 4 and KODIAC 5 trials, which assumed that patients in the 'non-OIC (on treatment)' state at 12 weeks stayed in this state for the remainder of the model (Table 100).

Transition B (OIC' state to 'non-OIC [untreated]' state) and transition C ('non-OIC [untreated]' state to 'OIC' state)

Estimates for transitions B and C 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 B and C estimates were used across the treatments included in the model.

For transition B, patients who had entered the 'OIC' state either at Week 4 or via transition A were followed until the time when they next became non-OIC. For transition C, patients in the non-OIC state were followed until time-to-next OIC state. The numerators (events) and denominators (number at risk) for each transition were used to compute 4-week transition probabilities utilised in the economic model.

Table 100: Transition probabilities B and C (source: analysis of KODIAC 4 and 5)

	Mean	SE
Transition B	28.98%	4.27%
Transition C	20.94%	5.44%

Abbreviations: standard error.

Mortality

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 (110). 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.

7.3.8 *Provide a list of all assumptions in the de novo economic model and a justification for each assumption.*

A list of the assumptions used in the economic model is provided in Table 101.

Table 101: List of assumptions used in the economic model

Variable	Assumption	Justification	Base Case or Scenario Analysis	Method
Maintenance of naloxegol and placebo response beyond KODIAC 4 and 5 trial duration	Treatment response can be maintained beyond the period observed in the trial, and that the extent of maintenance can be determined by extrapolating the response trends observed in the trial	KODIAC 8 discontinuation data Anticipated SPC	Base case and scenarios are available for alternative extrapolation methods	See section 7.3.7
Discontinuation	Once treatment fails, patients will discontinue therapy and do not try it again	[redacted] (28)	Base case and scenario analysis by varying the transition probability from OIC to non-OIC (on treatment) health states (transition D)	See section 6.9
Treatment when in non-OIC healthstate	Naloxegol treatment is maintained	When therapeutic effect maintained, patients persist on treatment.	Base Case and scenario analysis (section 7.7.7) by varying the transition probability from non-OIC (on treatment) to non-OIC (untreated) health states (transition E)	See section 7.7.7
Variable nature of OIC	The experience of OIC is variable, with patients moving between the OIC and non-OIC states over time	Ad-Board (29) Placebo arm on KODIAC 4 and 5 trials	Base case and scenario analysis considered in the sensitivity analysis by varying the transition probability from OIC to non-OIC (untreated) health states and from non-OIC (untreated) to OIC health states (transitions B and C).	See section 7.2.5
Utility	Health state utility is a function of OIC status, time and treatment	See section 7.4.3	Base case and scenario analysis considered in the sensitivity analysis by varying the utility by time, treatment and other tariff (section 7.7.7)	See section 7.4.3

Variable	Assumption	Justification	Base Case or Scenario Analysis	Method
Maintenance of comparator response beyond MTC end point	Response is maintained on comparator treatments (SC MNTX and OXN) in proportion to the rate it is maintained on naloxegol 25 mg, adjusted for the relative response on treatments at Week 4	Text above Table 97 in section 7.3.7	Base case and scenarios are available for alternative extrapolation methods	See section 7.3.7

Abbreviations: MTC, mixed treatment comparison; MNTX, methylnaltrexone; OIC, opioid-induced constipation; OXN, oxycodone plus naloxone; SC, subcutaneous.

7.4 *Measurement and valuation of health effects*

Patient experience

7.4.1 *Please outline the aspects of the condition that most affect patients' quality of life.*

The symptoms, discomfort and pain associated with OIC and the negative impact on daily life contribute to the overall quality of life (QoL) burden, regardless of the frequency of opioid use (7). The symptoms of the condition may range from rectal and/or lower abdominal pain, abdominal distension, straining during evacuation, bloating, and flatulence to obstructive symptoms with nausea and vomiting (111, 112). The physical sequelae of constipation are also important when assessing patients. Haemorrhoids, diverticular disease and faecal impaction contribute to the burden of the condition and often require treatment (38).

The longer-term consequences of constipation can result in substantial morbidity. For example, chronic constipation can lead to complications such as rectal pain and burning, bowel obstruction or rupture (14). Stool impaction is another unpleasant outcome of long-term constipation. Here, retained stools may form large, firm lumps that are impossible to defecate, which in turn may lead to bowel obstruction, stercoral ulcers and urinary retention (113). This stage of OIC necessitates manual disimpaction or even surgery.

The psychological distress caused by OIC includes general distress about the constipation itself as well as depressive symptoms and anticipatory anxiety, which may increase over time (112, 114). Symptoms of opioid-induced bowel dysfunction (OIBD) – including OIC – have a considerable negative impact on activities of daily living (7, 38). Additionally, increasing severity of constipation and multiple complications associated with the condition have been found to correlate with lower QoL (114). OIC can be disabling and troublesome to patients to the extent that some reduce the dose or even discontinue their opioid medication in order to facilitate having a bowel movement, thus compromising optimal pain management (7, 12, 13).

7.4.2 *Please describe how a patient's HRQL is likely to change over the course of the condition.*

The evidence indicates that OIC status is a key driver of HRQL in patients with OIC. For example:

- [redacted]) (115, 116).
- A regression analysis of utility data collected in the KODIAC 4 and KODIAC 5 trials demonstrated that OIC status and baseline utility were key predictors for change in utility (see section 7.4.3 for a description of this analysis).

Accordingly, patients who experience relief from OIC would be expected to also experience a HRQL improvement; conversely, patients who are initially non-OIC would be expected to experience worsening of HRQL if they become OIC later on (114).

HRQL data derived from clinical trials

7.4.3 ***If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.***

- ***Method of elicitation.***
- ***Method of valuation.***
- ***Point when measurements were made.***
- ***Consistency with reference case.***
- ***Appropriateness for cost-effectiveness analysis.***
- ***Results with confidence intervals.***

Table 102 summarises the utility inputs used in the model. The subsequent text describes these inputs in more detail.

Table 102: Summary of utility inputs (X indicates where the method was reported)

Scenario	Naloxegol 25 mg versus			
	Placebo	Placebo + rescue laxative	SC MNTX QAD	OXN
Treatment-specific health state utility, distinguishing utility used in Cycle 1 and 2 versus remaining model cycles (trial data, Dolan tariff) (**base case**)	X	X	-	-
Treatment-specific health state utility, distinguishing utility used in Cycle 1 and 2 versus remaining model cycles (trial data, Wittrup-Jensen tariff)	X	X	-	-
Treatment-specific health state utility (non-time dependent), (trial data, Dolan tariff.)	X	X	-	-
Health state specific (trial data, Dolan tariff)	X	X	X	X
Health state specific (trial data, Wittrup-Jensen tariff)	-	-	X	-
Health state specific (secondary literature)(117)	X	X	X	-

Abbreviations: MNTX, methylnaltrexone; OXN, naloxone-oxycodone; QAD, every other day; SC, subcutaneous.

The EQ-5D-3L instrument was included in the KODIAC 4, KODIAC 5 and KODIAC 7 trials. As KODIAC 7 did not collect data on constipation status, utility estimates were

derived from an analysis of KODIAC 4 and KODIAC 5 data. In both the KODIAC 4 and KODIAC 5 trials, the EQ-5D data were collected at 0, 4 and 12 weeks. These data were used with the Dolan algorithm to derive utility scores (118, 119).

Treatment- and time-specific utility inputs

Treatment- and time-specific estimates were used for naloxegol patients, as it was hypothesised that there would be a treatment and time impact of naloxegol 25 mg over and above its impact on OIC status, as:

- While OIC status is a key driver of utility, it is possible that treatment impacts utility via its effect on constipation symptoms independent of its effect on constipation status.

The model does not independently account for the impact of AEs on utility, which would not only vary between treatments, but would also be expected to vary over time if patients who experience the most AEs discontinue treatment.

To test the hypothesised treatment and time effects, a repeated measures mixed-effects (RMME) model was run for change in utility from baseline. The model used pooled KODIAC 4 and 5 data, and was run separately for the anticipated licensed population and anticipated licensed population on Step 3 opioids populations. The following variables were included in the model: time, treatment, baseline utility, OIC status, and an interaction between treatment and time. The results of the model are reported in Table 103.

Table 103: Random mixed effect model for change from baseline in utility

Effect	Anticipated licensed population (n=726)			Anticipated licensed population + Step 3 opioids (n=510)		
	Estimate	SE	Pr > |t|†	Estimate	SE	Pr > |t|†
Intercept	0.2945	0.0290	<.0001	0.2542	0.0346	<.0001
Baseline utility	-0.5049	0.0380	<.0001	-0.4824	0.0443	<.0001
Time (week 12 vs week 4)	-0.0229	0.0210	0.278	-0.0167	0.0266	0.532
Treatment (Naloxegol 25 mg vs placebo)	-0.0137	0.0260	0.597	0.0141	0.0316	0.656
OIC status (non-OIC vs OIC)	0.0514	0.0203	0.012	0.0543	0.0250	0.031
Interaction (treatment*time) Naloxegol 25 mg at week 12 vs other	0.0683	0.0300	0.024	0.0621	0.0376	0.100

Abbreviations: LIR, laxative inadequate responder; OIC, opioid-induced constipation; SE, standard error.
†Significance level for test.

The model identifies a strong relationship between change in utility and both baseline utility and OIC status. Furthermore, in the anticipated licensed population, a significant impact was identified between change in utility and a time-treatment interaction effect. Given this effect the economic model was run using time and

treatment specific utility effects. The model is constructed so that a treatment-specific and time-specific effect only applies to patients on Naloxegol treatment and during the time they are non OIC.

Further validation of a treatment effect was derived from an analysis of weekly SBMs, in the anticipated licensed population, from KODIAC 4 and 5 based on health state. In this analysis it was found that:

- In KODIAC 4 at week 12, when patients were nOIC on naloxegol 25 mg they experienced an average of 6.1 SBMs per week vs 5.8 SBMs per week for placebo. The change from baseline was 4.2 and 3.4 SBMs respectively

- In KODIAC 5 at week 12, when patients were nOIC on naloxegol 25 mg they experienced an average of 6.0 SBMs per week vs 5.1 SBMs per week for placebo. The change from baseline was 4.9 and 3.7 SBMs respectively

Table 104 summarises the data used to estimate utility in the different health states and treatment arms.

- Data from patients on naloxegol 25 mg in the non-OIC state, collected at 4 weeks, were used to estimate the utility of patients in the naloxegol 25 mg arm in the 'non-OIC (on treatment)' state in cycles 1 and 2.
- Data from patients on naloxegol 25 mg in the non-OIC state, collected at 12 weeks, were used to estimate the utility of patients in the naloxegol 25 mg arm in the 'non-OIC (on treatment)' state in cycles 3 onwards.
- Data from patients on placebo in the non-OIC state, pooled 4 and 12 week data, were used to estimate the utility of patients in the placebo arm in the 'non-OIC (on treatment)' state, and patients in both the naloxegol 25 mg and placebo arms in the 'non-OIC (untreated)' state, as the model assumed that patients discontinue active treatment in this state.
- Data from patients on placebo in the OIC state, pooled 4 and 12 week data, were used to estimate the utility of patients in both the naloxegol 25 mg and placebo arms in the 'OIC' state, as the model assumed that patients discontinue active treatment in this state.

Table 104: Summary of utility inputs (treatment and time-specific, Dolan tariff)

State	Treatment	Source (OIC status, treatment arm, and timepoint)	Anticipated licensed population (all)		Anticipated licensed population + Step 3 opioids	
			Mean	SE	Mean	SE
Non-OIC (on treatment) cycles 1 and 2	Naloxegol 25 mg	Non-OIC, naloxegol 25 mg, 4 weeks	0.620	0.025	0.594	0.030
Non-OIC (on		Non-OIC,	0.665	0.026	0.679	0.030

treatment) Cycles 3 onwards		naloxegol 25 mg, 12 weeks				
Non-OIC (on treatment)	Placebo	Non-OIC, placebo, 4 and 12 weeks pooled	0.613	0.021	0.572	0.027
OIC	Naloxegol l 25 mg and Placebo	OIC, placebo, 4 and 12 weeks pooled	0.553	0.022	0.537	0.027
Non-OIC (no treatment)		Non-OIC, placebo, 4 and 12 weeks pooled	0.613	0.021	0.572	0.027

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

The impact of running the model with health state specific utility inputs was tested in a scenario analysis (see below for further detail on these inputs).

Treatment-specific utility inputs

The model was also run using treatment-specific (non-time specific) utility inputs (see Table 105).

Table 105: Summary of utility inputs (treatment-specific, Dolan tariff)

State	Treatment	Source (OIC status, treatment arm, data point)	Anticipated licensed population (all)		Anticipated licensed population + Step 3 opioids	
			Mean	SE	Mean	SE
Non-OIC (on treatment)	Naloxegol 25 mg	Non-OIC, naloxegol 25 mg, 4 and 12 weeks pooled	0.642	0.018	0.634	0.021
Non-OIC (on treatments)	Placebo	Non-OIC, naloxegol 25 mg, 4 and 12 weeks pooled	0.613	0.021	0.572	0.027
OIC	Naloxegol 25 mg and Placebo	OIC, placebo, 4 and 12 weeks pooled	0.553	0.022	0.537	0.027
Non-OIC (no treatment)		Non-OIC, placebo, 4 and 12 weeks pooled	0.613	0.021	0.572	0.027

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

Health-state specific utility inputs

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

(Table 106). This was also used in a scenario of the model for naloxegol 25 mg versus placebo.

Table 106: Summary of utility inputs (non-treatment-specific, Dolan tariff)

State	Anticipated licensed population (all)		Anticipated licensed population + Step 3 opioids	
	Mean	SE	Mean	SE
OIC	0.564	0.017	0.546	0.021
Non-OIC	0.630	0.014	0.610	0.017

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

Alternative tariff

A scenario was also run using an alternative tariff. Unlike the Dolan tariff, the Wittrup-Jensen tariff (120) does not include a utility decrement associated with being in the worst state on any of the five dimensions of the EQ-5D. Given that the population being studied is on long-term opioid therapy and experiencing utility impacts, such as pain that are not targeted by OIC treatment, it is possible this underlying health state will cause patients to be at the worst level on one of the domains of the EQ-5D and that this will not change with a variation in OIC status. Consequently, a scenario was run using a tariff that does not include this extra decrement for being at the worst level of one of the domains. Table 107 and

Table 108 summarise the utility inputs generated with the Wittrup-Jensen tariff.

Table 107: Summary of utility inputs (treatment and time-specific, Wittrup-Jensen tariff)

State	Treatment	Anticipated licensed population (all)		Anticipated licensed population + Step 3 opioids)	
		Mean	SE	Mean	SE
Non-OIC (on treatment) cycles 1 and 2	Naloxegol 25 mg	0.691	0.019	0.672	0.022
Non-OIC (on treatment) Cycles 3 onwards		0.724	0.020	0.733	0.023
Non-OIC (on treatments)	Placebo	0.686	0.015	0.652	0.020
OIC	Naloxegol 25 mg and Placebo	0.643	0.015	0.632	0.020
Non-OIC (untreated)		0.686	0.015	0.652	0.020

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

Table 108: Summary of utility inputs (non-treatment-specific, Wittrup-Jensen tariff)

State	Anticipated licensed population (all)		Anticipated licensed population + Step 3 opioids	
	Mean	SE	Mean	SE
OIC	0.648	0.012	0.636	0.015
Non-OIC	0.698	0.010	0.681	0.012

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

Utility estimates from the literature

One set of utility estimates that was compatible with the health states included in the model was identified in the literature (121). These were from an observational study (that collected EQ-5D data) of patients in Holland who were prescribed opioids – 588 with non-advanced illnesses (which were disabling but not directly life-threatening), and 113 with advanced illnesses. The scenario analysis used estimates from the people with non-advanced illnesses, as this group best matched the model's patient population. Among these patients, 326 (55%) individuals self-reported being constipated. The study did not report which tariff was used to estimate utility using the EQ-5D data.

There are a number of limitations associated with the use of these literature-based estimates, thereby accounting for why the study data were used in a scenario analysis. First, the study focused on constipation in general in opioid-users, rather than OIC specifically. Second, the study was cross-sectional and not designed to assess the causal impact of OIC on utility and did not control for other factors that may influence utility. Third, the manuscript only provided estimates of median utility. Finally, constipation status was self-reported by patients.

Table 109 summarises the utility data extracted from Penning van Beest et al, 2010 (121).

Table 109: Summary of utility input

	Median utility (CI)
OIC	0.31 (0.17–0.73)
Non-OIC	0.65 (0.22–0.78)

Abbreviations: CI, confidence interval; OIC, opioid-induced constipation.
Source: Penning-van Beest et al, 2010 (121)

Mapping

7.4.4 *If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.*

- ***Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.***
- ***Details of the methodology used.***
- ***Details of validation of the mapping technique.***

No mapping was used to estimate utility.

HRQL studies

7.4.5 ***Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.***

A systematic review was conducted to identify HRQL studies from the published literature relevant to the decision problem.

In particular, EQ-5D health state utility values (in line with the NICE preferred method) relating to opioid-induced constipation (OIC) were searched for.

The following electronic databases were searched: Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (Ovid), The Cochrane Library (Ovid) and EconLit (Ovid).

Electronic searches were supplemented by hand searching the following sources: Research Papers in Economics (RePEc), the EQ-5D website, the Cost-Effectiveness Analysis (CEA) Registry, conference proceedings and NICE HTA submissions.

Full details of the search are provided in section 10.12.

In total, 1,784 papers were identified through the electronic searches. Upon the removal of duplicate papers, 1,510 titles and abstracts were reviewed. Ninety three were ordered for full paper review, of which 89 were excluded, resulting in 4 relevant papers for final inclusion (100, 121-123). Opioid-induced constipation and health state utility values (HSUV) related terms and combinations were used for the electronic database searches, with application of the following inclusion and exclusion criteria:

Inclusion criteria

- Population: patients with OIC, regardless of age, gender, and race
- Interventions and comparators: the SR will not be restricted by any particular intervention or comparator
- Outcomes: papers with the following HSUV outcomes will be included:
  - Euro-QoL 5 dimension (EQ-5D)
  - Directly-elicited utility scores (time trade off [TTO], standard gamble [SG])
  - Papers not conforming to the NICE reference case will not be of interest and will not be included

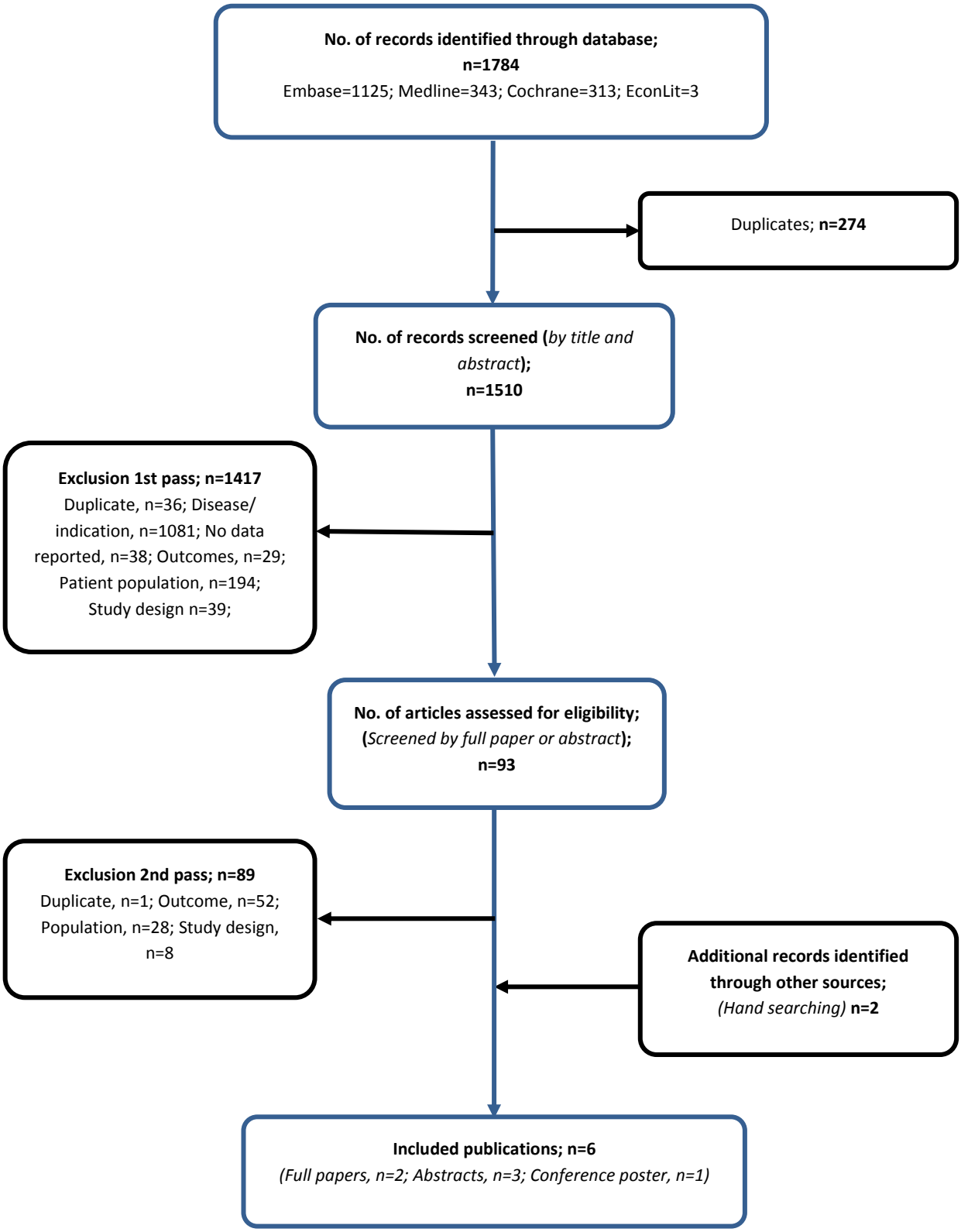
- Study designs
  - The type of study design will not be limited. It is expected that HSUVs will be reported in randomised controlled trials (RCTs), observational studies, and other cost-effectiveness evaluations, such as HTAs and economic evaluations. Any such study reporting relevant, non-treatment-specific HRQL data will be included.
  - Studies from any country will be included.

Exclusion criteria

- Patients without OIC or mixed populations in which outcomes for OIC patients are not reported separately
- Studies reporting ONLY non-HSUV outcomes (e.g. clinical, economic evaluations, costs) will not be included in this review

In addition, the following two studies were identified via hand searching: Dunlop et al, 2013 (100) and Van der Linden et al, 2008 (124). A scematic for the systematic review of HRQL evidence is shown in Figure 22.

Figure 22: Schematic for the systematic review of HRQL evidence



7.4.6 *Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.*

- ***Population in which health effects were measured.***
- ***Information on recruitment.***
- ***Interventions and comparators.***

- ***Sample size.***
- ***Response rates.***
- ***Description of health states.***
- ***Adverse events.***
- ***Appropriateness of health states given condition and treatment pathway.***
- ***Method of elicitation.***
- ***Method of valuation.***
- ***Mapping.***
- ***Uncertainty around values.***
- ***Consistency with reference case.***
- ***Appropriateness for cost-effectiveness analysis.***
- ***Results with confidence intervals.***
- ***Appropriateness of the study for cost-effectiveness analysis.***

Details of the studies that measured HRQL are provided in Table 110.

Table 110: Included HRQL studies

Study	Country	Population	Intervention(s)	Sample size	Elicitation method	Health states	Utility scores, mean [median]	Utility score, SD; (SE); [IQR]
Dunlop, 2012 (25)	UK	Adults required continuous opioid therapy for moderate to severe non-malignant pain, and had OIC.	Prolonged release oxycodone/naloxone (OXN) vs. prolonged release oxycodone (OXY)	322 patients: OXN (n=162) or OXY (n=160)	SF-36 scores converted to the EQ-5D utility values using Rowen mapping method†	Patients with moderate to severe non-malignant pain and OIC, baseline, OXN group	0.4776	-
						Patients with moderate to severe non-malignant pain and OIC, treated 12 weeks, OXN group	0.5032	-
						Patients with moderate to severe non-malignant pain and OIC, baseline, OXY group	0.4792	-
						Patients with moderate to severe non-malignant pain and OIC, treated 12 weeks, OXY group	0.4652	-
						Patients with moderate to severe non-malignant pain and OIC, baseline, OXN group	0.60169	-
						Patients with moderate to severe non-malignant pain and OIC, treated 12 weeks, OXN group	0.61901	-
						Patients with moderate to severe non-malignant pain and OIC, baseline, OXY group	0.59811	-

Study	Country	Population	Intervention(s)	Sample size	Elicitation method	Health states	Utility scores, mean [median]	Utility score, SD; (SE); [IQR]
						Patients with moderate to severe non-malignant pain and OIC, treated 12 weeks, OXY group	0.58664	-
Dunlop, 2013 (100)	UK	Patients with moderate to severe non-malignant pain and OIC	Prolonged release oxycodone/naloxone (OXN) vs. prolonged release oxycodone (OXY)	178	EQ-5D	Non advanced illness with constipation	0.31	-
						Non advanced illness without constipation	0.65	-
Guijarro, 2010 (122) (Data supplemented from poster; Viqueira, 2010 (125))	Spain	Recipients of opioids for at least 2 months prior to study entry‡	Unspecified opioids	347	CVE-20 overall	Patients with opioids at least 2 months	48	18.6
					EQ-VAS mean	Patients with opioids at least 2 months	51.3	19.3
					EQ-5D VAS tariff mean	Patients with opioids at least 2 months	0.45	0.25
					EQ-5D TE tariff mean	Patients with opioids at least 2 months	0.38	0.4
Iyer, 2009 (123)	USA	Patients on opioid therapy for chronic non-malignant pain with opioid-induced constipation	Methylnaltrexone daily	469	EQ-5D index	Baseline	0.45	0.33
			Methylnaltrexone daily	469	EQ-5D index	Treated 14 days	0.49	-
			Methylnaltrexone daily	469	EQ-5D index	Treated 28 days	0.53	-
			Methylnaltrexone every other day	469	EQ-5D index	Baseline	0.47	0.33
			Methylnaltrexone every other day	469	EQ-5D index	Treated 14 days	0.53	-
			Methylnaltrexone every other day	469	EQ-5D index	Treated 28 days	0.55	-
			Placebo	469	EQ-5D index	Baseline	0.44	0.35
			Placebo	469	EQ-5D index	Treated 14 days	0.46	-
			Placebo	469	EQ-5D index	Treated 28 days	0.43	-

Study	Country	Population	Intervention(s)	Sample size	Elicitation method	Health states	Utility scores, mean [median]	Utility score, SD; (SE); [IQR]
Penning-van Beest, 2010 (121)	Netherlands	Opioids users with advanced or non-advanced illness and OIC	Unspecified opioids	402	EQ-5D index	Non-advanced illness with OIC	0.31	[0.17-0.73]
					EQ-5D index	Advanced illness with OIC	0.41	[0.20-0.69]
Van der Linden, 2008 (124)	Netherlands	Cancer patients receiving opioids	Unspecified opioids	75	EQ-5D index	Patients with constipation	[0.39]	[0.19-0.69]
					EQ-5D index	Patients without constipation	[0.63]	[0.30-0.78]

Abbreviations: IQR, interquartile range; NA, not applicable; NR, not reported; OIC, opioid-induced constipation; OXN, oxycodone/ naloxone; OXY, oxycodone; PR, prolonged release; QoL, quality of life, SD, standard deviation; SE, standard error.
† Results with SF-6D mapping equation (Brazier) were also reported.
‡ All patients were free of constipation at baseline and received opioids for at least 2 months. The impact of OIC on patients' HRQL was determined in a cross-sectional phase of the study. Patients were evaluated depending on response to oral treatment for OIC

7.4.7 *Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.*

The utility inputs reported in the model for the anticipated licensed population and the anticipated licensed population + Step 3 opioids group were broadly similar to those utility values derived from the literature search (Table 110).

Adverse events

7.4.8 *Please describe how adverse events have an impact on HRQL.*

No direct estimates of the impact of AEs on utility were available to be included in the model. Clinicians (section 10.25) advised that AEs were unlikely to have a significant impact on the HRQL. However, the utility impact of AEs is captured by treatment-specific utility inputs which are detailed in section 7.4.3.

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

7.4.9 *Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in Sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.*

See section 7.4.3.

7.4.10 *If clinical experts assessed the applicability of values available or estimated any values, please provide details. Please provide the following details[f]:*

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).***

[f] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Clinical experts were consulted (see section 10.25) and agreed that the magnitude of the impact of OIC on utility had face validity.

7.4.11 ***Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?***

See sections 7.4.1 and 7.4.2.

7.4.12 ***Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?***

Besides the EQ-5D, the KODIAC 4 and KODIAC 5 trials also used the PAC-QoL and PAC-SYM instruments to capture the HRQL of patients with OIC. However, these data are not used in the model because they did not comply with the NICE reference case. A mapping from one of these instruments to EQ-5D would have been required to meet the reference case. Therefore, use of the EQ-5D data collected in the trial was preferred.

7.4.13 ***If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?***

In the base case analysis for the naloxegol 25 mg, naloxegol 25 mg and bisacodyl, placebo, and placebo and bisacodyl, HRQL varied within the health state by time point and by the treatment received (see section 7.4.3).

7.4.14 ***Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.***

In the model, HRQL depends on the OIC status of the patients (section 7.2.5). HRQL varies as patients move between the OIC and non-OIC health states. HRQL applied to health states after Week 12 are assumed to not change. Further to this, a time and treatment effect on HRQL has been assumed for naloxegol 25 mg (see Section 7.4.3)

7.4.15 ***Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.***

Not applicable.

7.5 *Resource identification, measurement and valuation*

NHS costs

7.5.1 ***Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.***

Two NHS costing codes are associated with the clinical management of OIC: FZ90a and FZ90b (126), as described in Table 111.

Table 111: NHS codes associated with management of OIC

Setting	Admission	Code	Description	Specialty	Average cost
Inpatient	Elective	FZ90a	Abdominal pain with intervention	Gastroenterology	£1950
Inpatient	Elective	FZ90b	Abdominal pain without intervention	Gastroenterology	£906
Inpatient	Non-elective	FZ90a	Abdominal pain with intervention	Gastroenterology	£2343
Inpatient	Non-elective	FZ90b	Abdominal pain without intervention	Gastroenterology	£1355
Outpatient	NA	FZ90a	Abdominal pain with intervention	General medicine	£310
Outpatient	NA	FZ90b	Abdominal pain without intervention	Gastroenterology	£345

Table 111 refers to the current HRG code associated with the hospitalisation of inpatients either elective or non-elective admission, or outpatients. Since no specific ICD-10 code exists for OIC, these codes have been selected due to their closest definition of an episode of OIC symptoms, especially as they are split into a – with intervention, or b- without intervention, where the intervention presumed would be either imagery or manual evacuation.

Under this HRG codes, AstraZeneca estimate the OIC-related weighted average outpatient and inpatient service cost respectively £344.65 to £1,606.98, depending of the occurrence of intervention or not (see section 10.28, Table 190)

7.5.2 ***Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.***

Based on the definition of HRG codes FZ90a and FZ90b, the NHS reference cost and PbR tariffs are appropriate for costing the interventions used to treat general constipation condition, which also includes OIC.

Resource identification, measurement and valuation studies

7.5.3 ***Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in Section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:***

- ***country of study***
- ***date of study***

- ***applicability to UK clinical practice***
- ***cost valuations used in study***
- ***costs for use in economic analysis***
- ***technology costs.***

No systematic research search for resource use was completed. Clinicians were consulted to estimate the resource use associated with the management of constipation and associated adverse events for use in the economic model.

7.5.4 ***If clinical experts assessed the applicability of values available or estimated any values, please provide details. Please provide the following details[g]:***

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).***

Clinicians were consulted to estimate the resource use associated with managing constipation (see section 7.5.6) and AEs (see section 7.5.7).

Intervention and comparators' costs

7.5.5 ***Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.***

For active treatments, the unit costs of drugs (per pill or per vial) were derived from the British National Formulary (BNF) database, and have not changed since these data were collated (127). The unit cost for the administration of SC methylnaltrexone was taken from the Personal Social Services Research Unit (PSSRU)'s Unit Costs of Health and Social Care (128). For placebo, the treatment cost is assumed to be zero.

[g] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

For the placebo and bisacodyl arm, the cost constitutes the rescue-bisacodyl component based on observed use in the KODIAC 4 and 5 trials.

Dosing regimens, as informed by product labels (129) or clinical trial publications (51, 52) were used to estimate the doses (in mg) required to treat patients with OIC. The daily treatment cost was estimated, followed by the calculation of treatment cost per cycle (28 days) which was used in the model. For SC methylnaltrexone, the cost associated with subcutaneous injection was also included as part of its treatment cost.

Table 112: Unit costs associated with the technology in the economic model (2014 £)

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**	**£51.81**	**£609.45**	**£ 125.54**	**£ 0**	**£ 0.29**

Abbreviations: MNTX, methylnaltrexone; OXN, naloxone-oxycodone; QAD, every other day; SC, subcutaneous.

Health-state costs

7.5.6 ***Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.***

The incremental cost of constipation

The incremental cost of managing constipation was included in the health states (Table 113). 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.

- '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.
- 'OIC': Laxatives were used upon treatment failure and movement to the 'OIC' state.
- 'Non-OIC (untreated)': Laxatives were used after the resolution of constipation as subsequent prophylaxis).

Survey work was undertaken to collect resource use data, as no systematic review of the literature was undertaken.

Two data sources were used to estimate costs related to constipation.

[redacted]

- [redacted] (see section 10.28 for further details).

As data estimating the healthcare costs associated with OIC is limited, AstraZeneca believes the base costs used in the model may be conservative particularly in comparison to the range of costs cited (25) of £42-£555 per cycle and Table 114, which present costs based on a burden of illness survey.

Table 113: 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

Abbreviations: OIC, opioid-induced constipation.
Source:.GP omnibus survey. See section 10.28 for further detail

Table 114: The incremental cost of constipation (scenario- BOI survey), per cycle (2014 £) where costs are different to Table 113.

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†		

Abbreviations: LIR, laxative inadequate response; OIC, opioid-induced constipation.
†The higher OIC costs identified is driven by inpatient stay
Source:BOI survey. See section 10.28 for further detail.

Opioid costs

Opioid use was assumed to be unaffected by OIC treatment in all comparisons except for naloxegol 25 mg versus naloxone-oxycodone. Since naloxone-oxycodone is a combination therapy that includes a Step 3 opioid (oxycodone) as part of its regimen, a true comparison with naloxegol 25 mg required that the cost of opioids be added to the cost of naloxegol 25 mg to ensure costing perspectives were comparable.

As naloxegol can be combined with any opioid, two approaches were used to incorporate opioid costs in the analysis of naloxegol 25 mg versus naloxone-oxycodone. In the base case the cost of the most commonly prescribed Step 3 opioid was added to naloxegol 25 mg. This was oral morphine (sustained release and instant release) at an average dose of 50mg per day.

In an alternative scenario reflecting the case where a clinician needs to prescribe oxycodone, all patients received oxycodone as their opioid. The cost of oxycodone reflects the average dose among patients enrolled in the oxycodone trials cited in the MTC.

The dose of opioid taken by patients taking either naloxegol 25 mg or naloxone-oxycodone in the ‘OIC’ and ‘non-OIC (untreated)’ states was assumed to be the same as that taken by patients in the ‘non-OIC (on treatment) state.

Table 115 summarises the opioid costs included in the model for the analysis of the naloxegol 25 mg arm when compared against 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).

Table 115: 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

Abbreviations: OIC, opioid-induced constipation; OXY, oxycodone.
†See section 10.25 for further detail
‡§Only applied when comparing naloxegol 25 mg and naloxone-oxycodone.
‡§In the model this cost is incorporated in the 'TreatmentInputs' tab.
§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-event costs

7.5.7 ***Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.***

Events of Grade 1/2 severity were assumed to be self-limiting and to result in no additional costs to the NHS (i.e. all such events were assumed to require minimal [over-the-counter medications] or no treatment). The Advisory Board (described in section 10.25) agreed that abdominal pain, flatulence, vomiting, nausea, headache and diarrhoea were the most clinically relevant AEs. Detailed resource use and unit costs are reported in section 10.28. These provided the typical resource use associated with treating each event of Grade 3/4 severity. The mean expected cost per AE was calculated as the weighted average of patients with Grade 3/4 events (and the corresponding unit cost) and patients with Grade 1/2 events (at a cost of £0). These costs were then summated to provide an overall total AE cost (see Table 116). As Grade 3/4 AE costs were not a driver in the model, and to aid simplification, all AE costs were assumed to be incurred in cycle 1 only.

Table 116: Adverse events costs† (2014 £)

	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

Abbreviations: MNTX, methylnaltrexone; OXN, naloxone-oxycodone; SC, subcutaneous; QAD, every other day.
†See section 10.28 for details.

Miscellaneous costs

7.5.8 ***Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.***

Not applicable.

7.6 *Sensitivity analysis*

7.6.1 ***Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.***

The impact of the following structural assumptions was explored in the analysis.

- The base case model allows utility to vary by constipation status, time and treatment. A number of utility input scenarios were run (see section 7.4.3).
- The base case model applies an exponential function to extrapolate the probability of remaining in a non-OIC state beyond the 12-week period observed in the KODIAC 4 and 5 data. Various scenarios were run to explore the impact of alternative extrapolation approaches (see section 7.3.7).
- The model assumes that once a patient stops responding to treatment they will discontinue therapy and not try it again. In the scenario analysis, the transition probability from 'OIC' to 'non-OIC (on treatment)' health states (transition D) was varied from 0% to 10%, to explore the impact of allowing patients to resume treatment after having experienced non-response and discontinued treatment as a result.
- It is assumed that if a patient is in the 'non-OIC (on treatment)' state and the underlying cause of their OIC resolves, they will not realise this is the case and so will continue on treatment. In the scenario analysis the transition probability from non-OIC (on treatment) to non-OIC (untreated) health states (transition E) was varied from 0% to 10%, to explore the impact of relaxing this assumption.
- It is assumed that patients' experience of OIC status varies over time, moving between the OIC and non-OIC health states, irrespective of treatment received. In the sensitivity analysis, the transition probability from non-OIC (on treatment) to OIC health states – and vice versa – (transition B and C) was varied, so the impact of variations in the way OIC is experienced over time could be explored.

7.6.2 *Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.*

Two sets of deterministic sensitivity analysis (DSA) were undertaken. First, Table 117 summarises the variables included in the tornado plot. Second, the five most sensitive parameters as determined from the tornado diagram were included in a threshold analysis.

Table 117: Relative variations on 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 7.6.3) and a variety of scenario analyses
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%	

Abbreviations: OIC, opioid-induced constipation; PSA, probabilistic sensitivity analysis.

7.6.3 *Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).*

Table 118 summarises the parameters included in the PSA and the distributions used to determine their values. These parameters were considered for PSA to investigate their collective impact on the ICER 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. All PSAs were run using 10,000 simulations.

Table 118: Values and distributions used in the probabilistic sensitivity analysis, anticipated licensed population (costs in 2014 £)

Variable	Base value	SE	Distribution
Probability of response at first cycle (Week 0–4) – Trial data (ITT)			
Naloxegol 25 mg	58.51%	3.17%	Beta
Naloxegol 25 mg + bisacodyl	72.20%	2.89%	Beta
Placebo	39.75%	3.17%	Beta
Placebo + bisacodyl	60.25%	3.17%	Beta
Probability of response at first cycle (Week 0 – 4) - MTC			
Naloxegol 25 mg	45.87%	7.66%	Beta
SC MNTX QAD	38.40%	9.74%	Beta
Placebo	31.11%	2.31%	Beta
Transition probabilities for subsequent cycles (after Week 4)			
Transition A	See below		
Transition B	28.98%	4.27%	Beta
Transition C	20.94%	5.44%	Beta
Probability of mortality (per cycle)			
All treatments	0.027%	0.001%	Beta
Frequency of adverse events per patient in the first cycle (Weeks 0–4)			
Naloxegol 25 mg	52.6%	7.57%	Beta
Naloxegol 25 mg + bisacodyl	52.6%	7.57%	Beta
SC MNTX QAD	43.1%	9.92%	Beta
Placebo	36.0%	2.40%	Beta
Placebo + bisacodyl	36.0%	2.40%	Beta
Non-laxative cost of constipation			
OIC	31.70	1.79	Gamma
Laxative cost			

Variable	Base value	SE	Distribution
OIC	4.12	1.79	Gamma
Non-OIC (on treatment)	0	1.59	Gamma
Non-OIC (untreated)	3.14	0.16	Gamma
Utilities – treatment and health state-specific (relevant for naloxegol 25 mg versus placebo and naloxegol 25 mg + bisacodyl versus placebo + bisacodyl)			
Non-OIC – naloxegol 25 mg (Cycles 1 and 2)	0.620	0.025	Gamma
Non-OIC – naloxegol 25 mg (Cycles 3+)	0.665	0.026	Gamma
Non-OIC – Placebo	0.613	0.021	Gamma
OIC	0.553	0.022	Gamma
Non-OIC (untreated)	0.613	0.021	Gamma
Utilities – health state specific (relevant for naloxegol 25 mg versus non-placebo comparators)			
OIC	0.564	0.017	Gamma
Non-OIC	0.630	0.014	Gamma
Parameters for transition curve for transition A (% non-OIC patients [responders at week 4] remaining over time) (base curve: exponential)			
Naloxegol 25 mg – intercept	5.474	0.204	Normal
Placebo - intercept	4.897	0.200	Normal

Abbreviations: ITT, intent-to-treat; MNTX, methylnaltrexone; OIC, opioid-induced constipation; QAD, every other day; SC, subcutaneous; SE standard error.

Table 119: Values and distributions used in the probabilistic sensitivity analysis, anticipated licensed population + Step 3 opioids (costs in 2014 £)

Variable	Base value	SE	Distribution
Probability of response at first cycle (Week 0–4) – Trial data (ITT)			
Naloxegol 25 mg	62.50%	3.65%	Beta
Naloxegol 25 mg + bisacodyl	73.86%	3.31%	Beta

Placebo	38.75%	3.85%	Beta
Placebo + bisacodyl	61.25%	3.85%	Beta
Probability of response at first cycle (Week 0–4) - MTC			
Naloxegol 25 mg	53.99%	9.18%	Beta
SC MNTX QAD	37.82%	10.97%	Beta
OXN	46.01%	6.59%	Beta
Transition probabilities for subsequent cycles (After Week 4)			
Transition A	See below		
Transition B	28.98%	4.27%	Beta
Transition C	20.94%	5.44%	Beta
Probability of mortality (per cycle)			
All treatments	0.027%	0.001%	Beta
Frequency of adverse events per patient in the first cycle (Weeks 0–4)			
Naloxegol 25 mg	56.9%	9.35%	Beta
Naloxegol 25 mg + bisacodyl	56.9%	9.35%	Beta
SC MNTX QAD	45.5%	12.12%	Beta
OXN	72.2%	2.32%	Beta
Placebo	38.2%	2.72%	Beta
Placebo + bisacodyl	38.2%	2.72%	Beta
Non-laxative cost of constipation			
OIC	36.90	2.05	Gamma
Laxative cost			
OIC	4.08	2.05	Gamma
Non-OIC (untreated)	3.12	0.16	Gamma
Opioid cost (relevant for naloxegol 25 mg versus OXN arm only)			

OIC and non-OIC (untreated) – naloxegol 25 mg	14.86	0.74	Gamma
OIC and non-OIC (untreated) - OXN	37.51	0.88	Gamma
Utilities – treatment and health state-specific (relevant for naloxegol 25 mg versus placebo and Naloxegol 25 mg + bisacodyl versus placebo + bisacodyl)			
Non-OIC – naloxegol 25 mg (Cycles 1 and 2)	0.594	0.030	Gamma
Non-OIC – naloxegol 25 mg (Cycles 3+)	0.679	0.030	Gamma
Non-OIC – Placebo	0.572	0.027	Gamma
OIC	0.537	0.027	Gamma
Non-OIC (un treated)	0.572	0.027	Gamma
Utilities – health state specific (relevant for naloxegol 25 mg versus non-placebo comparators)			
OIC	0.546	0.021	Gamma
Non-OIC	0.610	0.017	Gamma
Parameters for transition curve for transition A (% non-OIC patients [responders at week 4] remaining over time) (base curve: exponential)			
Naloxegol 25 mg - intercept	5.474	0.204	Normal
Placebo – intercept	4.897	0.200	Normal

Abbreviations: ITT, intent-to-treat; MNTX, methylnaltrexone; OIC, opioid-induced constipation; OXN, oxycodone plus naloxone; QAD, every other day; SC, subcutaneous; SE standard error.

7.7 *Results*

Overview

Table 120 provides an overview of the structure of the results section. The structure adopted to present the results of the models reflects not only the relevance of the comparators, but also the quality and nature of the data available to undertake comparisons. Placebo and placebo with rescue bisacodyl reflect the more relevant comparators for naloxegol 25 mg (see section 7.2.7 for further justification), and as a consequence, the KODIAC trials provide evidence for these comparisons. Furthermore, the use of different sources of evidence means that the ICERs generated for different comparators are not comparable.

Table 120: Structure of the results section

Analysis	Population	Comparators	Section
Base case	Anticipated licensed population (non-cancer)	• Placebo	7.7.1–7.7.8
Scenario analysis		• 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		

Abbreviations: LIR, laxative inadequate response; MNTX, methylnaltrexone; OXN, oxycodone plus naloxone; SC, subcutaneous.

Base case analysis (naloxegol 25 mg versus placebo)

Clinical outcomes from the model

7.7.1 ***For the outcomes highlighted in the decision problem (see Section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.***

The response rates used in the model and those reported in the clinical efficacy section differed as the two analyses adopted different response definitions (see section 7.3.1 for more detail on the definitions of response). The clinical efficacy analysis included a multifactor definition of response, including 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

intentionally focuses on absolute constipation status alone, without a measure of change in bowel movements from baseline which could be considered a more clinically relevant outcome. Thus, the model results may be interpreted as more optimistic than the clinical trial data.

Table 121: Summary of model results compared with clinical data (anticipated licensed population)

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

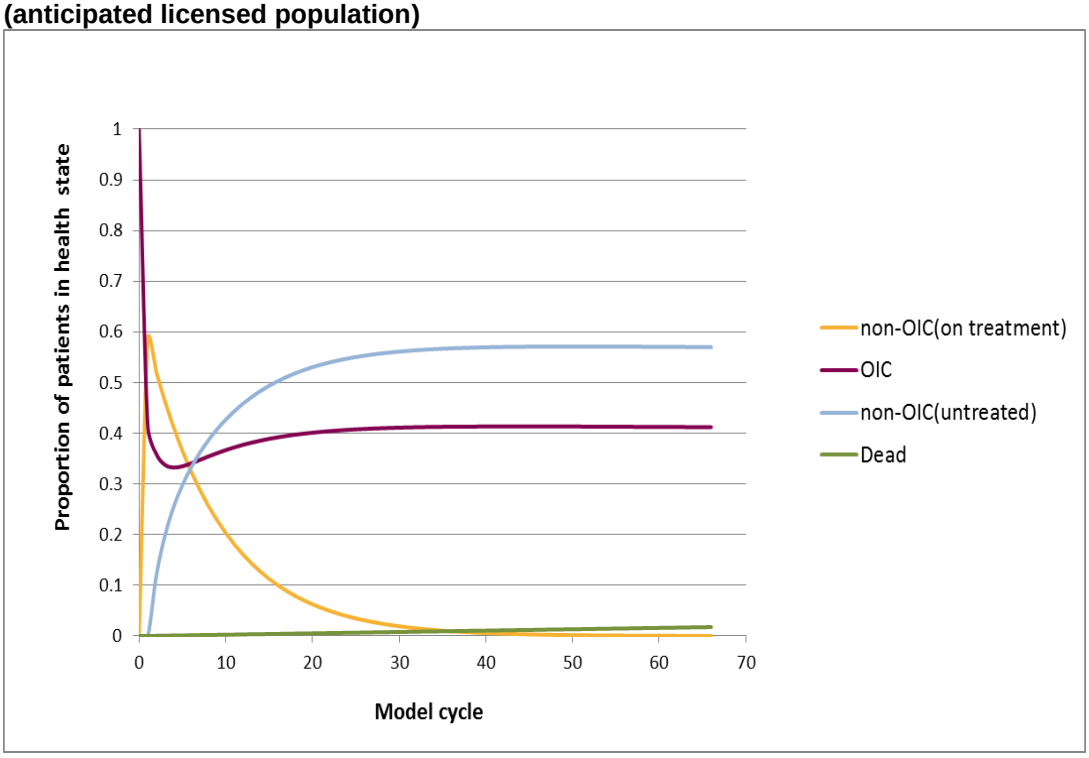
‡Response is defined as patients with ≥3 SBMs/week (%) over at least 3 out of past 4 weeks

7.7.2 *Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.*

The distribution of patients on naloxegol 25 mg and placebo across each of the four health states – non-OIC (on treatment), OIC, non-OIC (untreated), dead – over a time horizon of 5 years are presented in Figure 23 and Figure 24. All patients start in the 'OIC' state. The introduction of treatment causes patients to move to the 'non-OIC (on treatment)' state in cycle 1. Over the remainder of the model patients gradually discontinue treatment. This, and the variable nature of OIC, causes the model to reach a steady state (41% of patients OIC, 57% non-OIC). Both the naloxegol 25 mg and placebo models reach similar steady states, though the greater response rate associated with naloxegol 25 mg delays the point at which this state is reached.

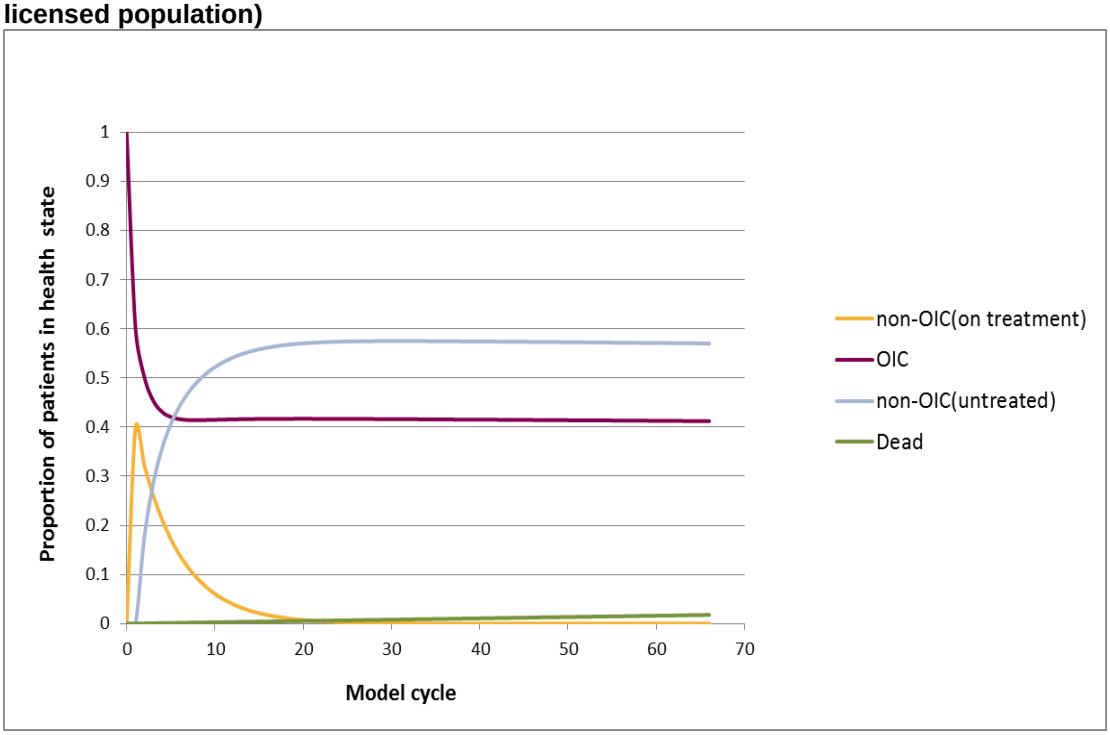
The impact of naloxegol 25 mg can be observed in the fewer patients in the 'OIC' state in the first 20 cycles of the model.

Figure 23: Number of naloxegol 25 mg patients in each health state over time (anticipated licensed population)



Abbreviations: OIC, opioid-induced constipation.

Figure 24: Number of placebo patients in each health state over time (anticipated licensed population)



Abbreviations: OIC, opioid-induced constipation.

7.7.3 *Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.*

Change in QALYs over time is driven by three factors:

- Change in OIC status
- Impact of naloxegol 25 mg on non-OIC
- Time horizon of model

7.7.4 *Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.*

See section 7.7.5.

7.7.5 *Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.*

Table 122 summarises the health and cost outcomes accrued by patients on naloxegol 25 mg and placebo. As expected, technology costs and AE costs increase with the use of naloxegol 25 mg. The cost of managing constipation reduces with naloxegol 25 mg as a consequence of less time being spent in the OIC state. In total, naloxegol 25 mg only increases costs by £185 per person over the 5 year model time horizon.

Table 122: Summary of QALYs and costs by health state and resource use by category of cost (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				

Item	Naloxegol 25 mg	Placebo	Absolute increment	% absolute increment
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	£ 1,202	£ 1,016	£ 185	18.3%

Abbreviations: LY, life year; OIC, opioid-induced constipation; QALY, quality adjusted life year.
†Including administration cost

Base-case analysis

7.7.6 ***Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.***

Through being more effective at relieving OIC, naloxegol improves HRQL, although it is not expected to impact on mortality, which is reflected in the same life years being accrued in by naloxegol 25 mg and placebo patients. The impact of naloxegol 25 mg on the reduced time that patient spend in OIC results in an improvement in QALYs for a cost increase of £185.

Table 123: Base case results – absolute (anticipated licensed population)

Technologies	Total LY	Total QALY	Total costs (£)
Naloxegol 25 mg	4.534	2.686	£1,272
Placebo	4.534	2.663	£1,016

Abbreviations: LY, life year; QALY, quality adjusted life year.

Table 124: Base case results - incremental (anticipated licensed population)

Naloxegol 25 mg vs	Incremental LY	Incremental QALY	Incremental costs (£)	ICER (£) (QALYs)
Placebo	0.000	0.024	£256	£10,849

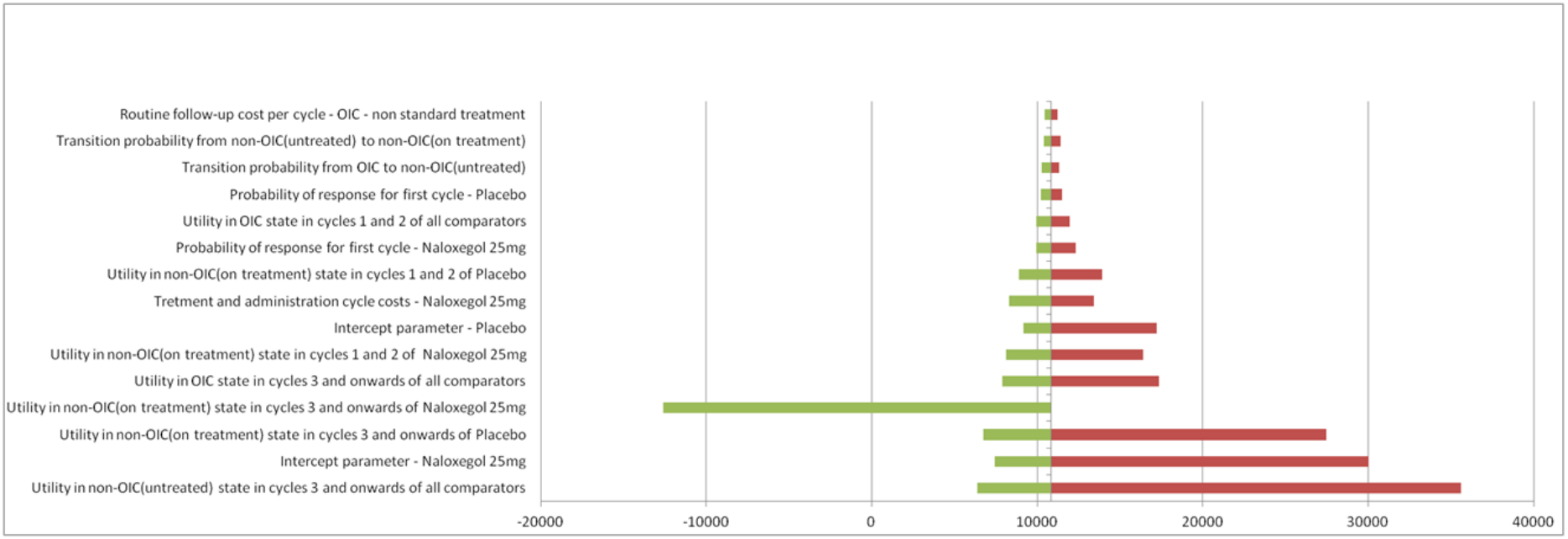
Abbreviations: ICER, incremental cost effectiveness ratio; LY, life year; OIC, opioid-induced constipation; QALY, quality adjusted life year.

Sensitivity analyses

7.7.7 ***Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.***

DSA was conducted for naloxegol 25 mg versus placebo, valuing a QALY gain at £20,000.

Figure 25: Tornado diagram (variation in ICER) for DSA of naloxegol 25 mg vs placebo (anticipated licensed population), parameters varied by ± 20%



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.

For five parameters to which the ICER is most sensitive based on the tornado diagram (Figure 25), threshold analysis was conducted to ascertain the input values that generate an ICER of £20,000 (Table 125).

Table 125: Threshold analysis for five parameters to which the ICER is most sensitive, naloxegol 25 mg versus placebo (anticipated licensed population)

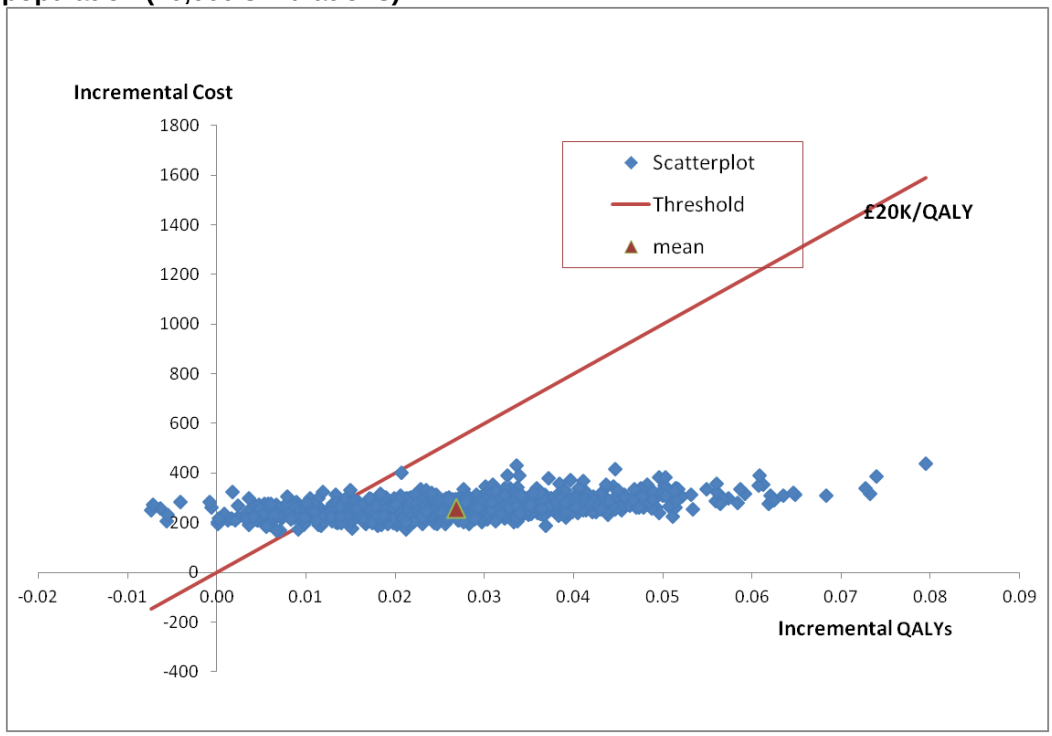
Input†	Base case value	Parameter value to give an ICER =£20,000.
Utility in non-OIC (on treatment) state in cycles 3 and onwards of naloxegol 25 mg	0.665	0.632
Utility in non-OIC(untreated) state in cycles 3 and onwards of all comparators	0.613	0.694
Utility in non-OIC(on treatment) state in cycles 3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

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.

7.7.8 *Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.*

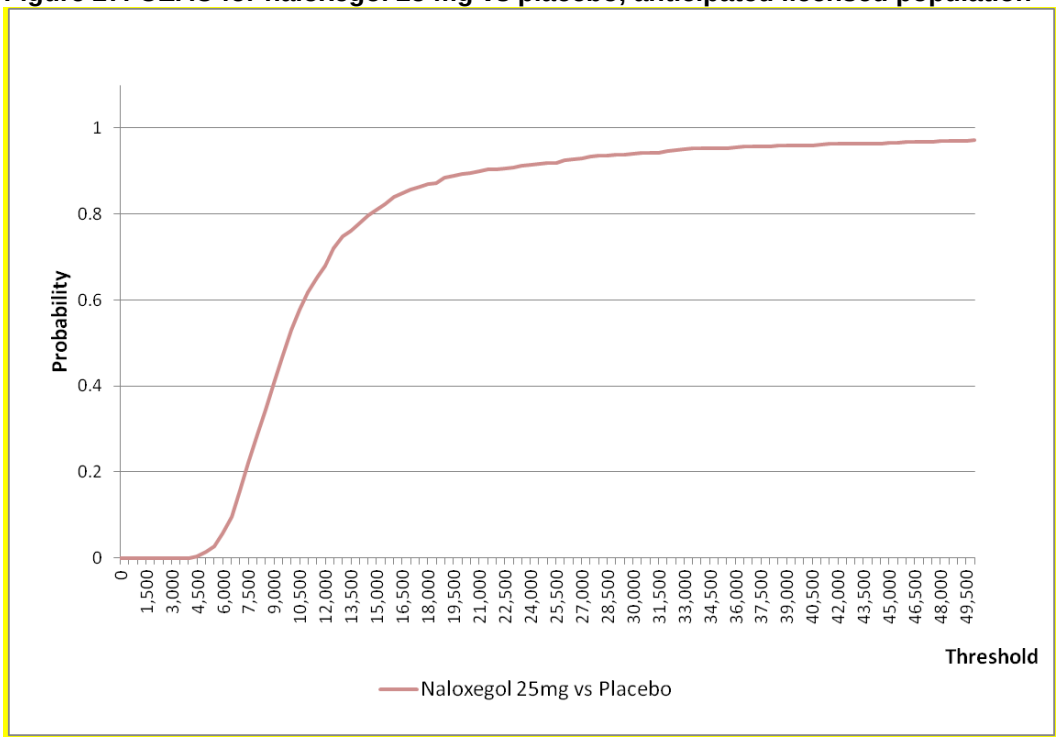
The PSA (Figure 26) and CEAC (Figure 27) suggest that the result that the ICER for naloxegol 25 mg is below the £20,000 threshold is robust in the face of parameter uncertainty. Naloxegol 25 mg has a 91% probability of being below the £20,000 willingness to pay threshold when compared with placebo.

Figure 26: PSA Scatterplot for naloxegol 25 mg vs placebo, anticipated licensed population (10,000 simulations)



Abbreviations: QALY, quality adjusted life year.

Figure 27: CEAC for naloxegol 25 mg vs placebo, anticipated licensed population



7.7.9 *Please present the results of scenario analysis. Include details of structural sensitivity analysis.*

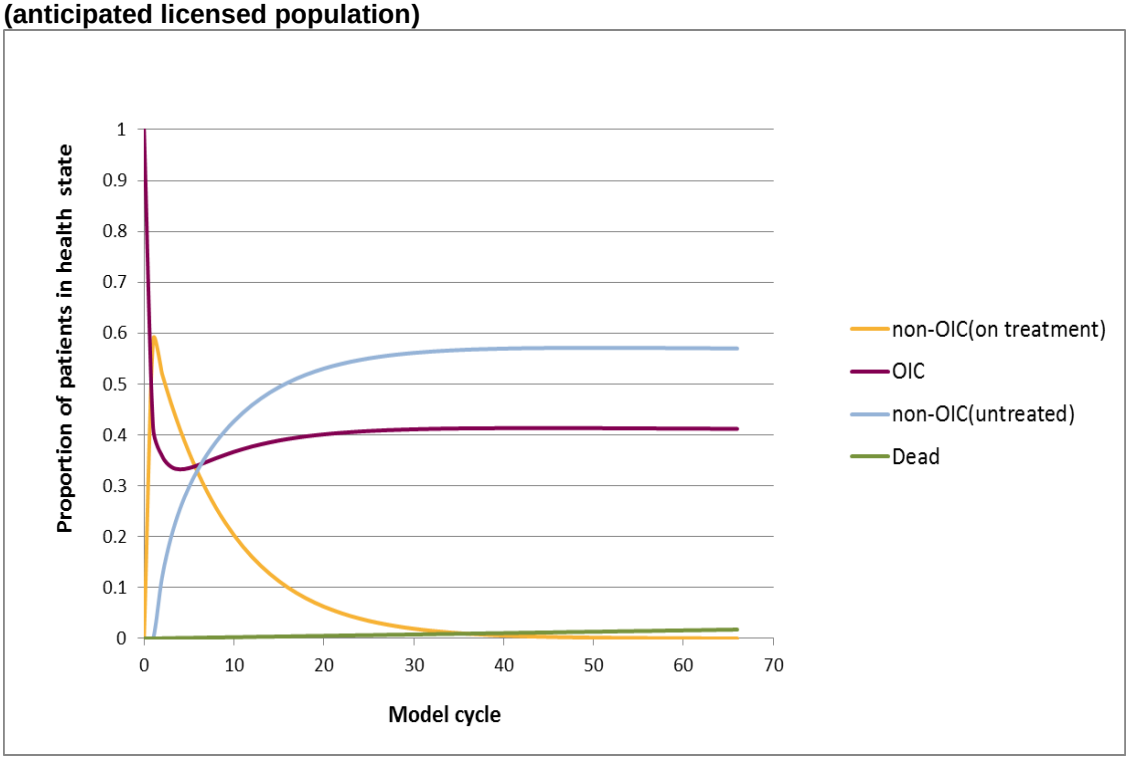
Two sets of scenario analyses were performed:

- Naloxegol 25 mg was compared with a range of treatments other than that for which the KODIAC pivotal trials were designed.
- A range of scenarios were run to explore uncertainty in model parameters.

Analysis of alternative treatments: naloxegol 25 mg (+ bisacodyl) versus placebo + bisacodyl

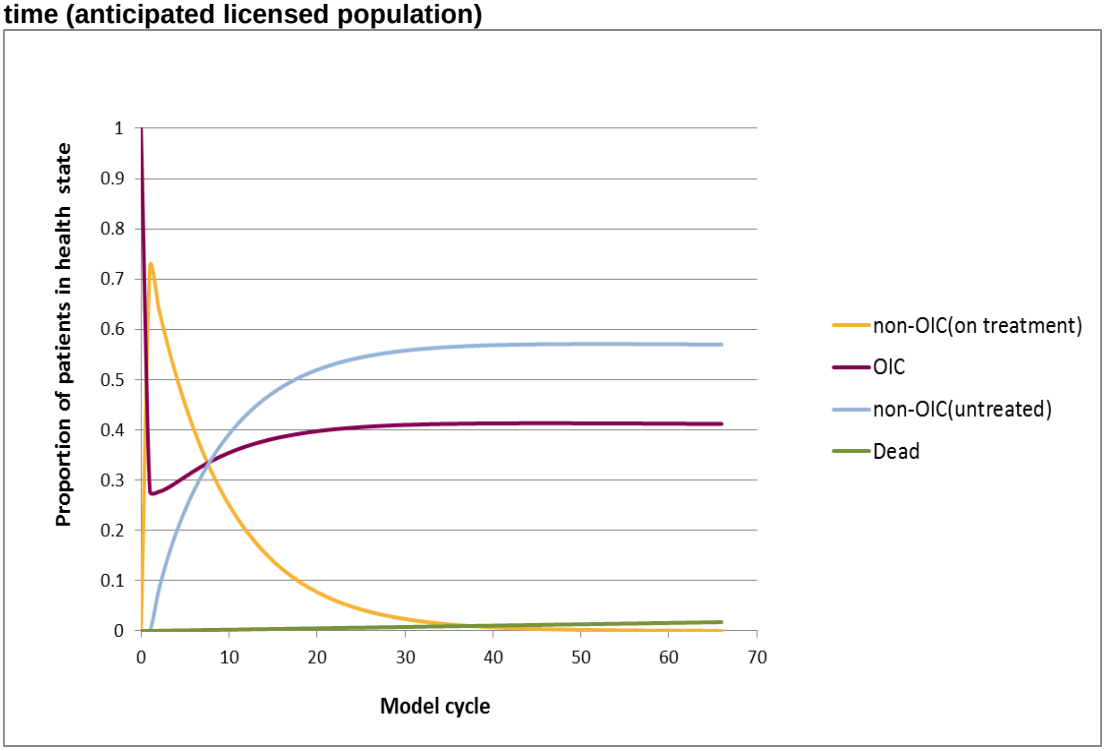
Figure 28–Figure 30 show the proportion of patients in each health state in the naloxegol 25 mg, naloxegol 25 mg + bisacodyl, and placebo + bisacodyl arms of the model. As with the base case model, all arms of the model reach similar steady states over the 5 year time horizon. The greater response of naloxegol 25 mg + bisacodyl compared with placebo + bisacodyl, causes more patients to enter the 'non-OIC (on treatment)' state in the early model cycles, delaying the point at which the model reached the steady state.

Figure 28: Proportion of naloxegol 25 mg patients in each health state over time (anticipated licensed population)



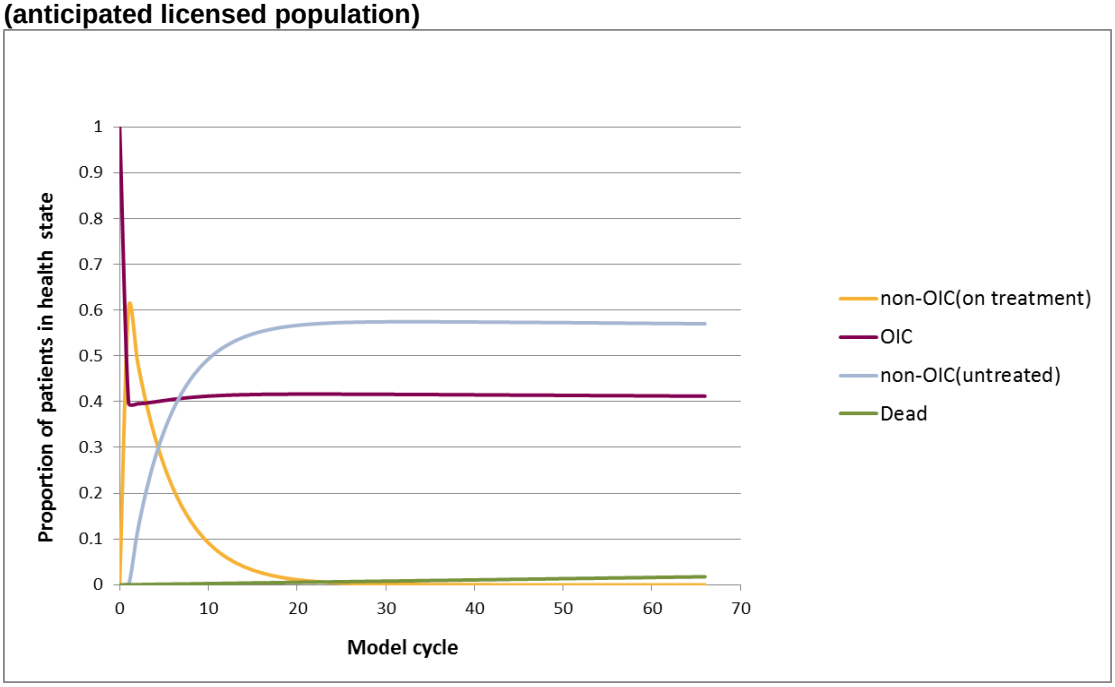
Abbreviations: OIC, opioid-induced constipation.

Figure 29: Proportion of naloxegol 25 mg + bisacodyl patients in each health state over time (anticipated licensed population)



Abbreviations: OIC, opioid-induced constipation.

Figure 30: Proportion of placebo + bisacodyl patients in each health state over time (anticipated licensed population)



Abbreviations: OIC, opioid-induced constipation.

A similar result is obtained when naloxegol 25 mg is compared against placebo + rescue bisacodyl. Naloxegol 25 mg and naloxegol 25 mg + rescue bisacodyl generate QALY gains when compared with placebo + bisacodyl. The cost associated with Naloxegol 25 mg results in a low ICER.

The cost of placebo + bisacodyl is lower than the cost of placebo alone as the increased cost of bisacodyl is offset by the reduced cost of managing constipation resulting from the higher response rate.

Table 126: Scenario analysis results (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

Abbreviations: LY, life years; QALY, quality adjusted life year.

Table 127: Scenario analysis results (anticipated licensed population)

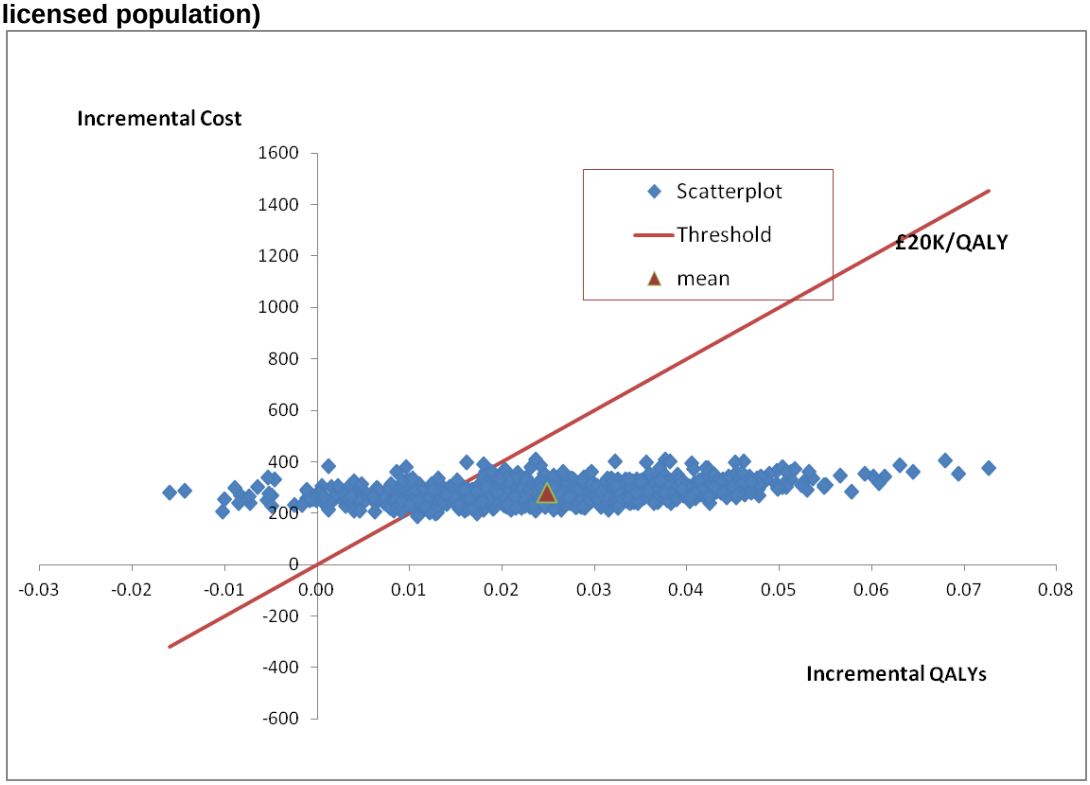
Treatment	Comparator	Incremental LY	Incremental QALY	Incremental costs (£)	ICER (£) (QALYs)
Naloxegol 25 mg	Placebo + bisacodyl	0.000	0.022	£272	£12,639
Naloxegol 25 mg + bisacodyl	Placebo + bisacodyl	0.000	0.028	£313	£11,175

Abbreviations: ICER, incremental cost effectiveness ratio; LY, life years; QALY, quality adjusted life year.

The PSA and CEAC suggest that the ICER for naloxegol 25 mg, when compared with placebo + bisacodyl, is below the £20,000 threshold and is robust in the face of parameter uncertainty:

- Naloxegol 25 mg has a probability of 83% of being below the £20,000 willingness to pay threshold when compared with placebo + bisacodyl (Figure 31 and Figure 32)
- Naloxegol 25 mg + bisacodyl has a probability of 87% of being below the £20,000 willingness to pay threshold when compared with placebo + bisacodyl (Figure 33 and Figure 34)

Figure 31: Scatter plots for naloxegol 25 mg versus placebo + bisacodyl (anticipated licensed population)



Abbreviations: QALY, quality adjusted life year.

Figure 32: CEAC for naloxegol 25 mg versus placebo + bisacodyl (anticipated licensed population)

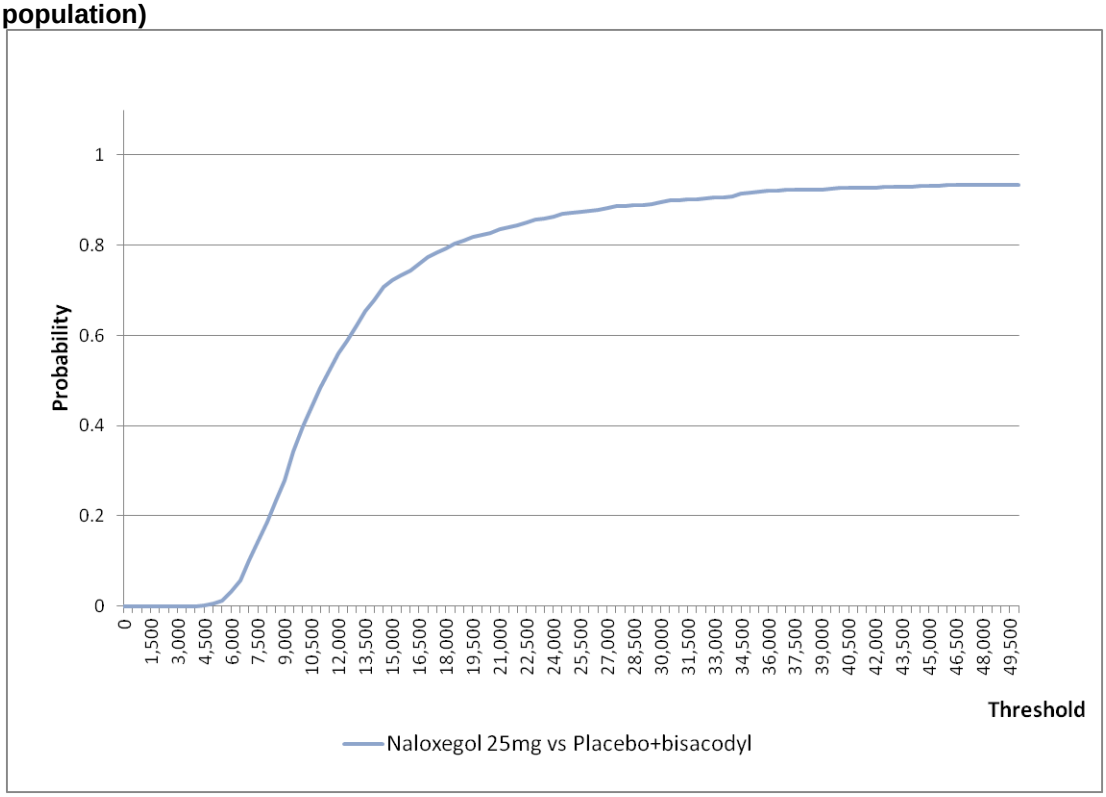
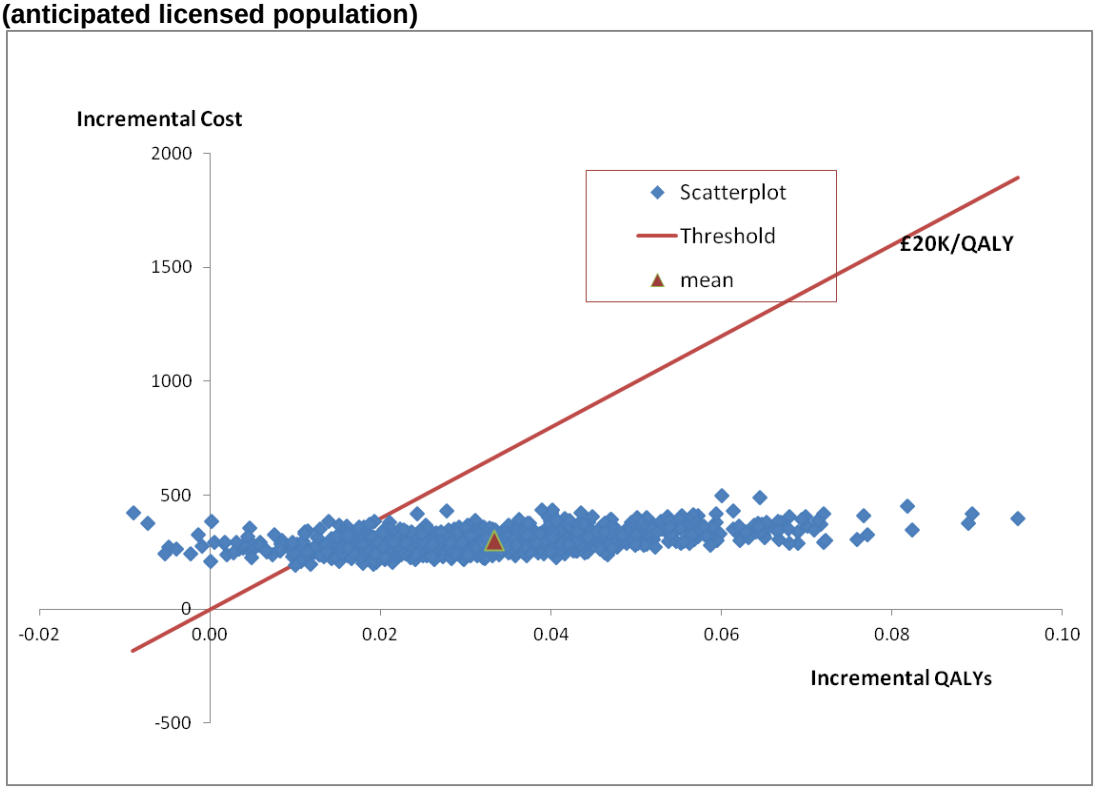
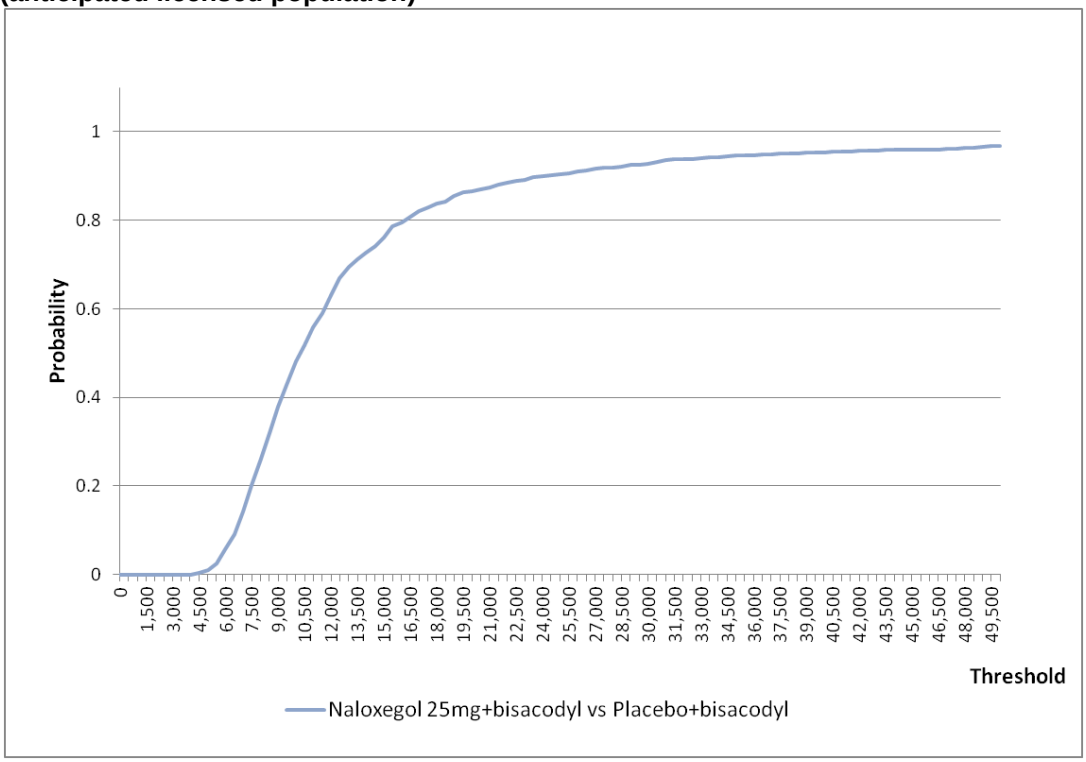


Figure 33: Scatter plots for naloxegol 25 mg + bisacodyl versus placebo + bisacodyl (anticipated licensed population)



Abbreviations: QALY, quality adjusted life year.

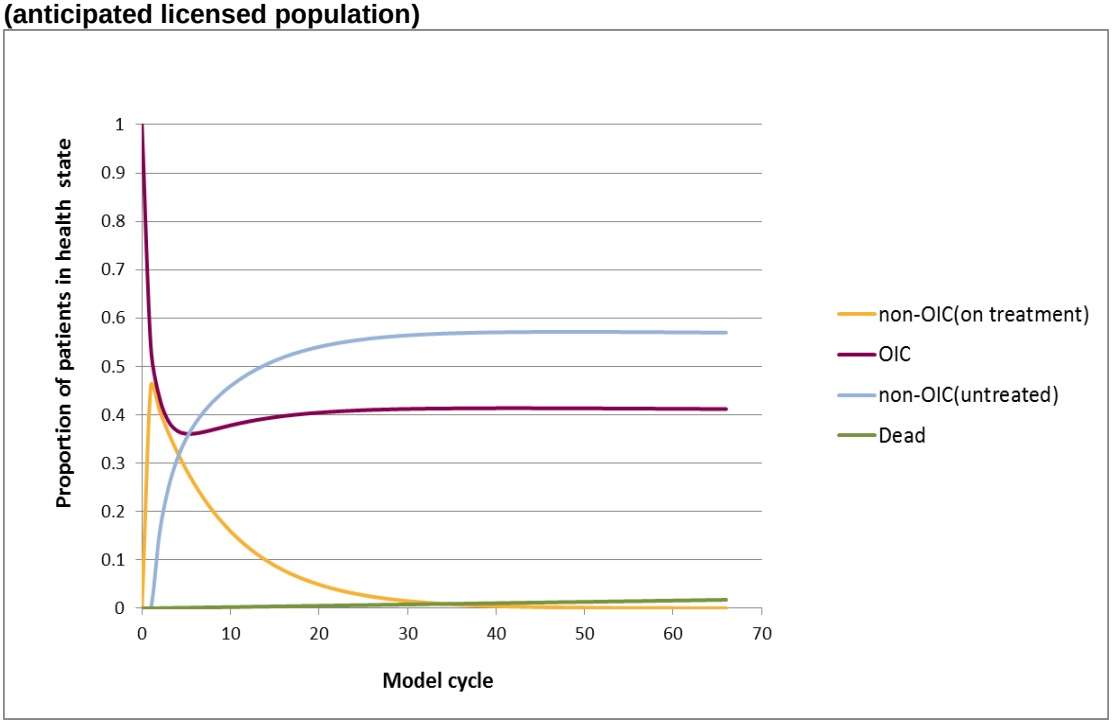
Figure 34: CEAC for naloxegol 25 mg + bisacodyl versus placebo + bisacodyl (anticipated licensed population)



Analysis of alternative treatments: naloxegol 25 mg versus SC methylnaltrexone QAD

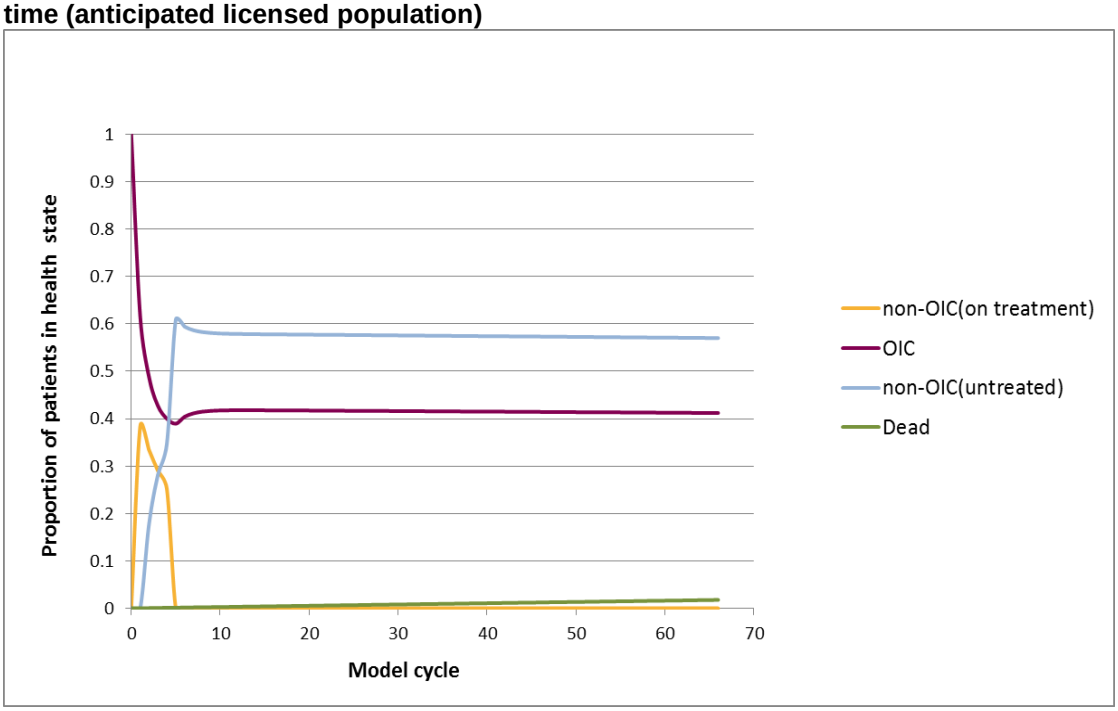
A greater proportion of patients respond with naloxegol 25 mg than SC methylnaltrexone (Figure 35 and Figure 36). The greater proportion of patients in the OIC state with SC methylnaltrexone is exacerbated by the stopping rule, which causes patients to stop SC methylnaltrexone after 16 weeks.

Figure 35: Proportion of naloxegol 25 mg patients in each health state over time (anticipated licensed population)



Abbreviations: OIC, opioid-induced constipation.

Figure 36: Proportion of SC methylnaltrexone QAD patients in each health state over time (anticipated licensed population)



Abbreviations: OIC, opioid-induced constipation.

Naloxegol 25 mg generates a greater number of QALYs in this scenario analysis (Table 128), than the base case, as the response data is taken from a different source, the MTC. The better response rate with naloxegol 25 mg generates a QALY gain compared with SC methylnaltrexone. In addition, the higher treatment cost of SC methylnaltrexone also means that naloxegol 25 mg is cost saving in this scenario, causing naloxegol 25 mg to be dominant (Table 129).

Table 128: Scenario analysis results (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

Abbreviations: LY, life year; MNTX, methylnaltrexone; QAD, every other day; QALY, quality adjusted life year; SC, subcutaneous.

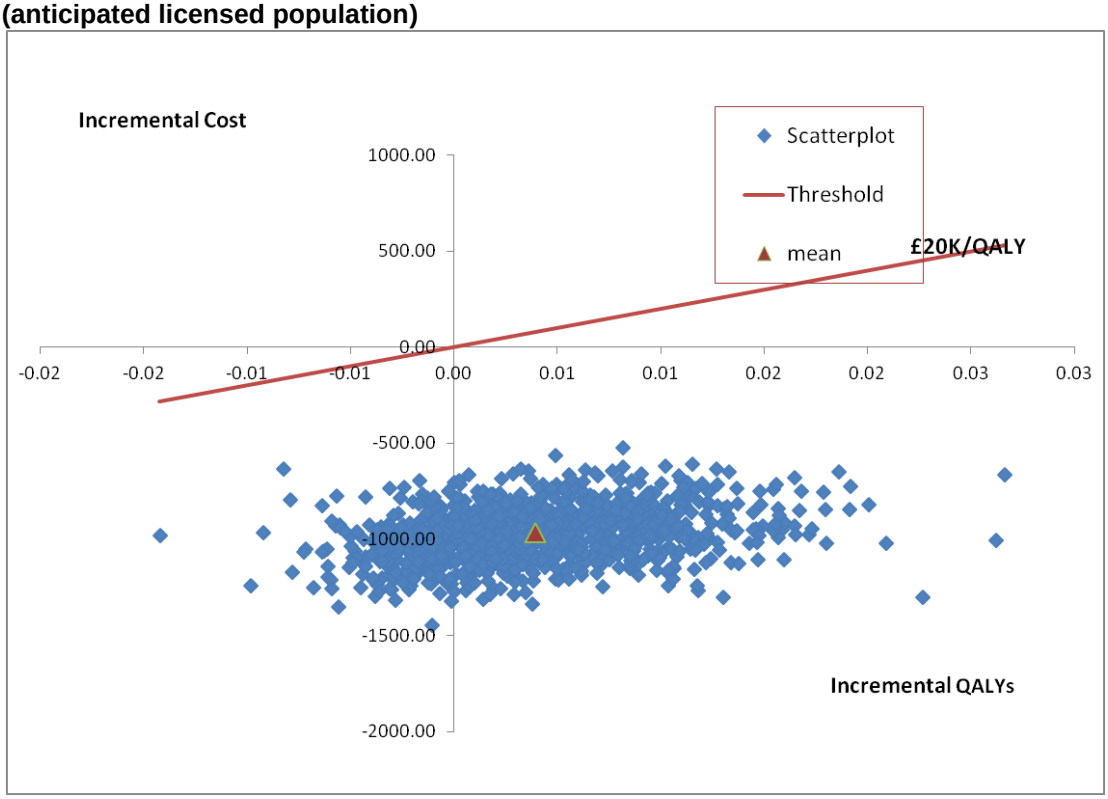
Table 129: Scenario analysis results (anticipated licensed population)

Treatment	Comparator	Incremental LY	Incremental QALY	Incremental costs (£)	ICER (£) (QALYs)
Naloxegol 25 mg	SC MNTX QAD	0.000	0.004	-£962	Naloxegol Dominant

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

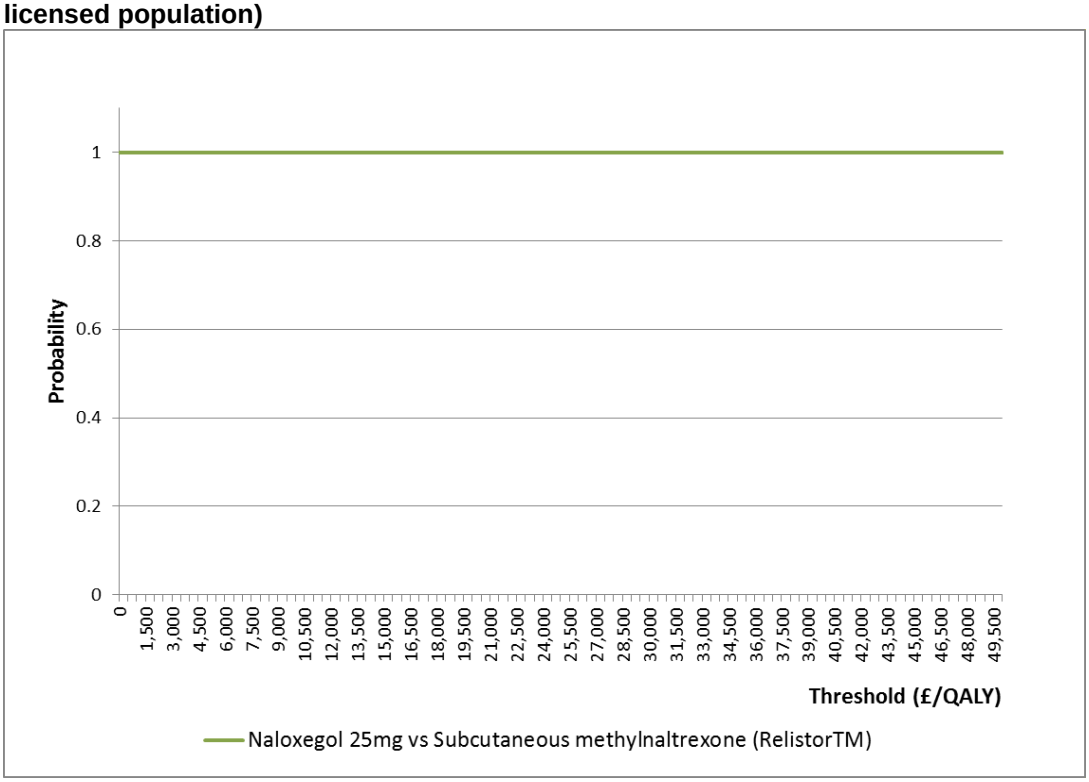
The PSA (Figure 37) and CEAC (Figure 38) suggest that the result that the ICER for naloxegol 25 mg, when compared with SC methylnaltrexone, is below the £20,000 threshold is robust in the face of parameter uncertainty. Naloxegol 25 mg has a 100% probability of being below the £20,000 willingness to pay threshold when compared with SC methylnaltrexone.

Figure 37: Scatterplot for Naloxegol 25 mg versus SC methylnaltrexone QAD (anticipated licensed population)



Abbreviations: QALY, quality adjusted life year.

Figure 38: CEAC for naloxegol 25 mg versus SC methylnaltrexone QAD (anticipated licensed population)



Abbreviations: QALY, quality adjusted life year.

Assessing structural uncertainty

Table 130: Transition A scenarios, anticipated licensed population (see section 7.3.7 for a description of the scenarios)

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
	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	

Scenario	Time horizon	ICER (£) (QALYs) for naloxegol 25 mg vs		
		Placebo	Placebo + bisacodyl	SC MNTX QAD
No extrapolation	12 weeks	£26,431	£43,400	
Hazard ratio = 1				Naloxegol Dominant

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

Table 131: Transition D (OIC – non-OIC [on treatment] and transition E (non-OIC [on treatment] – non-OIC (untreated) scenarios (anticipated licensed population)

Scenario	Value	ICER (£) (QALYs) for naloxegol 25 mg vs		
		Placebo	Placebo + rescue laxative	SC MNTX QAD
Transition D	0%*	£10,849	£12,639	Naloxegol Dominant
	2%	£10,472	£11,422	Naloxegol Dominant
	4%	£10,392	£11,041	Naloxegol Dominant
	6%	£10,395	£10,889	Naloxegol Dominant
	8%	£10,431	£10,830	Naloxegol Dominant
	10%	£10,482	£10,816	Naloxegol Dominant
Transition E	0%†	£10,849	£12,639	Naloxegol Dominant
	2%	£11,203	£13,372	Naloxegol Dominant
	4%	£11,554	£14,130	Naloxegol Dominant
	6%	£11,903	£14,914	Naloxegol Dominant
	8%	£12,249	£15,727	Naloxegol Dominant
	10%	£12,594	£16,573	Naloxegol Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; MNTX, methylnaltrexone; QAD, every other day; QALY, quality adjusted life year; SC, subcutaneous.
† Base case input

Table 132 that follows presents the resource use items and unit costs for managing constipation used in base case and scenario analyses.

Table 132: Resource use 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 consultation	£23.55	0.2900		£6.83	0.2900		£6.83
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

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
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				**£31.7**			**£371.32**

Abbreviations: BOI, burden of illness; GP, general practitioner.

Table 133: Non-laxative costs of managing constipation (anticipated licensed population)

Scenario	ICER (£) (QALYs) for naloxegol 25 mg versus		
	Placebo	Placebo + rescue laxative	SC MNTX QAD
Base case	£10,849	£12,639	Naloxegol Dominant
BOI survey data	Naloxegol Dominant	Naloxegol Dominant	Naloxegol Dominant

Abbreviations: BOI, burden of illness; ICER, incremental cost-effectiveness ratio; LY, life year; MNTX, methylnaltrexone; QAD, every other day; QALY, quality adjusted life year; SC, subcutaneous.

Table 134: 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)(117)	£7,555	£12,312	Naloxegol Dominant

Abbreviations: 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 135: Treatment response scenarios (anticipated licensed population)

Scenario	ICER (£) (QALYs) for naloxegol 25 mg vs	
	Placebo	Placebo + bisacodyl
Base case	£10,849	£12,639
Scenario (Denominator = Patient at risk)	£10,444	£11,884

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

7.7.10 *What were the main findings of each of the sensitivity analyses?*

The model demonstrates that naloxegol 25 mg is cost-effective when compared with treatments other than that for which the KODIAC trials were designed to assess, including:

- Placebo + rescue bisacodyl
- SC methylnaltrexone

The results of the model are robust in the face of uncertainty in both the parameter inputs, as well as the structural assumptions required to construct the model. Only two scenarios change the conclusion that the ICER for naloxegol 25 mg is lower than the £20,000 willingness to pay threshold:

- The worst case scenario, with 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 + bisacodyl. Naloxegol 25 mg remains dominant when compared with SC methylnaltrexone.
- When a health-state specific utility input is employed (rather than utility inputs that also vary with treatment and time), the ICER for naloxegol 25 mg increases to £38,921 compared with placebo and £63,423 when compared with placebo + bisacodyl (see section 7.4.3 for justification of the utility inputs employed in the base case).

7.7.11 *What are the key drivers of the cost-effectiveness results?*

The key model drivers are utility in non-OIC (on treatment) state and intercept parameter used in the exponential function to extrapolate response (Transition A) for naloxegol 25 mg (Figure 25 and Table 125).

7.8 *Validation*

7.8.1 *Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.*

The following steps were undertaken to validate the model:

[redacted]

- The modelling methodology was reviewed by three expert health economists.
- An assessment of the technical validity of the model was undertaken by the agency constructing the model to test the logic and accuracy of the programming, as well as the accuracy of the extraction of data inputs.

7.9 *Subgroup analysis*

7.9.1 *Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.*

Subgroup analysis was performed to assess naloxegol 25 mg for the anticipated licensed population on Step 3 opioids (see section 7.2.1 for further justification for the focus on this subgroup).

7.9.2 *Please clearly define the characteristics of patients in the subgroup.*

Subgroup analysis was conducted for non-cancer patients with OIC who at baseline were laxative inadequate responders (demonstrated ≥4 days of laxative use during the 14-days prior to the study screening period (see section 6.3.7 for further detail) and on Step 3 opioids (according to the WHO pain ladder(130)).

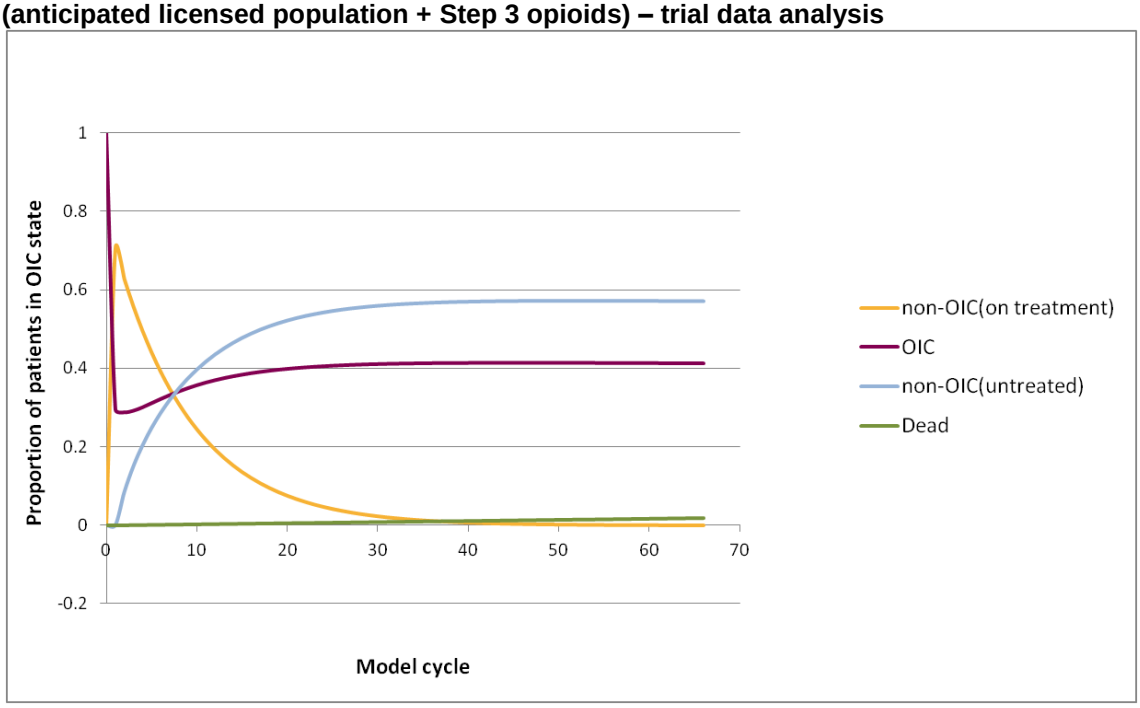
7.9.3 *Please describe how the statistical analysis was undertaken.*

Please refer to section 6.3.7.

7.9.4 *What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).*

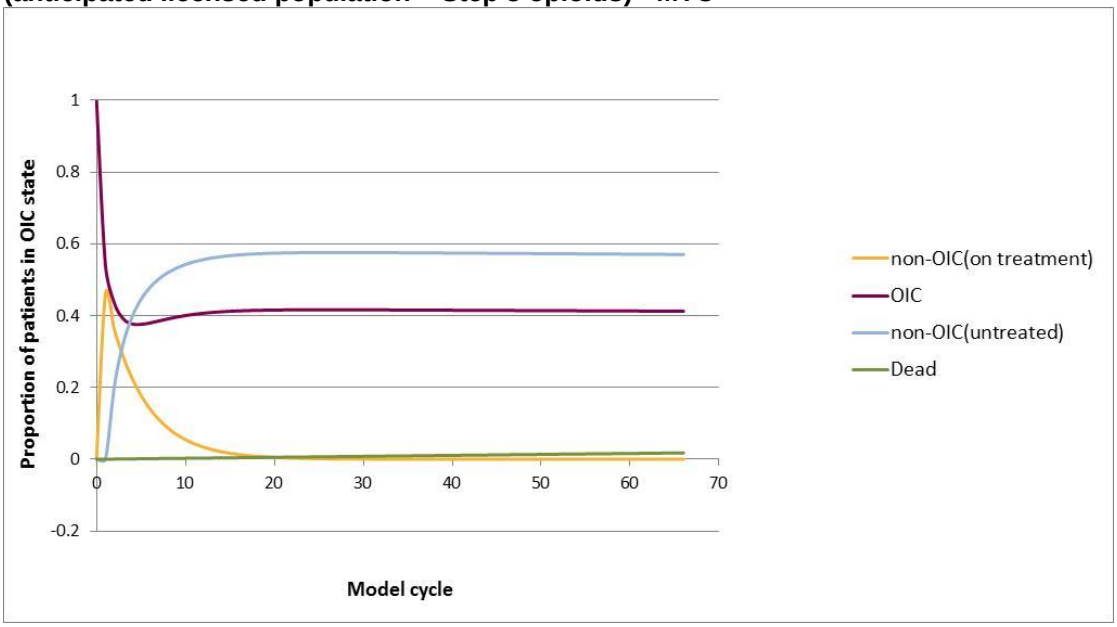
The proportion of patients in each health state displays a very similar pattern as that observed in the base case population (see section 7.7.2) (Figure 39–Figure 45).

Figure 39: Proportion of naloxegol 25 mg patients in each health state over time (anticipated licensed population + Step 3 opioids) – trial data analysis



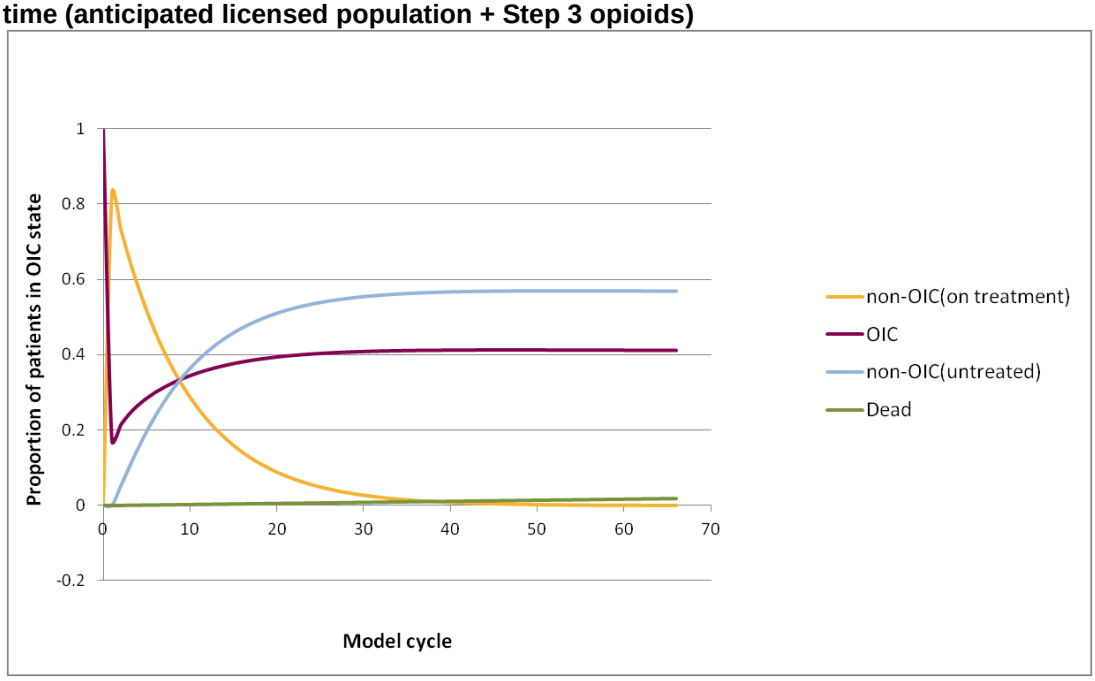
Abbreviations: OIC, opioid-induced constipation.

Figure 40: Proportion of naloxegol 25 mg patients in each health state over time (anticipated licensed population + Step 3 opioids) - MTC



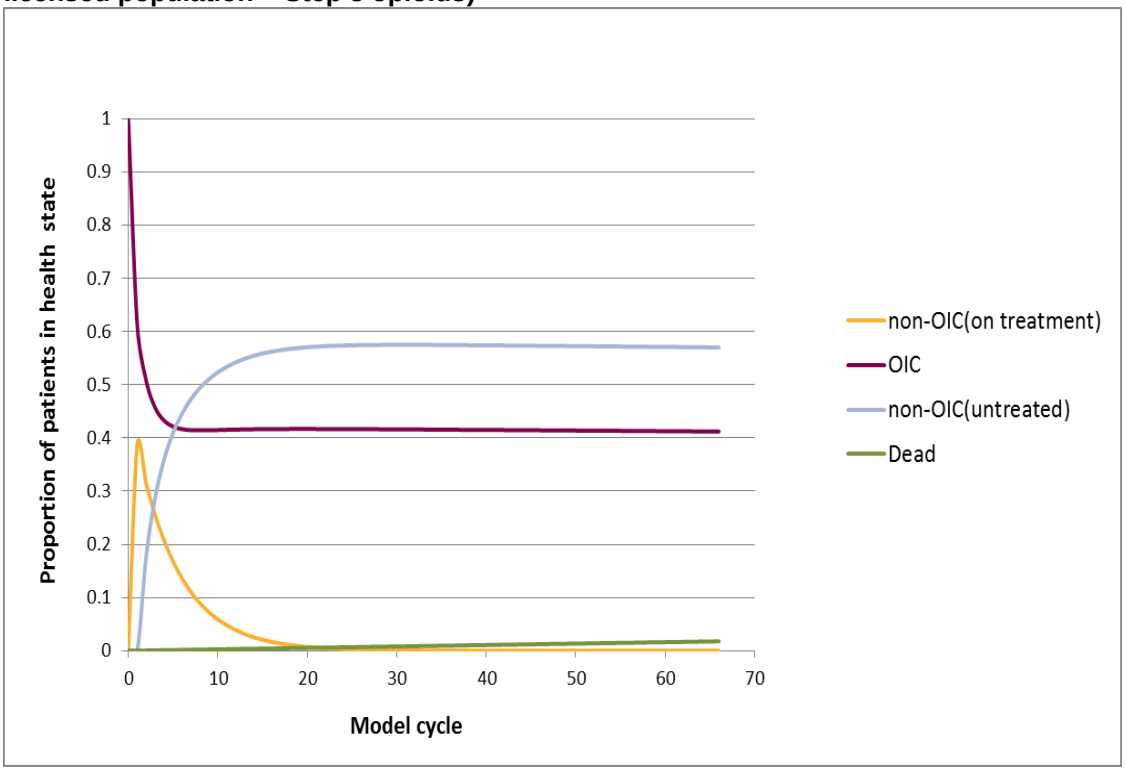
Abbreviations: OIC, opioid-induced constipation.

Figure 41: Proportion of naloxegol 25 mg + bisacodyl patients in each health state over time (anticipated licensed population + Step 3 opioids)



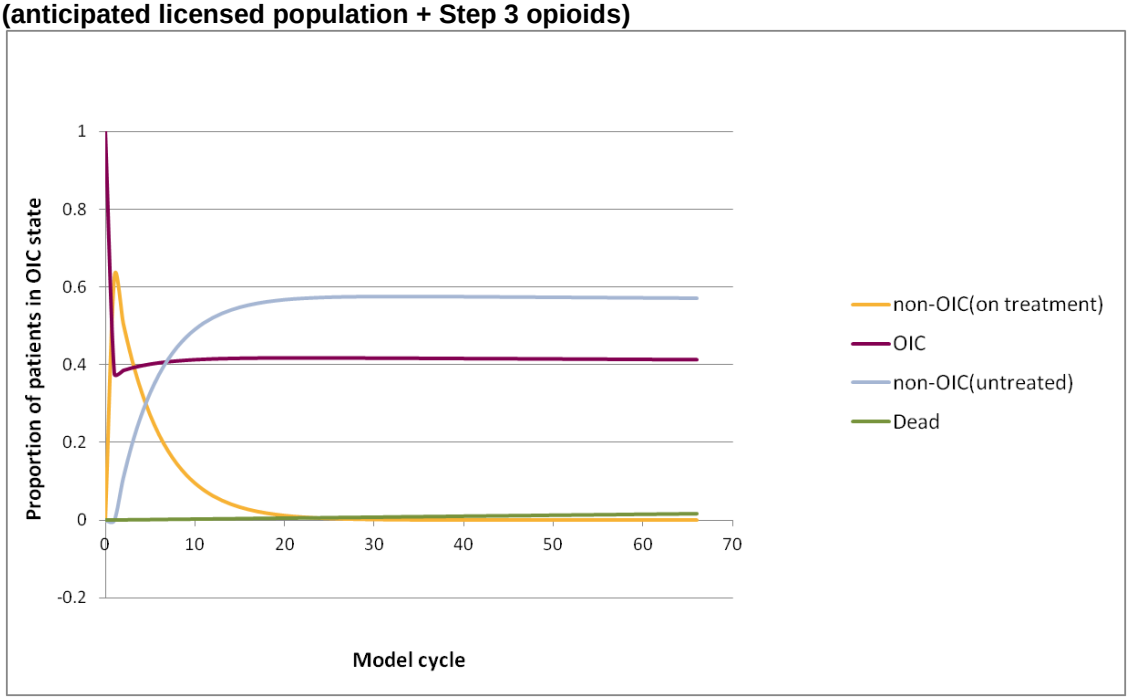
Abbreviations: OIC, opioid-induced constipation.

Figure 42: Proportion of placebo patients in each health state over time (anticipated licensed population + Step 3 opioids)



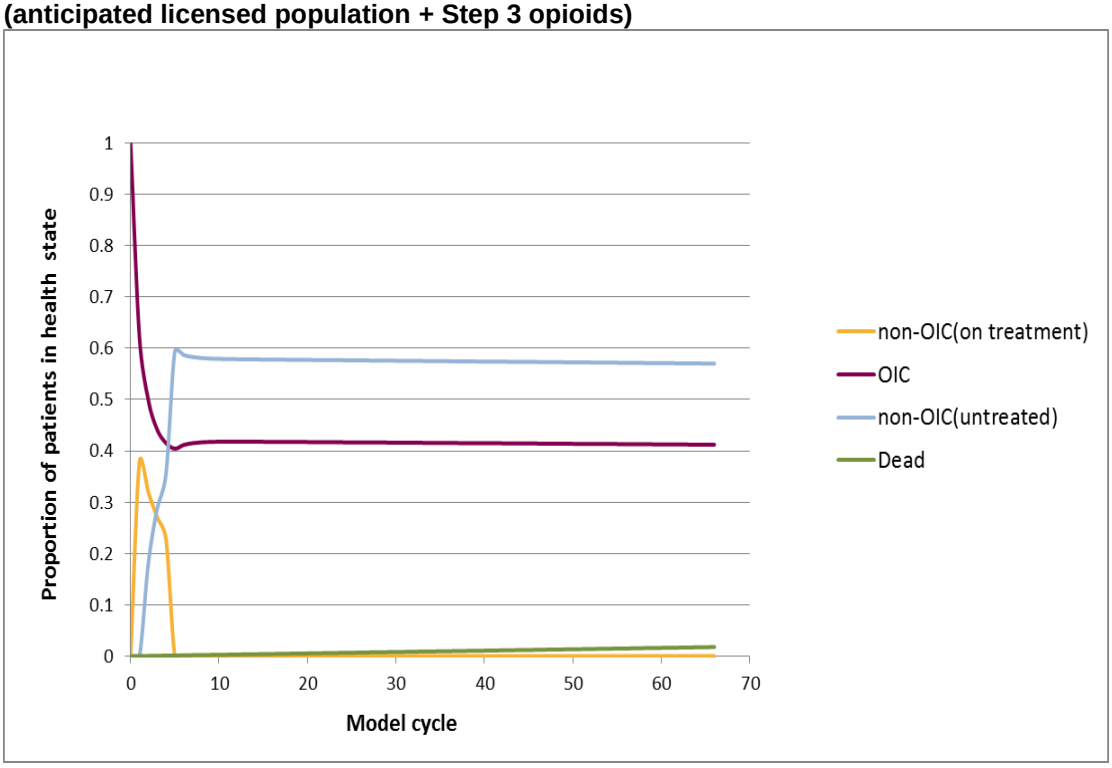
Abbreviations: OIC, opioid-induced constipation.

Figure 43: Proportion of placebo + bisacodyl patients in each health state over time (anticipated licensed population + Step 3 opioids)



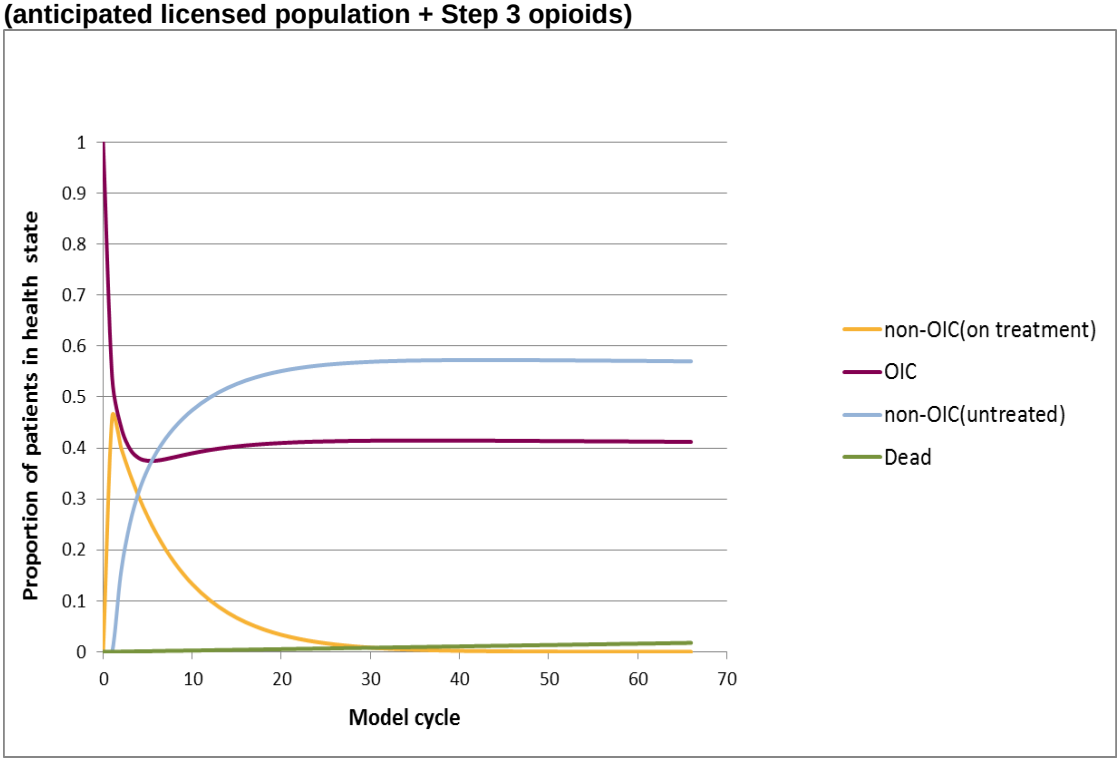
Abbreviations: OIC, opioid-induced constipation.

Figure 44: Proportion of SC methylnaltrexone QAD patients in each health state over time (anticipated licensed population + Step 3 opioids)



Abbreviations: OIC, opioid-induced constipation.

Figure 45: Proportion of naloxone-oxycodone patients in each health state over time (anticipated licensed population + Step 3 opioids)



Abbreviations: OIC, opioid-induced constipation.

The results of the analysis for the anticipated licensed population + Step 3 opioids (Table 136) mirror those for the broader anticipated licensed population (base case population). Comparison with placebo and placebo + bisacodyl produce ICERs below the threshold for cost effectiveness <£20,000 per QALY, and naloxegol 25 mg is dominant in the comparison with SC methylnaltrexone. A new comparator is introduced with the analysis of the anticipated licensed population + Step 3 opioids, naloxone-oxycodone. The comparison with naloxone-oxycodone in which naloxegol 25mg is taken in combination with oral morphine, naloxegol 25 mg is dominant. When naloxegol 25mg is taken in combination with oxycodone the ICER is £30,054

Table 136: Subgroup results (anticipated licensed population + Step 3 opioids)

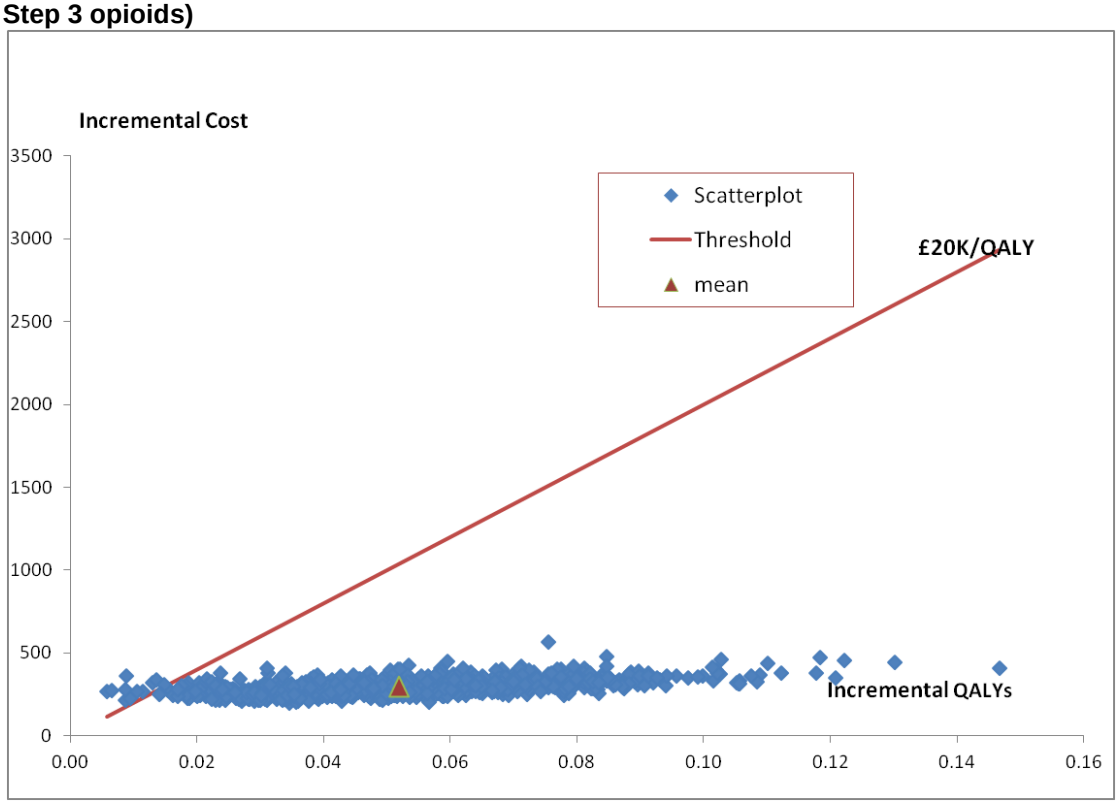
Treatment	Comparator	Incremental QALY	Incremental costs (£)	ICER (QALY) (£), treatment vs comparator
Naloxegol 25 mg	Placebo	0.043	£260	£6,015
Naloxegol 25 mg	Placebo + rescue bisacodyl	0.042	£280	£6,687
Naloxegol 25 mg + Rescue laxatives	Placebo + rescue bisacodyl	0.050	£312	£6,219
Naloxegol 25 mg	SC MNTX QAD	0.006	-£918	Naloxegol Dominant

Treatment	Comparator	Incremental QALY	Incremental costs (£)	ICER (QALY) (£), treatment vs comparator
Naloxegol 25 mg (morphine)†	OXN	0.0026	-£4,097	Naloxegol Dominant
Naloxegol 25 mg (OXY) ‡	OXN	0.0026	£78	£30,054

Abbreviations: ICER, incremental cost effectiveness ratio; MNTX, methylnaltrexone; OXN, naloxone-oxycodone; OXY, oxycodone; QAD, every other day; QALY, quality adjusted life year.
†Source: IMS Health (48)
‡Average dose of oxycodone = 59.3 mg. Source: (50, 54, 58)

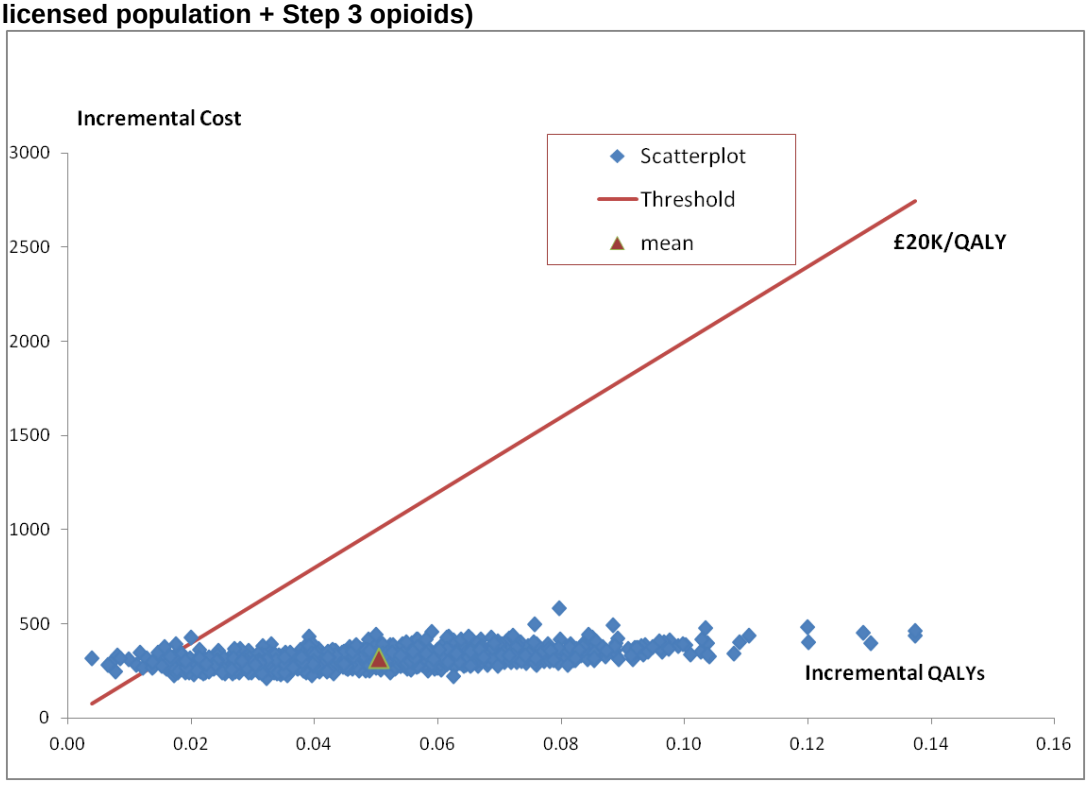
The PSAs and CEACs suggest that the results reported above are robust in the face of parameter uncertainty (Figure 46–Figure 57). With the comparison of naloxegol 25 mg (OXY) and naloxone-oxycodone, the probability of the ICER being lower than £20,000 is 46%.

Figure 46: Scatterplot for naloxegol 25 mg vs placebo (anticipated licensed population + Step 3 opioids)



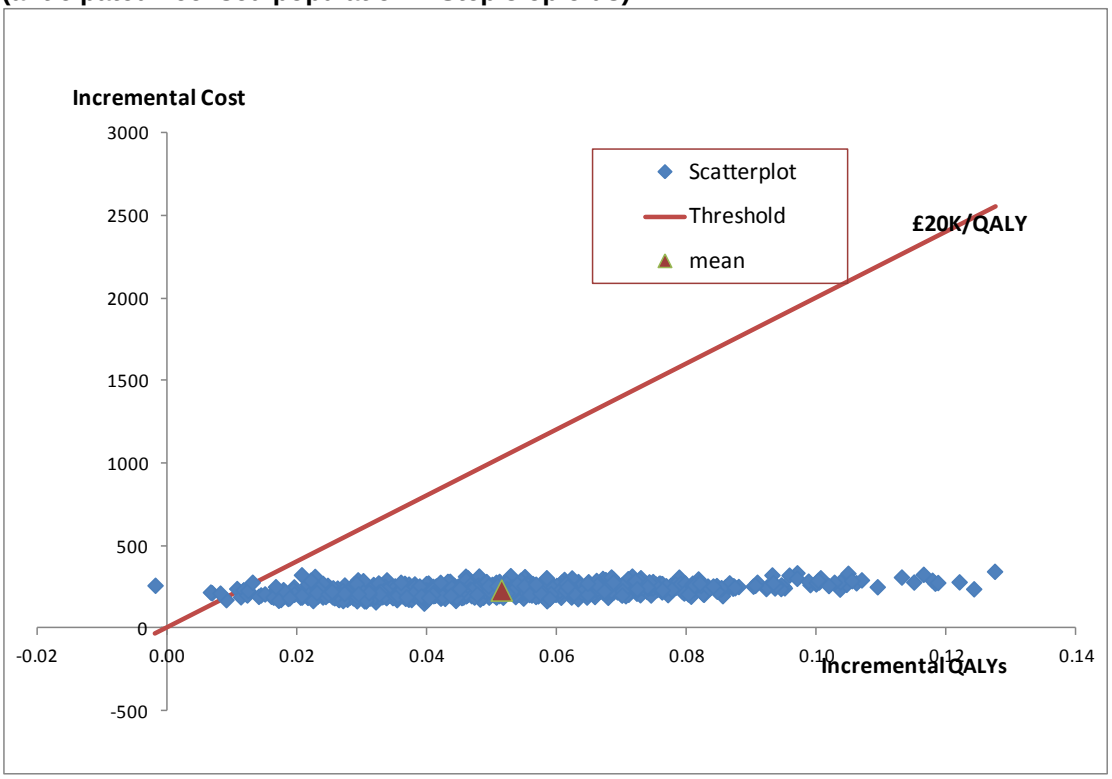
Abbreviations: QALY, quality adjusted life year.

Figure 47: Scatterplot for naloxegol 25 mg versus placebo + bisacodyl (anticipated licensed population + Step 3 opioids)



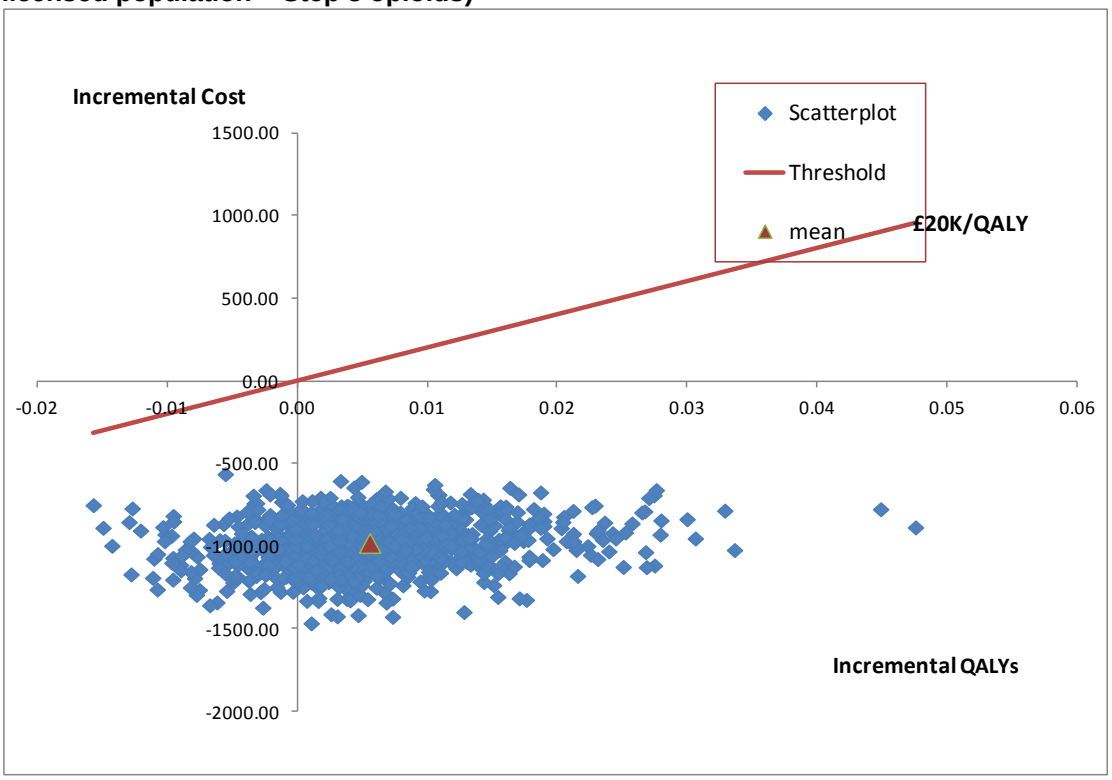
Abbreviations: QALY, quality adjusted life year.

Figure 48: Scatterplot for naloxegol 25 mg + bisacodyl versus placebo + bisacodyl (anticipated licensed population + Step 3 opioids)



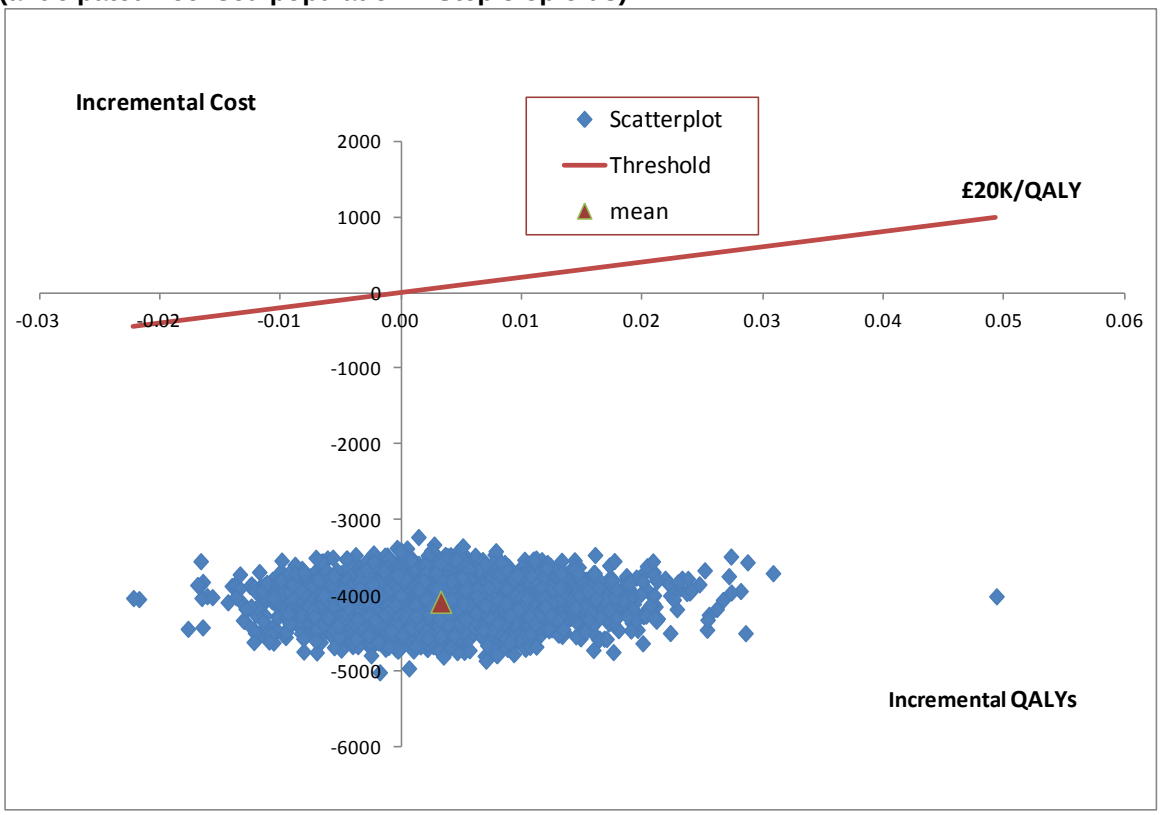
Abbreviations: QALY, quality adjusted life year.

Figure 49: Scatterplot for naloxegol 25 mg versus SC methylnaltrexone QAD (anticipated licensed population + Step 3 opioids)



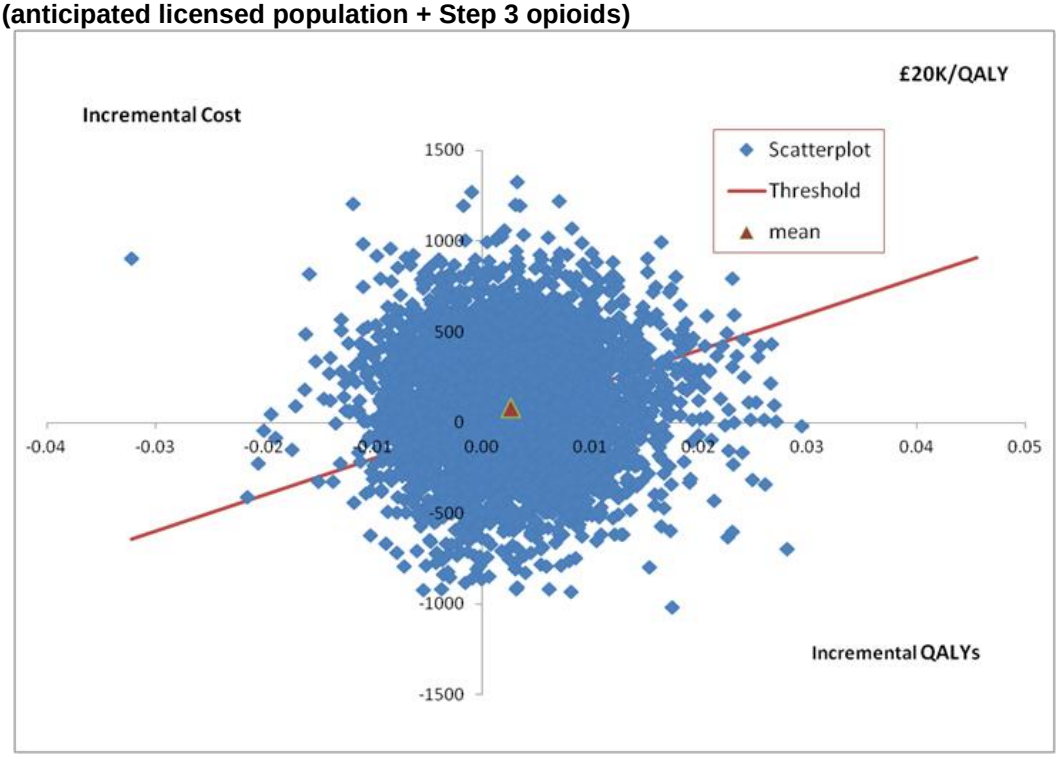
Abbreviations: QALY, quality adjusted life year.

Figure 50: Scatterplot for naloxegol 25 mg (+ morphine) versus naloxone-oxycodone (anticipated licensed population + Step 3 opioids)



Abbreviations: QALY, quality adjusted life year.

Figure 51: Scatterplot for naloxegol 25 mg (+ OXY) versus naloxone-oxycodone (anticipated licensed population + Step 3 opioids)



Abbreviations: QALY, quality adjusted life year.

Figure 52: CEAC for naloxegol 25 mg vs. placebo (anticipated licensed population + Step 3 opioids)

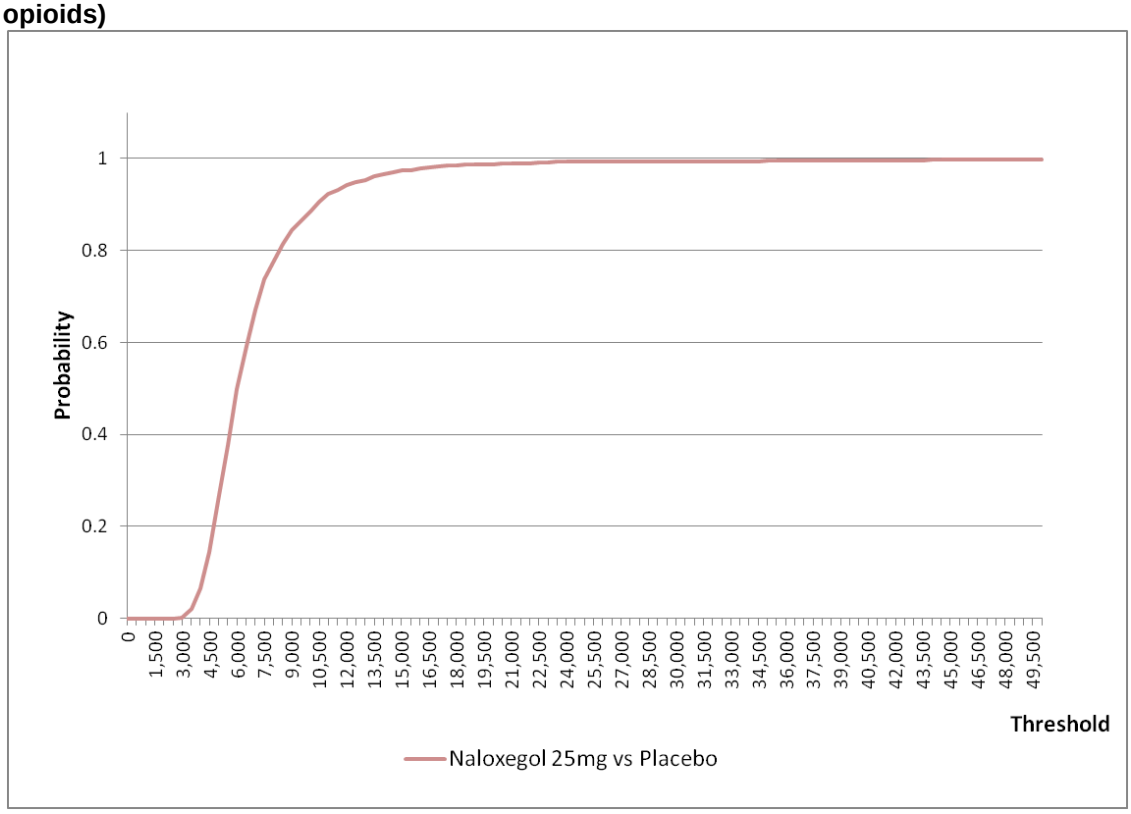


Figure 53: CEACs for naloxegol 25 mg versus placebo + bisacodyl (anticipated licensed population + Step 3 opioids)

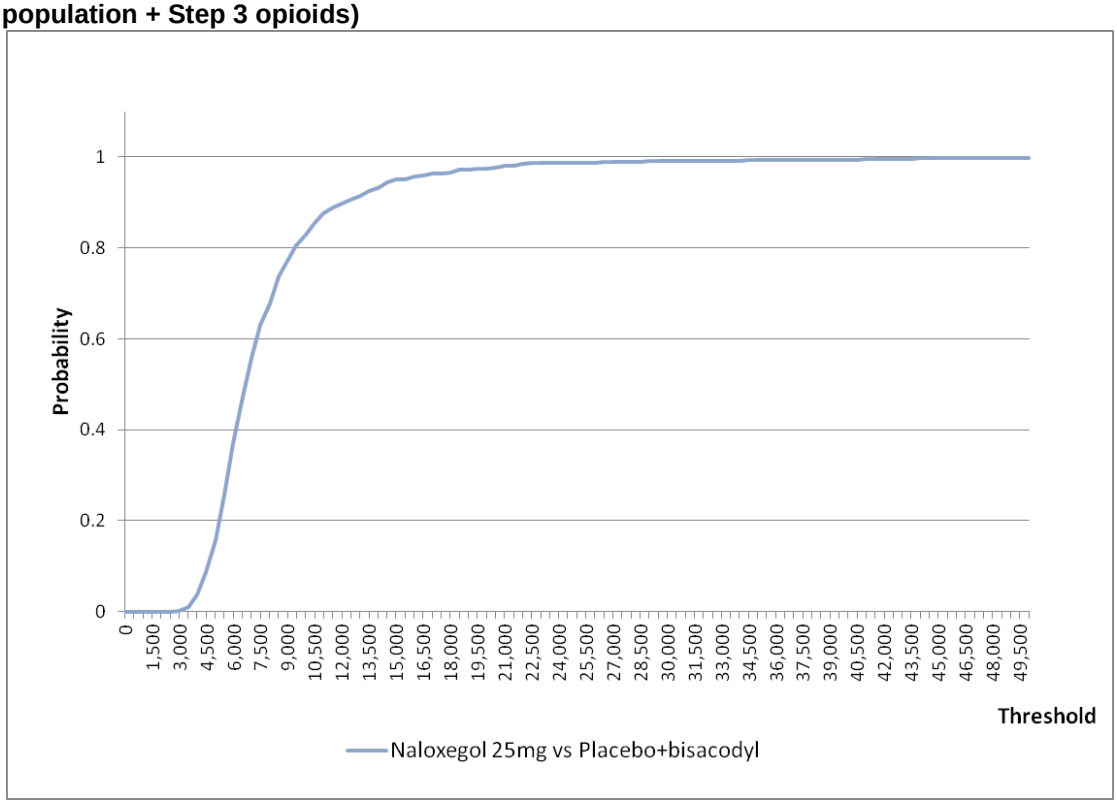


Figure 54: CEACs for naloxegol 25 mg + bisacodyl versus placebo + bisacodyl (anticipated licensed population + Step 3 opioids)

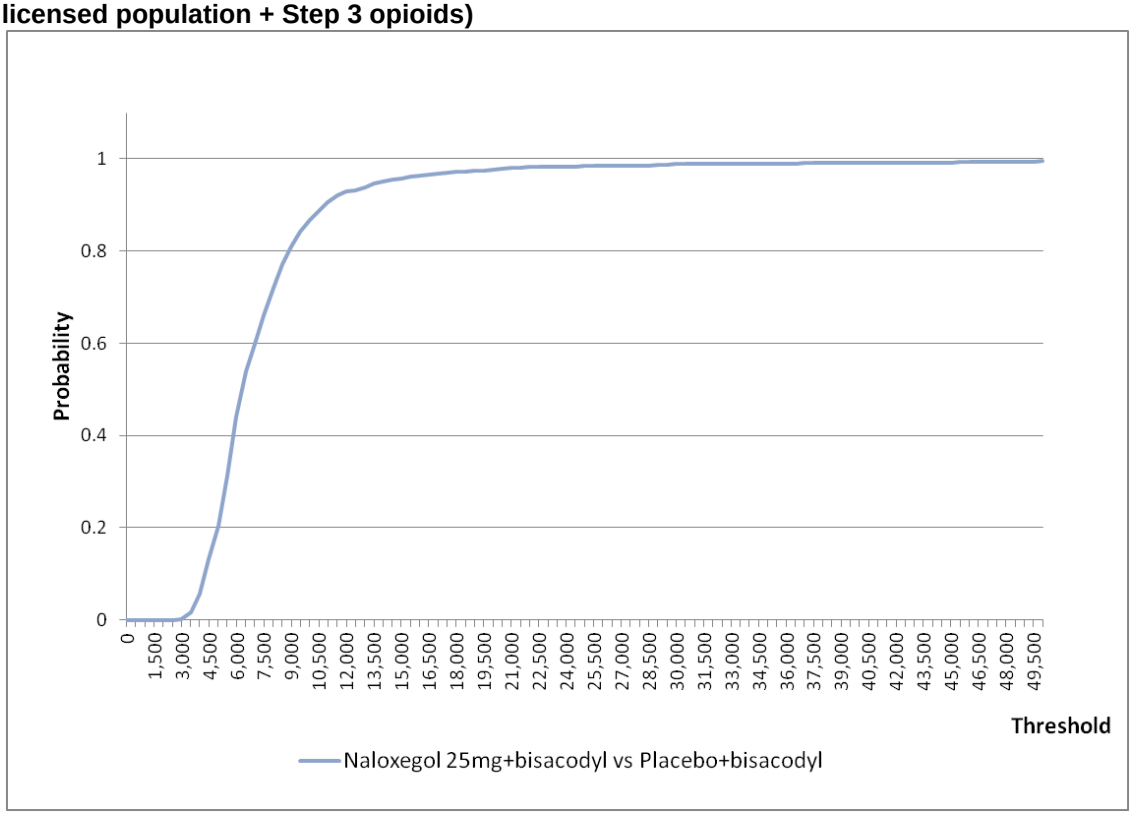


Figure 55: CEACs for naloxegol 25 mg versus SC methylnaltrexone (anticipated licensed population + Step 3 opioids)

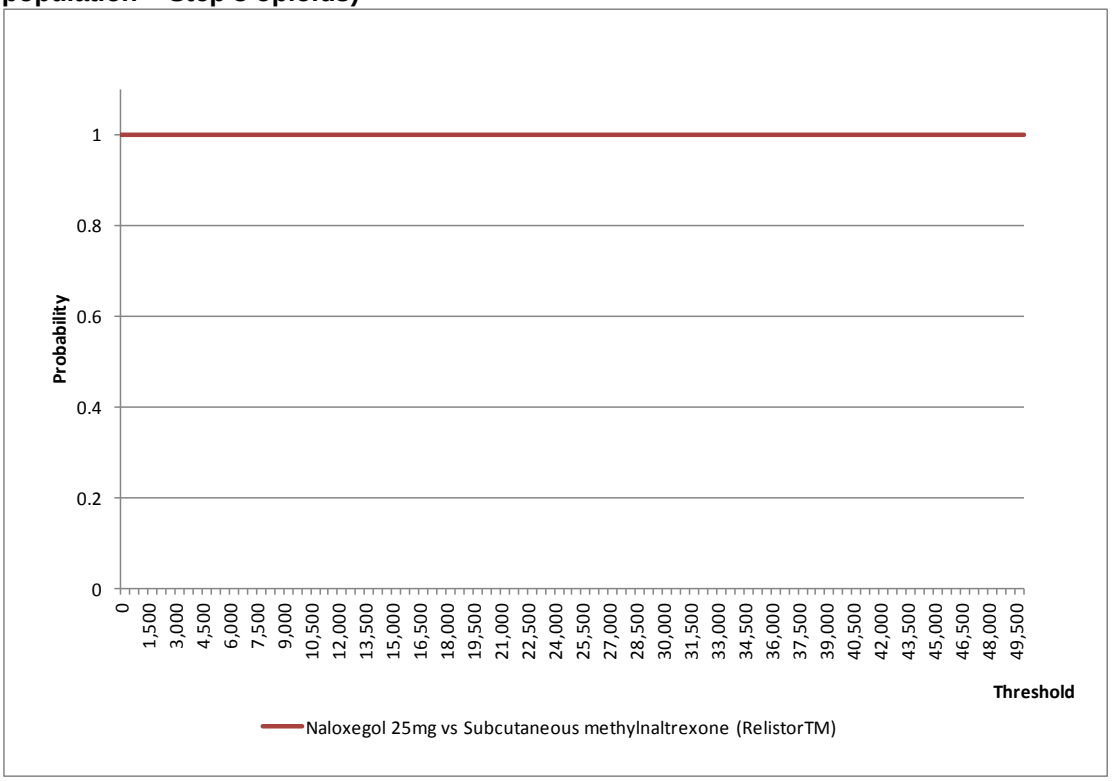
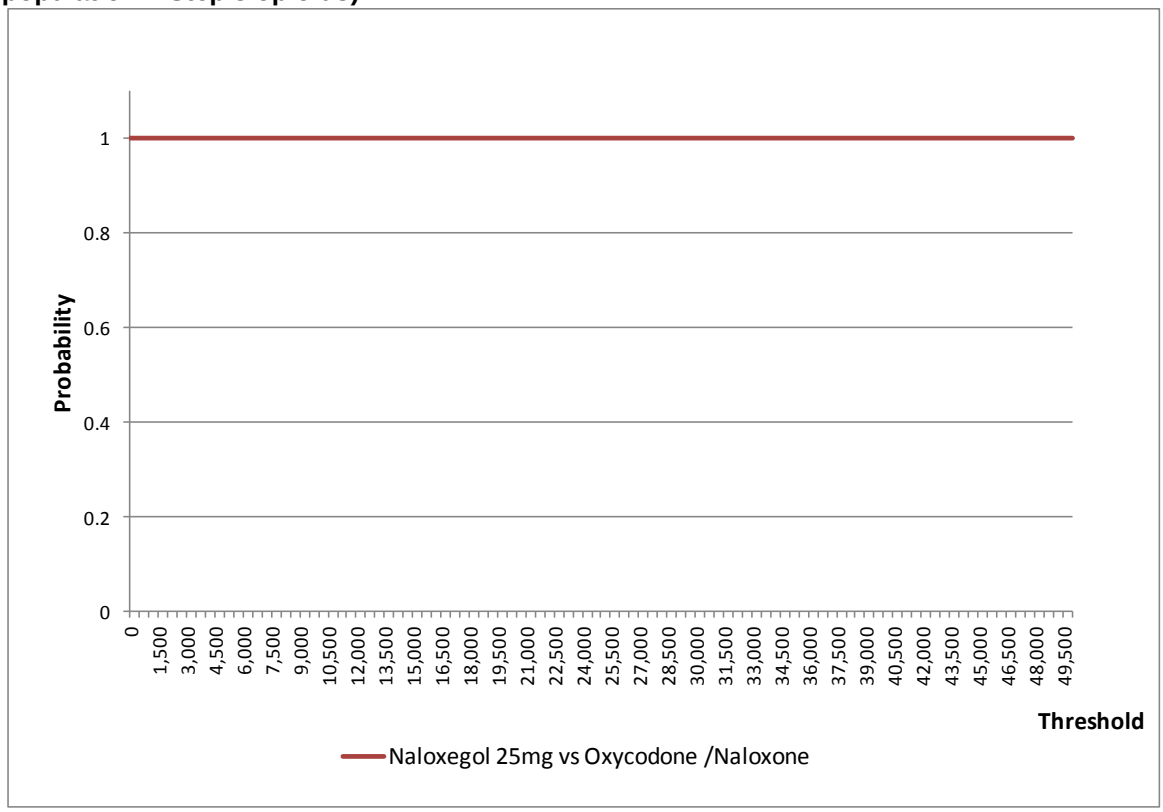
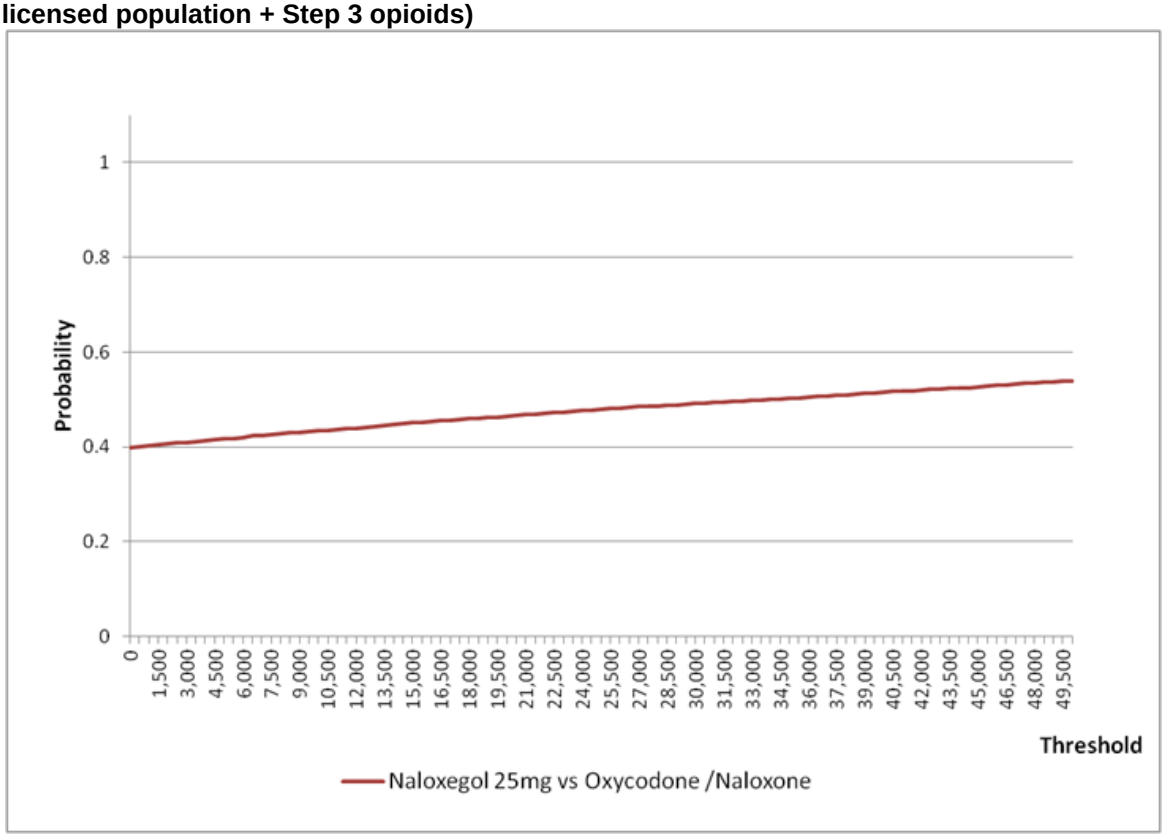


Figure 56: CEAC for naloxegol 25 mg (+ morphine) versus OXN (anticipated licensed population + Step 3 opioids)



Abbreviations: QALY, quality adjusted life year.

Figure 57: CEAC for naloxegol 25 mg (+ OXY) versus naloxone-oxycodone (anticipated licensed population + Step 3 opioids)



Cost minimisation analysis

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 137. According to an AstraZeneca internal 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 are presented in Table 138. The number of months expected per cost of one single intervention of naloxegol 25 mg for the cost of one rectal intervention are shown in Table 139. Compared with rectal interventions, naloxegol can be provided for 0.68 months for the same cost as a rectal intervention given at the patient's home and for 43.02 months if the rectal intervention is given in an inpatient care hospital setting.

Table 137: Unit costs of manual evacuation

Intervention	Unit cost	Reference
Community setting		
Nurse hourly cost	£ 70.00	PSSRU 2013, section 10.1. community nurse cost per hour of home visiting including travel
Hospital setting		
Outpatient care	£ 310.00	NHS Reference Cost 2012/2013 procedure FZ90a, abdominal pain with intervention, general medecine
Inpatient care	£ 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	AstraZeneca, Cost per 28 day cycle. £55.20 for a pack of 30 tablets, £1.84 per day

Table 138: Unit costs of conducting manual evacuation based on time required to perform the procedure

Intervention	Unit cost	Reference
Community setting		
Manual evacuation at patient home	£ 35.00	PSSRU 2013, section 10.1. community nurse cost per hour of home visiting including travel
Hospital setting		

Outpatient care	£ 310.00	NHS Reference Cost 2012/2013 procedure FZ90a, abdominal pain with intervention, general medicine
Inpatient care	£ 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	AstraZeneca, Cost per 28 day cycle. £55.20 for a pack of 30 tablets, £1.84 per day

Table 139: 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

7.9.5 *Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.*

The scope of the STA is adults with OIC and is therefore broader than the population included in the *de novo* economic model. Table 140 considers the generalisability to cancer patients of the results of the economic analysis undertaken for non-cancer patients.

As stated in section 6.10, while the absence of data on the treatment of OIC in cancer pain patients may be perceived as a limitation of the evidence base, it is AstraZeneca's position, and the position that the CHMP ultimately endorsed by granting naloxegol's positive opinion, which included cancer pain patients, that there is no scientific rationale to expect the pharmacodynamic properties of naloxegol to differ in this patient population. The underlying physiology of pain is the same regardless of the underlying cause of that pain. Therefore pain medications act on the same target receptors regardless of whether the trigger for the pain is cancer or non-cancer. Hence, the extrapolation of the available safety and efficacy data to the treatment of OIC in cancer pain patients is justified.

On the strength of these arguments it is therefore assumed that efficacy (MNTX as demonstrated in previous studies of methylnaltrexone and naloxone-oxycodone, see section 1.4), safety and utility estimates (as they include a time and treatment effect

interaction) should be unchanged from the de-novo patients to cancer pain patients. Therefore the model is generalisable for these inputs. Owing to maintaining efficacy and AE rates there would also be no change to the transition probabilities A, B, C, D and E.

In addition, a study of CPRD data demonstrates comparable opioid persistence irrespective of underlying cause of pain. Data from an analysis of the CPRD database 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 (89).

The cost to treat cancer pain patients (see section 7.7.6) would not be expected to be lower than the current base case, which as previously stated may represent a conservative estimate. Moreover, the GP survey (see section 10.28) from which the cost estimates are partly derived for the base case asked physicians to include both cancer and non-cancer pain when estimating resource use justifying the generalisability of the cost input.

However, AstraZeneca does accept that the average age of cancer pain patients will be higher than used in the base case of the model. Based on cancer statistics registration data, the average age of patients with a cancer diagnosis is 72 years. A description of how the average age of cancer pain patients in the model was derived is provided in section 10.29. Owing to this change in age, assumptions for all-cause mortality have been adjusted to reflect the rate at this age point. A mortality rate specifically reflecting cancer patients has been used. Input values and resulting ICERs can be seen in Table 140.

AstraZeneca believes that cancer patients will fit within the maximum and minimum ranges for the key model variables as seen in the threshold analysis shown in section 7.7.8, to maintain an ICER below £20,000.

Table 140: Generalisability to cancer patients of the results of the economic analysis undertaken for non-cancer patients

Variable	Value	How would the parameter differ in the cancer population?	Resultant ICER
Population age	52.2 years	Change = 72 years	£10,826
Mortality (per cycle)	0.027%	Change = 2.079%	£11,597
Naloxegol 25 mg 4 week response	58.51%	No change	NA
Transition A	See Section 7.3.7	No change	NA
Transition B	28.98%	No change	NA
Transition C	20.94%	No change	NA
Naloxegol cost	£ 39.48	No change	NA
Cost of adverse events with Naloxegol 25 mg	£ 17.85	No change	NA
Cost of OIC (non-laxatives)	£ 31.70	No change, potentially conservative estimate	NA
Utility impact of OIC	0.066	No change	NA

Abbreviations: ICER, incremental cost-effectiveness ratio; OIC, opioid-induced constipation.

7.10 *Interpretation of economic evidence*

7.10.1 *Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

No published literature relating to naloxegol 25 mg was identified.

7.10.2 *Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?*

The scope of the STA is adults with OIC and is thus broader than the population included in the *de novo* economic model. See section 7.9.4 for consideration of the generalisability to cancer patients of the results of the economic analysis undertaken for non-cancer patients.

7.10.3 *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

The model was designed to overcome a number of challenges identified with earlier models, including:

- Response rates
  - Response estimates were derived from two high quality RCTs, including several hundred patients.
  - Any MTC was undertaken to allow all potentially relevant comparators to the incorporated into the model.
- Utility: The clinical trials collected EQ-5D data to allow a direct estimate of utility impact in correspondence with NICE's reference case.
- Resource use: A survey of 1,000 GPs in the UK was undertaken to generate relevant resource use inputs.
- Model design: The model considers the likelihood that OIC patients can become non-OIC in the absence of treatment, thus avoiding the possibility that the analysis overestimates gains by assuming that patients' OIC is unresolved in the absence of effective treatment.
- Time horizon:
  - A 5 year time horizon was adopted to ensure all the impacts of treatment were captured in the model.
  - Standard techniques are employed to extrapolate treatment response beyond the trial period.
  - Scenario and sensitivity analysis: An extensive set of scenario and sensitivity analysis was undertaken to explore the implications of both structural and parameter uncertainty.

The model design was also informed by a consultation with clinical and health economic experts.

The model is subject to a number of sources of uncertainty, including:

- Varying definitions of response available in the literature, restricting the comparability of ICERs across treatment comparisons.
- The need to extrapolate over the 5 years of the model time horizon from short-term trial data.

7.10.4 *What further analyses could be undertaken to enhance the robustness/completeness of the results?*

The scenario and sensitivity analysis demonstrated that the model results are robust in the face of most sources of structural and parameter uncertainty. Further work could valuably support this conclusion by generating data to:

- Provide longer-term estimates of treatment response
- Provide further evidence on the factors that drive utility in OIC

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 ***How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.***

Anticipated licensed population

It is expected that the total number of patients eligible for treatment with naloxegol will be [redacted] in year 1, rising to [redacted] in year 5. These figures are estimates of the total population of patients with OIC who can be classified as laxative inadequate responders. Incidence and prevalence figures and the proportion of patients treatable were derived from IMS Disease Analyser (139). Mortality rates were derived from the ONS.

Table 141: Estimation of patients eligible for treatment, licensed population

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident cases, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net population with OIC, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of population treatable under the licence, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients eligible for treatment under the licence, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OIC, opioid-induced constipation

Anticipated licensed population + Step 3 opioids

It is expected that the total number of patients eligible for treatment with naloxegol who are also receiving a Step 3 opioid will be [redacted] in year 1, rising to [redacted] in year 5. Estimates of the percentage of the eligible patient cohort who are also receiving a Step 3 opioid are derived from IMS Disease Analyzer (139).

Table 142: Estimation of patients eligible for treatment, anticipated licensed population + Step 3 opioids

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in licensed population eligible for treatment, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sub-population of eligible patient cohort, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Potential number of eligible patients treated each year in sub-population, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.2 ***What assumption(s) were made about current treatment options and uptake of technologies?***

Anticipated licensed population

Naloxegol's displacement of existing therapies is assumed to be [redacted] for [redacted] respectively. For [redacted] For simplicity, constant annual proportions of patients switching from each therapy is also assumed. The tables below show the estimated displaced medicines cost per patient per annum.

Table 143: Estimated displaced medicine cost – methylnaltrexone (Relistor®)

Name of medicine displaced by naloxegol	[redacted]				
Estimated cost per patient per annum*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated % displaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated displaced medicine cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 144: Estimated displaced medicine cost – naloxone-oxycodone (Targinact®)

Name of medicine displaced by naloxegol	[redacted]				
Estimated cost per patient per	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

annum*					
Estimated % displaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated displaced medicine cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 145: Estimated displaced medicine cost – laxatives

Name of medicine displaced by naloxegol	[redacted]				
Estimated cost per patient per annum*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated % displaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated displaced medicine cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Anticipated licensed population + Step 3 opioids

The displacement of existing therapies is assumed to be the same in this subpopulation as for the total licensed population.

8.3 ***What assumption(s) were made about market share (when relevant)?***

Anticipated licensed population

AstraZeneca forecasts expect that naloxegol will have a total market share of [redacted] in year 1 rising to [redacted] in year 5. In addition, data from KODIAC 8 suggests that naloxegol will have a discontinuation rate of [redacted] per annum. The anticipated number of patients who will receive naloxegol is therefore [redacted] in year 1, rising [redacted] in year 5.

Table 146: Patients treated with naloxegol each year, anticipated licensed population

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients eligible for treatment, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Naloxegol uptake rate, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potential number of eligible patients treated each year, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Naloxegol discontinuation rate, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with naloxegol each year, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Anticipated licensed population + Step 3 opioids

AstraZeneca forecasts assume that uptake rates in this subpopulation will be slightly higher than in the overall licensed population. A market share of [redacted] is expected in year 1, rising to [redacted] in year 5. The discontinuation rate of [redacted] seen in KODIAC 8 was also applied to this population. The anticipated number of patients in this sub-group who will receive naloxegol is forecast to be [redacted] in year 1, rising to [redacted] in year 5.

Table 147: Patients treated with naloxegol each year, anticipated licensed population + Step 3 opioids

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients eligible for treatment, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Naloxegol uptake rate, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potential number of eligible patients treated each year, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Naloxegol discontinuation rate, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with naloxegol each year, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.4 ***In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).***

There are no other significant costs associated with naloxegol treatment.

8.5 ***What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?***

The unit costs for the comparators are as described in section 8.2.

8.6 ***Were there any estimates of resource savings? If so, what were they?***

There are no other additional resource savings expected from the use of naloxegol.

8.7 ***What is the estimated annual budget impact for the NHS in England and Wales?***

Anticipated licensed population

The net annual budget impact for the NHS in England and Wales following the introduction of naloxegol in the anticipated licensed population is estimated to be [redacted] in year 1 rising to [redacted] in year 5.

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10 Appendices

10.1 *Appendix 1*

10.1.1 *SPC/IFU, scientific discussion or drafts.*

Please see accompanying reference pack.

10.2 *Appendix 2: Search strategy for Section 6.1 (Identification of studies)*

10.2.1 *The specific databases searched and the service provider used:*

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- Embase (Ovid)
- The Cochrane Library

10.2.2 *The date on which the search was conducted*

The updated search was conducted on August 21, 2014.

10.2.3 *The date span of the search*

- Ovid MEDLINE(R) January 1, 2006 to present.
- Embase (Ovid), January 1, 2006 to present.
- The Cochrane Library, to present.

10.2.4 *The complete search strategy used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

All the following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to present; Searched on October 18, 2013

#	MEDLINE Search Algorithm	Hits
1	constipation OR ileus OR “gastrointestinal motility” OR “gastrointestinal transit” OR “gastrointestinal tract” OR “gastric emptying” OR “colonic diseases” OR (opioid[Title/Abstract] AND “bowel dysfunction”[Title/Abstract])	122,568

#	MEDLINE Search Algorithm	Hits
2	“narcotic antagonists” OR “opioid receptor” OR “opioid receptors” OR “opioid antagonist”[Title/Abstract] OR “opioid antagonists”[Title/Abstract] OR “pamora”[Title/Abstract] OR “pegylated naloxol conjugate”[Title/Abstract] OR secretagogue OR pentazocine[Title/Abstract] OR nalbuphine[Title/Abstract] OR buprenorphine[Title/Abstract] OR dezocine[Title/Abstract] OR butorphanol[Title/Abstract] OR methylnaltrexone[Title/Abstract] OR relistor[Title/Abstract] OR naloxone[Title/Abstract] OR narcan[Title/Abstract] OR nalone[Title/Abstract] OR narcanti[Title/Abstract] OR alvimopan[Title/Abstract] OR entereg[Title/Abstract] OR “adl 8 2698”[Title/Abstract] OR “adl 82698”[Title/Abstract] OR “ly 246736”[Title/Abstract] OR ly246736[Title/Abstract] OR naltrexone[Title/Abstract] OR antaxone[Title/Abstract] OR “pti 555”[Title/Abstract] OR celupan[Title/Abstract] OR morviva[Title/Abstract] OR revia[Title/Abstract] OR depade[Title/Abstract] OR vivitrol[Title/Abstract] OR nalmefene[Title/Abstract] OR nalmetrene[Title/Abstract] OR revex[Title/Abstract] OR cervene[Title/Abstract] OR arthrene[Title/Abstract] OR incystene[Title/Abstract] OR prucalopride[Title/Abstract] OR resolor[Title/Abstract] OR lubiprostone[Title/Abstract] OR amitiza[Title/Abstract] OR “ru 0211”[Title/Abstract] OR “td 1211”[Title/Abstract] OR “nktr 118”[Title/Abstract] OR linaclotide[Title/Abstract] OR tapentadol[Title/Abstract] OR nucynta[Title/Abstract] OR palexia[Title/Abstract] OR tapenta[Title/Abstract] OR targin[Title/Abstract] OR targinact[Title/Abstract] OR “alks 37”[Title/Abstract] OR adl5945[Title/Abstract] OR “adl 5945”[Title/Abstract]	59,092
3	Laxative OR purgative OR bisacodyl[Title/Abstract] OR senna[Title/Abstract] OR sennoside[Title/abstract] OR “polyethylene glycol 3350”[Title/Abstract] OR docusate[Title/abstract] OR lactulose[Title/Abstract] OR mannitol[Title/Abstract] OR sorbitol[Title/Abstract] OR “magnesium citrate”[Title/Abstract] OR “sodium picosulfate”[Title/Abstract] OR “magnesium hydroxide”[Title/Abstract] OR psyllium[Title/Abstract] OR methylcellulose[Title/Abstract] OR polycarbophil[Title/Abstract]	49,020
4	#1 AND #3 AND placebo[Title/Abstract]; Filters: Humans	235
5	#4 NOT #2	192

Embase 1980 to present; Searched on October 18 2013

#	EMBASE Search Algorithm	Hits

#	EMBASE Search Algorithm	Hits
1	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR 'allocated near/2 random' OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) OR placebo* OR 'prospective study'/de NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)	4,750,523
2	'constipation' OR 'constipation'/exp OR 'ileus'/exp OR 'gastrointestinal motility'/exp OR 'gastrointestinal transit'/de OR 'gastrointestinal tract'/exp OR 'gastric emptying'/exp OR 'colonic diseases, functional'/exp OR (opioid NEAR/2 'bowel dysfunction'):ab,ti	11,208
3	(non*selective NEAR/1 (opioid OR antagonists)):ab,ti OR 'narcotic antagonist'/exp OR 'opioid antagonist':ab,ti OR (opioid NEAR/1 receptor*):ab,ti OR 'opiate receptor'/exp OR 'delta opiate receptor'/de OR 'kappa opiate receptor'/de OR 'mu opiate receptor'/de OR 'pamora':ab,ti OR 'pegylated naloxol conjugate':ab,ti OR 'serotonin 4 agonist'/exp OR 'secretagogue' OR pentazocine:ab,ti OR nalbuphine:ab,ti OR buprenorphine:ab,ti OR dezocine:ab,ti OR butorphanol:ab,ti OR '17 methylnaltrexone'/exp OR methylnaltrexone:ab,ti OR relistor:ab,ti OR 'naloxone'/exp OR naloxone:ab,ti OR narcan:ab,ti OR nalone:ab,ti OR narcanti:ab,ti OR 'alvimopan'/exp OR alvimopan:ab,ti OR entereg:ab,ti OR 'adl 8 2698':ab,ti OR 'adl 82698':ab,ti OR 'ly 246736':ab,ti OR ly246736:ab,ti OR 'naltrexone'/exp OR naltrexone:ab,ti OR antaxone:ab,ti OR 'pti 555':ab,ti OR celupan:ab,ti OR morviva:ab,ti OR revia:ab,ti OR depade:ab,ti OR vivitrol:ab,ti OR 'nalmefene'/exp OR nalmefene:ab,ti OR nalmetrene:ab,ti OR revex:ab,ti OR cervene:ab,ti OR arthrene:ab,ti OR incystene:ab,ti	79,016
4	'prucalopride'/exp OR prucalopride:ab,ti OR resolor:ab,ti OR 'lubiprostone'/exp OR lubiprostone:ab,ti OR amitiza:ab,ti OR 'ru 0211':ab,ti OR 'td 1211':ab,ti OR 'nktr 118':ab,ti OR 'linaclotide'/exp OR linaclotide:ab,ti OR 'tapentadol'/exp OR tapentadol:ab,ti OR nucynta:ab,ti OR palexia:ab,ti OR tapenta:ab,ti OR targin:ab,ti OR targinact:ab,ti OR 'alks 37':ab,ti OR adl5945:ab,ti OR 'adl 5945':ab,ti	1,654
5	Laxative OR purgative OR bisacodyl:ab,ti OR senna:ab,ti OR sennoside:ab,ti OR “polyethylene glycol 3350”:ab,ti OR docusate:ab,ti OR lactulose:ab,ti OR mannitol:ab,ti OR sorbitol:ab,ti OR “magnesium citrate”:ab,ti OR “sodium picosulfate”:ab,ti OR “magnesium hydroxide”:ab,ti OR psyllium:ab,ti OR methylcellulose:ab,ti OR polycarbophil:ab,ti	36,856
6	#1 AND #2 AND #5 AND placebo:ab,ti	294
7	#6 AND [humans]/lim	259
8	#7 NOT (#3 OR #4)	186

The Cochrane Library, to present; Searched on October 18, 2013

#	CENTRAL Search Algorithm	Hits
1	MeSH descriptor Constipation explode all trees	813
2	MeSH descriptor Ileus explode all trees	117
3	MeSH descriptor Gastrointestinal Motility explode all trees	2,356
4	MeSH descriptor Gastrointestinal Transit, this term only	491
5	MeSH descriptor Gastrointestinal Tract explode all trees	9,088
6	MeSH descriptor Gastric Emptying explode all trees	1,097
7	MeSH descriptor Colonic Diseases, Functional explode all trees	694
8	(constipation) or (opioid NEAR/2 "bowel dysfunction"):ti,ab,kw	2,789
9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	13,324
10	MeSH descriptor Narcotic Antagonists explode all trees	816
11	MeSH descriptor Receptors, Opioid explode all trees	321
12	MeSH descriptor Receptors, Opioid, delta, this term only	5
13	MeSH descriptor Receptors, Opioid, kappa, this term only	52
14	MeSH descriptor Receptors, Opioid, mu, this term only	127
15	MeSH descriptor Serotonin 5-HT4 Receptor Agonists explode all trees	14
16	MeSH descriptor Naloxone explode all trees	1,470
17	MeSH descriptor Naltrexone explode all trees	694
18	(non*selective NEAR/1 (opioid OR antagonists)) OR "opioid antagonist" OR (opioid NEAR/1 receptor*) OR "pamora" OR "pegylated naloxol conjugate" OR "secretagogue" OR pentazocine OR nalbuphine OR buprenorphine OR dezocine OR butorphanol OR methylnaltrexone OR relistor OR naloxone OR narcan OR nalone OR narcanti OR alvimopan OR entereg OR "adl 8 2698" OR "adl 82698" OR "ly 246736" OR ly246736 OR naltrexone OR antaxone OR "pti 555" OR celupan OR morviva OR revia OR depade OR vivitrol OR nalmefene OR nalmetrene OR revex OR cervene OR arthrene OR incystene:ti,ab,kw	4,948
19	(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18), from 2006 to 2013	1,147
20	(prucalopride OR resolor OR lubiprostone OR amitiza OR "ru 0211" OR "td 1211" OR "nktr 118" OR linaclotide OR tapentadol OR nucynta OR palexia OR tapenta OR targin OR targinact OR "alks 37" OR adl5945 OR "adl 5945"):ti,ab,kw	106
21	(#19 OR #20)	1,238

#	CENTRAL Search Algorithm	Hits
22	(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,kw	3,230
23	#9 AND #22 AND placebo	242
24	#23 NOT #21	227
25	#24 in Cochrane Central Register of Controlled Trials	215

10.2.5 *Details of any additional searches, such as searches of company databases (include a description of each database).*

Additional studies were identified by hand searching the following conference proceedings (August 2010 to 2013):

- American Academy of Pain Medicine (AAPM), Annual Meeting (April 10–14)
- American Pain Society (APS), Annual Scientific Meeting (May 8–10)
- International Association for the Study of Pain (IASP), World Congress on Pain (NA, every 2 years)
- American College of Gastroenterology, Annual Scientific Meeting (Oct 11–16)
- United European Gastroenterology Week (Oct 12–16)
- Digestive Disease Week (DDW) (May 18–21)

Unpublished studies (i.e. clinical study reports) were provided by the manufacturer.

10.2.6 *The inclusion and exclusion criteria.*

	Description	Justification
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
Interventions	• Naloxegol	Consistent with the final scope
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)
Outcomes	• Change in SBMs at 4 weeks • 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	Consistent with the final scope and for use in the economic model (see section 5)
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.
Language restrictions	English language only	To reduce the number of hits and to identify studies in patient populations relevant to the UK setting
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
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

	Description	Justification
Comparators	Studies that do not include a treatment arm with any of the selected comparators of interest	Not relevant to the final scope
Outcomes	Studies lacking relevant data on any clinical efficacy, safety, and tolerability outcomes of interest	Not relevant to the final scope
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.

10.2.7 *The data abstraction strategy.*

After running the searches and removing duplicate articles, abstracts of the resulting publications were examined manually against the inclusion and exclusion criteria to identify whether the publications should be retrieved in full text for further review. During full-text review, these same inclusion and exclusion criteria were applied and studies meeting all inclusion criteria and no exclusion criteria were considered in the feasibility assessment for MTC analyses.

10.3 *Appendix 3: Quality assessment of RCT(s) (section 6.4)*

10.3.1 *A suggested format for the quality assessment of RCT(s) is shown below.*

Table 148: Quality assessment of pivotal RCTs (KODIAC 4 and KODIAC 5)

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	A unique randomisation code was used to randomly allocate patients to the three treatment groups. Codes were distributed and communicated to study sites by use of an IVRS. The randomisation procedure was structured to ensure that a minimum of 50% of patients were LIR. Eligible patients were randomised in balanced blocks to receive study drug or matching placebo in a 1:1:1 ratio.	Yes
Was the concealment of treatment allocation adequate?	Naloxegol tablets were identical in size and colour to their respective placebo tablets. Packaging and labelling was designed to maintain blinding throughout the study. Patients received two tablets per dose, irrespective of which randomised dose they received.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Demographic and disease baseline characteristics were similar between the three treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Participants and investigators were blinded to treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The treatment groups were generally balanced in terms of discontinuations in both KODIAC 4 and 5.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The outcomes for all variables to be assessed as listed in the clinical study report were reported.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary efficacy analysis set was based on the ITT analysis set, which was defined as all randomised patients. For patients with <4 days of diary data entered for a given week, the weekly SBM frequency was treated as missing for that week. A consistent approach was followed for the efficacy analysis of all eDiary data. For the calculation of responder status, any weeks where the SBM frequency was missing were automatically classified as weeks where no improvement in SBMs had been observed.	Yes

Abbreviations: eDiary, electronic diary; ITT, intent-to treat; IVRS, interactive voice response system; LIR, laxative inadequate responder; SBM, spontaneous bowel movement.

Table 149: Quality assessment of studies designed to primarily assess safety (KODIAC 7)

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	As KODIAC 7 was an extension study of KODIAC 4, patients kept the same randomisation number and enrolment number allocated to them in the previous study (see Table 148 for a summary of the randomisation procedure in KODIAC 4).	Yes
Was the concealment of treatment allocation adequate?	Naloxegol tablets were identical in size and colour to their respective placebo tablets. Packaging and labelling was designed to maintain blinding throughout the study. Patients received two tablets per dose, irrespective of which randomised dose they received.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Demographic and disease baseline characteristics were similar between the three treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Participants and investigators were blinded to treatment. Blinding was maintained throughout the study even after unblinding of KODIAC 4.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The treatment groups were generally balanced in terms of discontinuations.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The outcomes for all variables to be assessed as listed in the clinical study report were reported.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	An ITT analysis was included in the study and included all randomised patients. However, as KODIAC 7 was primarily designed to assess safety, all safety assessments were therefore based on the Safety analysis set which included all patients who participated in KODIAC 4 and received ≥1 dose of study drug in KODIAC 7.	NA

Table 150: Quality assessment of studies designed to primarily assess safety (KODIAC 8)

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Randomisation codes were distributed and communicated to study sites using an IVRS. Treatment assigned to individual patients was determined by the randomisation scheme. Patients were randomised in a 2:1 ratio to receive naloxegol 25 mg or Usual Care.	Yes
Was the concealment of treatment allocation adequate?	KODIAC 8 was an open-label study, therefore no procedures for blinding were applicable.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Demographic and disease baseline characteristics were similar between the two treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	KODIAC 8 was an open-label study, therefore no procedures for blinding were applicable.	N/A
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The treatment groups were generally balanced in terms of discontinuations.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The outcomes for all variables to be assessed as listed in the clinical study report were reported	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	KODIAC 7 was designed primarily to assess safety, therefore all analyses were based on the Safety analysis set defined as all patients who received ≥1 dose of study drug in the study.	N/A

Abbreviations: IVRS, interactive voice response system

10.4 *Appendix 4: Search strategy for Section 6.7 (Indirect and mixed treatment comparisons)*

The clinical search described in Section 6.1 and Section 10.2 was also designed to identify eligible studies for comparator interventions, relevant to the decision problem. Please refer to section 10.2 for full details of the specific databases searched, search dates and search strategies used.

10.5 *Appendix 5: Quality assessment of comparator RCT(s) in Section 6.7 (Indirect and mixed treatment comparisons)*

10.5.1 *A suggested format for the quality assessment of RCT(s) is shown below.*

Michna 2011 (56)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Patients were randomly assigned via a computer-generated randomisation schedule in a 1:1:1 ratio.	Yes
Was the concealment of treatment allocation adequate?	Allocation assignments were provided online to investigators, and randomisation assignments were distributed in blocks of 6 to mitigate the risk that investigators would be able to predict a patient's dosing regimen.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	No major differences existed between the treatment and placebo groups in baseline demographics or clinical characteristics.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Participants and investigators were blinded to treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Treatment groups were generally balanced with respect to discontinuations or withdrawals.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Efficacy and safety assessments listed in methods were reported.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The efficacy analysis included all patients who received at least one dose of study drug (modified intent-to-treat population).	Yes

Rauck 2012 (57)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Method of randomisation not described in abstract.	Not clear
Was the concealment of treatment allocation adequate?	Method not described in abstract.	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Demographic and baseline characteristics were similar among groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Study was not described as double-blinded.	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Discontinuations and withdrawals were not described in abstract.	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Efficacy and safety outcomes listed in methods were reported.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Method of analysis not described in methods.	Not clear

Meissner 2009 (55)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	The randomisation programme balanced the relation between the four naloxone dose groups (10, 20, 40 mg or placebo) in block sizes of four (1:1:1:1 randomisation).	Yes
Was the concealment of treatment allocation adequate?	Method of concealment of treatment allocation was not described.	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	All treatment groups were generally well balanced regarding demographic and baseline characteristics. No clinically relevant differences between the treatment groups or dose ratios concerning prior or concomitant medications were noted.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Participants and investigators were blinded to treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Treatment groups were generally balanced with respect to discontinuations or withdrawals.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Efficacy and safety assessments listed in methods were reported.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	An intent-to-treat analysis was performed for all efficacy endpoints. This included all randomised patients who received at least one dose of naloxone or corresponding naloxone placebo and had at least one efficacy assessment.	Yes

Lowenstein 2009 (54)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Method of randomisation was not described.	Not clear
Was the concealment of treatment allocation adequate?	Patients received either oxycodone /naloxone plus matched oxycodone placebo or oxycodone plus matched oxycodone/naloxone placebo.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	There were no relevant differences between the two treatment groups in terms of demographics and baseline characteristics.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Participants and investigators were blinded to treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Treatment groups were generally balanced with respect to discontinuations or withdrawals.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Efficacy and safety assessments listed in methods were reported.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analysis was based on the full analysis set which consisted of randomised patients who received at least one dose of study medication and who had at least one assessment of the primary efficacy variable. Last observation carried forward analyses of the primary efficacy results were performed using data from all patients in the full analysis population.	Yes

Simpson 2008 (58)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Method of randomisation not described.	Not clear
Was the concealment of treatment allocation adequate?	Method of concealment of treatment allocation not described.	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	There were no differences between the two groups at baseline with regards to demographics, bowel function index, and mean pain intensity.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Participants and investigators were blinded to treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Treatment groups were generally balanced with respect to discontinuations or withdrawals.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Efficacy and safety assessments listed in methods were reported.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy analyses were based on the full analysis population as it is the conservative approach for superiority trials. The full analyses set included randomised patients who received at least one dose of study medication and at least one assessment of the primary efficacy variable.	Yes

Arsenault 2014 (50)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Method of randomisation was not described.	Not clear
Was the concealment of treatment allocation adequate?	Method of concealment of treatment allocation was not described.	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Baseline group comparability was not described.	Not clear
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Participants and investigators were blinded to treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Withdrawals and discontinuations were not described.	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Efficacy and safety assessments were not listed in methods.	Not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analysis was appropriately based on intention-to-treat, but there was no description of how missing data were accounted for.	Yes

10.6 *Appendix 6: Search strategy for Section 6.8 (Non-RCT evidence)*

10.6.1 *The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:*

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library***

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- Embase (Ovid)
- The Cochrane Library
  - Cochrane Central Register of Controlled Trials
  - Cochrane Database of Systematic Reviews
  - Database of Abstracts of Reviews of Effects
  - Health Technology Assessment

10.6.2 *The date on which the search was conducted.*

The searches were conducted on September 29, 2014.

10.6.3 *The date span of the search.*

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), 1946 to present.
- Embase (Ovid), 1980 to 2014 Week 39.
- The Cochrane Library,
  - Cochrane Central Register of Controlled Trials, to August 2014;
  - Cochrane Database of Systematic Reviews, 2005 to August 2014;
  - Database of Abstracts of Reviews of Effects, to 3rd Quarter 2014;
  - Health Technology Assessment, to 3rd Quarter 2014)

10.6.4 *The complete search strategies used. including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

All the following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present; Searched on September 29, 2014

#	Searches	Results
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. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	20223

2	(Constipation or Dyschezia or obstipation or "rectal constipation" or "slow transit constipation").ti,ab.	16795
3	1 or 2	20584
4	(naloxegol or movantik or moventig or PEG$naloxol or NKTR$118 or AZ13337019 or UNII$6514TNM33 or naloxol).mp.	56
5	3 and 4	6

Embase 1980 to 2014 Week 39; Searched on September 29, 2014

#	Searches	Results
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. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	62828
2	(Constipation or Dyschezia or obstipation or "rectal constipation" or "slow transit constipation").ti,ab.	25254
3	1 or 2	63046
4	(naloxegol or movantik or moventig or PEG$naloxol or NKTR$118 or AZ13337019 or UNII$6514TNM33 or naloxol).mp.	158
5	3 and 4	44

EBM Reviews - Cochrane Central Register of Controlled Trials August 2014; Searched on September 29, 2014

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to August 2014; Searched on September 29, 2014

EBM Reviews - Database of Abstracts of Reviews of Effects 3rd Quarter 2014; Searched on September 29, 2014

EBM Reviews - Health Technology Assessment 3rd Quarter 2014; Searched on September 29, 2014

#	Searches	Results
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. [mp=ti, ot, ab, sh, hw,	4056

	kw, tx, ct]	
2	(Constipation or Dyschezia or obstipation or "rectal constipation" or "slow transit constipation").ti,ab.	2293
3	1 or 2	4079
4	(naloxegol or movantik or moventig or PEG$naloxol or NKTR$118 or AZ13337019 or UNII$6514TNM33 or naloxol).mp.	9
5	3 and 4	4

10.6.5 *Details of any additional searches (for example, searches of company databases [include a description of each database]).*

Additional studies were identified by hand searching the following resources:

- www.clinicaltrials.gov **(Search conducted: 30th September 2014)**
- World Health Organisation International Clinical Trials Registry Platform **(Search conducted: October 3, 2014)**
- Conference proceedings from 2012, 2013 and 2014, where available **(Searches conducted: September 30, 2014 except where stated otherwise):**
  - The American Academy of Pain Medicine (AAPM) Annual Meeting – 2014, 2013, 2012
  - American Pain Society (APS) Annual Scientific Meeting – 2014, 2013, 2012
  - American College of Gastroenterology Annual Scientific Meeting – 2013, 2012 (**2012 conference search conducted: October 3, 2014)**
  - United European Gastroenterology Week – 2013, 2012
  - Digestive Disease Week (DDQ) – 2014, 2013, 2012

The following search terms were used for each resource:

- Naloxegol
- Movantik
- Moventig
- Peg$naloxol
- NKTR$118
- AZ1337019
- UNII$6514TNM33

10.6.6 *The inclusion and exclusion criteria.*

	Description	Justification
Inclusion criteria		
Population	Patients with OIC, regardless of age, gender and race	As outlined in draft scope
Interventions	Naloxegol	As outlined in draft scope
Outcomes	Safety and efficacy	As outlined in draft scope
Study design	Non-RCT	RCT studies were identified in a separate review
Exclusion criteria		
Population	Patients without OIC or mixed populations in which outcomes for OIC patients are not reported separately	As outlined in draft scope

Abbreviations: OIC, opioid-induced constipation; RCT, randomised controlled trial.

10.6.7 *The data abstraction strategy.*

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. 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.

10.6.8 *Excluded second pass studies.*

Study	Exclusion code	Reason for exclusion
KODIAC-08, NCT01336205	Study Design	Reported data only on randomised patients

10.7 *Appendix 7: Quality assessment of non-RCT(s) in Section 6.8 (Non-RCT evidence)*

10.7.1 *Please tabulate the quality assessment of each of the non-RCTs identified.*

The study identified (KODIAC 16) is not yet recruiting patients (59).

10.8 *Appendix 8: Search strategy for Section 6.9 (Adverse events)*

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 and therefore a separate systematic review was not conducted.

10.9 *Appendix 9: Quality assessment of adverse event data in Section 6.9 (Adverse events)*

10.9.1 *Please tabulate the quality assessment of each of studies identified.*

N/A

10.10 *Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)*

10.10.1 *The specific databases searched and the service provider used was OVID SP:*

- **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)**
- **Embase (Ovid)**
- **NHS Economic Evaluation Database (NHS-EED, as part of The Cochrane Library)**
- **Econlit (Ovid)**

10.10.2 *The date on which the search was conducted.*

The searches were conducted on August 20, 2014.

10.10.3 *The date span of the search.*

- Ovid MEDLINE(R) 1946 to present.
- Embase (Ovid), 1980 to present.
- NHS EED (The Cochrane Library), to present.
- Econlit (Ovid) 1961 to present.

10.10.4 *The complete search strategies used, including all the search term textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

All the following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present; Searched on August 20, 2014

#	Searches	Results
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. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	20026
2	(Constipation or Dyschezia or obstipation or "rectal constipation" or "slow transit constipation").ti,ab.	16618
3	(non*selective adj2 opioid antagonists).ti,ab.	7
4	exp narcotic antagonist/	33067
5	opioid antagonist.ti,ab.	2929

6	(opioid adj2 receptor*).ti,ab. or exp opiate receptor/	29057
7	opioid antagonists.ti,ab.	1102
8	pamora.ti,ab.	1
9	pegylated naloxol conjugate.ti,ab.	0
10	secretagogue.ti,ab.	4679
11	(pentazocine or nalbuphine or buprenorphine or dezocine or butorphanol).ti,ab.	8089
12	(methylnaltrexone or relistor).ti,ab.	248
13	exp naloxone/	22924
14	(naloxone or narcan or nalone or narcanti).ti,ab.	20583
15	(alvimopan or entereg or adl 8 2698 or adl 82698 or ly 246736 or ly246736).ti,ab.	139
16	exp naloxone/	6791
17	(naloxone or antaxone or pti 555 or celupan or morviva or revia or depade or vivitrol).ti,ab.	5476
18	(nalmefene or nalmetrene or revex or cervene or arthrene or incystene).ti,ab.	247
19	(prucalopride or resolor).ti,ab.	199
20	(lubiprostone or amitiza or "ru 0211" or td 1211 or nktr 118).ti,ab.	260
21	linaclotide.ti,ab.	124
22	(tapentadol or nucynta or palexia or tapenta or targin or arginact or alks 37 or adl5945 or 'adl 5945).ti,ab.	204
23	(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.	32391
24	(naloxegol or MOVANTIK or moventig or NKTR-118).mp.	6
25	laxative.mp. or exp laxative/	2157
26	(suppositor* or enema*).mp.	16373
27	"manual evacuation".mp.	51
28	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,	504

	protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	
29	exp Cost-Benefit Analysis/	61136
30	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	62517
31	(cost utility analys* or (cost-utility adj1 analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1631
32	(cost consequence analys* or (cost-conseq* adj1 analys*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	125
33	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7389
34	or/28-33	64988
35	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	11294
36	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	50228
37	exp decision theory/ or exp decision trees/	9730
38	decision tree.mp.	3557
39	models, economic/	6455
40	(markov or deterministic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	24059
41	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare	142693

	disease supplementary concept word, unique identifier]	
42	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	396
43	(incremental-cost or incremental cost).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	6079
44	(ICER or QALY or DALY or WTP or TTO).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7586
45	35 and (or/36-44)	3932
46	34 or 45	66152
47	1 or 2	20385
48	or/3-27	111098
49	**46 and 47 and 48**	**20**

Embase 1980 to present; Searched on August 20, 2014

#	Searches	Results
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. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	62288
2	(Constipation or Dyschezia or obstipation or "rectal constipation" or "slow transit constipation").ti,ab.	24956
3	(non*selective adj2 opioid antagonists).ti,ab.	9
4	exp narcotic antagonist/	50165
5	opioid antagonist.ti,ab.	3161
6	(opioid adj2 receptor*).ti,ab. or exp opiate receptor/	35695
7	delta opiate receptor/	4740

8	kappa opiate receptor/ or mu opiate receptor/	11872
9	pamora.ti,ab.	5
10	pegylated naloxol conjugate.ti,ab.	0
11	exp serotonin 4 agonist/ or secretagogue/	783
12	(pentazocine or nalbuphineor buprenorphine or dezocine or butorphanol).ti,ab.	3496
13	exp 17 methylnaltrexone/	673
14	(methylnaltrexone or relistor).ti,ab.	366
15	exp naloxone/	33806
16	(naloxone or narcan or nalone or narcanti).ti,ab.	21689
17	exp alvimopan/	516
18	(alvimopan or entereg or adl 8 2698 or adl 82698 or ly 246736 or ly246736).ti,ab.	201
19	exp naltrexone/	10965
20	(naltrexone or antaxone or pti 555 or celupan or morviva or revia or depade or vivitrol).ti,ab.	6311
21	exp nalmefene/	938
22	(nalmefene or nalmetrene or revex or cervene or arthrene or incystene).ti,ab.	333
23	or/3-22	76039
24	exp prucalopride/	624
25	(prucalopride or resolor).ti,ab.	297
26	exp lubiprostone/	624
27	(lubiprostone or amitiza or "ru 0211" or td 1211 or nktr 118).ti,ab.	320
28	exp linaclotide/	371
29	linaclotide.ti,ab.	253
30	exp tapentadol/	647
31	(tapentadol or nucynta or palexia or tapenta or targin or arginact or alks 37 or adl5945 or 'adl 5945).ti,ab.	440

32	or/24-31	2084
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.	37091
34	(naloxegol or MOVANTIK or moventig or NKTR-118).mp.	50
35	exp naloxegol/	34
36	laxative.mp. or exp laxative/	113366
37	(suppositor* or enema*).mp.	23784
38	"manual evacuation".mp.	64
39	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2782
40	exp "cost benefit analysis"/	64471
41	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	66014
42	(cost utility analys* or (cost-utility adj1 analys*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	6266
43	"cost utility analysis"/ or economic evaluation/	14227
44	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	101339
45	"cost effectiveness analysis"/	99191
46	or/39-45	166590
47	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	21165
48	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	46067

49	exp decision theory/ or "decision tree"/	7366
50	decision tree.mp.	8533
51	economic model.mp.	1814
52	(markov or deterministic).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	24294
53	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	206269
54	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	637
55	(incremental-cost or incremental cost).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	8839
56	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	11953
57	or/48-56	287465
58	47 and 57	6368
59	46 or 58	167339
60	1 or 2	62505
61	or/33-38	158217
62	23 or 32 or 61	233558
63	**59 and 60 and 62**	**186**

NHS-EED, to present; Searched on August 20, 2014

#	Searches	Results
1	exp narcotic antagonist/	57
2	(opioid adj2 receptor*).ti,ab. or exp opiate receptor/	7

3	receptors, opioid, delta/	0
4	receptors, opioid, kappa/	0
5	receptors, opioid, mu/	5
6	pegylated naloxol conjugate.ti,ab.	0
7	exp serotonin 5_HT4 receptor agonists/	0
8	exp naloxone/	38
9	exp naltrexone/	23
10	(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.	11
11	(naloxegol or MOVANTIK or moventig or NKTR-118).mp.	1
12	laxative.mp. or exp laxative/	19
13	(suppositor* or enema*).mp.	56
14	"manual evacuation".mp.	1
15	exp constipation/	40
16	exp ileus/	7
17	exp gastrointestinal motility/	8
18	exp gastrointestinal transit/	3
19	exp gastrointestinal tract/	256
20	exp gastric emptying/	1
21	exp colonic diseases, functional/	26
22	(constipation or (opioid adj2 "bowel dysfunction")).mp. [mp=ti, tx, hw]	78
23	or/15-22	363
24	(Constipation or Dyschezia or obstipation or "rectal constipation" or "slow transit constipation").mp.	78
25	exp receptors, opioid/	7
26	((non*selective adj2 (opioid or antagonists)) or "opioid antagonist" or (opioid adj2	85

	receptor*) or "pamora" or "pegylated naloxol conjugate" or "secretagogue" or pentazocine or nalbuphine or buprenorphine or dezocine or butorphanol or methylnaltrexone or relistor or naloxone or narcan or nalone or narcanti or alvimopan or entereg or "adl 8 2698" or "adl 82698" or "ly 246736" or ly246736 or naltrexone or antaxone or "pti 555" or celupan or morviva or revia or depade or vivitrol or nalmefene or nalmetrene or revex or cervene or arthrene or incystene).mp. [mp=ti, tx, hw]	
27	(prucalopride or resolor or lubiprostone or amitiza or "ru 0211" or "td 1211" or "nktr 118" or linaclotide or tapentadol or nucynta or palexia or tapenta or targin or targinact or "alks 37" or adl5945 or "adl 5945").mp. [mp=ti, tx, hw]	20
28	23 or 24	363
29	or/1-14	141
30	or/25-27	100
31	29 or 30	179
32	**28 and 31**	**41**

Econlit 1961 to July 2014; Searched on August 20, 2014

#	Searches	Results
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. [mp=heading words, abstract, title, country as subject]	3
2	(Constipation or Dyschezia or obstipation or "rectal constipation" or "slow transit constipation").ti,ab.	3
3	(non*selective adj2 opioid antagonists).ti,ab.	0
4	opioid antagonist.ti,ab.	0
5	(opioid adj2 receptor*).ti,ab. or exp opiate receptor/	0
6	pamora.ti,ab.	0
7	pegylated naloxol conjugate.ti,ab.	0
8	(pentazocine or nalbuphineor buprenorphine or dezocine or butorphanol).ti,ab.	0
9	(methylnaltrexone or relistor).ti,ab.	0

10	(naloxone or narcan or nalone or narcanti).ti,ab.	0
11	(alvimopan or entereg or adl 8 2698 or adl 82698 or ly 246736 or ly246736).ti,ab.	0
12	(naltrexone or antaxone or pti 555 or celupan or morviva or revia or depade or vivitrol).ti,ab.	0
13	(nalmefene or nalmetrene or revex or cervene or arthrene or incystene).ti,ab.	0
14	(prucalopride or resolor).ti,ab.	0
15	(lubiprostone or amitiza or "ru 0211" or td 1211 or nktr 118).ti,ab.	0
16	linaclotide.ti,ab.	0
17	(tapentadol or nucynta or palexia or tapenta or targin or arginact or alks 37 or adl5945 or 'adl 5945).ti,ab.	0
18	(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.	5
19	(naloxegol or MOVANTIK or moventig or NKTR-118).mp.	0
20	laxative.mp. or exp laxative/	1
21	(suppositor* or enema*).mp.	4
22	"manual evacuation".mp.	0
23	1 or 2	3
24	or/3-22	9
25	**23 and 24**	**0**

10.10.5 *Details of any additional searches, (for example, searches of company databases [include a description of each database]).*

Additional studies were identified by hand searching the following resources:

- Reference lists of included studies
- ISPOR – International Society for Pharmacoeconomics and Outcomes Research for conference proceedings between 2012 to 2014
- NICE website for relevant HTA documentation (94)
- SMC website for relevant HTA documentation (93)

To identify previous relevant economic evaluations the following documentation was reviewed:

- NICE TA211: Prucalopride for the treatment of chronic constipation in women (95)

- NICE TA318: Lubiprostone for treating chronic idiopathic constipation (96)
- NICE Clinical Guideline No. 140, May 2012, 'Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults' (40)
- SMC Advice 977/14: Lubiprostone (Amitiza) - the treatment of chronic idiopathic constipation and associated symptoms in adults, when response to diet and other non-pharmacological measures (e.g. educational measures, physical activity) are inappropriate (97)
- SMC Advice 653/10: Prucalopride (Resolor) – chronic constipation (98)

10.10.6 *The inclusion and exclusion criteria.*

Selection criteria	Description
Inclusion criteria	
Population	Patients with opioid-induced constipation, Patient populations of OECD
Interventions	Naloxegol (MOVENTIG)
Comparators	• Oral laxative treatment without naloxegol. (for patient population with inadequate relief from oral laxatives) • Peripheral mu-opioid antagonists (methylnaltrexone and naloxone-oxycodone) • Rectal interventions (e.g. suppositories and enemas) • Manual evacuation
Outcomes	• QALYs (intervention/comparator) • Costs (intervention/comparator) • ICER per QALY gained • Country where study was performed • Patient population
Study design	Cost-utility analyses
Language restrictions	Non-English publications
Publication date	No date limit was applied
Exclusion criteria	
Population	Patients with constipation not related to opioid use, conditions associated with potential impairment of the structural integrity of the GI tract, surgery on the colon or abdomen, acute GI conditions, inadequate response to laxative rescue during OIC confirmation, treatment with opioids for cancer-related pain, history of cancer within 5 years of screening (except for basal cell or squamous cell skin cancer)

Abbreviations: GI, gastrointestinal; ICER, incremental cost-effectiveness ratio; OIC, opioid-induced constipation; QALY, quality adjusted life year

10.10.7 *The data abstraction strategy.*

Identified studies were independently assessed by an analyst to ascertain they met the pre-defined inclusion/exclusion criteria, any discrepancies were resolved by the project manager. Relevant information was extracted into the STA template/into a pre-defined

Microsoft Excel spreadsheet by an analyst. The included studies and key data elements were verified by the project manager. The data extraction was quality verified and any inconsistencies were resolved through discussion.

10.10.8 *Excluded second pass studies.*

Author	Title	Reason for exclusion
Health Technology Assessment (131)	Lubiprostone for opioid-induced constipation in people with chronic, non-cancer pain	No relevant outcomes reported and no relevant economic evaluations identified from the report
Galvez R 2012(132)	Economic analysis of PR oxycodone/naloxone in the management of severe pain and constipation associated with opioid treatment in Spain	Spanish full paper, English abstract of the paper has no outcome data reported
The Canadian Agency for Drugs and Technologies in Health (133)	Lubiprostone	No relevant outcomes reported and no relevant economic evaluations identified from the report
National Horizon Scanning Centre (134)	Naloxegol (NKTR-118) for opioid-induced constipation	No relevant outcomes reported and no relevant economic evaluations identified from the report
National Institute for Health Research (135)	Lubiprostone (Amitiza) for opioid-induced constipation in patients with chronic non-cancer pain	No relevant outcomes reported and no relevant economic evaluations identified from the report
National Institute for Health Research (136)	Methylnaltrexone bromide (Relistor) for opioid-induced constipation	No relevant outcomes reported and no relevant economic evaluations identified from the report

10.10.9 *Overview of studies included for in-depth review*

Cost-effectiveness evidence was submitted as a part of a SMC submission of OXN (Targinact®) (22), for the treatment of patients with severe pain.

A time horizon of one year was used. The clinical data used in the model such as average daily dose and average rates of laxative use was based on a single RCT. A decision tree model was developed comprising three health states. The utilities were derived from three different sources: 1) a study among neuropathic pain patients, for those receiving opioid treatment but not requiring laxatives; 2) a survey among 175 UK GPs using the EQ-5D for those receiving both opioid treatment and laxatives; and 3) standardised age weighted utilities for patients requiring neither analgesia nor laxatives.

- The cost per QALY for OXN vs OXY was estimated to be £4,712 per QALY.
- Patients treated with OXN incurred an additional opioid drug cost of £118. However, the higher costs were also associated with reduced laxative use and other resource use resulting in a net total cost of £93 for treatment with OXN.

- The treatment with OXN gave a QALY gain of 0.02. Sensitivity analysis was conducted with utility values obtained from SF-36 data collected during the trial, which resulted in a cost per QALY of £6,184.

Dunlop et al, 2012 (25) determined the cost-effectiveness of OXN compared to prolonged release oxycodone alone from a UK NHS perspective. The patient population in the model were adults receiving treatment for moderate/severe non-malignant pain with OIC. Clinical data for the population was based on a single RCT. The model evaluated the outcomes over a period of 301 days. Costs of treatment with OXN and OXY, laxative use in both treatment groups, and other healthcare costs such as physician consultations and home visits, hospital visits and procedures, outpatient appointments, enemas and manual evacuations were included. Cost and effects were not discounted because the time horizon was less than a year. The health states of the model were estimated using Bowel Function Index (BFI) data. The model included two health states; constipated and non-constipated in both treatment groups for a 12- week treatment period. The constipated state was modelled by defining normal bowel functioning as a BFI score ≤28.8. For the remainder of the time horizon the model assumed the BFI values achieved at the end of the 12th week remained constant until the 301st day. Utilities were derived by mapping SF-36 data to EQ-5D scores.

- The base case analyses reported an ICER of £5,841.56 for OXN versus OXY.
- The incremental costs of OXN versus OXY was £159.68 for the time horizon of 301 days.
- The base case analyses showed higher direct costs for OXN, however, this was offset by a higher quality of life gain.
- 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, 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%. Assuming a threshold of £20,000- £30,000 in the UK, treatment with OXN was estimated to be a cost-effective option for patients with OIC.

10.11 *Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)*

Study name	Earnshaw et al, 2010 (26)		Dunlop et al, 2012 (25)	
Study question	**Grade (yes/no/not clear/NA)**	**Comments**	**Grade (yes/no/not clear/NA)**	**Comments**
Study design				
1. Was the research question stated?	Yes		Yes	
2. Was the economic importance of the research question stated?	Yes		Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes		Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Not clear		Yes	
5. Were the alternatives being compared clearly described?	Yes		Yes	
6. Was the form of economic evaluation stated?	Yes		Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes		Yes	
Data collection				
8. Was/were the source(s) of effectiveness estimates used stated?	Yes		Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes		Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA		NA	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes		Yes	
12. Were the methods used to value health states and other benefits stated?	Yes		Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes		Yes	

Study name	Earnshaw et al, 2010 (26)		Dunlop et al, 2012 (25)	
Study question	**Grade (yes/no/not clear/NA)**	**Comments**	**Grade (yes/no/not clear/NA)**	**Comments**
14. Were productivity changes (if included) reported separately?	NA		NA	
15. Was the relevance of productivity changes to the study question discussed?	NA		NA	
16. Were quantities of resources reported separately from their unit cost?	No	Reported only for enema	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes		Yes	
18. Were currency and price data recorded?	Yes		Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Paper published in 2010 and all costs are reported in 2008 Euros. No details on inflation is reported in the paper	Yes	
20. Were details of any model used given?	Yes		Not clear	No details are reported on the type of model apart from stating that a 'cohort cost-utility model' was developed.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes		Not clear	
Analysis and interpretation of results				
22. Was the time horizon of cost and benefits stated?	Yes		Yes	
23. Was the discount rate stated?	NA		NA	
24. Was the choice of rate justified?	NA		NA	
25. Was an explanation given if cost or benefits were not discounted?	Yes		Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes		Yes	

Study name	Earnshaw et al, 2010 (26)		Dunlop et al, 2012 (25)	
Study question	**Grade (yes/no/not clear/NA)**	**Comments**	**Grade (yes/no/not clear/NA)**	**Comments**
27. Was the approach to sensitivity analysis described?	Yes		Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes		Yes	
29. Were the ranges over which the parameters were varied stated?	Yes		Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes		Yes	
31. Was an incremental analysis reported?	Yes		Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes		No	
33. Was the answer to the study question given?	Yes		Yes	
34. Did conclusions follow from the data reported?	Yes		Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes		Yes	
36. Were generalisability issues addressed?	Not clear		Not clear	

10.12 *Appendix 12: Search strategy for Section 7.4 (Measurement and valuation of health effects)*

10.12.1 *The specific databases searched and the service provider used:*

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- Embase (Ovid)
- The Cochrane Library (Ovid) , searching the following databases:
- EBM Reviews - Cochrane Central Register of Controlled Trials May 2014,
  - EBM Reviews - Health Technology Assessment 2nd Quarter 2014
  - EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 2014
  - EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2014
  - EBM Reviews – NHS Economic Evaluation Database 2nd Quarter 2014
- Econlit (Ovid)

10.12.2 *The date on which the search was conducted.*

The searches were conducted on August 18, 2014.

10.12.3 *The date span of the search.*

- Ovid MEDLINE(R) 1946 to present.
- Embase (Ovid), 1980 to 2014 week 33.
- The Cochrane Library (Ovid), to present.
- Econlit (Ovid) 1886 to July 2014.

10.12.4 *The complete search strategies used, including all the search terms textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

All the following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present; Searched on August 18, 2014

#	Searches	Results
1	Constipation.mp. or exp Constipation/	20016
2	(Constipation or Dyschezia or obstipation or "rectal constipation" or "slow transit constipation").ti,ab.	16607
3	(opioid adj2 constipation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	237
4	(chronic adj2 constipation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2416
5	1 or 2 or 3 or 4	20374
6	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	4509
7	(AQOL or "Assessment of Quality of Life").mp. [mp=title, abstract, original title, name of	1271

	substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	
8	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	6692
9	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	467
10	("15D" or "16D" or "17D").mp.	2004
11	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	379
12	"standard gamble".mp.	690
13	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	1233
14	disutilit$.mp.	240
15	(health adj1 stat*).mp. or exp Health Status/	161418
16	exp Models, Economic/	10369
17	(utility adj (value* or weight*)).mp.	920
18	preference$.mp.	106833
19	exp Patient Preference/	3139
20	(utilit* or "health utility index" or "utilities index").mp.	126219
21	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	968703
22	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	708
23	quality of life index.mp.	1182
24	quality adjusted life year.mp. or exp Quality-Adjusted Life Years/	8627
25	("qaly" or "daly" or "adjusted life").mp.	12006
26	("quality adjusted" or "disability adjusted").mp.	11665
27	exp Disability Evaluation/ or disability.mp.	159870
28	disabled person.mp. or exp Disabled Persons/	47450
29	life expectancy.mp. or exp Life Expectancy/	28516
30	(27 or 28) and 29	1348
31	("QoL" or "HRQL" or "HRQL" or "health related quality of life" or "health-related quality of life").mp.	41716
32	quality of life.mp. or exp "quality of life"/	202074
33	or/15-25,30	1334590
34	33 and (31 or 32)	49109
35	or/6-14	15618
36	34 or 35	59733
37	5 and 36	371
38	limit 37 to english	343

Embase 1980 to 2014 week 33; Searched on August 18, 2014

#	Searches	Results
1	Constipation.mp. or exp constipation/	62288
2	(Constipation or Dyschezia or obstipation or "rectal constipation" or "slow transit	24956

	constipation").ti,ab.	
3	(opioid adj2 constipation).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	436
4	(chronic adj2 constipation).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3485
5	1 or 2 or 3 or 4	62505
6	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	7389
7	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	4731
8	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	10420
9	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	746
10	(15D or 16D or 17D).mp.	2590
11	("standard gamble" or SG).mp.	8324
12	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	1598
13	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	450
14	disutilit$.mp.	383
15	(health adj1 stat*).mp. or exp Health Status/	183082
16	(utility adj1 (value* or weight*)).mp.	1517
17	exp statistical model/	102583
18	preference$.mp.	120070
19	*patient preference/	1423
20	(utilit* or "health utility index" or "utilities index").mp.	160481
21	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1004586
22	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	1025
23	quality of life index.mp. or exp "quality of life index"/	2953
24	quality adjusted life year.mp. or exp quality adjusted life year/	13318
25	(qaly or daly or "adjusted life").mp.	17950
26	("quality adjusted" or "disability adjusted").mp.	16452
27	disability.mp. or exp disability/	186261
28	disabled person.mp. or exp disabled person/	24870
29	life expectancy.mp. or exp life expectancy/	40482
30	(27 or 28) and 29	2112
31	(QoL or HRQL or HRQL or "health related quality of life" or "health-related quality of life").mp.	62458
32	quality of life.mp. or exp "quality of life"/	318995
33	or/15-26,30	1498807
34	33 and (31 or 32)	69215
35	or/6-14	33655

36	34 or 35	93299
37	5 and 36	1185
38	limit 37 to english	1125

The Cochrane Library, to present; Searched on August 18, 2014

#	Searches	Results
1	Constipation.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	4028
2	(Constipation or Dyschezia or obstipation or "rectal constipation" or "slow transit constipation").ti,ab.	2283
3	(opioid adj2 constipation).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	70
4	(chronic adj2 constipation).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	359
5	1 or 2 or 3 or 4	4051
6	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	2010
7	(AQOL or "Assessment of Quality of Life").mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	439
8	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	1042
9	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	139
10	("15D" or "16D" or "17D").mp.	114
11	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	279
12	"standard gamble".mp.	269
13	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	478
14	disutilit$.mp.	194
15	(health adj1 stat*).mp. or exp Health Status/	11239
16	exp Models, Economic/	1855
17	(utility adj (value* or weight*)).mp.	1862
18	preference$.mp.	8581
19	exp Patient Preference/	739
20	(utilit* or "health utility index" or "utilities index").mp.	10186
21	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	32389
22	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	43
23	quality of life index.mp.	349
24	quality adjusted life year.mp. or exp Quality-Adjusted Life Years/	4160
25	("qaly" or "daly" or "adjusted life").mp.	6328
26	("quality adjusted" or "disability adjusted").mp.	6190
27	exp Disability Evaluation/ or disability.mp.	12084
28	disabled person.mp. or exp Disabled Persons/	764
29	life expectancy.mp. or exp Life Expectancy/	2106
30	(27 or 28) and 29	154
31	("QoL" or "HRQL" or "HRQL" or "health related quality of life" or "health-related quality of life").mp.	9154
32	quality of life.mp. or exp "quality of life"/	37831

33	or/15-25,30	60468
34	33 and (31 or 32)	12582
35	or/6-14	4237
36	34 or 35	14269
37	5 and 36	319
38	limit 37 to english [Limit not valid in DARE,CLEED; records were retained]	313

Econlit 1886 to July 2014; Searched on August 18, 2014

#	Searches	Results
1	Constipation.mp. [mp=heading words, abstract, title, country as subject]	3

10.12.5 *Details of any additional searches (for example, searches of company databases [include a description of each database]).*

Additional studies were identified by hand searching the following resources:

- Conference proceedings: ISPOR (International Society for Pharmacoeconomics and Outcomes Research) and BSG (British Society of Gastroenterology), search between August 28–29, 2014.
- NICE HTA submissions (NICE TA211: Prucalopride for the treatment of chronic constipation in women; NICE TA318: Lubiprostone for treating chronic idiopathic constipation; and NICE Clinical Guideline No. 140: Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults), search on August 29, 2014.
- SMC submissions (SMC Advice 977/14: Lubiprostone (Amitiza) - the treatment of chronic idiopathic constipation and associated symptoms in adults, when response to diet and other non-pharmacological measures (e.g. educational measures, physical activity) are inappropriate; and SMC Advice 653/10: Prucalopride (Resolor) – chronic constipation), search on August 29, 2014
- Reference lists of included studies
- Research Papers in Economics (RePEc); https://research.tufts-nemc.org/cear4/Default.aspx, search between August 28–29, 2014
- The Cost-Effectiveness Analysis (CEA) Registry: http://repec.org/docs/RePEcINtro.html, search between August 28–29, 2014
- The EQ-5D website; www.euroqol.org, search between August 28–29, 2014

10.12.6 *The inclusion and exclusion criteria.*

	Description	Justification
Inclusion criteria		
Population	Patients with OIC, regardless of age, gender or race	In line with scope.
Interventions	The SR will not be restricted by any particular intervention	No restriction applied to ensure comprehensive data capture.
Comparators	The SR will not be restricted by any particular comparator	No restriction applied to ensure comprehensive data capture.
Outcomes	The papers with the following HSUV will be included: • Euro-QoL (EQ-5D) • Directly elicited utility scores (TTO, SG)	EQ-5D is the NICE preferred QoL utility tool.
Study design	The SR will not be limited by study design	No restriction applied to ensure comprehensive data capture.
Language restrictions	Only English language papers will be included	English language publications provide adequate data capture.
Publication date	The systematic review will not be restricted by any publication date	No restriction applied to ensure comprehensive data capture.
Exclusion criteria		
Population	Patients without OIC or mixed populations in which outcomes are not reported separately	In line with scope.
Outcomes	Studies reporting only non-HSUV outcomes (e.g. clinical, economic evaluations, costs)	In line with scope.

Abbreviations: TTO, time trade off; SR, systematic review; SG, standard gamble, OIC, opioid-induced constipation; HSUV, health state utility values

10.12.7 *The data abstraction strategy.*

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was abstracted into the STA template/ into a pre-defined Microsoft Excel spreadsheet by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

10.12.8 *Excluded second pass studies.*

Study	Exclusion code	Reason for exclusion
Abramowitz,, 2013	Study design	Validation of methods study
Ahmedzai,, 1995	Outcomes	QoL scores based on EORTC QLQ-C30, not EQ-5D and constipation reported as AE only
Ahmedzai,, 1997	Outcomes	QoL scores based on WHO scale and ECORTC QLQ-C30, not EQ-5D
Allan, 2001	Outcomes	QoL scores based on SF-36, not EQ-5D

Annemans, 2011	Outcomes	No QoL data reported
Ballantyne, 2007	Outcomes	QoL data not reported and constipation reported as AE only
Barrera-Chacon, 2011	Outcomes	Constipation reported as an AE only
Blanco, 2012	Outcomes	QoL data not reported
Bodukam, 2010	Outcomes	QoL data not reported
Bodukam, 2011	Outcomes	QoL scores based on UCLA SCTC GIT 2.0, not EQ-5D
Borggreven, 2007	Outcomes	QoL scores based on EORTC QLQ-C30, not EQ-5D
Breitbart, 1998	Outcomes	QoL score not based on EQ-5D
Bridoux, 2013	Population	Not OIC population
Brunner-La, 2012	Population	Not OIC population
Caissie, 2012	Outcomes	QoL scores based on QLQ-C15-PAL, not EQ-5D
Camps, 2011	Outcomes	Constipation reported as an AE only
Candy, 2011	Outcomes	QoL data not reported
Chancellor, 2010	Outcomes	Constipation related data not reported
Clark, 2014	Population	Not OIC population
Coluzzi, 2014	Study design	Economic study no QoL data reported
Cooley, 2013	Study design	Evaluation of web based service
Coyne, 2014	Outcomes	Baseline data only reported
Dellon, 2013	Population	Not OIC population
Dennison, 2005	Outcomes	Does not report EQ-5Q data
Dunlop, 2013	Outcomes	EQ-5D utility data not reported
Earnshaw, 2010	Outcomes	No original QoL data reported
El, 2010	Outcomes	EQ-5D data not reported
Farmer, 2011	Study design	Review article
Farmer, 2013	Population	Not OIC population
Ferreira, 2009	Outcomes	QoL scores based on EORTC QLQ-C30, not EQ-5D
For, 2014	Duplicate	
Galvez, 2013	Outcomes	EQ-5D data does not report constipation related data
Geels, 2000	Outcomes	QoL scores based on EORTC QLQ-C30, not EQ-5D
Gianesello, 2012	Outcomes	Constipation reported as an AE only
Gourlay, 2001	Outcomes	QoL data not reported
Gupta, 2014	Outcomes	QoL scores based on SF-36v2 and SF-6D, not EQ-5D
Gurland, 2010	Study design	Validation of methods study
Hadley, 2013	Outcomes	QoL data not reported
Hesselbarth, 2014	Population	Not 100% OIC population
Huang, 2012	Population	Not OIC population
Jephcott, 2004	Outcomes	QoL scores based on EORTC QLQ-C30 and EORTC QLQ-CR38, not EQ-5D
Jokinen, 2010	Population	Not OIC population
Jung, 2014	Study design	Validation of methods study
Karlsson, 2009	Outcomes	EQ-5D data not reported
Kerstens, 2011	Population	Not OIC population
Kivitz, 2006	Outcomes	Constipation reported as an AE only

Kuperwasser, 2010	Outcomes	Constipation reported as an AE only
Laugsand, 2010	Outcomes	QoL data not reported
LeeRobichaud, 2011	Population	Not OIC population
Li, 2014	Outcomes	QoL scores based on EORTC QLQ-C30, not EQ-5D
McNicol, 2011	Outcomes	QoL data not reported
Merchant, 2013	Outcomes	Constipation related QoL data based on PAC-SYM, not ED-5D
Milligan, 2001	Outcomes	QoL scores based not SF-36, not EQ-5D and constipation related data reported as an AE only
Mueller-Lissner, 2010	Population	Not OIC population
Mueller-Lissner, 2010	Population	Not OIC population
Muijsers, 2001	Outcomes	QoL scores based on EORTC QLQ-C30, not EQ-5D
Muriel, 2005	Outcomes	Constipation reported as an AE only
Nadstawek, 2008	Outcomes	QoL data not reported
Nadstawek, 2006	Outcomes	EQ-5D data not reported and constipation reported as AE only
Neil, 2013	Outcomes	QoL data not reported and constipation reported as AE only
Palese, 2010	Outcomes	QoL data not reported
Parker, 2011	Population	Not OIC population
Pennant, 2011	Population	Not OIC population
Qian, 2014	Population	Not OIC population
Queralto, 2013	Population	Not OIC population
Radford, 2014	Population	Not OIC population
Rajindrajith, 2013	Population	Not OIC population
Rauck, 2013	Outcomes	QoL data not reported
Rentz, 2011	Study design	Validation of methods study
SchmidtHansen, 2013	Study design	Protocol only, no QoL data reported
Shariff, 2009	Population	Not OIC population
Sima, 2010	Outcomes	QoL scores based on SF-6D, not EQ-5D
Speed, 2010	Population	Not OIC population
Sun, 2011	Outcomes	QoL scores based on SF-12v2, not EQ-5D.
Tanikella, 2010	Population	Not OIC population
Ten, 2006	Population	Not OIC population
Van Op Den Bosch, 2014	Outcomes	No utility data reported
Velazquez, 2012	Population	Not 100% OIC population
Wald, 2007	Population	Not OIC population
Wang, 2009	Population	Not OIC population
Wang, 2013	Population	Not OIC population
Watson, 2009	Outcomes	Constipation reported as an AE only
Watson,, 2012	Outcomes	QoL data based on SF12v2, not EQ-5D
Watson, 2010	Outcomes	QoL data based on SF12v2, not EQ-5D
Woodward, 2014	Population	Not OIC population
Wu, 2013	Outcomes	No relevant data reported
Zhao, 2012	Outcomes	Constipation related QoL data not reported

Zheng, 2013	Population	Not OIC population
Zugazabeitia, 2013	Outcomes	Constipation QoL data not reported

Abbreviations: AE, averse event; EQ-5D, EuroQoL 5 dimension; OIC, opioid-induced constipation; PAC-SYM, Patient Assessment of Constipation Symptoms; QoL, quality of life; SF-36, Short form 36 health survey; WHO scale, World Health Organisation Scale.

10.13 *Appendix 13: Resource identification, measurement and valuation (section 7.5)*

No systematic research search for resource use was completed. Clinicians were consulted to estimate the resource use associated with the management of constipation and associated adverse events for use in the economic model.

10.14 *Appendix14: Methodology of 29 clinician survey*

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10.17 *Appendix 16: KODIAC 4 and 5, ITT analysis set results*

Time to first post-dose SBM without the use of rescue medication within the last 24 hours

In KODIAC 4, the time to first post-dose SBM was statistically significantly shorter for both the naloxegol 12.5 mg and 25 mg groups compared with placebo (p<0.001 for both comparisons). Both treatment groups had a shorter median time to first post-dose SBM compared with placebo (20.4, 5.9, and 35.8 hours, respectively) (section 6.5).

In KODIAC 5, a significantly shorter time to first post-dose SBM was achieved in the naloxegol 12.5 mg and 25 mg groups vs placebo (p<0.001 for both comparisons). However, this improvement was not considered to be statistically significant when the multiple testing procedure was applied, although the nominal unadjusted p values are presented. As shown in Table 153, the median time to first post-dose SBM was shorter in the naloxegol 12.5 mg and 25 mg groups compared with placebo (19.3, 12.0, and 37.2 hours, respectively).

In both studies, Kaplan-Meier curves showed a clear separation between the naloxegol 12.5 mg and 25 mg groups and placebo indicating a clinically relevant improvement with naloxegol treatment (Figure 58 and Figure 59).

Mean number of days/week with ≥1 SBM

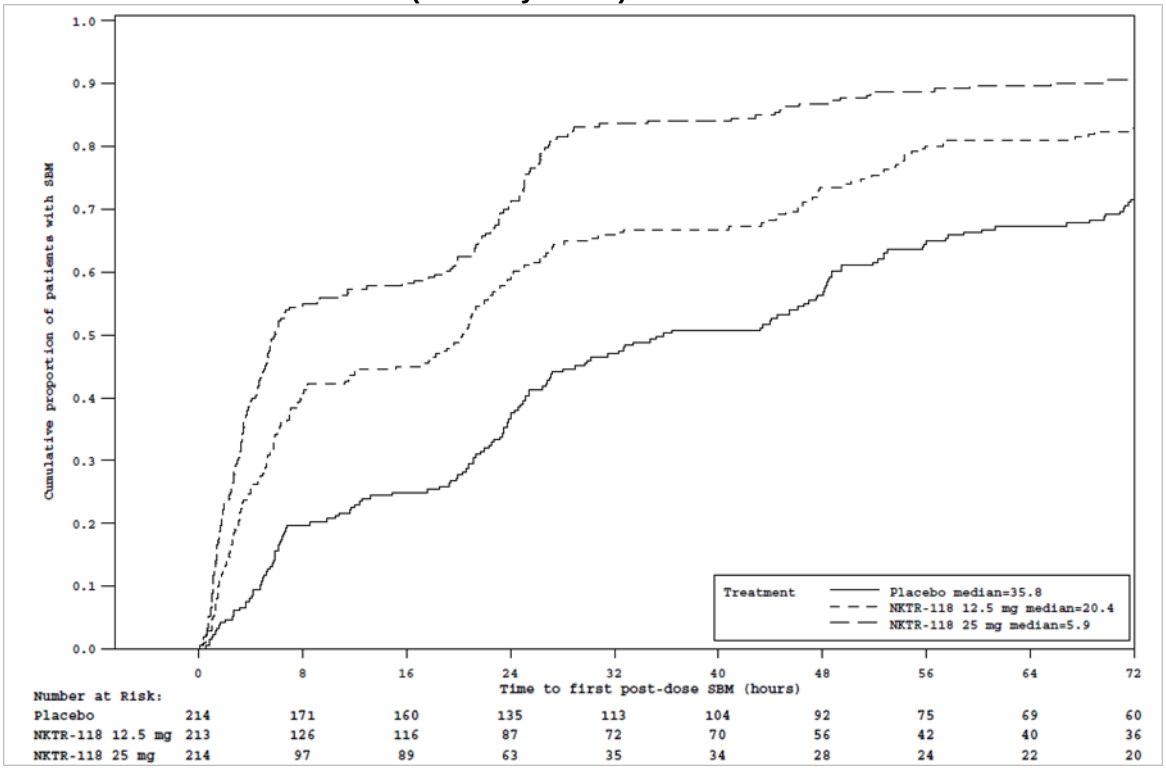
From Weeks 1–12 in KODIAC 4, there was a statistically significant increase in the mean number of days/week with ≥1 SBM in the naloxegol 12.5 mg and 25 mg groups compared with placebo (0.55; p<0.001 and 0.82; p<0.001, respectively) (Table 153). In KODIAC 5, there was a statistically significant increase in the mean number of days/week with ≥1 SBM in the naloxegol 25 mg group compared with placebo (0.68;p<0.001) from Weeks 1–12 (Table 153). In KODIAC 5, while there was an increase in the mean number of days/week with ≥ 1 SBM in the naloxegol 12.5 mg group compared with placebo (0.39; p=0.010), this increase was not considered to be statistically significant when the multiple testing procedure was applied.

Table 153: Key secondary outcomes in KODIAC 4 and KODIAC 5 (ITT analysis set)

Outcome	KODIAC 4			KODIAC 5		
	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo
Time to first post-dose SBM (ITT analysis set)						
Number of patients (n)	213	214	214	232	232	232
Median time to first SBM, hours, (95% CI)	20.4 (11.5, 22.7)	5.9 (4.8, 11.5)	35.8 (27.0, 48.1)	19.3 (9.4,22.3)	12.0 (7.0,21.5)	37.2 (30.0,46.9)
Patient with SBM by ≤6 hours (%)	72 (33.8)	109 (50.9)	33 (15.4)	80 (34.5)	91 (39.2)	40 (17.2)
Patient with SBM by ≤12 hours (%)	93 (43.7)	122 (57.0)	49 (22.9)	102 (44.0)	115 (49.6)	57 (24.6)
Patient with SBM by ≤24 hours (%)	125 (58.7)	150 (70.1)	79 (36.9)	136 (58.6)	142 (61.2)	85 (36.6)
Change from baseline in mean number of days/week with ≥1 SBM for Weeks 1–12 (ITT analysis set)						
Number of patients (n)	211	212	211	228	226	231
Least square means (SEM)	2.21 (0.13)	2.48 (0.13)	1.66 (0.13)	2.12 (0.12)	2.41 (0.13)	1.73 (0.12)
Least square mean (difference vs placebo)‡	0.55	0.82	N/A	0.39	0.68	N/A
95% CI	(0.24, 0.86)	(0.51, 1.13)	N/A	(0.09, 0.69)	(0.37, 0.98)	N/A
p value	<0.001*	<0.001*	N/A	0.010	<0.001*	N/A

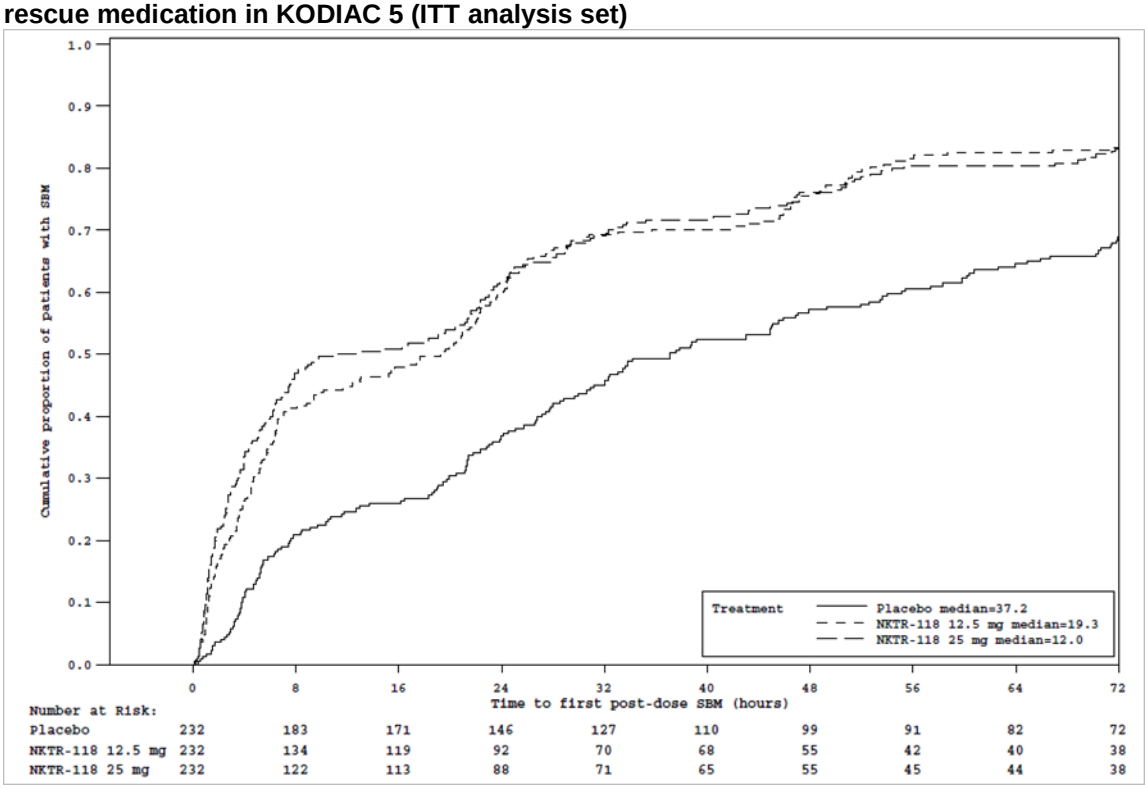
Abbreviations: CI, confidence interval; ITT, intent-to-treat; N/A, not applicable; RR, relative risk; SBM, spontaneous bowel movement; SEM, standard error of the mean.
†Analysed using the Chi-square test.
‡Analysis via MMRM with fixed effects for baseline, baseline laxative response, treatment and treatment time interaction. Study pooled centre is included as a random effect.
* Statistically significant under the multiple testing procedure

Figure 58: Kaplan-Meier curve of comparison to first post-dose SBM without the use of rescue medication in KODIAC 4 (ITT analysis set)



Source: KODIAC 4 CSR (51)

Figure 59: Kaplan-Meier curve of comparison to first post-dose SBM without the use of rescue medication in KODIAC 5 (ITT analysis set)



Source: KODIAC 5 CSR (52)

Other secondary efficacy results: ITT analysis set

Assessment of response incorporating symptom data

Based on advice from the CHMP (Scientific Advice Letter, July 2011) that improvement of OIC symptoms are an important outcome when assessing the success of a treatment for the condition, an additional supporting analysis was conducted which used a definition of responder that takes symptoms into account. In addition to the definition of response for the primary outcome, patients were required to demonstrate symptom improvement and no clinically relevant symptom deterioration during the study period of KODIAC 4 and 5. Symptom improvement/deterioration was defined as meeting ≥1 of the following criteria (based on the mean change from baseline over the 12 week treatment period):

- Improvement/worsening from baseline in mean BSS by ≥1 point
- Improvement/worsening from baseline in mean straining score by ≥0.5 points
- Improvement/worsening from baseline in mean number of days/week with ≥1 complete SBM by ≥1 day

In both studies, analysis of response incorporating symptom data supported the statistically significant improvements observed for the primary endpoint for the naloxegol 25 mg treatment groups compared with the placebo groups (p=0.003 and p=0.006 for KODIAC 4 and 5, respectively) (Table 154).

Table 154: Analysis of response rate incorporating symptom data for Weeks 1–12 in KODIAC 4 and KODIAC 5 (ITT analysis set)

Outcome	KODIAC 4			KODIAC 5		
	Naloxegol 12.5 mg n=213	Naloxegol 25 mg n=214	Placebo n=214	Naloxegol 12.5 mg n=232	Naloxegol 25 mg n=232	Placebo n=232
n (%) of patients responding	71 (33.3)	83 (38.8)	54 (25.2)	65 (28.0)	80 (34.5)	53 (22.8)
RR (comparison vs placebo)†	1.312	1.538	N/A	1.221	1.499	N/A
95% CI	0.974, 1.768	1.156, 2.046	N/A	0.894, 1.669	1.117, 2.012	N/A
p value	0.072	0.003	N/A	0.209	0.006	N/A

Abbreviations: CI, confidence interval; N/A, not applicable; RR, relative risk.
†Analysed using the Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR)
Source: Naloxegol summary of clinical efficacy. Data on file (67)

OIC symptom-related secondary outcomes (ITT analysis set)

In KODIAC 4 and 5, naloxegol treatment was associated with improvements versus placebo in other secondary outcomes as presented in Table 155. In both studies, there was a greater improvement in the degree of straining from baseline in patients receiving naloxegol 12.5 mg and 25 mg compared with placebo: -0.73 (0.05), -0.64 (0.05), and -0.54 (0.05) for the 25 mg, 12.5 mg, and placebo groups in KODIAC 4, respectively; and -0.80 (0.06), -0.67 (0.06), and -0.48 (0.06) for the 25 mg, 12.5 mg, and placebo groups in KODIAC 5, respectively.

In both studies, an improvement in Bristol Stool Scale (BSS) ratings was observed in patients receiving naloxegol 25 mg compared with placebo (p=0.042 in KODIAC 4, and p<0.001 in KODIAC 5). In the KODIAC 4 study, the naloxegol 12.5 mg group showed a similar improvement in BSS ratings to that observed in the placebo group while in KODIAC 5, the 12.5 mg group showed a significantly greater improvement in BSS ratings compared with placebo (p=0.001).

In KODIAC 4, the naloxegol 25 mg group showed an increase in the percent number of days with a complete SBM/week vs placebo (p<0.001), while a small increase was observed in the 12.5 mg treatment group vs placebo (p=0.094). An increase in the percent number of days with a complete SBM /week was observed in both the naloxegol 12.5 mg and the 25 mg groups compared with placebo in the KODIAC 5 study (p=0.002 and p<0.001, respectively).

In both studies, the use of rescue medication was low over the 12 week treatment period. In KODIAC 4, the mean weekly bisacodyl dose was 5.9 mg, 5.8 mg, and 10.3 mg in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively. In the naloxegol 12.5 mg and 25 mg groups, 63.4% and 54.7% of patients used bisacodyl at least once compared with 72.0% of placebo patients. The number of patients that that used an enema ≥1 times during the study was low in the ITT analysis set and similar across treatment groups; 3, 5 and 6 patients in the naloxegol 12.5 mg, 25 mg and placebo groups used an enema once during the treatment period.

In KODIAC 5, the mean weekly bisacodyl dose for the naloxegol 12.5 mg, 25 mg and placebo groups was 6.1 mg, 6.6 mg, and 7.9 mg, respectively. The proportions of patents that used bisacodyl at least once were 57.3%, 57.3%, and 70.7% in the naloxegol 12.5 mg, 25 mg, and placebo groups, respectively. As observed in KODIAC 4, the number of patients that used an enema ≥1 times during the treatment period was low in the ITT analysis set; 4, 2, and 5 patients in the naloxegol 12.5 mg, 25 mg and placebo groups, respectively.

Patient-reported outcomes (ITT analysis set)

In KODIAC 4, patients in the naloxegol 12.5 mg and 25 mg groups showed numerically greater changes from baseline in the severity of constipation symptoms in the Patient Assessment of Constipation Symptoms (PAC-SYM) domains of total score, rectal symptoms and stool symptoms. Changes from baseline in the severity of abdominal symptoms sub-scores were comparable across treatment groups.

In KODIAC 5, numerically greater improvements in PAC-SYM scores were observed in the naloxegol 12.5 mg and 25 mg groups compared with placebo, with the largest differences seen in the stool symptoms domain (12.5 mg, p=0.002; 25 mg, p<0.001).

In both KODIAC 4 and 5, the average baseline value for the satisfaction domain score of the Patient Assessment of Constipation Quality of Life (PAC-QoL) questionnaire described patients as being only “a little satisfied with their bowel function”. At Week 12 in KODIAC 4, there were no differences in the change from baseline in the satisfaction domain of the PAC-QoL between treatment groups. In KODIAC 5, the change from baseline in the patients satisfaction domain of the PAC-QoL was numerically greater for the naloxegol 12.5 mg and 25 mg groups compared with placebo at Week 12 (p=0.011 ad p<0.001, respectively). In both studies, changes from baseline in the PAC-QoL

domains of total score, physical discomfort, psychosocial discomfort and worries and concerns were comparable with placebo and were not formally analysed.

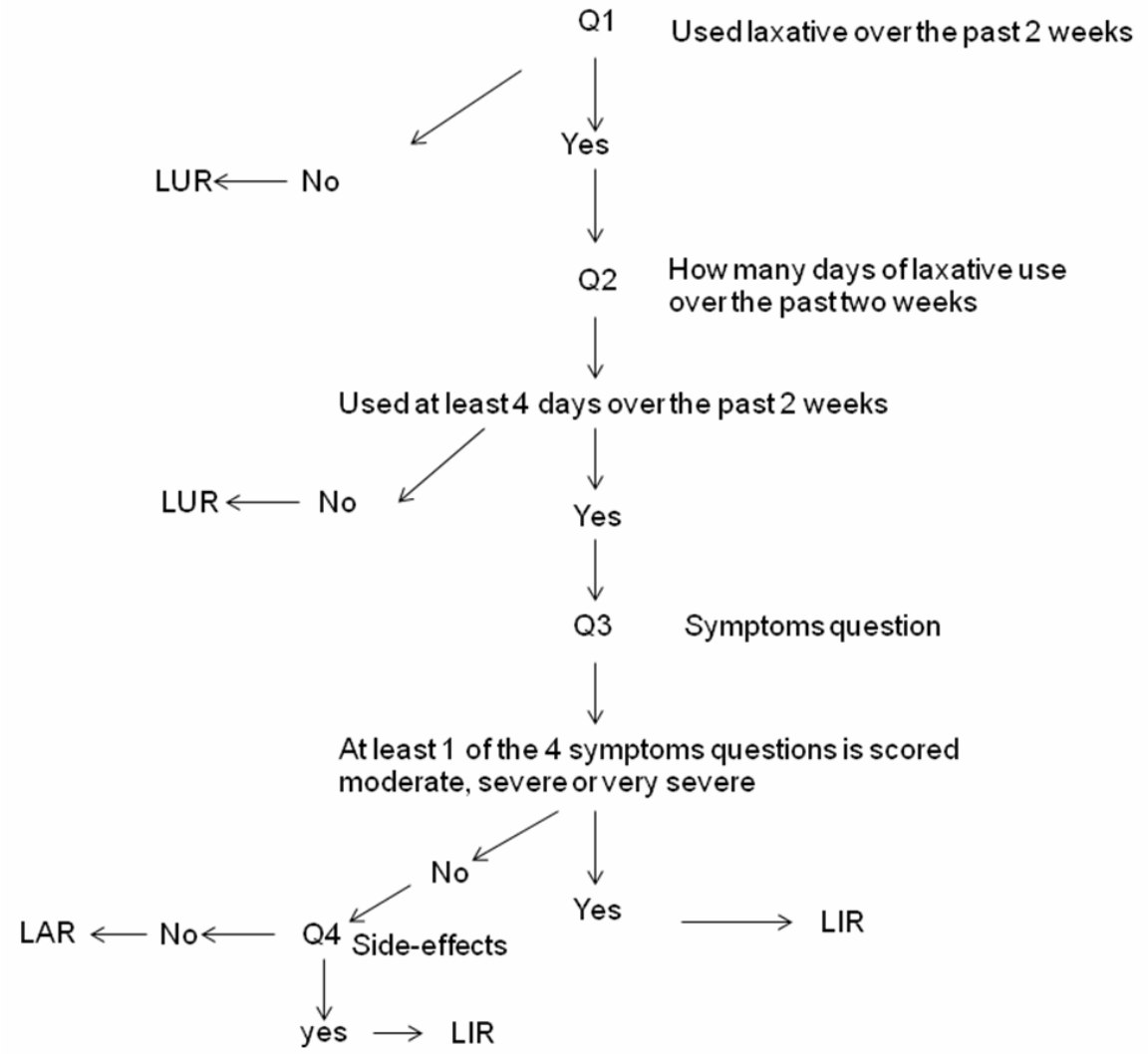
Table 155: OIC symptom-related secondary outcomes from Weeks 1–12 in KODIAC 4 and KODIAC 5 (ITT analysis set)

Outcome	KODIAC 4			KODIAC 5		
	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo
Change from baseline in mean degree of straining/week (ITT analysis set)						
Number of patients (n)	211	212	211	228	226	231
Least square means (SEM)	-0.64 (0.05)	-0.73 (0.05)	-0.54 (0.05)	-0.67 (0.06)	-0.80 (0.06)	-0.48 (0.06)
Least square mean (difference vs placebo)†	-0.09	-0.18	N/A	-0.19	-0.32	N/A
95% CI	(-0.23, 0.04)	(-0.32, -0.05)	N/A	(-0.32, -0.06)	(-0.45, -0.18)	N/A
p value	0.176	0.008	N/A	0.005	<0.001	N/A
Change from baseline in mean stool consistency/week (ITT analysis set)						
Number of patients (n)	211	212	211	228	226	231
Least square means (SEM)	0.53 (0.07)	0.66 (0.07)	0.47 (0.07)	0.54 (0.07)	0.71 (0.07)	0.26 (0.06)
Least square mean (difference vs placebo)†	0.05	0.18	N/A	0.28	0.45	N/A
95% CI	(-0.12, 0.23)	(0.01, 0.36)	N/A	(0.12, 0.45)	(0.29, 0.62)	N/A
p value	0.564	0.042	N/A	0.001	<0.001	N/A
Change from baseline in percent days/week with a complete SBM (ITT analysis set)						
Number of patients (n)	211	212	211	228	226	231
Least square means (SEM)	22.31 (1.73)	27.04 (1.75)	18.45 (1.72)	23.48 (1.88)	27.20 (1.93)	16.76 (1.86)
Least square mean (difference vs placebo)†	3.87	8.59	N/A	6.72	10.43	N/A
95% CI	(-0.66, 8.39)	(4.04, 13.14)	N/A	(2.37, 11.06)	(6.03, 14.84)	N/A
p value	0.094	<0.001	N/A	0.002	<0.001	N/A

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N/A, not applicable; SBM, spontaneous bowel movement; SEM, standard error of the mean.
†Analysis via MMRM with fixed effects for baseline, baseline laxative response (LIR, non-LIR), treatment and treatment time interaction. Study pooled centre is included as a random effect.

10.18 *Appendix 17: Guidelines for determination of laxative response status*

Figure 60: Determination of laxative response status



Abbreviations: LAR, laxative adequate responder; LIR, laxative inadequate responder; LUR, laxative unknown responder.

10.19 *Appendix 18: OpenBUGS model for the MTC analysis (section 6.7.5)*

OpenBUGS Model: Odds Ratios

```
#Random effects model
model{
for (i in 1:ns){                # ns = Number of studies
 w[i,1] <-0
            delta[i,1]<-0      # treatment effect is zero for control arm
            for (k in 1:na[i]) { # Loop through arms within studies (na[i] = # arms in study [i]
            Outcome[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
                                 logit(p[i,k])<-mu[i] + delta[i,k]
                        }
# Adjustment for multi-arm trials
                        for (k in 2:na[i]) {
 delta[i,k] ~ dnorm(md[i,k],taud[i,k])
 md[i,k] <- dd[ntreat[i,k]] - dd[ntreat[i,1]] + sw[i,k]

 taud[i,k] <- prec*2*(k-1)/k
 w[i,k] <- (delta[i,k] - dd[ntreat[i,k]] + dd[ntreat[i,1]])
 sw[i,k] <-sum(w[i,1:k-1])/(k-1) }              }

#Give priors for treatment effects -- nt = number of treatments
            dd[1]<-0
            for (k in 2:nt){dd[k] ~ dnorm(0,0.0001) }

tau<-1/prec
tau.sqrt<-sqrt(tau)
prec <- 1/(sd*sd)
sd ~ dunif(0,1) # Prior for random-effects variance of treatment effects

# Unconstrained baseline effect (study-specific baselines)
 for (j in 1:ns) {
 mu[j] ~ dnorm(0.0,0.0001)          }

#All pairwise log odds ratios and odds ratios, as well as probability that a given log-odds ratio is
greater than 0.
for (c in 1:nt-1){
            for (k in (c+1):nt){
 lor[c,k] <- dd[k] - dd[c]
                        log(or[c,k]) <- lor[c,k]
                        lorprob[c,k] <- step(lor[c,k])
                        }
            }
}
```

OpenBUGS Model: Mean Differences

```
#Random effects model
model{
for (i in 1:ns){                # ns = Number of studies
 w[i,1] <-0
            delta[i,1]<-0      # treatment effect is zero for control arm
            for (k in 1:na[i]) { # Loop through arms within studies (na[i] = # arms in study [i]
                        prec.Outcome[i,k] <- n[i,k]/Outcome.var[i,k]
                        Outcome[i,k]~dnorm(theta[i,k],prec.Outcome[i,k])
            theta[i,k]<-mu[i] + delta[i,k]
                        }
# Adjustment for multi-arm trials
                         for (k in 2:na[i]) {
 delta[i,k] ~ dnorm(md[i,k],taud[i,k])
 md[i,k] <- dd[ntreat[i,k]] - dd[ntreat[i,1]] + sw[i,k]

 taud[i,k] <- prec*2*(k-1)/k
 w[i,k] <- (delta[i,k] - dd[ntreat[i,k]] + dd[ntreat[i,1]])
 sw[i,k] <-sum(w[i,1:k-1])/(k-1) }              }

#Give priors for treatment effects -- nt = number of treatments
            dd[1]<-0
            for (k in 2:nt){dd[k] ~ dnorm(0,0.0001) }

tau<-1/prec
tau.sqrt<-sqrt(tau)
prec <- 1/(sd*sd)
sd ~ dunif(0,XXX) # Prior for random-effects variance of treatment effects (XXX used is twice the
                                median within-subject SD across the trials)

# Unconstrained baseline effect (study-specific baselines)
 for (j in 1:ns) {
 mu[j] ~ dnorm(0.0,0.0001)          }

#All pairwise mean differences, as well as probability that a given mean difference is greater than
0.
for (c in 1:nt-1){
            for (k in (c+1):nt){
                        meandif[c,k] <- dd[k] - dd[c]
                        meandifprob[c,k] <- step([c,k])                }
            }
}
```

10.20 *Appendix 19: Square output tables of the MTC analysis*

Table 156–Table 167 are designed to provide all results from each MTC in the base-case analysis and are presented by outcome. These tables can be interpreted as the comparison between each row and column. As an example, in Table 156, in the second row and first column, the mean difference is 0.8 [95% CrI: 0.37, 1.22]. This value can be read as naloxegol 12.5 mg compared with placebo, and it indicates that naloxegol had fewer SBMs per week than placebo.

Table 156: Bayesian MTC results grid for the mean change in SBMs from baseline to the average over four weeks in the anticipated licensed population (mean difference [95% CrI])

Placebo							
0.79 [-0.67, 2.23]	**Naloxegol (12.5 mg)**						
1.85 [0.34, 3.33]	1.05 [-0.43, 2.48]	**Naloxegol (25 mg)**					
1.6 [-0.48, 3.6]	0.8 [-1.74, 3.33]	-0.25 [-2.84, 2.29]	**Methylnaltrexone (12 mg OD)**				
0.16 [-1.82, 2.17]	-0.63 [-3.07, 1.9]	-1.68 [-4.13, 0.87]	-1.43 [-4.28, 1.46]	**Methylnaltrexone (150 mg OD)**			
0.67 [-1.38, 2.75]	-0.12 [-2.62, 2.4]	-1.17 [-3.63, 1.37]	-0.93 [-3.75, 1.99]	0.51 [-1.52, 2.53]	**Methylnaltrexone (300 mg OD)**		
0.68 [-1.34, 2.72]	-0.11 [-2.55, 2.37]	-1.17 [-3.63, 1.36]	-0.92 [-3.73, 1.94]	0.52 [-1.5, 2.55]	0.01 [-2, 1.99]	**Methylnaltrexone (450 mg OD)**	
0.59 [-1.43, 2.62]	-0.2 [-2.7, 2.33]	-1.26 [-3.76, 1.32]	-1.01 [-3.02, 1.1]	0.43 [-2.45, 3.27]	-0.08 [-2.96, 2.76]	-0.09 [-2.95, 2.79]	**Methylnaltrexone (12 mg QAD)**

Abbreviations: OD, once daily; QAD, every other day.

Table 157: Bayesian MTC results grid for the mean change in SBMs from baseline to the average over four to twelve weeks in the anticipated licensed population (mean difference [95% CrI])

Placebo							
0.55 [-0.81, 1.96]	**Naloxegol (12.5 mg)**						
1.46 [0.02, 2.93]	0.91 [-0.51, 2.33]	**Naloxegol (25 mg)**					
1.6 [-0.41, 3.54]	1.05 [-1.39, 3.48]	0.13 [-2.29, 2.59]	**Methylnaltrexone (12 mg OD)**				
0.17 [-1.77, 2.15]	-0.37 [-2.8, 2.08]	-1.28 [-3.77, 1.16]	-1.42 [-4.23, 1.39]	**Methylnaltrexone (150 mg OD)**			
0.69 [-1.31, 2.71]	0.14 [-2.25, 2.56]	-0.76 [-3.27, 1.7]	-0.91 [-3.73, 1.9]	0.51 [-1.46, 2.46]	**Methylnaltrexone (300 mg OD)**		
0.68 [-1.32, 2.67]	0.14 [-2.26, 2.54]	-0.77 [-3.22, 1.64]	-0.91 [-3.77, 1.96]	0.52 [-1.48, 2.48]	0 [-1.96, 1.98]	**Methylnaltrexone (450 mg OD)**	
0.61 [-1.36, 2.58]	0.05 [-2.4, 2.48]	-0.85 [-3.35, 1.61]	-1 [-3, 1]	0.43 [-2.4, 3.29]	-0.08 [-2.96, 2.73]	-0.08 [-2.9, 2.73]	**Methylnaltrexone (12 mg QAD)**

Abbreviations: OD, once daily; QAD, every other day.

Table 158: Bayesian MTC results grid for the proportion of patients with SBM response in the anticipated licensed population (median OR [95% CrI])

Placebo				
1.98 [0.98, 4.06]	**Naloxegol (12.5mg)**			
1.88 [0.93, 3.78]	0.95 [0.47, 1.9]	**Naloxegol (25mg)**		
2.33 [0.91, 5.95]	1.18 [0.35, 3.78]	1.24 [0.38, 3.92]	**Methylnaltrexone (12mg OD)**	
1.36 [0.51, 3.46]	0.69 [0.2, 2.22]	0.73 [0.22, 2.34]	0.58 [0.22, 1.51]	**Methylnaltrexone (12mg QAD)**

Abbreviations: CrL, credible interval; OD, once daily; QAD, every other day.

Table 159: Bayesian MTC results grid for the proportion of patients with CSBM response in the anticipated licensed population (median OR [95% CrI])

Placebo		
2.78 [1.61, 4.83]	**Naloxone PR (FRC OD)**	
2.42 [1.25, 4.74]	0.87 [0.38, 2.11]	**Naloxegol (25mg)**

Abbreviations: FRC, fixed ration combination; OD, once daily.

Table 160: Bayesian MTC results grid for the proportion of patients with DAEs in the anticipated licensed population (median OR [95% CrI])

Placebo								
0.72 [0.26, 2.38]	**Naloxone PR (FRC OD)**							
0.66 [0.18, 2.21]	0.9 [0.15, 4.36]	**Naloxegol (12.5mg)**						
2.13 [0.71, 6.57]	2.97 [0.59, 13.14]	3.26 [1.06, 11.35]	**Naloxegol (25mg)**					
2.93 [0.59, 16.49]	4.08 [0.54, 28.79]	4.42 [0.61, 39.37]	1.36 [0.19, 10.88]	**Methylnaltrexone (12mg OD)**				
6.86 [0.68, 205.82]	9.5 [0.69, 323.44]	10.85 [0.73, 401.02]	3.23 [0.25, 117.45]	2.33 [0.13, 98.1]	**Naloxone (10mg BD)**			
8.75 [0.87, 246.41]	11.87 [0.92, 395.05]	13.74 [0.92, 474.38]	4.13 [0.31, 136.46]	2.95 [0.16, 119.58]	1.24 [0.22, 7.34]	**Naloxone (20mg BD)**		
14.44 [1.56, 407.08]	20.09 [1.59, 642.26]	22.69 [1.62, 817.29]	6.82 [0.54, 224.75]	4.97 [0.29, 199.74]	2.06 [0.4, 11.72]	1.66 [0.33, 8.46]	**Naloxone (40mg BD)**	
3.93 [0.84, 21.74]	5.5 [0.76, 38.9]	6 [0.81, 52.51]	1.86 [0.27, 14.44]	1.36 [0.31, 5.91]	0.58 [0.01, 10.62]	0.45 [0.01, 7.97]	0.27 [0.01, 4.67]	**Methylnaltrexone (12mg QAD)**

Abbreviations: FRC, fixed ratio combination; OD, once daily; QAD, every other day.

Table 161: Bayesian MTC results grid for the proportion of patients with TEAEs in the anticipated licensed population (median OR [95% CrI])

Placebo				
1.06 [0.53, 2.13]	**Naloxegol (12.5mg)**			
1.98 [0.99, 3.99]	1.87 [0.94, 3.72]	**Naloxegol (25mg)**		
1.56 [0.6, 4.03]	1.48 [0.46, 4.73]	0.79 [0.24, 2.52]	**Methylnaltrexone (12mg OD)**	
1.33 [0.52, 3.4]	1.26 [0.39, 3.99]	0.68 [0.21, 2.16]	0.85 [0.33, 2.2]	**Methylnaltrexone (12mg QAD)**

Abbreviations: OD, once daily; QAD, every other day.

Table 162: Bayesian MTC results grid for the mean change in SBMs from baseline to the average over four weeks in the anticipated licensed population + Step 3 opioids (mean difference [95% CrI])

Placebo							
1.08 [-0.78, 2.92]	**Naloxegol (12.5 mg)**						
2.29 [0.43, 4.16]	1.2 [-0.63, 3.06]	**Naloxegol (25 mg)**					
1.6 [-1.02, 4.17]	0.51 [-2.7, 3.75]	-0.68 [-3.89, 2.52]	**Methylnaltrexone (12 mg OD)**				
0.17 [-2.35, 2.78]	-0.91 [-4, 2.31]	-2.12 [-5.29, 1.12]	-1.43 [-5.08, 2.28]	**Methylnaltrexone (150 mg OD)**			
0.69 [-1.82, 3.3]	-0.4 [-3.5, 2.78]	-1.6 [-4.77, 1.64]	-0.91 [-4.58, 2.85]	0.51 [-2.08, 3.06]	**Methylnaltrexone (300 mg OD)**		
0.68 [-1.88, 3.33]	-0.4 [-3.52, 2.82]	-1.6 [-4.75, 1.62]	-0.91 [-4.56, 2.9]	0.52 [-2.05, 3.11]	0 [-2.54, 2.65]	**Methylnaltrexone (450 mg OD)**	
0.6 [-2.05, 3.14]	-0.5 [-3.7, 2.65]	-1.69 [-4.91, 1.51]	-1.01 [-3.57, 1.6]	0.43 [-3.31, 4.03]	-0.08 [-3.86, 3.53]	-0.09 [-3.87, 3.54]	**Methylnaltrexone (12 mg QAD)**

Abbreviations: OD, once daily; QAD, every other day.

Table 163: Bayesian MTC results grid for the mean change in SBMs from baseline to the average over four to twelve weeks in the anticipated licensed population + Step 3 opioids (mean difference [95% CrI])

Placebo							
0.78 [-1.06, 2.7]	**Naloxegol (12.5 mg)**						
1.93 [0.06, 3.85]	1.14 [-0.76, 3.07]	**Naloxegol (25 mg)**					
1.6 [-1.06, 4.23]	0.82 [-2.49, 4.02]	-0.33 [-3.61, 2.93]	**Methylnaltrexone (12 mg OD)**				
0.17 [-2.45, 2.79]	-0.62 [-3.85, 2.54]	-1.76 [-5.09, 1.48]	-1.43 [-5.19, 2.26]	**Methylnaltrexone (150 mg OD)**			
0.68 [-2, 3.34]	-0.1 [-3.38, 3.07]	-1.25 [-4.52, 2.03]	-0.91 [-4.63, 2.85]	0.51 [-2.09, 3.18]	**Methylnaltrexone (300 mg OD)**		
0.68 [-1.97, 3.31]	-0.1 [-3.33, 3.1]	-1.25 [-4.52, 1.98]	-0.91 [-4.66, 2.96]	0.52 [-2.08, 3.19]	0 [-2.63, 2.63]	**Methylnaltrexone (450 mg OD)**	
0.6 [-2.05, 3.29]	-0.19 [-3.47, 3.1]	-1.33 [-4.67, 2]	-1 [-3.65, 1.7]	0.43 [-3.34, 4.21]	-0.09 [-3.88, 3.69]	-0.09 [-3.88, 3.66]	**Methylnaltrexone (12 mg QAD)**

Abbreviations: OD, once daily; QAD, every other day.

Table 164: Bayesian MTC Results Grid for the Proportion of Patients with SBM Response in the LIR with Step 3 Opioids Population (Median OR [95% CrI])

Placebo				
2.62 [1.13, 6.13]	**Naloxegol (12.5mg)**			
2.65 [1.15, 6.19]	1.01 [0.45, 2.3]	**Naloxegol (25mg)**		
2.3 [0.76, 6.97]	0.87 [0.22, 3.42]	0.86 [0.21, 3.45]	**Methylnaltrexone (12mg OD)**	
1.33 [0.44, 4.06]	0.51 [0.13, 2.02]	0.5 [0.12, 1.99]	0.58 [0.19, 1.75]	**Methylnaltrexone (12mg QAD)**

Abbreviations: OD, once daily; QAD, every other day.

Table 165: Bayesian MTC results grid for the proportion of patients with CSBM response in the anticipated licensed population + Step 3 opioids (median OR [95% CrI])

Placebo		
2.81 [1.63, 4.73]	**Naloxone PR (FRC OD)**	
3.92 [1.94, 8.05]	1.39 [0.59, 3.5]	**Naloxegol (25mg)**

Abbreviations: OD, once daily.

Table 166: Bayesian MTC results grid for the proportion of patients with DAEs in the anticipated licensed population + Step 3 Opioids (median OR [95% CrI])

Placebo								
0.73 [0.26, 2.36]	**Naloxone PR (FRC OD)**							
0.6 [0.13, 2.58]	0.82 [0.12, 4.8]	**Naloxegol (12.5mg)**						
3.01 [0.96, 10.33]	4.17 [0.79, 19.69]	5.02 [1.41, 20.21]	**Naloxegol (25mg)**					
3.01 [0.6, 17.81]	4.14 [0.55, 31.28]	5.18 [0.57, 51.68]	1 [0.13, 8.38]	**Methylnaltrexone (12mg OD)**				
7.65 [0.71, 270.43]	10.64 [0.73, 402.62]	12.82 [0.81, 547.85]	2.49 [0.18, 101.49]	2.56 [0.13, 123.97]	**Naloxone (10mg BD)**			
9.62 [0.9, 309.51]	13.32 [0.91, 498.7]	16.25 [1.02, 717.66]	3.13 [0.22, 129.15]	3.25 [0.16, 160.61]	1.27 [0.22, 7.06]	**Naloxone (20mg BD)**		
16.2 [1.66, 535.39]	22.31 [1.69, 793.93]	26.9 [1.76, 1167.94]	5.28 [0.4, 213.15]	5.46 [0.3, 264.28]	2.16 [0.41, 11.46]	1.7 [0.34, 8.59]	**Naloxone (40mg BD)**	
4.07 [0.83, 23.45]	5.7 [0.76, 41.85]	6.95 [0.78, 69.2]	1.35 [0.18, 11.21]	1.35 [0.32, 5.91]	0.52 [0.01, 10.26]	0.42 [0.01, 8.41]	0.25 [0.01, 4.53]	**Methylnaltrexone (12mg QAD)**

Abbreviations: BD, twice daily; FRC, fixed ratio combination; OD, once daily; QAD, every other day.

Table 167: Bayesian MTC results grid for the proportion of patients with TEAEs in the anticipated licensed population + Step 3 opioids (median OR [95% CrI])

Placebo				
1.11 [0.46, 2.67]	**Naloxegol (12.5mg)**			
2.16 [0.91, 5.11]	1.95 [0.82, 4.61]	**Naloxegol (25mg)**		
1.58 [0.5, 5.11]	1.42 [0.33, 6.08]	0.73 [0.17, 3.13]	**Methylnaltrexone (12mg OD)**	
1.33 [0.42, 4.3]	1.2 [0.29, 5.29]	0.62 [0.15, 2.64]	0.85 [0.27, 2.73]	**Methylnaltrexone (12mg QAD)**

Abbreviations: OD, once daily; QAD, every other day.

10.21 *Appendix 20: Random and fixed effects model results for the MTC and direct meta-analysis*

The Bayesian MTC results for the random effects model are presented in Table 168–Table 179. Results are presented by evaluated outcome. Comparisons with placebo are presented first followed by comparisons for naloxegol 12.5 or 25 mg with other treatments.

Table 168: Bayesian MTC results for the mean change in SBMs per week from baseline to average over 4 weeks in the anticipated licensed population

				Placebo SBMs Median % [95% CrI]	
Random	---			1.70 [1.51, 1.87]	---
Fixed	---			1.69 [1.51, 1.87]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients Evaluated**	**Active Treatment Median SBMs [95% CrI]**	**Mean Difference [95% CrI]**
Random	Naloxegol 12.5 mg vs. placebo	2	240	2.49 [1.02, 3.92]	0.79 [-0.67, 2.24]
Fixed	Naloxegol 12.5 mg vs. placebo	2	240	2.49 [2.11, 2.87]	0.79 [0.37, 1.22]
Random	Naloxegol 25 mg vs. placebo	2	241	3.54 [2.03, 5.02]	1.85 [0.34, 3.33]
Fixed	Naloxegol 25 mg vs. placebo	2	241	3.54 [3.08, 3.99]	1.85 [1.35, 2.33]
Random	Methylnaltrexone 12 mg OD vs. placebo	1	150	3.29 [1.21, 5.31]	1.60 [-0.48, 3.60]
Fixed	Methylnaltrexone 12 mg OD vs. placebo	1	150	3.29 [2.79, 3.79]	1.60 [1.06, 2.14]
Random	Methylnaltrexone 12 mg QAD vs. placebo	1	148	2.28 [0.25, 4.30]	0.59 [-1.43, 2.62]
Fixed	Methylnaltrexone 12 mg QAD vs. placebo	1	148	2.29 [1.78, 2.79]	0.60 [0.04, 1.14]
Random	Methylnaltrexone 150 mg OD vs. placebo	1	201	1.85 [-0.13, 3.87]	0.16 [-1.82, 2.17]
Fixed	Methylnaltrexone 150 mg OD vs. placebo	1	201	1.86 [1.48, 2.24]	0.17 [-0.23, 0.57]
Random	Methylnaltrexone 300 mg OD vs. placebo	1	201	2.36 [0.31, 4.44]	0.67 [-1.38, 2.75]
Fixed	Methylnaltrexone 300 mg OD vs. placebo	1	201	2.40 [1.92, 2.82]	0.68 [0.22, 1.14]
Random	Methylnaltrexone 450 mg OD vs. placebo	1	200	2.37 [0.36, 4.43]	0.68 [-1.34, 2.72]
Fixed	Methylnaltrexone 450 mg OD vs. placebo	1	200	2.38 [1.78, 2.79]	0.69 [0.26, 1.12]
Heterogeneity (sqrt [tau]) Random model (median)				---	0.3127

Abbreviations: CrI, credible interval; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement.

Table 169: Bayesian MTC results for the mean change in SBMs per week from baseline to average over 4 to 12 weeks in the anticipated licensed population

				Placebo SBMs Median % [95% CrI]	
Random	---			1.81 [1.63, 1.99]	---
Fixed	---			1.81 [1.63, 1.99]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients Evaluated**	**Active Treatment Median SBMs [95% CrI]**	**Mean Difference [95% CrI]**
Random	Naloxegol 12.5 mg vs. placebo	2	240	2.36 [1.00, 3.75]	0.55 [-0.81, 1.96]
Fixed	Naloxegol 12.5 mg vs. placebo	2	240	2.36 [2.01, 2.71]	0.55 [0.14, 0.95]
Random	Naloxegol 25 mg vs. placebo	2	241	3.26 [1.84, 4.72]	1.46 [0.02, 2.93]
Fixed	Naloxegol 25 mg vs. placebo	2	241	3.26 [2.81, 3.71]	1.45 [0.95, 1.94]
Random	Methylnaltrexone 12 mg OD vs. placebo	1	150	3.40 [1.40, 5.35]	1.6 [-0.41, 3.54]
Fixed	Methylnaltrexone 12 mg OD vs. placebo	1	150	3.41 [2.91, 3.91]	1.6 [1.06, 2.14]
Random	Methylnaltrexone 12 mg QAD vs. placebo	1	148	2.41 [0.46, 4.37]	0.61 [-1.36, 2.58]
Fixed	Methylnaltrexone 12 mg QAD vs. placebo	1	148	2.41 [1.9, 2.91]	0.6 [0.04, 1.14]
Random	Methylnaltrexone 150 mg OD vs. placebo	1	201	1.98 [0.02, 3.96]	0.17 [-1.77, 2.15]
Fixed	Methylnaltrexone 150 mg OD vs. placebo	1	201	1.98 [1.6, 2.36]	0.17 [-0.23, 0.57]
Random	Methylnaltrexone 300 mg OD vs. placebo	1	201	2.5 [0.50, 4.51]	0.69 [-1.31, 2.71]
Fixed	Methylnaltrexone 300 mg OD vs. placebo	1	201	2.49 [2.04, 2.94]	0.68 [0.22, 1.14]
Random	Methylnaltrexone 450 mg OD vs. placebo	1	200	2.49 [0.49, 4.49]	0.68 [-1.32, 2.67]
Fixed	Methylnaltrexone 450 mg OD vs. placebo	1	200	2.5 [2.09, 2.92]	0.69 [0.26, 1.12]
Heterogeneity (sqrt [tau]) Random model (median)				---	0.3106

Abbreviations: CrI, credible interval; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement.

Table 170: Bayesian MTC results for proportion of patients with SBM response in the anticipated licensed population

					Placebo SBMs Median % [95% CrI]	
Random	---				0.31 [0.27, 0.36]	---
Fixed	---				0.31 [0.27, 0.36]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients with SBM Response**	**Number of Patients Evaluated**	**Active Treatment SBMs Median % [95% CrI]**	**Median Odds Ratio [95% CrI]**
Random	Naloxegol 12.5 mg vs. placebo	2	99	240	0.47 [0.31, 0.64]	1.98 [0.98, 4.06]
Fixed	Naloxegol 12.5 mg vs. placebo	2	99	240	0.47 [0.39, 0.55]	1.98 [1.35, 2.93]
Random	Naloxegol 25 mg vs. placebo	2	96	241	0.46 [0.3, 0.62]	1.88 [0.93, 3.78]
Fixed	Naloxegol 25 mg vs. placebo	2	96	241	0.46 [0.38, 0.54]	1.87 [1.27, 2.76]
Random	Methylnaltrexone 12 mg OD vs. placebo	1	88	150	0.51 [0.29, 0.72]	2.33 [0.91, 5.95]
Fixed	Methylnaltrexone 12 mg OD vs. placebo	1	88	150	0.51 [0.41, 0.61]	2.3 [1.47, 3.62]
Random	Methylnaltrexone 12 mg QAD vs. placebo	1	67	148	0.38 [0.19, 0.61]	1.36 [0.51, 3.46]
Fixed	Methylnaltrexone 12 mg QAD vs. placebo	1	67	148	0.38 [0.29, 0.47]	1.34 [0.85, 2.1]
Heterogeneity (sqrt [tau]) Random model (median)					---	0.2372

Abbreviations: CrI, credible interval; OD, once daily; QAD, every other day; SBM, spontaneous bowel movement.

Table 171: Bayesian MTC results for proportion of patients with CSBM response in the anticipated licensed population

					Placebo CSBMs Median % [95% CrI]	
Random	---				0.25 [0.21, 0.28]	---
Fixed	---				0.25 [0.21, 0.28]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients with CSBM Response**	**Number of Patients Evaluated**	**Active Treatment CSBMs Median % [95% CrI]**	**Median Odds Ratio [95% CrI]**
Random	Naloxegol 25 mg vs. placebo	2	91	241	0.44 [0.3, 0.6]	2.42 [1.25, 4.74]
Fixed	Naloxegol 25 mg vs. placebo	2	91	241	0.44 [0.36, 0.53]	2.43 [1.61, 3.68]
Random	Naloxone PR (FRC) vs. placebo	3	177	333	0.48 [0.35, 0.6]	2.78 [1.61, 4.83]
Fixed	Naloxone PR (FRC) vs. placebo	3	177	333	0.48 [0.42, 0.55]	2.81 [2.05, 3.9]
Heterogeneity (sqrt [tau]) Random model (median)					---	0.219

Abbreviations: CrI, credible interval; CSBM, complete spontaneous bowel movement; FRC, fixed ratio combination; PR, prolonged release.

Table 172: Bayesian MTC results for proportion of patients with DAEs in the anticipated licensed population

					Placebo DAEs Median % [95% CrI]	
Random	---				0.05 [0.04, 0.07]	---
Fixed	---				0.05 [0.04, 0.07]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients with DAEs**	**Number of Patients Evaluated**	**Active Treatment DAEs Median % [95% CrI]**	**Median Odds Ratio [95% CrI]**
Random	Naloxegol 12.5 mg vs. placebo	2	8	237	0.03 [0.01, 0.1]	0.66 [0.18, 2.21]
Fixed	Naloxegol 12.5 mg vs. placebo	2	8	237	0.03 [0.01, 0.08]	0.65 [0.25, 1.64]
Random	Naloxegol 25 mg vs. placebo	2	24	241	0.1 [0.04, 0.25]	2.13 [0.71, 6.57]
Fixed	Naloxegol 25 mg vs. placebo	2	24	241	0.1 [0.06, 0.19]	2.12 [1.05, 4.5]
Random	Methylnaltrexone 12 mg OD vs. placebo	1	10	150	0.14 [0.03, 0.47]	2.93 [0.59, 16.49]
Fixed	Methylnaltrexone 12 mg OD vs. placebo	1	10	150	0.14 [0.05, 0.37]	2.97 [0.95, 11.18]
Random	Methylnaltrexone 12 mg QAD vs. placebo	1	13	148	0.18 [0.05, 0.54]	3.93 [0.84, 21.74]
Fixed	Methylnaltrexone 12 mg QAD vs. placebo	1	13	148	0.18 [0.07, 0.43]	4.04 [1.37, 14.64]
Random	Naloxone PR (FRC) vs. placebo	2	15	292	0.04 [0.01, 0.11]	0.72 [0.26, 2.38]
Fixed	Naloxone PR (FRC) vs. placebo	2	15	292	0.03 [0.02, 0.06]	0.66 [0.33, 1.29]
Random	Naloxone (10 mg BD) vs. placebo	1	5	51	0.27 [0.04, 0.92]	6.86 [0.68, 205.82]
Fixed	Naloxone (10 mg BD) vs. placebo	1	5	51	0.27 [0.05, 0.93]	6.92 [0.95, 248.1]
Random	Naloxone (20 mg BD) vs. placebo	1	6	51	0.32 [0.05, 0.93]	8.75 [0.87, 246.41]
Fixed	Naloxone (20 mg BD) vs. placebo	1	6	51	0.32 [0.06, 0.94]	8.63 [1.22, 308.6]
Random	Naloxone (40 mg BD) vs. placebo	1	9	50	0.44 [0.08, 0.96]	14.44 [1.56, 407.08]
Fixed	Naloxone (40 mg BD) vs. placebo	1	9	50	0.44 [0.11, 0.96]	14.54 [2.28, 500.8]
Heterogeneity (sqrt [tau]) Random model (median)					---	0.4957

Abbreviations: BD, twice daily; CrI, credible interval; DAE, discontinuation due to adverse event; FRC, fixed ratio combination; OD once daily; QAD, every other day; PR, prolonged release.

Table 173: Bayesian MTC results for proportion of patients with TEAEs in the anticipated licensed population

					Placebo Response Median % [95% CrI]	
Random	---				0.36 [0.31, 0.41]	---
Fixed	---				0.36 [0.31, 0.41]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients with TEAEs**	**Number of Patients Evaluated**	**Active Treatment TEAEs Median % [95% CrI]**	**Median Odds Ratio [95% CrI]**
Random	Naloxegol 12.5 mg vs. placebo	2	85	237	0.37 [0.23, 0.54]	1.06 [0.53, 2.13]
Fixed	Naloxegol 12.5 mg vs. placebo	2	85	237	0.37 [0.3, 0.45]	1.06 [0.73, 1.55]
Random	Naloxegol 25 mg vs. placebo	2	122	241	0.53 [0.36, 0.69]	1.98 [0.99, 3.99]
Fixed	Naloxegol 25 mg vs. placebo	2	122	241	0.52 [0.45, 0.6]	1.96 [1.35, 2.83]
Random	Methylnaltrexone 12 mg OD vs. placebo	1	74	150	0.47 [0.26, 0.69]	1.56 [0.6, 4.03]
Fixed	Methylnaltrexone 12 mg OD vs. placebo	1	74	150	0.47 [0.37, 0.57]	1.58 [1.01, 2.48]
Random	Methylnaltrexone 12 mg QAD vs. placebo	1	67	148	0.43 [0.23, 0.65]	1.33 [0.52, 3.4]
Fixed	Methylnaltrexone 12 mg QAD vs. placebo	1	67	148	0.43 [0.33, 0.53]	1.34 [0.85, 2.11]
Heterogeneity (sqrt [tau]) Random model (median)					---	0.2298

Abbreviations: CrI, credible interval; OD once daily; QAD, every other day; TEAE, treatment-emergent adverse event.

Table 174: Bayesian MTC results for the mean change in SBMs per week from baseline to average over 4 weeks in the anticipated licensed population + Step 3 opioids

				Placebo SBMs Median % [95% CrI]	
Random	---			1.66 [1.47, 1.85]	---
Fixed	---			1.66 [1.47, 1.85]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients Evaluated**	**Active Treatment Median SBMs [95% CrI]**	**Mean Difference [95% CrI]**
Random	Naloxegol 12.5 mg vs. placebo	2	157	2.74 [0.88, 4.58]	1.08 [-0.78, 2.92]
Fixed	Naloxegol 12.5 mg vs. placebo	2	157	2.74 [2.26, 3.22]	1.08 [0.56, 1.59]
Random	Naloxegol 25 mg vs. placebo	2	176	3.94 [2.08, 5.81]	2.29 [0.43, 4.16]
Fixed	Naloxegol 25 mg vs. placebo	2	176	3.93 [3.37, 4.49]	2.27 [1.67, 2.85]
Random	Methylnaltrexone 12 mg OD vs. placebo	1	150	3.26 [0.65, 5.82]	1.6 [-1.02, 4.17]
Fixed	Methylnaltrexone 12 mg OD vs. placebo	1	150	3.26 [2.76, 3.75]	1.6 [1.06, 2.14]
Random	Methylnaltrexone 12 mg QAD vs. placebo	1	148	2.26 [-0.41, 4.77]	0.6 [-2.05, 3.14]
Fixed	Methylnaltrexone 12 mg QAD vs. placebo	1	148	2.25 [1.76, 2.75]	0.6 [0.04, 1.14]
Random	Methylnaltrexone 150 mg OD vs. placebo	1	201	1.83 [-0.69, 4.44]	0.17 [-2.35, 2.78]
Fixed	Methylnaltrexone 150 mg OD vs. placebo	1	201	1.83 [1.46, 2.2]	0.17 [-0.23, 0.57]
Random	Methylnaltrexone 300 mg OD vs. placebo	1	201	2.34 [-0.17, 4.96]	0.69 [-1.82, 3.3]
Fixed	Methylnaltrexone 300 mg OD vs. placebo	1	201	2.34 [1.89, 2.78]	0.68 [0.22, 1.14]
Random	Methylnaltrexone 450 mg OD vs. placebo	1	200	2.34 [-0.24, 4.99]	0.69 [-1.88, 3.33]
Fixed	Methylnaltrexone 450 mg OD vs. placebo	1	200	2.35 [1.94, 2.76]	0.69 [0.26, 1.12]
Heterogeneity (sqrt [tau]) Random model (median)				---	0.4677

Abbreviations: CrI, credible interval; OD once daily; QAD, every other day; SBM, spontaneous bowel movement.

Table 175: Bayesian MTC results for the mean change in SBMs per week from baseline to average over 4 to 12 weeks in the anticipated licensed population + Step 3 opioids

				Placebo SBMs Median % [95% CrI]	
Random	---			1.73 [1.55, 1.92]	---
Fixed	---			1.73 [1.55, 1.92]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients Evaluated**	**Active Treatment Median SBMs [95% CrI]**	**Mean Difference [95% CrI]**
Random	Naloxegol 12.5 mg vs. placebo	2	157	2.52 [0.67, 4.45]	0.78 [-1.06, 2.7]
Fixed	Naloxegol 12.5 mg vs. placebo	2	157	2.51 [2.07, 2.95]	0.77 [0.29, 1.25]
Random	Naloxegol 25 mg vs. placebo	2	176	3.66 [1.78, 5.58]	1.93 [0.06, 3.85]
Fixed	Naloxegol 25 mg vs. placebo	2	176	3.66 [3.1, 4.21]	1.93 [1.33, 2.51]
Random	Methylnaltrexone 12 mg OD vs. placebo	1	150	3.33 [0.67, 5.95]	1.6 [-1.06, 4.23]
Fixed	Methylnaltrexone 12 mg OD vs. placebo	1	150	3.33 [2.84, 3.82]	1.6 [1.06, 2.14]
Random	Methylnaltrexone 12 mg QAD vs. placebo	1	148	2.33 [-0.3, 5.01]	0.6 [-2.05, 3.29]
Fixed	Methylnaltrexone 12 mg QAD vs. placebo	1	148	2.33 [1.83, 2.82]	0.6 [0.04, 1.14]
Random	Methylnaltrexone 150 mg OD vs. placebo	1	201	1.9 [-0.72, 4.51]	0.17 [-2.45, 2.79]
Fixed	Methylnaltrexone 150 mg OD vs. placebo	1	201	1.9 [1.53, 2.28]	0.17 [-0.23, 0.57]
Random	Methylnaltrexone 300 mg OD vs. placebo	1	201	2.42 [-0.25, 5.07]	0.68 [-2, 3.34]
Fixed	Methylnaltrexone 300 mg OD vs. placebo	1	201	2.41 [1.97, 2.86]	0.68 [0.22, 1.14]
Random	Methylnaltrexone 450 mg OD vs. placebo	1	200	2.42 [-0.23, 5.05]	0.68 [-1.97, 3.34]
Fixed	Methylnaltrexone 450 mg OD vs. placebo	1	200	2.42 [2.02, 2.84]	0.69 [0.26, 1.12]
Heterogeneity (sqrt [tau]) Random model (median)				---	0.475

Abbreviations: CrI, credible interval; OD once daily; QAD, every other day; SBM, spontaneous bowel movement.

Table 176: Bayesian MTC results for proportion of patients with SBM response in the anticipated licensed population + Step 3 opioids

					Placebo SBMs Median % [95% CrI]	
Random	---				0.31 [0.26, 0.36]	---
Fixed	---				0.31 [0.26, 0.36]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients with SBM Response**	**Number of Patients Evaluated**	**Active Treatment SBMs Median % [95% CrI]**	**Median Odds Ratio [95% CrI]**
Random	Naloxegol 12.5 mg vs. placebo	2	68	157	0.54 [0.34, 0.72]	2.62 [1.13, 6.13]
Fixed	Naloxegol 12.5 mg vs. placebo	2	68	157	0.54 [0.43, 0.64]	2.61 [1.62, 4.29]
Random	Naloxegol 25 mg vs. placebo	2	78	176	0.54 [0.34, 0.73]	2.65 [1.15, 6.19]
Fixed	Naloxegol 25 mg vs. placebo	2	78	176	0.54 [0.44, 0.64]	2.68 [1.68, 4.33]
Random	Methylnaltrexone 12 mg OD vs. placebo	1	88	150	0.5 [0.26, 0.75]	2.3 [0.76, 6.97]
Fixed	Methylnaltrexone 12 mg OD vs. placebo	1	88	150	0.5 [0.41, 0.6]	2.29 [1.46, 3.63]
Random	Methylnaltrexone 12 mg QAD vs. placebo	1	67	148	0.37 [0.17, 0.64]	1.33 [0.44, 4.06]
Fixed	Methylnaltrexone 12 mg QAD vs. placebo	1	67	148	0.37 [0.29, 0.47]	1.34 [0.85, 2.1]
Heterogeneity (sqrt [tau]) Random model (median)					---	0.3379

Abbreviations: CrI, credible interval; OD once daily; QAD, every other day; SBM, spontaneous bowel movement.

Table 177: Bayesian MTC results for proportion of patients with CSBM response in the anticipated licensed population + Step 3 opioids

					Placebo CSBMs Median % [95% CrI]	
Random	---				0.24 [0.21, 0.28]	---
Fixed	---				0.24 [0.21, 0.28]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients with CSBM Response**	**Number of Patients Evaluated**	**Active Treatment CSBMs Median % [95% CrI]**	**Median Odds Ratio [95% CrI]**
Random	Naloxegol 25 mg vs. placebo	2	75	176	0.55 [0.39, 0.72]	3.92 [1.94, 8.05]
Fixed	Naloxegol 25 mg vs. placebo	2	75	176	0.55 [0.44, 0.67]	3.89 [2.33, 6.65]
Random	Naloxone PR (FRC) vs. placebo	3	177	333	0.47 [0.35, 0.59]	2.81 [1.63, 4.73]
Fixed	Naloxone PR (FRC) vs. placebo	3	177	333	0.47 [0.41, 0.54]	2.81 [2.05, 3.9]
Heterogeneity (sqrt [tau]) Random model (median)					---	0.1987

Abbreviations: CrI, credible interval; CSBM, complete spontaneous bowel movement; FRC, fixed ratio combination; PR, prolonged release.

Table 178: Bayesian MTC results for proportion of patients with DAEs in the anticipated licensed population + Step 3 opioids

					Placebo DAEs Median % [95% CrI]	
Random	---				0.05 [0.04, 0.07]	---
Fixed	---				0.05 [0.04, 0.07]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients with DAEs**	**Number of Patients Evaluated**	**Active Treatment DAEs Median % [95% CrI]**	**Median Odds Ratio [95% CrI]**
Random	Naloxegol 12.5 mg vs. placebo	2	5	156	0.03 [0.01, 0.12]	0.6 [0.13, 2.58]
Fixed	Naloxegol 12.5 mg vs. placebo	2	5	156	0.03 [0.01, 0.09]	0.61 [0.18, 1.93]
Random	Naloxegol 25 mg vs. placebo	2	23	176	0.14 [0.05, 0.35]	3.01 [0.96, 10.33]
Fixed	Naloxegol 25 mg vs. placebo	2	23	176	0.14 [0.07, 0.27]	3 [1.32, 7.4]
Random	Methylnaltrexone 12 mg OD vs. placebo	1	10	150	0.14 [0.03, 0.49]	3.01 [0.6, 17.81]
Fixed	Methylnaltrexone 12 mg OD vs. placebo	1	10	150	0.14 [0.05, 0.37]	2.98 [0.93, 11.47]
Random	Methylnaltrexone 12 mg QAD vs. placebo	1	13	148	0.18 [0.04, 0.55]	4.07 [0.83, 23.45]
Fixed	Methylnaltrexone 12 mg QAD vs. placebo	1	13	148	0.18 [0.07, 0.44]	4.03 [1.34, 15]
Random	Naloxone PR (FRC) vs. placebo	2	15	292	0.04 [0.01, 0.11]	0.73 [0.26, 2.36]
Fixed	Naloxone PR (FRC) vs. placebo	2	15	292	0.03 [0.02, 0.06]	0.66 [0.33, 1.29]
Random	Naloxone (10 mg BD) vs. placebo	1	5	51	0.29 [0.04, 0.94]	7.65 [0.71, 270.43]
Fixed	Naloxone (10 mg BD) vs. placebo	1	5	51	0.27 [0.05, 0.9]	6.75 [0.9, 171]
Random	Naloxone (20 mg BD) vs. placebo	1	6	51	0.34 [0.05, 0.94]	9.62 [0.9, 309.51]
Fixed	Naloxone (20 mg BD) vs. placebo	1	6	51	0.31 [0.06, 0.92]	8.34 [1.19, 203.6]
Random	Naloxone (40 mg BD) vs. placebo	1	9	50	0.47 [0.09, 0.97]	16.2 [1.66, 535.39]
Fixed	Naloxone (40 mg BD) vs. placebo	1	9	50	0.43 [0.11, 0.95]	13.99 [2.19, 338.1]
Heterogeneity (sqrt [tau]) Random model (median)					---	0.3929

Abbreviations: BD, twice daily; CrI, credible interval; DAE, discontinuation due to adverse event; FRC, fixed ratio combination; OD once daily; QAD, every other day; PR, prolonged release.

Table 179: Bayesian MTC Results for proportion of patients with TEAEs in the anticipated licensed population + Step 3 opioids

					Placebo Response Median % [95% CrI]	
Random	---				0.38 [0.33, 0.44]	---
Fixed	---				0.38 [0.33, 0.44]	---
Analysis Model	**Comparison**	**Number of Studies**	**Number of Patients with TEAEs**	**Number of Patients Evaluated**	**Active Treatment TEAEs Median % [95% CrI]**	**Median Odds Ratio [95% CrI]**
Random	Naloxegol 12.5 mg vs. placebo	2	64	156	0.41 [0.23, 0.61]	1.11 [0.46, 2.67]
Fixed	Naloxegol 12.5 mg vs. placebo	2	64	156	0.41 [0.32, 0.51]	1.12 [0.71, 1.76]
Random	Naloxegol 25 mg vs. placebo	2	100	176	0.57 [0.36, 0.75]	2.16 [0.91, 5.11]
Fixed	Naloxegol 25 mg vs. placebo	2	100	176	0.57 [0.48, 0.66]	2.17 [1.4, 3.36]
Random	Methylnaltrexone 12 mg OD vs. placebo	1	74	150	0.49 [0.24, 0.76]	1.58 [0.5, 5.11]
Fixed	Methylnaltrexone 12 mg OD vs. placebo	1	74	150	0.49 [0.4, 0.59]	1.58 [1, 2.47]
Random	Methylnaltrexone 12 mg QAD vs. placebo	1	67	148	0.45 [0.21, 0.72]	1.33 [0.42, 4.3]
Fixed	Methylnaltrexone 12 mg QAD vs. placebo	1	67	148	0.45 [0.36, 0.55]	1.33 [0.85, 2.1]
Heterogeneity (sqrt [tau]) Random model (median)					---	0.482

Abbreviations: CrI, credible interval; OD once daily; QAD, every other day; TEAE, treatment-emergent adverse event.

10.22 *Appendix 21: Forest plots for the MTC analysis*

Forest plots were generated for the MTC analysis of the anticipated licensed population and the anticipated licensed population + Step 3 opioids subgroup. The relative treatment effect can be visualised against other comparisons for 1) each treatment versus placebo, 2) naloxegol 12.5 mg versus other treatments, and 3) naloxegol 25 mg versus other treatments. These forest plots are provided in the embedded file below.

Forest Plots.zip

10.23 *Appendix 22: non-RCT studies identified in the systematic review*

Summary of methodology of relevant non-RCTs: KODIAC 16 (59)

The methodology of KODIAC 16 is presented in Table 180.

Table 180: Methodology of KODIAC 16

Study no. (acronym)	**KODIAC 16 (D3820C00016)**
Study objective	To characterise the PK of naloxegol after single oral dose and through population PK in paediatric patients with OIC
Location	Conducted at eight sites in The Netherlands, Spain, and the UK
Design	Phase I, open-label, multicentre study
Inclusion criteria	• Ages 6 months to 18 years • Receiving, or are about to receive, acute or chronic treatment with opioids for malignant or non-malignant pain • Newly diagnosed constipation, a history of constipation treated with laxatives, or expected to develop constipation after opioid treatment
Exclusion criteria	• Current acute or chronic use of methadone • History of neoplasm or an ongoing gastrointestinal-related issue • Signs or symptoms of gastrointestinal obstruction • History of prolonged neutropenia or thrombocytopenia with clinical sequelae • Need for mechanical ventilation • Patients currently receiving the first cycle of chemotherapy
Duration of study	• Study start date: July 2014 • Estimated study completion date: January 2017
Method of randomisation	N/A: non-randomised
Method of blinding (care provider, patient and outcome assessor)	N/A: open-label study
Interventions, N randomised	• 12.5 mg naloxegol – age group ≥12yr to <18yr – Lower dose • 25 mg naloxegol – age group ≥12yr to <18yr – Higher dose • 12.5 mg naloxegol – age group 6yr to <12yr – Lower dose • 25 mg naloxegol – age group 6yr to <12yr – Higher dose • 12.5 mg naloxegol – age group 6months to <6yr – Lower dose • 25 mg naloxegol – age group 6months to <6yr – Higher dose 8 patients per arm planned; study is not yet recruiting
Comparators, N randomised	None
Permitted concomitant medications	Not stated
Disallowed	Not stated

Study no. (acronym)	KODIAC 16 (D3820C00016)
concomitant medications	
Discontinuation of study therapy	N/A – study not yet recruiting
Assessments	Not stated
Primary outcomes (including scoring methods and timings of assessments)	• Pharmacokinetics after single oral dose o Timings of assessments: Day 1: pre-dose (within 30 minutes prior to drug dosing), 0.5, 1, 2, 4, 6, 8, 10 and 24 hours o Scoring methods: ▪ AUC from zero extrapolated to infinity ▪ AUC from zero to the last quantifiable concentration ▪ Maximum plasma concentration (Cmax) ▪ Terminal half-life (t1/2λz) ▪ Maximum plasma concentration (tmax) ▪ MRT ▪ Oral clearance (CL/F) ▪ Volume of distribution during the terminal phase (Vz) ▪ Apparent volume of distribution at steady state (Vss/F)
Secondary outcomes (including scoring methods and timings of assessments)	• Pharmacokinetics after multiple, once-daily oral dosing o Timings of assessments: Day 7 pre-dose (within 30 min prior to drug dosing) and after 4 hours. o Scoring methods: accumulation ratio calculated from AUC of Day 7/AUC of Day 1, determined by population PK modelling • Palatability of naloxegol liquid drug formulation using VAS, willingness to swallow, etc. o Timings of assessments: Day 1 and Day 2 after dose. o Scoring methods: ▪ For age group ≥6 years to <18 years: VAS with facial hedonic scale. ▪ For age group ≥6 months to <6 years: willingness to swallow, patients' behaviour indicative of a negative response and the response to the taste of naloxegol liquid formulation compared to patients' response to all other oral medications currently being given. • Ability of the patient to swallow the tablet o Timings of assessment: Day 1 and Day 2 after dose o Scoring methods: Study nurse assessment • Safety in terms of adverse events o Timings of assessments: from the point ICF is signed until the follow-up visit (Week 26) o Scoring methods: ▪ Laboratory tests (clinical chemistry, haematology, urinalysis), physical examination, vital signs ▪ ECG ▪ Pain (pain intensity scale: e.g. 21 numbered VAS, facial pain scales and FLACC scales) ▪ Opioid withdrawal (withdrawal assessment tool-1 (WAT-1) assessments. Time frame: adverse event will be collected

Study no. (acronym)	KODIAC 16 (D3820C00016)

	from the point ICF is signed until the follow-up visit (Week 26)
	• Clinical outcome measures (by assessment of BM)
	  ○ Timings of assessments: from Day 1 until Week 26
	  ○ Scoring methods:
	  ▪ Time (hours) to first post dose BM
	  ▪ Number of days with BM per week
	  ▪ % days with BM during treatment
	• Clinical outcome measures (by assessment of laxative use)
	  ○ Timings of assessments: from Day 1 to Week 26
	  ○ Scoring methods:
	  ▪ Laxative use within 24 hours prior to first dose
	  ▪ Number of days with laxative use per week
	  ▪ % days with laxative use during treatment
	• Pharmacokinetics after multiple, once-daily, oral dosing
	  ○ Timings of assessments: Day 7. If patient discontinues treatment before Day 7, samples will be taken on the last day of study drug but not earlier than Day 4, after 3 full days of naloxegol treatment. Pre-dose (within 30 min prior to drug dosing) and after 4 hours.
	  ○ Scoring methods:
	  ▪ Accumulation ratio calculated from Cmax of day 7. Cmax of Day 1 will be determined by population pharmacokinetic modelling

Duration of follow-up	Final data collection for primary outcome measure: January 2017 (estimated)
Analysis populations	Not stated
Statistical methods	Not stated

Abbreviations: AUC, assessment of area under the plasma concentration-time curve; ECG, electrocardiogram; FLACC, face, legs, activity, cry, consolability; ICF, informed consent form; MRT, mean residence time; OIC, opioid-induced constipation; PK, pharmacokinetics; VAS, visual analogue scale

Critical appraisal of relevant non-RCTs

A critical appraisal of KODIAC 16 is presented in section 10.6.1.

Results of relevant non-RCTs

There are currently no results from KODIAC 16 as patients are not yet being recruited.

10.24 *Appendix 23: Efficacy results from KODIAC 7*

Key efficacy results

Although KODIAC 7 was primarily designed as a safety extension study of KODIAC 4, patient reported outcome results as measured by the PAC-SYM, PAC-QoL and EQ-5D questionnaires were assessed in addition to the safety evaluations. In KODIAC 7, assessment of the PAC-SYM and PAC-QoL was based on the mITT analysis set, a subset of the ITT analysis set that included patients in the safety analysis set who had at least 1 assessment for PAC-SYM or PAC-QoL beyond Day 1 of the current study.

Patient reported outcome results: PAC-SYM

Across all three treatment groups, mean baseline domain scores indicated that patients were most affected by symptoms in the stool domain (moderate to severe). The improvement in mean domain scores of the PAC-SYM that were observed in the 12 week KODIAC 4 RCT were maintained across all three treatment groups in the KODIAC 7 extension study. In general, differences in PAC-SYM change from baseline scores observed between the naloxegol 12.5 mg and 25 mg groups vs placebo were of small magnitude and were in favour of greater improvement for naloxegol.

Patient reported outcome results: PAC-QoL

At baseline in the KODIAC 4 RCT, the lowest scores were observed in the satisfaction domain of the PAC-QoL, describing patients as being only “a little satisfied with their bowel function”. The improvements in PAC-QoL domains observed in KODIAC 4 were maintained across all treatment groups in KODIAC 7. In general, differences in change from baseline scores between naloxegol treatment groups and placebo were of small magnitude.

Patient reported outcome results: EQ-5D

The mean EQ-5D visual analogue scale (VAS) scores increased, from enrolment in KODIAC 4 to the end of treatment (Week 24) in KODIAC 7 for all three treatment groups. At Week 24, small improvements in the change from baseline were observed for the naloxegol 12.5 mg, 25 mg and placebo groups (4.2, 2.6 and 2.1 on a 100 point VAS scale, respectively).

10.25 *Appendix 24: X*

10.26 *Appendix 25: Estimation of AE management cost*

This section provides details of the inputs used to determine costs per episode of AE associated with OIC. Unit costs were gathered from official published UK sources (Table 181) and frequency of medical resource use associated with each AE was obtained by consulting KOLs (n=3) with expertise in management of OIC (Table 182). Where resource-use estimates differed between the KOLs, each person's answers were weighted according to his or her confidence in them and then the average calculated.

To calculate a weighted cost of AE per treatment arm, the sum of the costs of each AE and the distribution of AEs across each event of interest was evaluated and multiplied by the percentage of patients experiencing any AE (details of which are given in section 6.9.2). The distribution of AEs for each treatment arm is presented in Table 183.

Table 181: Unit costs of medical resource use items used in adverse event management

Item	Unit cost	Source
Inpatient care (per stay)	£1606,98	National Schedule of Reference Costs Year: 2012-13 - NHS Trusts and PCTs combined. Weighted average of Elective and Non-Elective Inpatient HRG Data (codes FZ90A, FZ90B).
Outpatient care (per visit)	£344.65	National Schedule of Reference Costs Year: 2012-13 - NHS Trusts and PCTs combined. Weighted average of Day Cases HRG Data (codes FZ90A, FZ90B).
Emergency care (per visit)	£112.00	Unit Costs of Health & Social Care 2012. PSSRU. Section 7.1 A&E services weighted average.
GP visit	£45.00	Unit Costs of Health & Social Care 2013. PSSRU section 10.8b, Per patient contact lasting 11.7 minutes
Nurse visit	£18.08	Unit Costs of Health & Social Care 2013. PSSRU, section 10.1, Community nurse per hour of home visiting of £73. average duration of nurse visit in GP practice of 15.5 min, section 10.8b
Specialist visit	£140.00	National Schedule of Reference Costs Year: 2012-13 - NHS Trusts and PCTs combined, Total outpatient attendance, Consultant lead outpatient attendance (code 301M, gastrology).
Stemetil (per mg)	£0.01	British National Formulary (BNF) December 2013. Available by subscription. Accessed 17Dec2013.
Paracetamol (per mg)	£0.00	British National Formulary (BNF) December 2013. Available by subscription. Accessed 17Dec2013.
Abdominal x-ray	£28.00	National Schedule of Reference Costs Year : 2012-13 - NHS Trusts and PCTs combined, Directly Accessed Diagnostic Services, Direct Access Plain Film
MRI scan	£169.00	National Schedule of Reference Costs - Year 2012-13 - NHS trusts and NHS foundation trusts, diagnostic imaging (code RA01A).
Liver function tests	£1.00	National Schedule of Reference Costs - Year 2012-13 - NHS trusts and NHS foundation trusts, Directly Accessed Pathology Services, clinical biochemistry (code DAPS04).

Table 182: Medical resource use frequency per adverse event†

Adverse events	Items	% of patients with OIC using	# used per adverse event‡
Abdominal pain	Inpatient care	5.37%	1.49
	Outpatient care	3.24%	1.29
	Emergency care	6.44%	1.94
	Physician consultation	25.84%	2.69
	Nurse visit	11.92%	3.34
	Specialist visit	0.86%	0.20
	Abdominal X-ray	13.80%	1.00
	MRI scan	0.80%	0.40
	Liver function tests	1.20%	0.40
Flatulence	Outpatient care	0.34%	0.60
	Emergency care	0.34%	0.60
	Physician consultation	1.79%	1.44
	Nurse visit	2.11%	1.64
Vomiting	Inpatient care	4.42%	1.75
	Outpatient care	3.93%	1.77
	Emergency care	5.59%	2.14
	Physician consultation	3.81%	4.15
	Nurse visit	2.68%	5.99
	Specialist visit	1.11%	0.67
	Stemetil	5.00%	30 mg for 5 days
	Abdominal X-ray	3.00%	0.6
Nausea	Inpatient care	2.65%	0.72
	Outpatient care	1.02%	0.66
	Emergency care	2.52%	0.70

	Physician consultation	3.13%	2.61
	Nurse visit	3.92%	2.17
	Stemetil	10.00%	30 mg for 5 days
Headache	Outpatient care	0.34%	0.55
	Emergency care	0.34%	0.55
	Physician consultation	1.45%	0.80
	Nurse visit	2.38%	0.87
	Paracetamol	10.00%	4,000 mg for 3 days
Diarrhoea	Inpatient care	1.52%	1.56
	Outpatient care	2.56%	0.60
	Emergency care	2.30%	1.66
	Physician consultation	3.80%	2.66
	Nurse visit	1.15%	2.05
	Specialist visit	0.86%	0.26
	Abdominal X-ray	3.00%	0.60

†Source: Key opinion leader (KOL) inputs (n = 3).
‡Among patients who used the resource.

Table 183: Distribution of adverse events by treatment arm for which grade?

	Abdominal pain	Flatulence	Vomiting	Nausea	Headache	Diarrhoea
Naloxegol 25 mg (51, 52)	33.18%	12.15%	9.35%	16.82%	9.35%	19.16%
SC MNTX QAD(56)	33.82%	0.00%	16.18%	25.00%	0.00%	25.00%
OXN(54, 58)	12.15%	12.15%	6.54%	30.84%	15.98%	22.43%
Placebo (51, 52)	25.00%	11.00%	13.00%	20.00%	12.00%	19.00%
Placebo + rescue laxative	25.00%	11.00%	13.00%	20.00%	12.00%	19.00%

Abbreviations: MNTX, methylnaltrexone; OXN, naloxone-oxycodone; QAD, every other day; SC, subcutaneous.

Table 184: Adverse events costs

Resource use items	Abdominal pain	Flatulence	Vomiting	Nausea	Headache	Diarrhoea
Inpatient care	£0.08	-	£0.70	£0.02	-	£0.02
Outpatient care	£14.40	£0.70	£0.23	£2.32	£0.64	£5.29
Emergency care	£13.99	£0.23	£1.16	£1.98	£0.21	£4.28
GP visit	£31.28	£1.16	£0.63	£3.68	£0.52	£4.55
Nurse visit	£7.20	£0.63	£0.70	£1.54	£0.37	£0.43
Specialist visit	£0.24	**-**	£0.23	-	-	£0.31
Stemetil	£3.86	**-**	£1.16	-	-	-
Paracetamol	£0.54	**-**	-	-	£0.12	-
Abdominal x-ray	£0.00	**-**	£0.50	-	-	£0.50
MRI scan	£0.08	**-**	**-**	**-**	**-**	**-**
Liver function tests	£14.40	**-**	**-**	**-**	**-**	**-**
Total (2013 £)	**£71.61**	**£2.72**	**£49.09**	**£9.68**	**£1.87**	**£15.39**
Total (inflated to 2014 £)	**£72.71**	**£2.76**	**£49.85**	**£9.83**	**£1.90**	**£15.62**

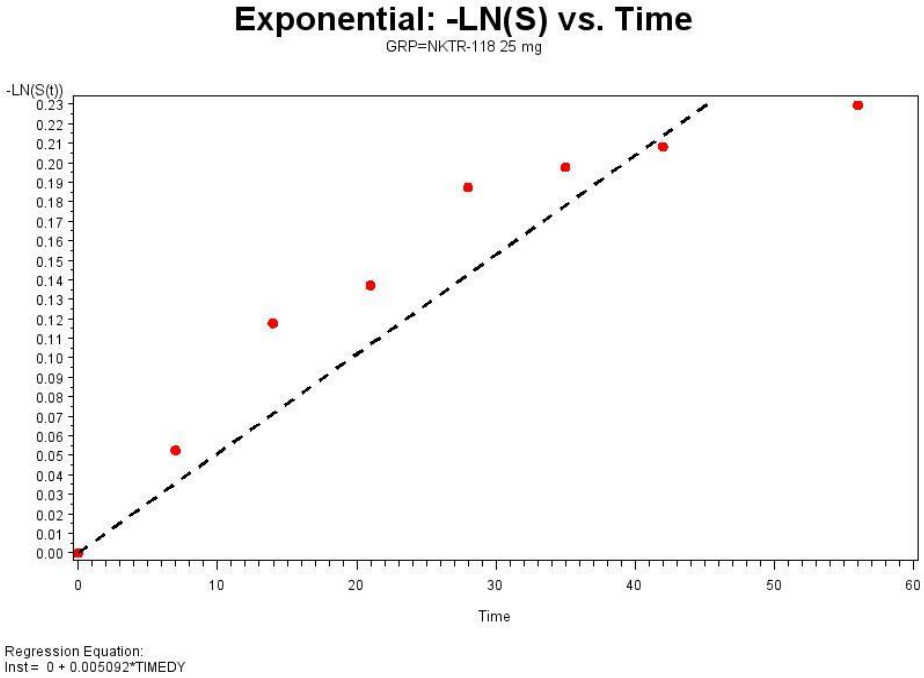
Abbreviations: GP, general practitioner; MRI, magnetic resonance imaging.

10.27 *Appendix 26: Diagnostic plots for transition A*

A linear pattern in these graphs indicates a good fit and suggests that the underlying distribution is possibly the one being tested. Conversely, a deviation from linearity indicates poor fit.

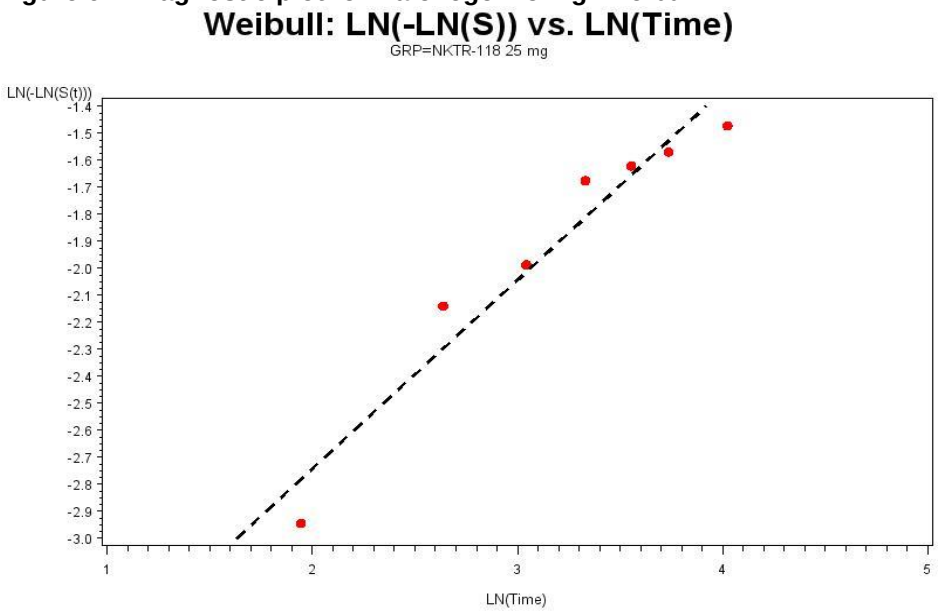
The parametric plot for the exponential distribution (Figure 61) tests the negative natural log of survival against time. The dashed line represents the trend line which the observed data points should follow. In this plot it can be seen that the observed data points (red) do not follow the linear trend of the dashed line, suggesting that the underlying distribution is not likely to be exponential.

Figure 61: Diagnostic plot for Naloxegol 25 mg: exponential



The parametric plot for the Weibull distribution (Figure 62) tests the natural log of the negative natural log of survival against natural log of time. The dashed line represents the trend line which the observed data points should follow. The observed points deviate from a linear trend only slightly, especially in the beginning and tail sections of the curve, suggesting that the underlying distribution for the observed data may be Weibull.

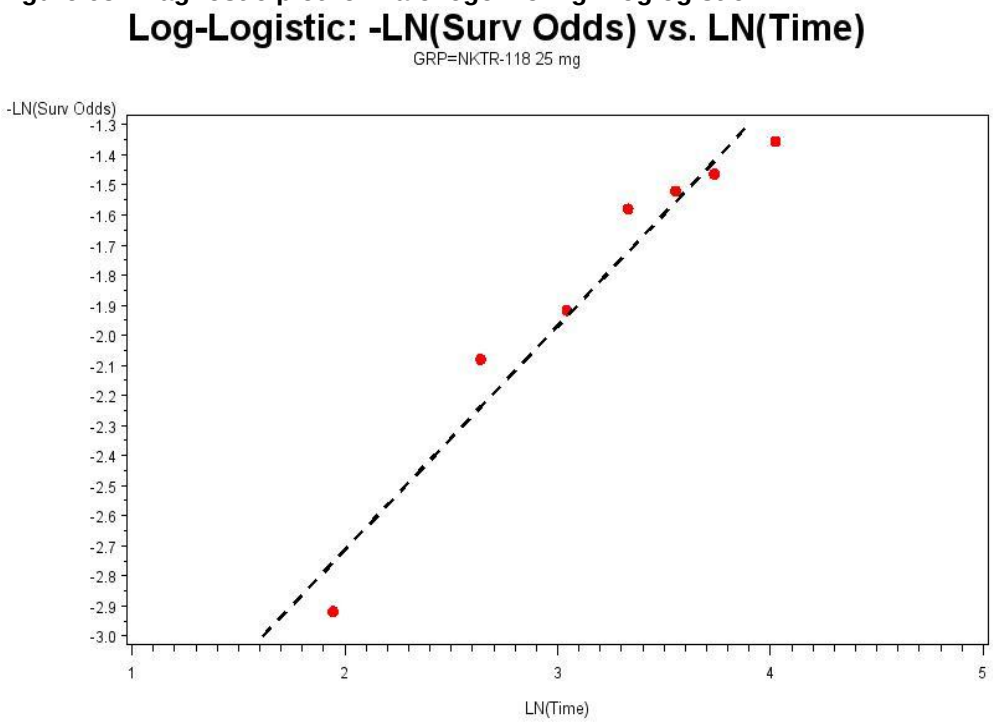
Figure 62: Diagnostic plot for Naloxegol 25 mg: Weibull



Regression Equation:
lnlnst = -4.142514 + 0.699877*lnt

The parametric plot for the Log-Logistic distribution (Figure 63) tests the negative natural log of the survival odds against natural log of time. The dashed line represents the trend line which the observed data points should follow. The observed points only deviate from the linear trend slightly, suggesting that the underlying distribution for the observed data may be log logistic.

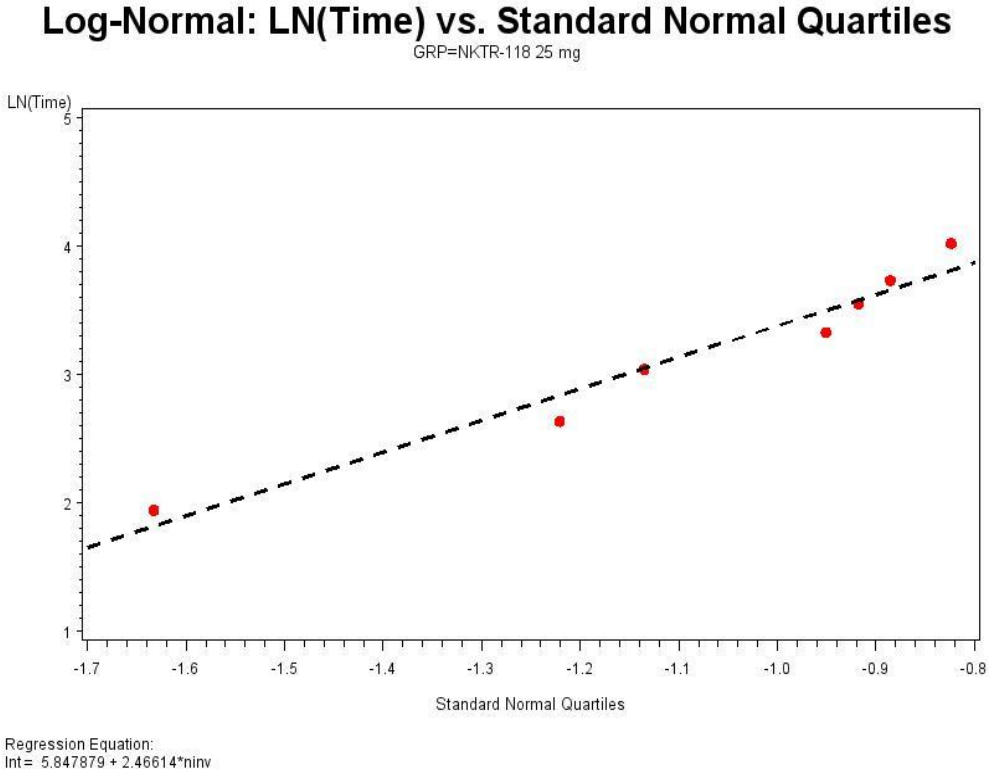
Figure 63: Diagnostic plot for Naloxegol 25 mg: Loglogistic



Regression Equation:
lnodds = -4.201964 + 0.744317*lnt

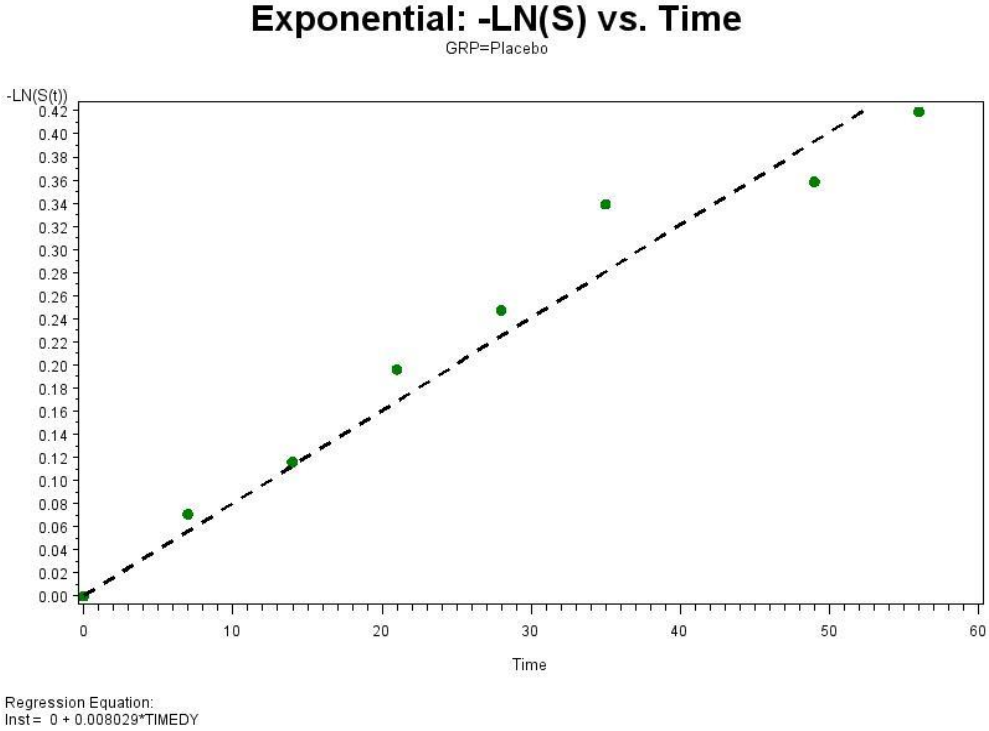
The parametric plot for the log-normal distribution (Figure 64) tests the natural log of time against standard normal quartiles. The dashed line represents the trend line which the observed data points should follow. The observed points are very much aligned with the dashed trend line which suggests that this distribution may be the best fitting parametric distribution to the observed data.

Figure 64: Diagnostic plot for Naloxegol 25 mg: lognormal



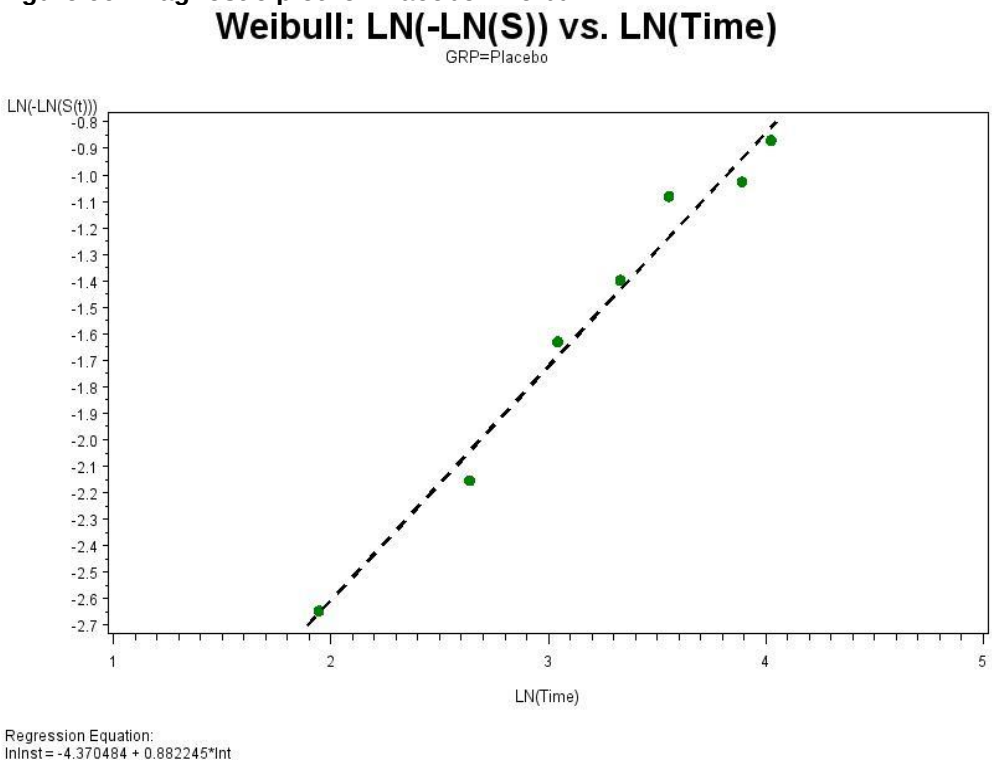
Similarly, in the placebo arm, parametric plot for the exponential distribution (Figure 65) tests the negative natural log of survival against time. The dashed line represents the trend line which the observed data points should follow. In this plot it can be seen that the observed data points (green) diverge slightly from the linear trend of the dashed line, suggesting that the underlying distribution may not be exponential.

Figure 65: Diagnostic plot for Placebo: Exponential



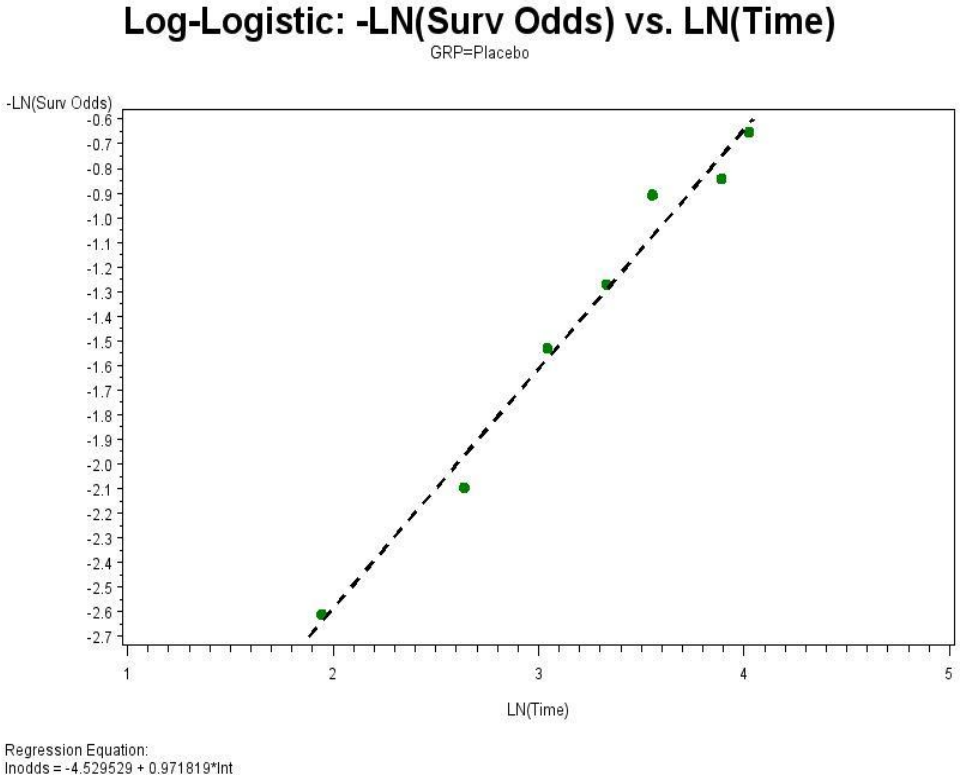
The parametric plot for the Weibull distribution (Figure 66) tests the natural log of the negative natural log of survival against natural log of time. The dashed line represents the trend line which the observed data points should follow. The observed points are closely aligned with the trend line, suggesting that the distribution underlying the data may be Weibull.

Figure 66: Diagnostic plot for Placebo: Weibull



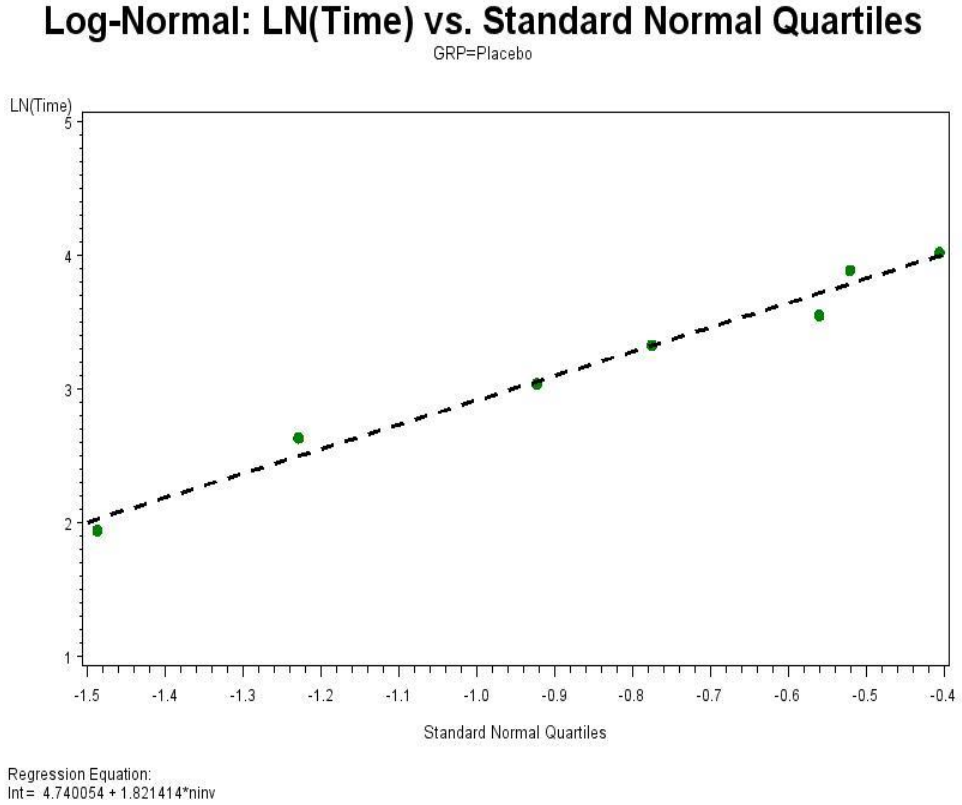
The parametric plot for the log-logistic distribution (Figure 67) tests the negative natural log of the survival odds against natural log of time. The dashed line represents the trend line which the observed data points should follow. The observed points follow the linear trend of the dashed line, which suggests that the underlying distribution for the observed data may be log logistic.

Figure 67: Diagnostic plot for Placebo: Loglogistic



The parametric plot for the log-normal distribution (Figure 68) tests the natural log of time against standard normal quartiles. The dashed line represents the trend line which the observed data points should follow. The observed points are very well aligned with the dashed trend line suggesting that log-normal distribution may be the best fit among the other distributions tested.

Figure 68: Diagnostic plot for Placebo: Lognormal



10.28 *Appendix 27: Health state cost data inputs*

GP omnibus data

Table 185: Constipation related resource use in the OIC state, excluding laxatives (Source: GP Omnibus Survey)

Items	Anticipated licensed population		Anticipated licensed population + Step 3 opioids	
	Frequency (per cycle)	Duration (days)	Frequency (per cycle)	Duration (days)
Inpatient care	0	0	0	0
Outpatient care	0.01	-	0.02	-
Emergency care	0.01	1	0.01	1
Physician consultation	0.39	-	0.41	-
Nurse visit	0.13	-	0.16	-
Specialist visit	0	-	0	-
GP telephone consultation	0.29	-	0.3	-
Enema	0	-	0	-
Manual evacuation	0	-	0	-
Haemorrhoid stapling	0	-	0	-
Endoscopy	0	-	0	-
Colonoscopy	0	-	0	-
Abdominal X-ray	0	-	0	-
Urea and electrolytes	0	-	0	-
Full blood count	0	-	0	-
Liver function tests	0	-	0	-

Abbreviations: GP, general practitioner.
Source GP omnibus survey (137)

Table 186: Laxative use in the OIC state (source: GP Omnibus Survey)

Laxative	Anticipated licensed population		Anticipated licensed population + Step 3 opioids	
	Proportion patients receiving	Dose (mg) per cycle	Proportion patients receiving	Dose (mg) per cycle
Bisacodyl	6.2%	213	4.4%	207
Polyethylene glycol 3350 / macrogol	40.7%	58	42.6%	63
Senna	17.0%	353	15.3%	283
Docusate sodium	10.9%	6182	9.1%	6324
Lactulose	15.5%	553	14.2%	586
Co-danthramer	3.4%	42	6.7%	44
Bisacodyl suppository	1.1%	263	1.8%	287
Glycerol suppository	5.1%	51	5.9%	54

Abbreviations: GP, general practitioner.

Table 187 describes the inputs used to estimate the percentage change in laxative use that occurs when patients move from OIC to non-OIC (untreated) state, based on the various ways the patients may change their laxative usage.

Table 187: Change in laxative use with constipation relief (source: GP Omnibus Survey)

	Proportion of patients in whom you would:	% of the initial laxative dose
Continue laxative unchanged	51.2%	100%
Change to increased laxative dose	4.0%	131.2%
Change to reduced laxative dose	35.0%	56.8%
Stop laxative	9.8%	0%

Burden of illness data

A prospective hybrid longitudinal study was conducted in 98 patients with OIC in the UK to estimate the healthcare resource utilisation associated with the condition. The study used a combination of a web-based, longitudinal patient survey, with retrospective data abstraction from medical records. For resource use items informed by patient survey, frequency per cycle is calculated from the weighted average estimates of baseline (t=0) survey and eight follow-up surveys over 24 weeks. For resource use items identified by the retrospective chart review, frequency per cycle is calculated in a similar fashion based on a total of 18 months of chart review data. Specifically, the weighted average estimate of chart review data collected from 12 months prior to the baseline patient visit

and again at the end of the prospective study period (Week 24) for each patient are considered in the analysis.

Table 188: Constipation related resource use in the OIC state, excluding laxatives

Items	Anticipated licensed population		Anticipated licensed population + Step 3 opioids	
	Frequency (per cycle)	Duration (days)	Frequency (per cycle)	Duration (days)
Inpatient care	0.03	4.67	0.1000	9.00
Outpatient care	0.28	-	0.6112	-
Emergency care	0.03	1.00	0.1000	1.00
Physician consultation	0.01	-	0.0000	-
Nurse visit	0.00	-	0.0085	-
Specialist visit	0.00	-	0.0000	-
GP telephone consultation†	0.29	-	0.30	-
Enema	0.00	-	0.00	-
Manual evacuation	0.00	-	0.00	-
Haemorrhoid stapling	0.00	-	0.00	-
Endoscopy	0.00	-	0.00	-
Colonoscopy	0.00	-	0.00	-
Abdominal X-ray	0.00	-	0.00	-
Urea and electrolytes	0.00	-	0.00	-
Full blood count	0.00	-	0.00	-
Liver function tests	0.00	-	0.00	-

Abbreviations: GP, general practitioner; LIR, laxative inadequate response.
†Value from BOI data is 0; in the model, GP omnibus data is used instead.
Source: BOI study

IMS data

Please see section 10.15.

Table 189: Profile of Opioid Use for Naloxegol 25 mg

Scenario	Proportion of patients receiving	Average dose per cycle (mg) *
1. Exclusive use of morphine	100%	56.0
2. Exclusive use of oxycodone	100%	45.8

Source: AstraZeneca IMS data

Table 190: Unit Cost inputs

Items	Unit cost	Source
Inpatient care	£1,631.81	National Schedule of Reference Costs Year: 2012-13 - NHS Trusts and PCTs combined. Weighted average of Elective and Non-Elective Inpatient HRG Data (codes FZ90A, FZ90B). Inflated to 2014
Outpatient care	£349.98	National Schedule of Reference Costs Year: 2012-13 - NHS Trusts and PCTs combined. Weighted average of Day Cases HRG Data (codes FZ90A, FZ90B). Inflated to 2014.
Emergency care	£116.50	Unit Costs of Health & Social Care 2012. PSSRU. Inflated to 2014.
GP visit	£45.70	Unit Costs of Health & Social Care 2013. PSSRU. Inflated to 2014.
Nurse visit at the surgery	£18.36	Unit Costs of Health & Social Care 2013. PSSRU. Inflated to 2014.
Community nurse hourly rate for home visit	£71.08	Unit Costs of Health & Social Care 2013. PSSRU. Inflated to 2014.
GP telephone consultation	£23.55	Unit Costs of Health & Social Care 2011. PSSRU. Inflated to 2014.
Enema	£35.54	Unit Costs of Health & Social Care 2013. PSSRU (code 10.1). Inflated to 2014. – correspond to 30 min of a community nurse home visit
Manual evacuation – assumed to correspond to Intermediate Large Intestine Procedures 19 years and over (FZ50Z)	£149.85	National Schedule of Reference Costs Year : 2012–13 - NHS Trusts and PCTs combined (code FZ50Z). Inflated to 2014.
Haemorrhoid stapling – assumed to correspond to Intermediate Anal Procedures 19 years and over (FZ22A)	£125.05	National Schedule of Reference Costs Year : 2012–13 - NHS Trusts and PCTs combined (code FZ22A). Inflated to 2014.
Endoscopy	£161.07	National Schedule of Reference Costs Year : 2012–13 - NHS Trusts and PCTs combined (code FZ27C). Inflated to 2014.
Colonoscopy	£282.83	National Schedule of Reference Costs Year : 2012–13 - NHS Trusts and PCTs combined (code FZ51Z and FZ53Z). Inflated to 2014.
Abdominal X-ray	£28.72	National Schedule of Reference Costs Year: 2012–13 - NHS Trusts and PCTs combined (code DAPF). Inflated to 2014.

Items	Unit cost	Source
Urea and electrolytes	£1.00	National Schedule of Reference Costs - Year 2012–13 - NHS trusts and NHS foundation trusts (code DAPS04). Inflated to 2014.
Full blood count	£3.00	National Schedule of Reference Costs - Year 2012–13 - NHS trusts and NHS foundation trusts (code DAPS05). Inflated to 2014.
Liver function tests	£1.00	National Schedule of Reference Costs - Year 2012–13 - NHS trusts and NHS foundation trusts (code DAPS04). Inflated to 2014.
Bisacodyl (per mg, as a rescue laxative)	£0.0075	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Polyethylene glycol 3350 / macrogol (per mg)	£0.0170	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Senna (per mg)	£0.0286	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Docusate sodium (per mg)	£0.0007	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Lactulose (per mg)	£0.0141	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Co-danthramer	£0.0007	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Bisacodyl suppository	£0.0294	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Glycerol suppository	£0.0490	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Morphine oral immediate release	£0.0095	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Morphine oral controlled release	£0.0095	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Morphine injectable	£0.0443	British National Formulary (BNF) September 2014.

Items	Unit cost	Source
		Available by subscription. Accessed 22 September 2014.
Oxycodone	£0.0630	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Fentanyl (transdermal)	£0.1459	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Buprenorphine (transdermal)	£0.4543	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22Sep2014.
Hydrocodone or dihydrocodeine	£0.0065	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Methadone	£0.0101	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.
Hydromorphone	£0.1212	British National Formulary (BNF) September 2014. Available by subscription. Accessed 22 September 2014.

10.29 *Appendix 26: Calculation of average age of cancer pain patients in the model*

Age 72 years was chosen as the starting age in the model for patients with cancer pain. This value was derived using data from the Office for National Statistics (ONS) for registrations of newly diagnosed cancer cases for England (138). Ideally, data corresponding to the typical age for pain onset in UK cancer patients would have been used but no such data were found. The ONS dataset presents age of registration of newly diagnosed cancer by 5 year age band, for 'all registrations' (ICD-10 codes C00-C97, D00-D48), 'all cancers' (C00-C97) and by individual cancer site. Data for 'all cancers' were chosen for purposes of simplicity, as naloxegol's contraindications have not yet been confirmed. The median age was found to lie in the 70-74 years age band and the mean age, calculated using the midpoint of each 5 years age band, was found to be 72.3 years. As such, age 72 years was applied as the starting age in the model.