National Institute for Health and Clinical Excellence

Single technology appraisal (STA)

Prucalopride (Resolor®) for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief

29th March 2010

Contents

Contents 2
List of figures 3
List of tables 3
List of abbreviations 6
Executive summary 7
Section A – Decision problem 13
1 Description of technology under assessment 13
2 Context 18
3 Equity and equality 22
4 Statement of the decision problem 23
Section B – Clinical and cost effectiveness 25
5 Clinical evidence 25
6 Cost effectiveness 115
Section C – Implementation 158
7 Assessment of factors relevant to the NHS and other parties 158
8 References 164
9 Appendices 167
10 Related procedures for evidence submission 236

List of figures

Figure 1: Participant flow in PRU-INT-6 (18) 52
Figure 2: Participant flow in PRU-USA-11 (20) 53
Figure 3: Participant flow in PRU-USA-13 (22) 54
Figure 4: Participant flow in PRU-INT-12 (24) 55
Figure 5: Participant flow in PRU-INT-8 (25) 56
Figure 6: Participant flow in PRU-USA-28 (26) 57
Figure 7: Participant flow in the Phase II RCT PRU-USA-26 (1, 2) 89
Figure 8: Cost and outcomes of constipation treatment – decision tree analysis, UK model 118
Figure 9: PAC-QOL satisfaction scores in the open label phase 119
Figure 10: Mapping PAC-QOL, SF-36 and EQ-5D 134
Figure 11: CEAC for all female patients 148
Figure 12: CEAC for all adult patients (18-65 years) 149
Figure 13: CEAC for elderly patients (>65 years) 150
Figure 14: Prucalopride patient population estimate (000's) 159

List of tables

Table 1: Overview of prucalopride Phase II and III studies 27
Table 2: List of relevant RCTs 34
Table 3: List of relevant non-RCTs 35
Table 4: Methodology of the pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13) (18-23) 36
Table 5: Methodology of RCT in elderly subjects (PRU-INT-12) (24) 37
Table 6: Methodology of RCT in subjects with opioid-induced constipation (PRU-INT-8) (25) 37
Table 7: Methodology of the retreatment study (PRU-USA-28) (26) 38
Table 8: Eligibility criteria in the pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13) (18-23) 39
Table 9: Eligibility criteria in the RCT in elderly subjects (PRU-INT-12) (24) 39
Table 10: Eligibility criteria in the RCT in subjects with opioid-induced constipation (PRU-INT-8) (25) 40
Table 11: Eligibility criteria in the retreatment study PRU-USA-28) (26) 40
Table 12: Baseline patient characteristics pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13) (18-23) 41
Table 13: Baseline patient characteristics RCT in elderly subjects (PRU-INT-12) (24) 43
Table 14: Baseline patient characteristics RCT in subjects with opioid-induced constipation (PRU-INT-8) (25) 44
Table 15: Baseline patient characteristics retreatment study (PRU-USA-28) (26) 44
Table 16: Primary and secondary outcomes of the pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13) (18-23) 45

Table 17: Primary and secondary outcomes of the RCT in elderly subjects (PRU-INT-12) (24) 46
Table 18: Primary and secondary outcomes of the RCT in subjects with opioid-induced constipation (PRU-INT-8) (25) 47
Table 19: Primary and secondary outcomes of the retreatment study (PRU-USA-28) (26) 48
Table 20: Statistical analyses in the pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13) (18-23) 49
Table 21: Statistical analyses in the RCT in elderly subjects (PRU-INT-12) (24) 49
Table 22: Statistical analyses in the RCT in subjects with opioid-induced constipation (PRU-INT-8) (25) 50
Table 23: Statistical analyses in the retreatment study (PRU-USA-28) (26) 50
Table 24: Quality assessment of pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13)(18-23) 58
Table 25: Efficacy data derived from diaries and patient global assessment questionnaires: Pivotal trials PRU-INT-6 (18, 19), PRU-USA-11 (20, 21), PRU-USA-13 62
Table 26: Efficacy data derived from PAC-SYM questionnaires: Pivotal RCTs PRU-INT-6 (18, 19), PRU-USA-11 (20, 21), PRU-USA-13 (22, 23) 65
Table 27: Quality of life data derived from PAC-QOL and SF-36 questionnaires: Pivotal RCTs PRU-INT-6 (18, 19), PRU-USA-11 (20, 21), PRU-USA-13 (22, 23) 65
Table 28: Efficacy data derived from diaries and patient global assessment questionnaires: PRU-INT-12 (24) 68
Table 29: Efficacy data derived from PAC-SYM questionnaires: PRU-INT-12 (24) 69
Table 30: Quality of life data derived from PAC-QOL questionnaires: PRU-INT-12 (24) 69
Table 31: Efficacy data derived from diaries and patient global assessment questionnaires: PRU-INT-8 (25) 71
Table 32: Efficacy data derived from PAC-SYM questionnaires: PRU-INT-8 (25) 73
Table 33: Quality of life data derived from PAC-QOL and SF-36 questionnaires: PRU-INT-8 (25) 73
Table 34: Primary and key secondary efficacy data: PRU-USA-28 (26) 75
Table 35: Further secondary efficacy data: PRU-USA-28 (26) 77
Table 36: Non-RCTs relevant to the submission 80
Table 37: Methodology of relevant non-RCTs (PRU-INT-10, PRU-USA-22, PRU-INT-17) (27-29) 81
Table 38: Patient disposition over time (PRU-INT-10, PRU-USA-22, PRU-INT-17) (27-29) 82
Table 39: Patient demographic data and reasons for discontinuation (PRU-INT-10, PRU-USA-22, PRU-INT-17) (27-29) 82
Table 40: Summary of efficacy results for relevant non-RCTs (PRU-INT-10, PRU-USA-22, PRU-INT-17) (27-29) 83
Table 41: Summary of methodology of PRU-USA-26 (1, 2) 86
Table 42: Eligibility criteria in PRU-USA-26 (1, 2) 86
Table 43: Characteristics of participants in PRU-USA-26 (1, 2) 87
Table 44: Primary and secondary outcomes of PRU-USA-26 (1, 2) 88
Table 45: Quality assessment of PRU-USA-26 (1, 2) 90
Table 46: TEAEs occurring in ≥ 5% of patients in any PRU treatment arm 92
Table 47: TEAEs occurring in ≥ 5% of patients in any PRU treatment arm 99
Table 48: TEAEs occurring in ≥ 5% of patients in any PRU treatment arm 100

Table 49: TEAEs occurring in ≥ 5% of patients 102
Table 50: TEAEs occurring in ≥ 5% of patients in any PRU treatment arm 103
Table 51: Summary of incidence and most frequently reported treatment related adverse events (PRU-INT-10, PRU-USA-22 and PRU-INT-17) (27-29) 104
Table 52: Key features of analysis 121
Table 53: Clinical trial data incorporated in the model 124
Table 54: Summary of variables applied in the economic model 128
Table 55: Mean utility scores 133
Table 56: Unit costs associated with the technology in the economic model 142
Table 57: Cost and QALY data for SmPC Base Case (treatment compliance 80%) 148
Table 58: Cost and QALY data for ≥3 SCBM responders (primary clinical endpoint) 149
Table 59: Cost and QALY data for partial responders (≥1 improvement in SCBM responders = secondary clinical endpoint) 150
Table 60: CEACs for patients achieving ≥3 SCBMs – baseline adjusted 151
Table 61: CEACs for patients achieving ≥3 SCBMs – without baseline constipation-severity-related treatment effect 151
Table 62: Cost and QALY data for ≥3 SCBM responders (primary clinical endpoint) 155
Table 63: Female population England and Wales (000's) - mid-2008 estimated population (40) 158
Table 64: National tariffs 162
Table 65: Cumulative budget impact over 5 years (£000) 163

List of abbreviations

AE	Adverse event
b.i.d.	Twice daily
BM	Bowel movement
CC	Chronic constipation
CMH	Cochran-Mantel-Haenszel test
CPMP	Committee for Proprietary Medicinal Products
CSR	Clinical study report
DB	Double blind
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EMA	European Medicines Agency
GI	Gastrointestinal
ITT	Intent-to-treat
JRF	Janssen Research Foundation
o.d.	Once daily
OIC	Opioid induced constipation
OL	Open label
PAC-QOL	Patient Assessment of Constipation – Quality of Life
PAC-SYM	Patient Assessment of Constipation – Symptoms
QOL	Quality of life
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia
SAE	Serious adverse event
SBM	Spontaneous, non-laxative induced bowel movement
SCBM	Spontaneous, non-laxative induced complete bowel movement
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SF-36	36-item Short Form Health Survey
VAS	Visual Analogue Scale
vs	versus

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Burden of disease

Constipation is a common, complex and debilitating medical problem with symptoms including infrequent defecation (typically fewer than three per week), excessive straining with defecation, lumpy or hard stools, sensation of incomplete evacuation, abdominal bloating and abdominal pain or discomfort (3-5). Constipation can be defined as either primary (idiopathic or functional) or secondary (due to systemic or neurologic disorders, or medications). Different working groups have recognised that constipation is a multifactorial phenomenon with a complex symptomatology and thus, have stressed the importance of considering the different symptoms in its definition.

Although chronic constipation is not-life threatening, the bothersome nature of the symptoms, the chronic nature of the disease and inadequate control with current laxative treatment options constitute a significant burden to the patient, society and the NHS. From a patient perspective, chronic constipation may have significant impact on quality of life (QoL) in term of impaired psychological well-being and daily life restrictions. In a study spanning 7 countries and over 2,500 patients, the detrimental effect of chronic constipation on QoL was similar to that seen in women with a history of diabetes, heart disease or depression (6). Work absenteeism due to chronic constipation is considerable as many patients are under the age of 65. There is a substantial and inefficient utilisation of health resource by those patients who remain dissatisfied with their current treatment. These patients often unsuccessfully seek an alternative treatment that may relieve their symptoms, translating into repeat medical visits, tests, expensive diagnostic procedures and medication costs.

Epidemiology and risk factors

The prevalence of constipation in the population is difficult to accurately estimate as it is highly dependent on whether constipation is self-assessed by the patient or diagnosed by the physician. However, estimates indicate that 10-15% of the general population in Europe, USA and Canada suffer from any type of (chronic) constipation. Worldwide, constipation is more frequent in women, children and the elderly. All studies on constipation have found that females have a higher incidence of constipation compared with males (range 2.1-3 to 1). In Europe, risk factors associated with the development of chronic constipation have been studied in a sample of more than 20,000 subjects randomly selected from the General Practice Research Database (GPRD) on the basis of having a diagnosis of constipation (7). According to these data, female gender, increasing age, multiple sclerosis, parkinsonism, and dementia are independent risk factors for chronic constipation. Most medications assessed, particularly aluminium containing antacids, diuretics, opioids, antidepressants, antispasmodics, and anticonvulsants, were associated with a higher risk of chronic constipation.

Current management and unmet need

Multiple guidelines for the management of chronic constipation have been published; most of them recommend a stepped approach based on life style changes and use of laxatives in adults and the elderly. If functional or idiopathic constipation is suspected, non-pharmacologic measures, such as diet modification and exercise, are recommended in the first instance. Pharmacologic measures should be prescribed only when the non-pharmacologic measures fail to alleviate the constipation. There is no clear evidence regarding which laxative is superior (8-12). The goals of management include improving symptoms, restoring normal bowel function, increasing colonic transit if abnormal, and facilitating defecation (13). Further to the increase in the frequency of bowel movements, relief of constipation-related symptoms is an important and much desired treatment goal for many patients.

Systematic reviews (10, 14-16) have highlighted the lack of high quality clinical effectiveness data for laxatives. Many of the trials are based on small sample sizes and lack the power to establish the efficacy of individual agents. In addition, one review (10) reported that inter-trial comparisons or pooling of results in meta-analyses were not feasible because of the wide variation in definitions of constipation and the outcomes being assessed.

Most laxatives act by binding water, increasing stool mass/volume or improving stool consistency and as such they induce more bowel movements. As they work only directly on stool mass, they have a lack of effect on delayed gastric emptying, impaired colon motility or reduced sensory pain thresholds that are frequently also present in these patients. Their short term effect on increasing the number of bowel movements is documented but the evidence towards consistent and long term symptom relief, or on producing sustained complete and satisfactory bowel movements is scarce and controversial at best. While the absolute number of bowel movements is considered important from the physician's point of view, the patient him/herself tends to focus less on bowel frequency and is more concerned about bothersome symptoms. Data support that bloating, straining, hard stool, abdominal discomfort, low number of bowel movements and sensation of incomplete evacuation are particularly bothersome (17).

In search for relief, patients switch between drugs, combine drugs and increase dosages beyond recommended doses. Inappropriate treatment leads to complications such as haemorrhoids, volvulus, acute constipation and faecal impaction. Some sources have linked persistent constipation to polyps and colon cancer. Different epidemiology studies support the high degree of dissatisfaction with current laxatives (between 30-55%) mainly due to lack of efficacy and unpleasant posology. Evidence shows that the most difficult problem relates to the many patients who have been suffering for a significant length of time (median 20 years in the prucalopride pivotal studies) and have exhausted the available therapeutic options.

Prucalopride is targeted at patients with a clear unmet medical need and is intended to be used in the patient population, in which laxatives have failed to provide adequate relief. Use of prucalopride in refractory patients should facilitate a reduction in the use of NHS resource and reduce the use of inefficient laxatives.

Prucalopride

Resolor® (prucalopride succinate), is a highly selective high affinity serotonin (5-HT4) receptor agonist with enterokinetic activities that predominantly stimulates colonic motility, thereby restoring bowel function, improving symptoms and quality of life. Prucalopride belongs to the therapeutic and pharmacological WHO ATC subgroup class (A03AE04) of drugs for the treatment of functional bowel disorders that are acting on serotonin receptors. ***Prucalopride belongs to a different therapeutic and pharmacological class to laxatives (A06).***

Prucalopride has an enterokinetic mechanism of action, meaning that it restores impaired gut motility. Prucalopride increases AcH release through stimulation of 5-HT4 receptors predominantly located in the gut, thereby inducing High Amplitude Propagating Contractions (HAPC) that propels colonic mass. Prucalopride is predominantly active on the colon and has some effect on gastric motility. In contrast to other 5-HT4 agonists prucalopride has no effect on other receptors or cardiovascular channels (such as HERG channels).

On October 23rd 2009 Movetis obtained approval from the European commission for the commercialisation of prucalopride in the European Economic Area (EU/1/09/581/001 and EU/1/09/581/002). Prucalopride was launched in the UK at the British Society of Gastroenterology meeting on 23rd March 2010.

Prucalopride is indicated for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. Prucalopride is supplied as 1 mg and 2 mg film coated tablets. The licensed dose for adults (18-65 years) is 2 mg once daily and for the elderly (>65 years) a starting dose of 1 mg once daily; if needed the dose can be increased to 2 mg once daily. Both the 1 mg and 2 mg tablets are supplied as a pack of 28 tablets at a cost of £38.69 and £59.52 per pack, respectively. The daily cost of the 1 mg tablet is therefore £1.38 and for the 2 mg tablet is £2.13. Aggregated data from the three phase III pivotal trials suggest that approximately one third of patients will not satisfactorily respond to enterokinetic therapy and will cease medication after one pack of prucalopride (28 tablets). These patients are suspected not to have motility disorders and other causes should be considered. A further one third of patients will have a clinically meaningful benefit (as supported by QoL data) and are expected to use the medication. In this sub-set it is anticipated that patients will not take medication when they are free of symptoms, recommencing their medication only when symptoms return. Approximately one third of patients will experience normalisation of disease (primary endpoint in the trials) and are expected to use medication almost continuously.

Efficacy and safety

- The efficacy and safety of prucalopride has been studied in the largest clinical programme ever conducted in chronic constipation to date. All the clinical trials were placebo controlled and as such the comparator arm was intended to represent those patients who had failed to achieve adequate relief with laxatives
- Patients included in the studies had a high degree of severity of constipation; they had a long standing history of chronic constipation of 20 years and > 85 % were dissatisfied with available treatment (laxatives). The mean number of SCBMs per week prior to entry into the trials was 0.5, approximately 57% had no SCBM and quality of life was very low.
- Three large pivotal, double-blind, randomised, placebo-controlled studies evaluated the efficacy and safety of prucalopride in adults (≥ 18 years) with chronic constipation
- Consistent results from the three studies demonstrated that a statistically significantly higher proportion of patients in the prucalopride 2 mg treatment group achieved the

stringent primary efficacy endpoint of ≥ 3 SCBMs per week ('normalisation') when compared with placebo, 23.6% vs 11.3% (pooled results)

- The positive effect of treatment was evident over the first 4 weeks and maintained over the 12 weeks of the double blind studies. Long-term follow-up studies demonstrated that efficacy, as measured by PAC-QOL, was maintained for up to 2.6 years
- In all three pivotal studies prucalopride showed a statistically significant and consistent effect on a wide range of secondary endpoints that assessed all clinically relevant aspects of chronic constipation
- Pooled results showed that 43.1% of patients that received 2 mg prucalopride compared with 24.6% of placebo-treated patients had an increase of at least 1 SCBM per week
- Prucalopride significantly improved bowel movement symptoms (consistency, straining during defecation), shortened the time to first SCBM, and reduced the use of laxatives. When all bowel movements were considered, prucalopride decreased stool hardness and severe staining, without increasing the number of watery stools
- A consistent significant improvement in patient satisfaction with treatment and their bowel habits (subscale of PAC-QOL) was observed with prucalopride across the pivotal phase III studies; 45.3% of prucalopride-treated patients compared with 21.3% of placebo-treated patients achieved a ≥ 1 point improvement in the satisfaction subscale score (5 point Likert scale)
- The improvement with prucalopride was also statistically significant when compared with placebo for the overall PAC-QOL and each of the remaining subscales (physical discomfort, psychosocial discomfort, worries and concerns) at every time point ($p < 0.001$)
- Evidence that efficacy is maintained when patients restart treatment after a period off medication comes from the treatment study where two treatment periods of one month were separated by a washout of at least two weeks. Response rates on the primary and secondary endpoints were similar in both treatment periods. In the period between treatments, there was no evidence of a rebound effect on bowel movements or disease symptoms and there was no increase in laxative use beyond the initial baseline levels. The lack of rebound effect is further supported by data from the follow-up phase from a dose-response study that showed a gradual disappearance of effect after cessation of treatment
- Specific studies in elderly patients with long-standing chronic constipation demonstrated that prucalopride 1 mg and 2 mg were more efficacious than placebo, with benefits generally more pronounced with prucalopride 1 mg. Decreased renal clearance in the elderly is believed to explain this effect
- Data from the opioid-induced constipation population supports the results obtained in the pivotal studies. The studies are smaller and consequently do not always show statistical significance, however the numerical superiority for the prucalopride groups are consistent with the results from the pivotal studies and suggest that there may be a role for prucalopride in this patient population
- Prucalopride was well tolerated in patients with chronic constipation
- The most frequently reported adverse events (AEs) associated with prucalopride treatment were headache and GI symptoms (nausea, diarrhoea and abdominal pain), these were expected from the type of medicinal product and occurred predominantly in the first day of treatment. As of day two the incidence of these AEs was similar in both prucalopride and placebo groups

- The AEs were generally mild to moderate in severity and the proportion of patients discontinuing due to AEs was low
- Long-term treatment with prucalopride was well-tolerated with an adverse event profile similar to that observed in the phase III pivotal studies. No new safety signals emerged during the long term studies
- Data from all studies suggest that there is no difference between placebo and prucalopride on QT interval and other ECG. This conclusion is supported by results from two placebo controlled studies and a thorough (positive controlled) QT study, all of which confirmed that prucalopride had no effect on QT interval

Cost-effectiveness

Highlighted results

Using the model, the probability of prucalopride costing more than £20,000 per QALY in the target population is unlikely (<50%). In the adult female population (18-65 years), which suffers the greatest reduction in quality of life as a consequence of laxative refractory chronic constipation, prucalopride has the most reliable cost effectiveness outcome. The 4-week early stopping rule, recommended in the SmPC, allows non-responders to be identified and removed from treatment at the earliest opportunity, which avoids wasting resources on ineffective medication.

The Cost and QALY for responders (defined as ≥3 SCBMs/week = primary clinical endpoint)

≥3 SCBM responders	Average incremental cost/year (SD)	Average QALY gained per year (SD)	Average cost/QALY (SD)
All females (base case)	£498(108)	0.0316 (0.1124)	£15,700 (961)
Adult females (18-65 yrs)	£622 (0)	0.0369 (0.0450)	£16,800 (—)
Elderly females (>65 yrs)	£403 (0)	0.0342 (0.1495)	£11,700 (—)

The cost effectiveness model

A de-novo economic evaluation of the cost effectiveness of prucalopride (plus rescue medication) versus placebo (plus rescue medication) was undertaken in patients suffering from long term chronic constipation who had failed on prior laxative therapy. As the licensed indication for prucalopride is restricted to females the economic model takes into account the female population from the prucalopride clinical trials. Specific trials were conducted in the elderly population (65+ years) and the licensed dose of prucalopride for this group of patients is 1 mg daily, the adult (18-65 years) daily licensed dose is 2 mg. The model was therefore designed to evaluate the cost effectiveness of prucalopride in two populations; adults (18-65 years) and the elderly (65+ years). A decision analytical framework was used to develop the economic model, which used patient level data taken directly from the clinical trials. The model time horizon was 52 weeks.

All the available patient data from the clinical trials were identified for adult female patients receiving 2 mg prucalopride and for elderly female patients receiving 1 mg prucalopride. For the first 12 weeks of the economic model in the adult patients the analysis uses patient level data from the trials identified. Observational data collected for an additional 40 weeks beyond the initial trial period emphasised that patient satisfaction with prucalopride therapy was maintained to 52 weeks. The elderly clinical trials only covered a 4 week period and therefore observational data was utilised to extend the analysis out to 52 weeks.

Mapping to EQ-5D

Quality of life was measured in the prucalopride trials using the patient assessment of constipation outcome measures (PAC-SYM and PAC-QOL) and generic SF-36. The latter was applied at multiple time periods. The relationship between SF-36 and the PAC measures enabled mapping to EQ-5D.

Drug acquisition costs

Drug acquisition costs incorporated into the model reflect the full list price for prucalopride, average duration of treatment was calculated as 220 days per year based on data taken from the clinical trials. The duration of prucalopride use varies for each patient depending on response/non-response to treatment. In order to optimise and realistically assess the cost effectiveness of prucalopride a treatment continuation rule has been implemented to ensure the treatment is focused entirely on patients who are responding to treatment (returned to normal bowel movements). The development of a treatment continuation rule for prucalopride is facilitated by two important characteristics of the drug. Firstly, the speed of the clinical response to prucalopride and secondly the visibility and ease of assessment of the physical response. As such the treatment continuation rule suggests reassessment of the patient after four weeks by a GP if patients are not responding to treatment at this timepoint they discontinue prucalopride. In addition patients who have responded in the initial four weeks are reassessed after 12 weeks to ensure that treatment effectiveness is sustained.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

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.

Resolor® (prucalopride succinate), is a highly selective high affinity serotonin (5HT4) receptor agonist with enterokinetic activities that predominantly stimulates colonic motility. Prucalopride belongs to the therapeutic and pharmacological WHO ATC subgroup class (A03AE04) of drugs for the treatment of functional bowel disorders that are acting on serotonin receptors. Prucalopride belongs to a different therapeutic and pharmacological class to laxatives (A06).

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

Prucalopride has an enterokinetic mechanism of action meaning that it restores impaired gut motility. Prucalopride increases AcH release through stimulation of 5-HT4 receptors predominantly located in the gut, thereby inducing High Amplitude Propagating Contractions (HAPC) that propels colonic mass. Prucalopride is predominantly active on the colon and has some effect on gastric motility. In contrast to other 5 HT4 agonists prucalopride has no effect on other receptors or cardiovascular channels (such as HERG channels) with clinical doses, and with doses far in excess of clinical doses.

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).

On October 23rd 2009 Movetis obtained approval from the European commission for the commercialization of prucalopride in the European Economic Area (EU/1/09/581/001 and EU/1/09/581/002).

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 initially proposed therapeutic indication was: Prucalopride is indicated for the treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief.

After review of the dossier the indication has been revised and endorsed by CHMP to become: Prucalopride is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. Female only: **(EPAR pp 47/49)**

Three discussions have guided that revision:

- **Chronic Constipation in Males:** The majority of patients included in the 3 pivotal phase III trials were females, Caucasian with a mean age of approximately 50 years; 227 (11.4%) of the patients were male. A comprehensive Pharmacokinetic (PK) and pharmacodynamic (PD) (time to first bowel movement and total gut transit time) analysis was performed confirming there was no gender difference. Despite this evidence, EMA considered that there were insufficient data to conclude on the efficacy of prucalopride in males.

  A further sub-group analysis that corrected for a statistically significant difference in disease severity at entry between the males 2 mg group and other treatment groups in males (placebo, 4 mg of prucalopride) and females (placebo, 2 mg and 4 mg prucalopride group) supported the efficacy of 2 mg of prucalopride in males. This analysis was only partly accepted by EMA.

  Although the available data suggest that prucalopride 2 mg may be equally effective in males and females, Movetis has agreed to perform a confirmatory extra trial in males to be started in H 1 2010.

- **Treatment duration**: Treatment duration in the pivotal phase III trials was, after scientific advice from EMA, set at 3 months. Based upon analysis of the QOL data on patient-reported satisfaction with bowel function and treatment in the long term open label trials, no specific time limitation was put on treatment duration. It was deemed important to add a statement in the label that responders can be identified after 4 weeks or one pack of prucalopride and that regular reassessment during chronic use is advisable. In addition, a statement has been added in the SmPC that data from open label studies up to 2.6 years offer some evidence for longer-term safety and efficacy; however, no placebo controlled efficacy data for treatments longer than 12 weeks duration are available. Movetis has agreed to perform a confirmatory long term (6 months treatment duration) trial to be initiated in 2010. Treatment duration: Long term efficacy EPAR pp 37-38, 40 (patient exposure), and 47/49

- **Opioid Induced Constipation (OIC)**: Results from a Phase II clinical trial indicate that prucalopride is effective and well tolerated in patients with constipation due to the intake of opioids. It was considered by EMA that secondary causes of chronic constipation such as OIC are a separate sub-set of the target patient population and no specific statements were added in the SmPC. In the EPAR (*Population with "Opioid-Induced Constipation"* **EPAR: pp 38-39/49)** the results of the only completed phase II trial (196 patients) are summarized. It showed an increase in the percentage of patients that had an improvement of ≥ 1 SCBM per week (primary endpoint) of 35.9% (pru 2 mg) vs. 23.4% on placebo. Pooled data from all controlled data (n = 274) confirmed that the % of patients with clinically meaningful improvement of ≥ 1 point on patient-reported satisfaction was higher on PRU 2 mg (32.5%, p ≤ 0.05) compared to placebo (19.0%) after 4 weeks of treatment. Movetis has agreed to perform a phase III programme both in cancer and non-cancer patients with constipation due to the intake of opioids, to be started in H1 2010.

In addition questions were asked on the toxicity profile, further work was done to confirm that prucalopride has not revealed any relevant toxicology signals for humans. No further monitoring or actions were requested.

An extra thorough QTc study was also performed that confirmed a lack of QT effect for Prucalopride. It was therefore agreed that, above normal PV activities, no specific QT related monitoring was required..

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

Prucalopride is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. It is anticipated that with further research the indication will be extended to include:

- Patients with opioid Induced constipation.
- Children
- Chronic constipation in males in whom laxatives fail to provide adequate relief.

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.

A drug interaction study with oral contraceptives is currently ongoing to evaluate the effect of prucalopride on plasma levels of oral contraceptives (ethinylestradiol and norethisterone) in healthy subjects.

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

Prucalopride was launched in the UK at the British Society of Gastroenterology meeting on 23rd March 2010.

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

EMA approval has been obtained for the 27 countries of the EU and Iceland, Liechtenstein, Norway

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 intend to appraise prucalopride imminently.

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 A1 Unit costs of technology being appraised

Pharmaceutical formulation	Prucalopride succinate film coated tablets containing 1mg or 2mg of prucalopride succinate as active substance. The excipients used include lactose monohydrate microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate
Acquisition cost (excluding VAT)	1mg £38.69 / 28 tablets 2 mg £59.52 /28 tablets
Method of administration	Oral
Doses	1mg and 2mg
Dosing frequency	Once daily
Average length of a course of treatment	150 days*
Average cost of a course of treatment	Daily average cost: 1mg £1.38 (estimated 30% of patients) 2mg £2.13 (estimated 70% of patients)
Anticipated average interval between courses of treatments	Treatment is for a chronic condition and is likely to be continuous*
Anticipated number of repeat courses of treatments	Treatment is for a chronic condition and is likely to be continuous*
Dose adjustments	1mg initial dose in elderly patients and patients with renal or hepatic impairment

* Aggregated data from three phase III trials suggest that approximately one third of patients will not satisfactorily respond to enterokinetic therapy and will cease medication after one pack of prucalopride (28 tablets). These patients are expected not to have a motility disorders and other causes should be suspected. A further one third of patients will have a clinically meaningful benefit (as supported by QOL data) and are expected to use the medication for an average 150 days out of 365 (comparable to other drugs for this indication). In this sub set it is anticipated that patients will not take medication when they

are free of symptoms, recommencing their medication only when symptoms return. Approximately one third of patients will experience normalization of disease (primary endpoint in the trials) and are expected to use medication almost continuously (treatment duration in open long term follow-up trials in responders was in excess of 200 days).

Patients, who respond to initial treatment with prucalopride but cease treatment, will respond to medication if restarted.

Changes to lifestyle such as improved diet, increased exercise, and weight loss may result in reduced need for therapy.

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, not a medical device.

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

None expected.

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

No need for monitoring.

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?

None anticipated.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

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.

Chronic constipation is a complex problem that may have different underlying aetiologies including primary or idiopathic (slow or normal) transit constipation, to secondary causes such as drug usage (opioid induced constipation), neuromuscular conditions and metabolic diseases that impair colonic motility and result in low number and low amplitude of contractions.

According to the Rome III criteria, chronic constipation is defined as the presence of 2 or more of the following symptoms for at least 3 months with symptom onset at least 6 months prior to diagnosis:

- Straining during at least 25% of defecations;
- Lumpy or hard stools in at least 25% of defecations;
- Sensation of incomplete evacuation for at least 25% of defecations;
- Sensation of anorectal obstruction/blockage for at least 25% of defecations;
- Manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor);
- Fewer than 3 defecations per week.

In addition, the patient should not meet the suggested criteria for irritable bowel syndrome (IBS) and loose stools are rarely present without the use of laxatives.
Chronic constipation should be differentiated from acute constipation episodes that may follow a short-term administration of certain medications or transient changes in lifestyle for example during holidays. In these conditions, the decrease in bowel frequency may be accompanied by constipation-related symptoms but it usually reverses once the medication is stopped or the individual resumes his/her normal lifestyle.

The prevalence of constipation in the population is difficult to accurately estimate as it is highly dependent on whether constipation is self-assessed by the patient or diagnosed by the physician. However, estimates indicate that 10-15% of the general population in Europe, USA and Canada suffer from any type of (chronic) constipation. Worldwide, constipation is more frequent in women, children and the elderly. All studies on constipation have found that females have a higher incidence of constipation compared to males (range 2.1-3 to 1). It is estimated that males represent between 25-30 % of the total population of chronically constipated patients. Data also support that females are twice as likely to consult a doctor rather than males.

Although chronic constipation is not a life-threatening medical problem, its high prevalence, the bothersome nature of the symptoms, the chronic nature of the disease and the inadequate control with current laxative treatment options makes chronic constipation a public health concern. Chronic constipation inflicts a heavy burden to the patient (in terms of an impaired psychological well-being and overall QOL), to the society (due to work

absenteeism) and to the health system (due to the substantial and inefficient health resource utilisation by these patients who remain dissatisfied and often unsuccessfully seek an alternative treatment that may relief better their constipation). This translates into frequent visits to the treating physician and the unnecessary performance of expensive diagnostic procedures to rule out other causes of constipation.

2.2 How many patients are assumed to be eligible? How is this figure derived?

The total potential eligible patient group that might benefit from prucalopride in the UK is estimated at 363,000. This represents approximately 25% of the 1.5 million patients that are actively followed by physicians for treatment of chronic constipation in the UK. The estimate of uptake is derived for the total UK population of 59 million of which approximately 20% are children (for whom prucalopride is not currently licensed), 65% are adults and 15% are elderly (OECD 2007), and has been calculated assuming an average prevalence of chronic constipation of 7.7% amongst adult and elderly patients and further assuming that 10 % of constipation patients are dissatisfied or refractory to laxatives.

2.3 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 its licensed indication there are no current NICE Guidelines for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.

2.4 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 constipation are managed in primary care. Multiple guidelines for the first line management of chronic constipation have been published. If functional or idiopathic constipation is suspected, non-pharmacologic measures such as a diet modification and exercise are recommended in the first instance. Pharmacologic measures should be prescribed when the non-pharmacologic measures fail to alleviate the constipation. The goals of management include improving symptoms, restoring normal bowel function (by improving colonic transit and facilitating defecation) and ultimately improving patient satisfaction, functioning, and psycho-social well-being. More than the increase in the frequency of bowel movements alone, is the relief of constipation-related symptoms an important and much desired treatment goal for many patients.
Chronic (> several years) and severe constipation (the population studied by prucalopride) is a much more complex condition to manage. Especially those patient that do not get adequate relief with laxatives have limited options left. In such circumstances, referral to specialist services may be required where a wider range of diagnostic and more appropriate use of treatment options may be beneficial.

Because prucalopride is intended for use in laxative refractory patients, the current initial primary care guidelines are not expected to change.

Prucalopride is intended to be used as a substitute for laxatives in this patient population, by definition; laxatives have been identified as being ineffective or inadequate. Use of Prucalopride in refractory patients should show a reduction in the use of NHS resource and reduce use of inefficient laxatives.

Identification of the target patients by physicians will be based upon the clinical trial data and include following 4 criteria:

- Onset of symptoms at least 6 months prior to diagnosis
- Should have tried at least one laxative with unsatisfactory symptomatic response
- Fewer than three satisfactory defecations per week on laxative treatment
- Breakthrough symptoms on laxative treatment must include two or more of the following in at least 25% of defecations:
    - Straining
    - Lumpy or hard stools
    - Sensation of incomplete evacuation
    - Sensation of anorectal obstruction/blockage

Within the target patient population potential non-responders can be rapidly identified using an early stopping rule (if no response is seen within 4 weeks prucalopride is stopped) which ensures that prucalopride can be accurately targeted on responders, thus optimizing the use of scarce NHS resources. In addition, the easy and early identification of non-responders enables clinicians to more accurately identify patients with potentially organic or non-primary motility aetiology in order to cease prucalopride and take appropriate alternative action to effectively treat the patient.

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

While the absolute number of bowel movements itself is widely used and a recognized endpoint from a regulatory or clinical development standpoint, the patient herself seldom focuses on bowel movements only, but is more concerned about bothersome symptoms. Patients with constipation go to the doctor because they complain of (in order of importance) straining, gas, abdominal discomfort, low number of BM, bloating and incomplete bowel movements. Bloating, abdominal discomfort, straining and sensation of incomplete bowel movements in particular are bothersome symptoms that are not adequately relieved by laxatives and affect adversely QOL.

Despite widespread usage, there is little evidence to support the long term use of laxatives. Different epidemiology studies support the high degree of dissatisfaction with current laxatives (between 30-55 %) mainly due to lack of efficacy and unpleasant posology. Evidence shows the most difficult problem relates to the many patients who have been suffering for a significant length of time (> 20 years in our studies) and have exhausted the available therapeutic options. In search for relief people switch between drugs, combine drugs and increase dosages beyond recommended doses (IMS data). Inappropriate treatment leads to complications such as haemorrhoids, volvulus, acute constipation and

faecal impaction. Some sources have linked persistent constipation to polyps and colon cancer.

Healthcare resources are inefficiently used (partly or not effective treatments are still used because of lack of alternatives) which is expected to result in unnecessary visits and examinations. Significant numbers of patients with faecal impaction continue to be admitted today to hospitals despite the availability and widespread use of laxatives. Prucalopride may have a beneficial effect on the number of these events.

Only these patients who are considered to have 'failed' on laxatives will be considered for treatment with prucalopride.

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

Given its licensed indication - symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief - no comparators can be defined.

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

The most common adverse reactions with prucalopride in the clinical studies were headache, nausea, diarrhoea, and abdominal pain. Episodes of headache related to prucalopride are mainly mild to moderate, transient in nature and resolve without additional treatment. Similar to headache, the episodes of diarrhoea, nausea and abdominal pain are mainly mild to moderate, transient in nature and resolve without additional treatment.

2.8 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.

The resource use associated with prucalopride will mainly be visits to gastroenterology clinicians and general practitioners. A potential reduction in hospital admissions for complications (e.g. faecal impaction) – prevalent problem in laxative non-responders - is being investigated.

It is anticipated that the use of prucalopride within the licensed indication will release resource currently being utilised inefficiently on a suite of unproductive physician visits, investigative procedures and tests.

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

Existing infrastructure will be sufficient and will not need changing.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

N/A

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

The licensed indication restricts the use of prucalopride to women with chronic constipation in whom laxatives fail to provide adequate relief; this may appear to discriminate against males however the burden of this condition is far greater in women. The gender mix of patients recruited into the phase III clinical trials suggests that approximately 85% of patients with chronic constipation are female. At some time in the future the indication may extend to include males with chronic constipation who fail to achieve adequate relief with laxatives. This trial is planned to start in 2010.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

The Health Economic model focuses on costs and benefits for the treated female population, analyzing the patient reported outcomes from the total female population in the phase III trials. These patient reported outcome data are converted into standardized EQ-5D metrics and used to calculate QALY values. QALY values have been calculated for various sub-groups within the total data set, these show that prucalopride produces cost effective improvements in the health of all of the treated female population.

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief, and for whom more invasive procedures, such as direct rectal intervention, are being considered	Women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief	The population treated with prucalopride would be as per the indication. None responders to prucalopride may be referred for more invasive procedures
Intervention	Prucalopride	Prucalopride	none
Comparator(s)	• standard therapy without prucalopride • invasive procedures such as rectal interventions (including enemas, suppositories and manual evacuation) • bowel surgery	• standard therapy without prucalopride	Invasive procedures and bowel surgery are not direct comparators with prucalopride. Invasive procedures provide short term relief only. Bowel surgery may be necessary as a last resort
Outcomes	The outcome measures to be considered include: • proportion of patients with ≥ 3 SCBM per week • number of spontaneous complete bowel movements per week • improvement in symptoms of constipation • adverse effects of treatment	• Proportion of patients with ≥ 3 SCBM per week • Frequency of (spontaneous complete) bowel movements • Alleviation of chronic constipation symptoms including abdominal pain or discomfort, bloating and straining as measured with the validated patient-reported PAC-SYM symptom severity index • Long term safety data (including potential CV	N/A

	• health-related quality of life	and CNS events) • Satisfaction with bowel movements, bowel function and treatment and clinically meaningful improvement in health-related quality of life outcomes, as measured with the validated PAC-QOL questionnaire	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost utility analysis using the disease-specific patient reported outcome measure PAC-QOL derived from the clinical trial programme being 'mapped' on to EQ-5D to generate a ICER Overall period of analysis is 52 weeks. Perspective of the NHS	
Subgroups to be considered		Elderly women (65 years and older)	Of the total adult female population, elderly women (65 years and older) with chronic constipation are a specific sub-group that need special consideration The burden of disease sits unequally in this group of society
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation.	N/A	N/A

Section B – Clinical and cost effectiveness

5 Clinical evidence

Summary of clinical evidence

- The efficacy and safety of prucalopride has been studied in the largest clinical programme ever conducted in chronic constipation to date.
- Patients included in the studies had a high degree of severity of constipation; they had a long standing history of chronic constipation of 20 years and > 85 % were dissatisfied with available treatment (laxatives). The mean number of SCBMs per week prior to entry into the trials was 0.5, approximately 57% had no SCBM and quality of life was very low.
- Three large pivotal, double-blind, randomised, placebo-controlled studies evaluated the efficacy and safety of prucalopride in adults (≥ 18 years) with chronic constipation
- Consistent results from the three studies demonstrated that a statistically significantly higher proportion of patients in the prucalopride 2 mg treatment group achieved the stringent primary efficacy endpoint of ≥ 3 SCBMs per week ('normalisation') when compared with placebo, 23.6% vs. 11.3% (pooled results)
- The positive effect of treatment was evident over the first 4 weeks and maintained over the 12 weeks of the double blind studies. Long-term follow-up studies demonstrated that efficacy, as measured by PAC-QOL, was maintained for up to 2.6 years
- In all three pivotal studies prucalopride showed a statistically significant and consistent effect on a wide range of secondary endpoints that assessed all clinically relevant aspects of chronic constipation
- Pooled results showed that 43.1% of patients that received 2 mg prucalopride compared with 24.6% of placebo-treated patients had an increase of at least 1 SCBM per week
- Prucalopride significantly improved bowel movement symptoms (consistency, straining during defecation), shortened the time to first SCBM, and reduced the use of laxatives. When all bowel movements were considered, prucalopride decreased stool hardness and severe staining, without increasing the number of watery stools
- A consistent significant improvement in patient satisfaction with treatment and their bowel habits (subscale of PAC-QOL) was observed with prucalopride across the pivotal phase III studies; 45.3% of prucalopride-treated patients compared with 21.3% of placebo-treated patients achieved a ≥ 1 point improvement in the satisfaction subscale score (5 point Likert scale)
- The improvement with prucalopride was also statistically significant when compared with placebo for the overall PAC-QOL and each of the remaining subscales (physical discomfort, psychosocial discomfort, worries and concerns) at every time point ($p < 0.001$)
- Long-term follow-up studies demonstrated that efficacy, as measured by PAC-QOL, was maintained for at least 12 months. Patients have been treated successfully for up to 2.6 years
- Evidence that efficacy is maintained when patients restart treatment after a period off medication comes from the treatment study where two treatment periods of one month were separated by a washout of at least two weeks. Response rates on the primary and secondary endpoints were similar in both treatment periods. In the period between

treatments, there was no evidence of a rebound effect on bowel movements or disease symptoms and there was no increase in laxative use beyond the initial baseline levels. The lack of rebound effect is further supported by data from the follow-up phase from a dose-response study that showed a gradual disappearance of effect after cessation of treatment

- Specific studies in elderly patients with long-standing chronic constipation demonstrated that prucalopride 1 mg and 2 mg were more efficacious than placebo, with benefits generally more pronounced with prucalopride 1 mg. Decreased renal clearance in the elderly is believed to explain this effect
- Data from the opioid-induced constipation population supports the results obtained in the pivotal studies. The studies are smaller and consequently do not always show statistical significance, however the numerical superiority for the prucalopride groups are consistent with the results from the pivotal studies and suggest that there may be a role for prucalopride in this patient population
- Prucalopride was well tolerated in patients with chronic constipation
- The most frequently reported adverse events (AEs) associated with prucalopride treatment were headache and GI symptoms (nausea, diarrhoea and abdominal pain), these were expected from the type of medicinal product and occurred predominantly in the first day of treatment. As of day two the incidence of these AEs was similar in both prucalopride and placebo groups
- The AEs were generally mild to moderate in severity and the proportion of patients discontinuing due to AEs was low
- Long-term treatment with prucalopride was well-tolerated with an adverse event profile similar to that observed in the phase III pivotal studies. No new safety signals emerged during the long term studies
- Data from all studies suggest that there is no difference between placebo and prucalopride on QT interval and other ECG. This conclusion is supported by results from two placebo controlled studies and a thorough (positive controlled) QT study, all of which confirmed that prucalopride had no effect on QT interval

5.1 Identification of studies

Table 1 outlines all Phase II and III studies from the prucalopride clinical trial programme.

Table 1: Overview of prucalopride Phase II and III studies

Study	Phase	Study title	Intervention	Study length	Number randomised patients
Phase II dose-response trials					
PRU-INT-1	II	A double-blind placebo-controlled dose-finding trial to evaluate the efficacy and safety of R093877 in patients with chronic constipation	Placebo, prucalopride 0.5 mg, 1 mg, 2 mg o.d.; Capsules, oral	4 weeks	N=174
PRU-INT-2	II	A double-blind placebo-controlled dose-finding trial to evaluate the efficacy and safety of R093877 in patients with chronic constipation	Placebo, prucalopride 0.5 mg, 1 mg, 2 mg b.i.d.; Capsules, oral	12 weeks	N=253
PRU-USA-3	II	A double-blind placebo-controlled, dose-finding trial to evaluate the efficacy and safety of prucalopride (R093877) in subjects with chronic constipation	Placebo, prucalopride 0.5 mg, 1 mg, 2 mg, 4 mg o.d.; Capsules, oral	4 weeks	N=231
Pivotal phase III double-blind, placebo-controlled trials in chronic constipation					
PRU-INT-6	III	A double-blind placebo-controlled trial to evaluate the efficacy and safety of prucalopride tablets in subjects with chronic constipation	Placebo, prucalopride 2 mg, 4 mg o.d.; Tablets, oral	12 weeks	N=720
PRU-USA-11	III	A double-blind placebo-controlled trial to evaluate the efficacy and safety of prucalopride tablets in subjects with chronic constipation	Placebo, prucalopride 2 mg, 4 mg o.d.; Tablets, oral	12 weeks	N=628
PRU-USA-13	III	A double-blind placebo-controlled trial to evaluate the efficacy and safety of prucalopride tablets in subjects with chronic constipation	Placebo, prucalopride 2 mg, 4 mg o.d.; Tablets, oral	12 weeks	N=651
Other phase II/III double-blind, placebo-controlled trials in chronic constipation					
PRU-USA-25	III	A double-blind placebo-controlled trial to evaluate the effect of dose-titration on the safety and efficacy of prucalopride tablets in subjects with chronic constipation	Prucalopride 1 mg for 2 days, 2 mg for 2 days, 4 mg thereafter; or 4 mg, placebo o.d.; Capsules, oral	4 weeks	N=347

Study	Phase	Study title	Intervention	Study length	Number randomised patients
PRU-USA-28	III	A 2-period, double-blind placebo-controlled study to evaluate the effects of retreatment of prucalopride on efficacy and safety in subjects with chronic constipation	Placebo, prucalopride 4 mg o.d.; Tablets, oral	2 periods of 4 weeks	N=516
PRU-BEL-6	II	A double-blind placebo-controlled trial to evaluate the efficacy and safety of R093877 in patients with severe chronic constipation	Placebo, prucalopride 4 mg o.d.; Capsules, oral	4 weeks	N=53
PRU-GBR-4	II	Study to evaluate the effect of a 1 mg o.d. dose of prucalopride in patients with chronic constipation	Placebo, prucalopride 1 mg o.d.; Capsules, oral	4 weeks	N=77
PRU-FRA-1 Part 1	II	Study to evaluate effect of prucalopride on GI transit and the colonic response to eating in subjects with objective chronic constipation	Placebo, prucalopride 1 mg and 2 mg o.d.; Tablets, oral	4 wks DB, 24 wks LT FU	N=37
PRU-USA-21	II	Dose-related effects of prucalopride on GI and colonic transit in subjects with chronic constipation	Placebo, prucalopride 2 mg and 4 mg o.d.; Tablets, oral	1 week	N=40
PRU-NED-13	II	The effect of prucalopride on colonic transit and on colonic motility as measured by prolonged ambulatory colonic manometry. A randomized placebo-controlled crossover study in patients with chronic constipation	Placebo, prucalopride 4 mg o.d.; Tablets, oral	2 periods of 10 days	N=8
PRU-NED-2	II	A placebo controlled study to evaluate the effect of repeated oral dosing of prucalopride, given once daily, on gastrointestinal transit, on anorectal manometry and on safety/tolerability in patients with chronic idiopathic constipation	Placebo, prucalopride 1 mg, 2 mg o.d.; Capsules, oral	2 periods of 2 weeks	N=28
Phase II/III double-blind, placebo-controlled trials in elderly patients					
PRU-USA-26	II	A double-blind placebo-controlled trial to evaluate the safety and tolerability of oral once-daily prucalopride (R108512) solution in constipated elderly patients living in a nursing facility	Placebo, prucalopride 0.5 mg, 1 mg, 2 mg, 4 mg o.d.; Solution, oral	4 weeks	N=100
PRU-INT-12	III	A double-blind placebo-controlled trial to evaluate the efficacy, safety, and quality of life of prucalopride (R108512) tablets in elderly subjects with chronic constipation	Placebo, prucalopride 1 mg, 2 mg, 4 mg o.d.; Tablets oral	4 weeks	N=305
Phase II/III open-label trials in patients with chronic constipation					
PRU-INT-10	III	A study to evaluate the long-term tolerability and safety of oral prucalopride administered to subjects with chronic constipation. Long-term follow-up of PRU-INT-6/ PRU-INT-12	Prucalopride 2 mg up to 4 mg o.d.; Tablets, oral	24 months	N=693

Study	Phase	Study title	Intervention	Study length	Number randomised patients
PRU-USA-22	III	A study to evaluate the long-term tolerability and safety, patient satisfaction, pharmacokinetics and use of patterns of oral prucalopride tablets in patients with chronic constipation. Long-term follow-up of PRU-USA-3/ PRU-USA-11/ PRU-USA-13/ PRU-USA-21/ PRU-USA-25/ PRU-USA-27/ PRU-USA-28/ PRU-USA-35	Prucalopride 1 mg to 4 mg o.d.; Tablets, oral	36 months	N=1775
PRU-BEL-8	II	Trial to evaluate the long-term tolerability, safety and efficacy of oral prucalopride (R093877) administered to patients with chronic constipation. Long-term follow-up of PRU-BEL-6	Prucalopride 1 mg to 4 mg o.d.; Capsules, oral	30 months	N=44
PRU-INT-3	II	Trial to evaluate the long-term tolerability, safety and efficacy of oral prucalopride administered to patients with chronic constipation. Long-term follow-up of PRU-INT-2	Prucalopride 1 mg b.i.d.; Capsules and tablets, oral	24 months	N=142
PRU-INT-4	II	Trial to evaluate the long-term tolerability, safety and efficacy of oral prucalopride (R093877) administered to patients with chronic constipation. Long-term follow-up of PRU-INT-1	Prucalopride 2 mg o.d.; Capsules, oral	30 months	N=72
PRU-NED-4	II	Study to evaluate the long-term effect of oral prucalopride on GI transit, on anorectal manometry and on safety and tolerability, in patients with chronic constipation. Long-term follow-up of PRU-NED 2	Prucalopride 2 mg o.d.; Capsules and tablets, oral	24 months	N=17
PRU-FRA-1 Part 2	II	Study of the effect of prucalopride on GI transit and the colonic response to eating in patients with objective chronic constipation	Prucalopride 2 mg o.d.; Tablets. oral	24 weeks	N=34
PRU-INT-13	III	Long-term follow-up of PRU-INT-3/ PRU-INT-4/ PRU-INT-9/ PRU-INT-10/ PRU-BEL-8/ PRU-NED-4/ PRU-GBR-4; open-access for subjects unable to enter PRU-INT-6 or PRU-INT-12	Prucalopride 1 mg to 4 mg o.d.; Tablets oral	20 months	N=242
PRU-SWE-2	III	Long-term follow-up of PRU-INT-3/ PRU-INT-10	Prucalopride 1 mg to 4 mg o.d.; Tablets, oral	20 months	N=5

Study	Phase	Study title	Intervention	Study length	Number randomised patients
Phase II/III double-blind, placebo-controlled trials in patients with opioid-induced constipation					
PRU-USA-8	II	A pilot study of once-daily oral prucalopride capsules vs. placebo in opioid-induced constipation in cancer patients	Placebo, prucalopride 2 mg, 4 mg o.d.; Capsules, oral	4 weeks	N=5
PRU-INT-14	II	A double-blind, placebo-controlled trial to evaluate the efficacy and safety of prucalopride in patients with chronic cancer pain, suffering from opioid-induced constipation	Placebo, prucalopride 2 mg, 4 mg o.d.; Tablets, oral	4 weeks	N=53
PRU-INT-8	II	A double-blind, placebo-controlled trial to evaluate the efficacy and safety of prucalopride in subjects with chronic non-cancer pain, suffering from opioid-induced constipation	Placebo, prucalopride 2 mg, 4 mg o.d.; Tablets, oral	4 weeks	N=196
PRU-USA-27	II	A study of once-daily oral prucalopride tablets vs. placebo in patients with opioid-induced constipation	Placebo, prucalopride 2 mg, 4 mg o.d.; Tablets, oral	4 weeks	N=88
Phase II open-label trial in patients with opioid-induced constipation					
PRU-INT-17	II	A study to evaluate the long-term tolerability and safety and the pattern of use of prucalopride in patients with chronic pain (cancer and non-cancer pain), suffering from opioid-induced constipation	Prucalopride 1 to 4 mg o.d.; Tablets, oral	12 months	N=96
Phase II trials in patients with multiple sclerosis or spinal cord injury					
PRU-BEL-18	II	A double-blind placebo-controlled trial to evaluate safety and tolerability and pilot efficacy of R093877 in subjects with constipation due to MS	Placebo, prucalopride 1 mg, 2 mg o.d.; Capsules, oral	4 weeks	N=22
PRU-DEN-2	II	A double-blind placebo-controlled trial to evaluate safety and tolerability and pilot efficacy of R093877 in subjects with constipation subsequent to SCI	Placebo, prucalopride 1 mg, 2 mg o.d.; Capsules, oral	4 weeks	N=23
PRU-INT-9	II	A study to evaluate long-term tolerability, safety and efficacy of oral prucalopride in patients with constipation due to SCI or MS	Prucalopride 1 mg, 2 mg o.d.; Capsules, oral	12 months	N=22

Study	Phase	Study title	Intervention	Study length	Number randomised patients
Phase II double-blind, placebo-controlled trial in subjects with chronic intestinal pseudo-obstruction					
PRU-GBR-7	II	Safety and efficacy of prucalopride in patients with chronic intestinal pseudo-obstruction	Prucalopride 2 mg to 4 mg o.d.; Capsules, oral	2 periods of 2 weeks	N=7
Phase II double-blind, placebo-controlled trials with i.v./s.c. formulations for treatment of postoperative ileus in patients undergoing major abdominal surgery of elective partial colectomies					
PRU-GER-1	II	Evaluation of safety, tolerability and efficacy of R093877 (enterokinetic) given i.v. in patients undergoing major abdominal surgery	Placebo, prucalopride 0.5 mg, 1 mg, 2 mg, 4 mg o.d.; Solution, i.v.	3 days (each 24h; max. 48h)	N= 66
PRU-USA-5	II	Evaluation of the efficacy, safety, and tolerability of prucalopride (enterokinetic) given s.c. in patients undergoing elective partial colectomies	Placebo, prucalopride 0.5 mg, 2 mg, 4 mg o.d.; Solution, s.c.	4 days	N=317

Abbreviations: b.i.d., Twice daily; i.v., Intravenous; LT FU, long term follow-up; o.d., Once daily; s.c., Subcutaneous; SCI, Spinal cord injury; MS, Multiple Sclerosis

5.2 Study selection

The clinical evidence section within this submission provides full details of the pivotal trials (three phase III pivotal trials, two elderly trials, one opioid induced trial and the main long-term open label studies, see Table 3 and Table 4). The dose finding trials are excluded from a full description in this submission a brief overview is provided for completeness. The retreatment study has been included in full as it was designed to assess whether efficacy is maintained when patients restart treatment after a period off treatment.

Summary of dose finding studies

In order to determine the prucalopride dose for the Phase III studies, 3 double-blind, placebo-controlled Phase II studies in adult (≥ 18 years) patients with chronic constipation who failed to respond adequately to laxatives were conducted. The doses evaluated ranged between 0.5 and 4 mg per day for 4 to 12 weeks.

In PRU-INT-1 and PRU-INT-2 efficacy was evaluated by means of a visual analogue scale (VAS), diary data (self-assessment), symptom evaluation and colonic transit time (investigator assessment). Daily doses of 2 mg and 4 mg of prucalopride consistently resulted in a statistically significant improvement of bowel habit, i.e. increased stool frequency, decreased stool consistency and straining, and reduction of severity of constipation at 4 weeks of treatment.

In PRU-USA-3 the primary endpoint used was the percentage of patients with ≥ 3 spontaneous complete bowel movements (SCBM) per week. A bowel movement was defined as spontaneous if no laxatives were taken in the 24 hours preceding the bowel movement and complete if associated with the feeling of complete evacuation. This endpoint was used in the later pivotal Phase III studies. The results of PRU-USA-3 provided the primary basis for Phase III dose selection. Both prucalopride 2 mg and 4 mg o.d. significantly increased the percentage of patients with ≥ 3 SCBM per week at the end of the 4 week double-blind treatment period. No statistically significant improvements in response rate were observed for the prucalopride 0.5 mg and 1 mg groups compared with placebo at any time-point, although the lower doses were associated with a clinically favourable trend throughout the double-blind treatment period. A statistically significant improvement of all secondary endpoints including frequency of SCBM and bowel movements, stool hardness, straining and the patient's assessment of efficacy and disease severity, was also observed for the 2 mg and 4 mg groups. Improvement in secondary endpoints was also observed among patients treated with 1 mg o.d., but the magnitude of the changes was lower than with 2 mg or 4 mg. Based on the results of PRU-USA-3 on the primary endpoint, 2 mg o.d. was considered the lowest effective dose in the adult population.

An additional Phase III study (PRU-INT-12) was conducted in an elderly population (64–95 years) to evaluate the effects of 3 doses of prucalopride (1, 2 and 4 mg o.d.). At the end of the 4 week treatment period all doses, including the 1 mg o.d., were superior to placebo for the primary endpoint (patients with ≥ 3 SCBM/week) and all secondary endpoints in the elderly population with chronic constipation. Since prucalopride is mainly excreted unchanged in the urine, the efficacy of prucalopride 1 mg in the elderly may relate to a lower glomerular filtration rate which results in a more sustained exposure to prucalopride in this subgroup. Based on the results of PRU-INT-12 on the primary endpoint, 1 mg o.d. was considered the lowest effective dose in the elderly population.

In conclusion, the Phase II dose-finding studies in adult patients not adequately relieved by laxatives indicated a significant improvement versus placebo on primary and secondary endpoints for the 2 mg and 4 mg o.d. doses with a numerically higher response at 4 mg. 1 mg did not provide statistically significant improvement versus placebo on the primary endpoint. Based on these findings, the 2 and 4 mg daily doses were selected for further investigation in Phase III studies. For elderly patients, the efficacy data indicated that a lower dose of 1 mg o.d. is appropriate and this was supported by the pharmacokinetic data showing an increase in exposure in this population.

The licensed dose for prucalopride in adults is 2 mg o.d. and in the elderly 1 mg o.d., if needed the dose can be increased to 2 mg o.d.

Complete list of relevant RCTs

A complete list of the relevant RCTs that are discussed in this submission are summarised in Table 2. The studies primarily designed to evaluate efficacy outcomes are discussed in sections 5.3- 5.5. The study designed primarily to assess safety outcomes (PRU-USA-26) is presented in section 5.9.

Table 2: List of relevant RCTs

Study	Intervention	Comparator	Population	Primarily assessed for efficacy or safety	Primary study ref.
Pivotal phase III double-blind, placebo-controlled trials in chronic constipation					
PRU-INT-6	Prucalopride 2 mg or 4 mg o.d.	Placebo	Subjects with chronic constipation (≤ 2 SCBM/ week)	Efficacy	Tack et al (2009) (18) CSR (19)
PRU-USA-11				Efficacy	Camilleri et al (2008) (20) CSR (21)
PRU-USA-13				Efficacy	Quigley et al (2009) (22) CSR (23)
Phase II/III double-blind, placebo-controlled trials in elderly patients with chronic constipation					
PRU-USA-26	Prucalopride 0.5 mg, 1 mg, 2 mg and 4 mg o.d.	Placebo	Constipated elderly patients in a nursing facility	Safety	Camilleri et al (2009) (1) CSR (2)
PRU-INT-12	Prucalopride 1 mg, 2 mg and 4 mg o.d.	Placebo	Elderly subjects with chronic constipation	Efficacy	CSR (24)
Phase III double-blind, placebo-controlled trial in patients with opioid-induced constipation					
PRU-INT-8	Prucalopride 2 mg or 4 mg o.d.	Placebo	Subjects with chronic non-cancer pain suffering from opioid-induced constipation	Efficacy	CSR (25)
Phase III double-blind, placebo-controlled, retreatment study in chronic constipation					
PRU-USA-28[†]	Prucalopride 4 mg o.d.	Placebo	Subjects with chronic constipation	Efficacy	CSR (26)

Abbreviations: CSR, clinical study report; o.d., once daily; SCBM, Spontaneous complete bowel movements

[†]The licensed dose of prucalopride was not evaluated in PRU-USA-28. However, this study is a retreatment study that demonstrates that if a patient is taken off treatment (after 4 weeks) and then restarted after a break of 2 weeks, the response level in the second treatment period is at a similar level to that seen in the first period. This data was considered relevant and consequently this study has been included for further discussion in this submission.

List of relevant non-RCTs

Non-RCTs that are relevant to this submission are summarised in Table 3. Non-RCT evidence is presented in Section 5.8.

Table 3: List of relevant non-RCTs

Study	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
PRU-INT-10	Prucalopride 2 mg up to 4 mg o.d.	Subjects with chronic constipation	Long-term tolerability/ safety	CSR (27)	Long-term follow-up of PRU-INT-6/ PRU-INT-12; population relevant to decision problem
PRU-USA-22	Prucalopride 1 mg to 4 mg o.d.	Subjects with chronic constipation	Long-term tolerability, safety, patient satisfaction, pharmacokinetics and pattern of use	CSR (28)	Long-term follow-up study including patients from pivotal trials; population relevant to decision problem
PRU-INT-17	Prucalopride 1 mg to 4 mg o.d.	Subjects with chronic pain (cancer and non-cancer pain), suffering from opioid-induced constipation	Long-term tolerability/safety and pattern of use	CSR (29)	Long-term follow-up in population relevant to decision problem

Abbreviations: CSR, clinical study report; o.d., Once daily

5.3 Summary of methodology of relevant RCTs

5.3.1 Methods

The methodology of the relevant RCTs is summarised in the following tables.

Pivotal studies

Table 4: Methodology of the pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13) (18-23)

Study	PRU-INT-6	PRU-USA-11	PRU-USA-13
Location	International multicentre - sites in Australia (7), Belgium (5), Canada (11), Great Britain (11), Netherlands (11), Norway (4), South Africa (8), Sweden (8)	Multicentre - sites in the US (38)	Multicentre - sites in the US (41)
Design	Phase III, randomised, double-blind, placebo-controlled, parallel-group trial		
Duration of study	12 weeks (preceded by 2-week run-in phase)		
Method of randomisation	A randomisation code was used to randomly allocate patients to the treatment groups, with balancing per centre to obtain approximately equal numbers per group. Patient numbers were consecutively assigned (lowest number first)		
Method of blinding	Group assignment was concealed from investigators and participants. Tablets were identical in appearance, taste and smell. Containers were identical in appearance. In the case of an emergency, the investigator could obtain treatment details (per patient) from sealed code envelopes		
Intervention(s) (n =) and comparator(s) (n =)	Prucalopride 2 mg o.d. (n = 238) Prucalopride 4 mg o.d. (n = 238) Placebo o.d. (n = 240)	Prucalopride 2 mg o.d. (n = 207) Prucalopride 4 mg o.d. (n = 204) Placebo o.d. (n = 209)	Prucalopride 2 mg o.d.: (n = 214) Prucalopride 4 mg o.d. (n = 215) Placebo o.d. (n = 212)
Rescue medication	Laxatives were not allowed. However, if the patient did not have a bowel movement for ≥ 3 consecutive days he/she was allowed bisacodyl as a rescue medication. A maximum single dose of 15mg (3 tablets) was prescribed. If this standard dose was insufficient, an increase was allowed. If no bowel movements passed after an increase in bisacodyl an enema could be administered. No bisacodyl was to be taken or enemas used within 48 hours prior to and 48 hours after the start of the double blind treatment period		
Primary outcomes	Proportion of patients having ≥ 3 SCBM/week, averaged over 12 weeks: assessed using patient-reported daily diaries		
Key secondary outcome	Proportion of patients with an average increase of ≥ 1 SCBM/week as compared with the baseline number: assessed using patient-reported daily diaries. Improvement of QoL		

Abbreviations: o.d., once daily; SCBM, Spontaneous Complete Bowel Movements

Elderly subjects

Table 5: Methodology of RCT in elderly subjects (PRU-INT-12) (24)

Study	PRU-INT-12
Location	International multicentre – conducted at sites in Austria (2), Canada (9), Germany (7), Great Britain (13), Netherlands (11), Norway (2) and South Africa (4)
Design	Phase III, randomised, double-blind, placebo-controlled, parallel-group trial
Duration of study	4 weeks (preceded by 2-week run-in phase)
Method of randomisation	As per pivotal trials
Method of blinding	As per pivotal trials
Intervention(s) (n =) and comparator(s) (n =)	Prucalopride 1 mg o.d. (n = 76) Prucalopride 2 mg o.d. (n = 75) Prucalopride 4 mg o.d. (n = 80) Placebo o.d. (n = 72)
Rescue medication	As per pivotal trials
Primary outcomes	Proportion of patients having ≥ 3 SCBM/week over the entire 4 week period: assessed using patient-reported daily diaries
Key secondary outcome	As per pivotal trials

Abbreviations: o.d., once daily; SCBM, Spontaneous Complete Bowel Movements

Opioid-induced constipation

Table 6: Methodology of RCT in subjects with opioid-induced constipation (PRU-INT-8) (25)

Study	PRU-INT-8
Location	International multicentre – sites in Belgium (5), Canada (8), Denmark (3), France (10), Germany (15), Great Britain (3), Netherlands (7), Poland (3)
Design	Phase II, randomised, double-blind, placebo-controlled, parallel-group, trial
Duration of study	4 weeks (preceded by 14 ± 3 day run in, and an additional 7 day period for subjects taking agents which influence bowel habits)
Method of randomisation	As per pivotal trials
Method of blinding	Group assignment was concealed from investigators and participants. Tablets and containers were identical in appearance. In the case of an emergency, the investigator could obtain treatment details (per patient) from sealed code envelopes.
Intervention(s) (n =) and comparator(s) (n =)	Prucalopride 2 mg o.d. (n = 66) Prucalopride 4 mg o.d. (n = 64) Placebo o.d. (n = 66)
Rescue medication	Laxative use was stopped at visit 1 and subjects switched to the bisacodyl rescue rule: if subjects had not had a bowel movement within the previous 48 hours, they were allowed bisacodyl as rescue medication. No bisacodyl was allowed within 24 hours prior to and 24 hours following the first intake of study medication. Rescue medication was provided throughout the trial; one single dose of 10 mg maximum bisacodyl was allowed, if insufficient one increase in dose was allowed. If no bowel movements passed after an increase in bisacodyl an enema could be

Study	PRU-INT-8
	administered.
Primary outcomes	Proportion of patients having an increase of ≥ 1 SCBM/week from baseline to 4 week double-blind period: assessed using patient-reported daily diaries
Key secondary outcome	Proportion of patients having ≥ 3 SCBM/week: assessed using patient-reported daily diaries

Abbreviations: o.d., once daily; SCBM, Spontaneous Complete Bowel Movements

Retreatment study

Table 7: Methodology of the retreatment study (PRU-USA-28) (26)

Study	PRU-USA-28
Location	National multicentre – 33 centres in the USA
Design	Phase III, randomised, double-blind, placebo-controlled, parallel-group trial
Duration of study	2-week drug-free run-in phase followed by a randomised, 4-week, double-blind, placebo-controlled treatment phase, a drug-free washout period of at least 2 weeks, and a second 4-week double-blind treatment period
Method of randomisation	As per pivotal trials
Method of blinding	As per pivotal trials
Intervention(s) (n =) and comparator(s) (n =)	Prucalopride 4 mg o.d. (n = 257) Placebo o.d. (n = 253)
Rescue medication	As per pivotal trials
Primary outcomes	Proportion (%) of responders, defined as patients who had an average of ≥ 3 SCBM/week
Key secondary outcome	Proportion (%) of patients with an average increase of ≥ 1 SCBM/week

Abbreviations: o.d., once daily; SCBM, spontaneous complete bowel movement

5.3.2 Participants

Inclusion and exclusion criteria for the relevant RCTs are summarised in the following tables.

Pivotal studies

Table 8: Eligibility criteria in the pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13) (18-23)

Study	Inclusion criteria	Exclusion criteria
PRU-INT-6 **PRU-USA-11** **PRU-USA-13**	• Male or female (≥ 18 years of age) with a history of chronic constipation[†], as well as one or more of the following[‡]: very hard or hard stools, a sensation of incomplete evacuation, or straining during defecation with at least 25% of bowel movements	• Constipation secondary to drugs, endocrine, metabolic or neurologic disorders, surgery, organic disorders of the large intestine or megacolon • Patients with uncontrolled cardiovascular, liver, psychiatric, or lung diseases, a serum creatinine level of > 180 µmol/L (2.0 mg per decilitre), or clinically significant abnormal laboratory (based on pre-specified values)

Abbreviations: SCBM, Spontaneous Complete Bowel Movements; [†] Defined as ≤ 2 SCBM/week ; [‡] For a minimum of 6 months before the screening visit

Elderly subjects

Table 9: Eligibility criteria in the RCT in elderly subjects (PRU-INT-12) (24)

Study	Inclusion criteria	Exclusion criteria
PRU-INT-12	• Male and female (≥ 65 years of age) with a history of constipation[†], as well as ≥ 1 of the following[‡]: very hard or hard stools, a sensation of incomplete evacuation, or straining during defecation with at least 25% of bowel movements	• Constipation secondary to drugs, or uncontrolled endocrine, metabolic or neurologic disorders, surgery, organic disorders of the large intestine or megacolon • Main complaint of abdominal pain • Known serious illnesses: malignancies, AIDS, clinically significant cardiovascular, lung, GI, endocrine, neurological, psychiatric or metabolic disturbances • Serum creatinine concentration >2 mg/dL (>180 µmol/L) or clinically significant abnormal laboratory values • Patients who received an investigational drug in the 30 days preceding run-in

Abbreviations: GI, Gastrointestinal; SCBM, Spontaneous Complete Bowel Movements; [†] Defined as ≤ 2 SCBM/week (not preceded within a period of 24 hours by use of laxative or enema; [‡] For a minimum of 6 months before the screening visit

Opioid-induced constipation

Table 10: Eligibility criteria in the RCT in subjects with opioid-induced constipation (PRU-INT-8) (25)

Study	Inclusion criteria	Exclusion criteria
PRU-INT-8	Male or female (≥ 18 years of age) with opioid-induced chronic constipation† with no history of chronic constipation prior to opioid use Chronic pain (except cancer pain) requiring daily maintenance therapy with opioids Taking a minimum total daily maintenance dose of opioids and expected to stay on the same opioid for maintenance therapy for ≥ 6 weeks Laxative regimen (if applicable) was switched to rescue rule‡ Willing to maintain lifestyle and diet unaltered ≤ 2 SCBM with a feeling of complete evacuation and constipation was bothering them	History of chronic constipation prior to opioid treatment Constipation secondary to drugs (excluding opioids), or uncontrolled endocrine, metabolic or neurologic disorders, surgery, organic disorders of the large intestine or megacolon Known serious illnesses:, AIDS, clinically significant cardiovascular, lung, endocrine, neurological, psychiatric, metabolic disturbances or cancer, Serum creatinine concentration >2 mg/dL (>180 µmol/L) or clinically significant abnormal laboratory values Patients who received an investigational drug in the 30 days preceding run-in; and previously received R093877 or R108512

Abbreviations: SCBM, Spontaneous Complete Bowel Movements; †Constipation was clearly secondary to chronic daily opioid use, started ≥ 2 weeks prior to Visit 1 and was expected to last ≥ 6 weeks following Visit 1); ‡ Bisacodyl/enemas

Retreatment study

Table 11: Eligibility criteria in the retreatment study PRU-USA-28) (26)

Study	Inclusion criteria	Exclusion criteria
PRU-USA-28 (26)	Male or female adults (≥ 18 years of age) with a history of chronic constipation†, as well as one or more of the following‡: very hard or hard stools, a sensation of incomplete evacuation, or straining during defecation with at least 25% of bowel movements	• Constipation secondary to drugs, endocrine, metabolic or neurological disorders, surgery, organic disorders of the large intestine or megacolon • Known/suspected organic disorders of the large bowel • Known serious, uncontrolled illnesses • HIV positive or cancer in the last 5 years • Impaired renal function or significant abnormalities of haematology, urinalysis, or blood chemistry • Females without adequate contraception

† Defined as ≤ 2 SCBM/week (not preceded within a period of 24 hours by use of laxative or enema; ‡ For a minimum of 6 months before the screening visit

5.3.3 Patient characteristics at baseline

Baseline characteristics of patients in the relevant RCTs are summarised in the following tables.

Pivotal studies

Table 12: Baseline patient characteristics pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13) (18-23)

PRU-INT-6	Prucalopride 2 mg¶ (n = 236)	Prucalopride 4 mg (n = 237)	Placebo (n = 240)
Age (years), mean (SE)	42.7 (0.98)	45.4 (0.97)	43.7 (0.99)
Sex, n (%)			
Male	25 (10.5)	23 (9.7)	18 (7.5)
Female	213 (89.5)	215 (90.3)	222 (92.5)
Race, n (%)			
White	223 (93.7)	220 (92.4)	226 (94.2)
Black	3 (1.3)	4 (1.7)	2 (0.8)
Hispanic	0 (0)	2 (0.8)	2 (0.8)
Oriental	5 (2.1)	1 (0.4)	2 (0.8)
Other	7 (2.9)	11 (4.6)	8 (3.3)
Height (cm), mean (SE)	165.8 (0.5)	165.7 (0.52)	165.1 (0.45)
Weight (kg), mean (SE)	68.8 (0.93)	68.0 (0.88)	66.7 (0.84)
Duration of constipation (years), mean (SE)	15.9 (0.97)	18.3 (0.99)	18.5 (0.90)
Average frequency of spontaneous stools/week, n (%)			
0	86 (36.1)	91 (38.2)	99 (41.3)
> 0 to ≤ 1	78 (32.8)	69 (29.0)	84 (35.0)
> 1 to ≤ 3	65 (27.3)	70 (29.4)	51 (21.3)
> 3	9 (3.8)	8 (3.4)	6 (2.5)
Use of previous therapy (laxative, enema), n (%)			
Yes	191 (80.3)	183 (76.9)	198 (82.5)
No	47 (19.7)	55 (23.1)	42 (17.5)
Overall assessment of therapeutic efficacy of previous treatment of constipation, n (%)†			
Adequate	48 (21.1)	34 (15.4)	32 (14.0)
Inadequate	180 (78.9)	187 (84.6)	196 (86.0)
PRU-USA-11	**Prucalopride 2 mg¶ (n = 207)**	**Prucalopride 4 mg (n = 204)**	**Placebo (n = 209)**
Age (years), mean (SE)	48.2 (1.0)	47.8 (1.0)	48.9 (0.9)
Sex, n (%)			
Male	19 (9.2)	30 (14.7)	26 (12.4)
Female	188 (90.8)	174 (85.3)	183 (87.6)
Race, n (%)			
White	188 (90.8)	186 (91.2)	182 (87.1)
Black	13 (6.3)	9 (4.4)	18 (8.6)
Hispanic	5 (2.4)	8 (3.9)	4 (1.9)
Asian	1 (0.5)	1 (0.5)	2 (1.0)
Other	0	0	3 (1.4)
Height (cm), mean (SE)	164.7 (0.6)	165.0 (0.6)	164.7 (0.6)
Weight (kg), mean (SE)	69.3 (1.0)	68.6 (1.0)	68.4 (1.0)
Duration of constipation (years), mean (SE)	21.1 (1.1)	20.5 (1.1)	21.6 (1.2)
Average frequency of spontaneous stools/week, 6 months before study entry, n (%)			
0	77 (37.2)	76 (37.3)	79 (37.8)

> 0 to ≤ 1	79 (38.2)	77 (37.7)	78 (37.3)
> 1 to ≤ 3	50 (24.2)	46 (22.5)	49 (23.4)
> 3	1 (0.5)	5 (2.5)	3 (1.4)
Use of previous therapy (laxative, enema), n (%)			
Yes	185 (89.4)	180 (88.2)	183 (87.6)
No	22 (10.6)	24 (11.8)	26 (12.4)
Overall assessment of therapeutic efficacy of previous treatment of constipation, n (%)‡			
Adequate	34 (16.9)	32 (16.1)	32 (15.8)
Inadequate	167 (83.1)	167 (83.9)	170 (84.2)
PRU-USA-13	**Prucalopride 2 mg¶ (n = 214)**	**Prucalopride 4 mg (n = 215)**	**Placebo (n = 212)**
Age (years), mean (SE)	48.6 (0.97)	49.1 (0.93)	46.2 (0.89)
Sex, n (%)			
Male	33 (15.4)	30 (14.0)	23 (10.8)
Female	181 (84.6)	185 (86.0)	189 (89.2)
Race, n (%)			
White	183 (85.5)	184 (85.6)	197 (92.9)
Black	24 (11.2)	21 (9.8)	9 (4.2)
Hispanic	3 (1.4)	7 (3.3)	5 (2.4)
Oriental	3 (1.4)	0 (0)	0 (0)
Other	1 (0.5)	3 (1.4)	1 (0.5)
Height (cm), mean (SE)	165.2 (0.6)	165.7 (0.62)	165.3(0.58)
Weight (kg), mean (SE)	71.1 (1.04)	69.6 (1.03)	70.7 (0.99)
Duration of constipation (years), mean (SE)	22.7 (1.08)	22.0 (1.17)	21.4 (1.06)
Average frequency of spontaneous stools/week, 6 months before study entry, n (%)			
0	96 (44.9)	101 (47.0)	85 (40.1)
> 0 to ≤ 1	73 (34.1)	66 (30.7)	65 (30.7)
> 1 to ≤ 3	43 (20.1)	43 (20.0)	60 (28.3)
> 3	2 (0.9)	5 (2.3)	2 (0.9)
Use of previous therapy (laxative, enema), n (%)			
Yes	189 (88.3)	192 (89.3)	189 (89.2)
No	25 (11.7)	23 (10.7)	23 (10.8)
Overall assessment of therapeutic efficacy of previous treatment of constipation, n (%)§			
Adequate	39 (18.6)	39 (18.4)	46 (22.1)
Inadequate	171 (81.4)	173 (81.6)	162 (77.9)

Abbreviations: SE, Standard Error; [†]39 patients had not received previous treatment; [‡]18 patients had not received previous treatment; [§]11 patients had not received previous treatment; [¶]Licensed dose

Elderly subjects

Table 13: Baseline patient characteristics RCT in elderly subjects (PRU-INT-12) (24)

PRU-INT-12	Prucalopride 1 mg (n = 76)	Prucalopride 2 mg (n = 75)	Prucalopride 4 mg (n = 80)	Placebo (n = 72)
Age (years), mean (SE)	76.7 (0.9)	75.6 (0.83)	77.1 (0.91)	76 (0.87)
Age groupings, n (%)				
< 65	0 (0)	1 (1.3)	0 (0)	0 (0)
65 - 74	34 (44.7)	37 (49.3)	33 (41.3)	33 (45.8)
75 - 84	28 (36.8)	26 (34.7)	33 (41.3)	29 (40.3)
≥ 85	14 (18.4)	11 (14.7)	14 (17.5)	10 (13.9)
Sex, n (%)				
Male	18 (23.7)	24 (32.0)	20 (25.0)	30 (41.7)
Female	58 (76.3)	51 (68.0)	60 (75.0)	42 (58.3)
Race, n (%)				
Caucasian	74 (97.4)	74 (98.7)	78 (97.5)	67 (93.1)
Black	1 (1.3)	0 (0)	1 (1.3)	1 (1.4)
Other	1 (1.3)	1 (1.3)	1 (1.3)	4 (5.6)
Height (cm), mean (SE)	164.1 (0.90)	164.9 (1.26)	161.9 (1.10)	165.2 (1.28)
Weight (kg), mean (SE)	66.7 (1.55)	69.3 (2.00)	68.0 (1.85)	67.5 (1.57)
Duration of constipation (years), mean (SE)	18.7 (2.02)	21.6 (2.36)	23.5 (2.56)	22.4 (2.33)
Average frequency of spontaneous stools/week, 6 months before study entry, n (%)				
0	24 (31.6)	34 (45.3)	32 (40.0)	32 (44.4)
> 0 to ≤ 1	22 (28.9)	15 (20.0)	17 (21.3)	11 (15.3)
> 1 to ≤ 3	26 (34.2)	20 (26.7)	25 (31.3)	23 (31.9)
> 3	4 (5.3)	6 (8.0)	6 (7.5)	6 (8.3)
Use of laxative, n (%)				
Yes	63 (82.9)	60 (80.0)	67 (83.8)	62 (86.1)
No	13 (17.1)	15 (20.0)	13 (16.3)	10 (13.9)
Overall assessment of therapeutic efficacy of previous treatment of constipation, n (%)				
Adequate	13 (17.3)	20 (28.6)	18 (23.4)	9 (12.7)
Inadequate	62 (82.7)	50 (71.4)	59 (76.6)	62 (87.3)

Abbreviations: SE, Standard Error

Opioid-induced constipation

Table 14: Baseline patient characteristics RCT in subjects with opioid-induced constipation (PRU-INT-8) (25)

PRU-INT-8	Prucalopride 2 mg (n = 66)	Prucalopride 4 mg (n = 64)	Placebo (n = 66)
Age (years), mean (SE)	42 (63.6)	33 (51.60	50.6 (1.48)
Sex, n (%)			
Male	24 (36.4)	31 (48.4)	21 (31.8)
Female	42 (63.6)	33 (51.6)	45 (62.8)
Age groupings, n (%)			
18 – 40	6 (9.1)	11 (7.2)	13 (19,7)
41 - 64	54 (81.8)	47 (73.4)	43 (65.2)
≥ 65 years	6 (9.1)	6 (9.4)	10 (15.2)
Race			
Caucasian	65 (98.5)	63 (98.4)	66 (100)
Black	1 (1.5)	1 (1.6)	0 (0)
Height (cm), mean (SE)	168.2 (1.12)	170.1 (1.0)	167.7 (1.16)
Weight (cm), mean (SE)	74 (1.87)	74.4 (1.9)	70.9 (1.9)
Difficulty in defecation, n (%)	27 (40.9)	29 (45.3)	24 (36.4)
Hard stools, n (%)	18 (27.3)	25 (39.1)	21 (31.8)
Straining, n (%)	26 (39.4)	24 (37.5)	22 (33.3)
Bloating, n (%)	22 (33.3)	21 (32.8)	16 (24.2)
Abdominal pain, n (%)	14 (21.2)	19 (29.7)	16 (24.2)
Feeling not completely empty, n (%)	21 (31.8)	19 (29.7)	16 (24.2)
Irregular stools, n (%)	11 (6.7)	16 (25.0)	13 (9.7)
Continuous laxative use, n (%)	12 (18.2)	9 (14.1)	13 (9.7)
Decreased stool frequency, n (%)	7 (10.6)	9 (14.1)	6 (9.1)

Abbreviations: SE, Standard Error

Retreatment study

Table 15: Baseline patient characteristics retreatment study (PRU-USA-28) (26)

PRU-USA-28	Prucalopride 4 mg (n = 253)	Placebo (n = 257)
Age (years), mean (SE)	45.9 (0.85)	46.3 (0.86)
Age groupings, n (%)		
< 18	2 (0.8)	1 (0.4)
[18, 40]	82 (32.4)	91 (35.4)
[41, 64]	146 (57.7)	140 (54.5)
≥ 64	23 (9.1)	25 (9.7)
Sex, n (%)		
Male	23 (9.1)	31 (12.1)
Female	230 (90.9)	226 (87.9)
Race, n (%)		
Caucasian	206 (81.4)	206 (80.2)
Black	29 (11.5)	38 (14.8)
Hispanic	13 (5.1)	11 (4.3)
Oriental	0	2 (0.8)
Other	5 (2.0)	0
Height (cm), mean (SE)	164.2 (0.59)	164.5 (0.64)
Weight (kg), mean (SE)	70.1 (0.97)	71 (0.98)

5.3.4 Outcomes

Pivotal studies

Table 16: Primary and secondary outcomes of the pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13) (18-23)

Study	Primary outcome(s) and measures	Secondary outcome(s) and measures	Other outcomes and measures	Reliability/validity/ current use in clinical practice
PRU-INT-6 **PRU-USA-11** **PRU-USA-13**	• Proportion of patients having ≥ 3 SCBMs/week, evaluated over the first 4 weeks and averaged over 12 weeks - assessed using patient-reported daily	Key secondary outcome: • Proportion of patients with an average increase of ≥ 1 SCBM/week versus baseline Other secondary outcomes: • Average number of SCBMs/SBMs week • Symptoms (including % BM with normal consistency, with no straining, with severe or very severe straining, with sensation of complete evacuation • Average time to first (S)BM or SCBM after first intake of study drug • Average number of bisacodyl† tablets or enemas used/week All the above were assessed using patient - reported daily diaries • Patient's global assessment of efficacy of treatment – at weeks 2, 4, 8, and 12 using a 5-point Likert scale:"not at all effective" (0) to "extremely effective" (4) • Patient's global assessment of severity of constipation - assessed at baseline and weeks 2, 4, 8, and 12 using a 5-point Likert scale: "none" (0) to "very severe" (4)	• Constipation related symptoms assessed using the PAC-SYM at baseline and weeks 2, 4, 6, 8 and 12 • Effect of constipation on daily life assessed using the PAC-QOL at weeks 4 and 12 • General health status assessed using the SF-36 at baseline, and weeks 4 and 12	• SCBM is a rigorous and clinically meaningful measure of evaluating efficacy of a treatment in chronic constipation. SCBM combines both a measureable endpoint (number of spontaneous stools) and a qualitative measure of each bowel movement based on the patients' assessment of the completeness of evacuation. Consequently, SCBM identifies bowel movements that fully relieve the symptoms caused by chronic constipation(18) • Patient Assessment of Constipation –symptoms (PAC-SYM) and Patient Assessment of Constipation – Quality of Life (PAC-QOL) are validated constipation specific instruments that measure patients' experience of constipation over time. • The PAC-SYM has been previously validated in patients with opioid-induced constipation (30) and was shown to be a 'reliable, valid and responsive measure of the presence and severity of constipation-related symptoms' (30) • The PAC-QOL is described as 'a brief but comprehensive assessment of the burden of constipation on patients' everyday functioning and well-being' and has been demonstrated via multinational studies to be 'internally consistent, reproducible, valid, and responsive to improvements over time' (31)

Abbreviations: BM, Bowel Movement; SBM, Spontaneous Bowel Movement; SCBM, Spontaneous, Complete Bowel Movements ; PAC-SYM, Patient Assessment of Constipation Symptoms; PAC-QOL, Patient Assessment of Constipation Quality of Life; SF-36, Medical Outcomes Study 36-item Short-Form General Health Survey; † If patients did not have a bowel movement for ≥ 3 consecutive days during the trial, they were permitted to take up to 15 mg of bisacodyl, followed by an enema if bisacodyl was ineffective

Elderly subjects

Table 17: Primary and secondary outcomes of the RCT in elderly subjects (PRU-INT-12) (24)

Study	Primary outcome(s) and measures	Secondary outcome(s) and measures	Other outcomes and measures	Reliability/validity/ current use in clinical practice
PRU-INT-12	• Proportion of patients having ≥ 3 SCBMs/week, evaluated over the entire 4-week study period- assessed using patient-reported daily	Key secondary outcome: • Proportion of patients with an average increase of ≥ 1 SCBM/week versus baseline Other secondary outcomes: • Average number of SCBMs/SBMs week • Symptoms (including % BM with normal consistency, with no straining, with severe or very severe straining, with sensation of complete evacuation • Average time to first (S)BM or SCBM after first intake of study drug • Average number of bisacodyl† tablets or enemas used/week All the above were assessed using patient - reported daily diaries • Patient's global assessment of efficacy of treatment – at weeks 2 and 4 using a 5-point Likert scale, ranging from "not at all effective" (0) to "extremely effective" (4) • Patient's global assessment of severity of constipation - assessed at baseline and weeks 2 and 4 using a 5-point Likert scale: "none" (0) to "very severe" (4)	• Constipation related symptoms assessed using the PAC-SYM at baseline and weeks 2, and 4 • Effect of constipation on daily life assessed using the PAC-QOL at baseline and week and 4 • General health status assessed using the SF-36 at Visit 2 and 4	• As for pivotal trials

Abbreviations:BM, Bowel Movement; SBM, Spontaneous Bowel Movement; SCBM, Spontaneous, Complete Bowel Movements ; PAC-SYM, Patient Assessment of Constipation Symptoms; PAC-QOL, Patient Assessment of Constipation Quality of Life;
†If patients did not have a bowel movement for ≥ 3 consecutive days during the trial, they were permitted to take up to 15 mg of bisacodyl, followed by an enema if bisacodyl was ineffective

Opioid-induced constipation

Table 18: Primary and secondary outcomes of the RCT in subjects with opioid-induced constipation (PRU-INT-8) (25)

Study	Primary outcome(s) and measures	Secondary outcome(s) and measures	Other outcomes and measures	Reliability/validity/ current use in clinical practice
PRU-INT-8	• Proportion of patients having an increase of ≥ 1 SCBM/week from baseline to 4 week double-blind period: assessed using patient-reported daily diaries	Key secondary outcome: • Proportion of patients having ≥ 3 SCBM/week: assessed using patient-reported daily diaries Other secondary outcomes: • Average number of SCBMs/SBMs week • Symptoms (average score for BM consistency, with straining, with sensation of complete evacuation • Average frequency of laxatives taken; and average number of days with bisacodyl tablets or other laxative tablet intake used/week All the above were assessed using patient - reported daily diaries • Patient's self assessment most bothersome constipation complaint (Visit 2), severity of constipation (Visits 2, 3 and 4), extent of being bothered by constipation (Visits 2, 3 and 4), efficacy of treatment (Visit 3 and 4)	• Constipation related symptoms assessed using the PAC-SYM at Visit 2, 3 and 4 • Effect of constipation on daily life assessed using the PAC-QOL at Visit 2 and 4	• As for pivotal trials

Abbreviations: BM, Bowel Movement; SBM, Spontaneous Bowel Movement; SCBM, Spontaneous, Complete Bowel Movements ; PAC-SYM, Patient Assessment of Constipation Symptoms; PAC-QOL, Patient Assess

Retreatment study

Table 19: Primary and secondary outcomes of the retreatment study (PRU-USA-28) (26)

Study	Primary outcome(s) and measures	Secondary outcome(s) and measures	Other outcomes and measures	Reliability/validity/ current use in clinical practice
PRU-USA-28	• Proportion of patients with an average of ≥ 3 SCBM/week	Key secondary parameter: • Proportion of patients with an average increase of ≥ 1 SCBM/week Other secondary parameters: • Average number of SCBM/(S)BM/week • Symptoms (consistency, straining, sensation of complete evacuation) • Average time to first (S)BM or SCBM after first intake • Laxative use • Patient global evaluation of drug efficacy and of constipation severity	• PAC-SYM	• As for pivotal trials

Abbreviations: BM, Bowel Movement; SBM, Spontaneous Bowel Movement; SCBM, Spontaneous, Complete Bowel Movements ; PAC-SYM, Patient Assessment

5.3.5 Statistical analysis and definition of study groups

A summary of the statistical analysis and definition of study groups for the relevant RCTs is presented in the following tables.

Pivotal studies

Table 20: Statistical analyses in the pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13) (18-23)

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PRU-INT-6 PRU-USA-11 PRU-USA-13	To compare the percentage of patients reaching ≥ 3 SCBM/week	• CMH test with Holm's procedure to correct for the multiple pairwise comparisons • Analysis of covariance to evaluate differences among groups for continuous data, (including factors: baseline value, and centre) with Dunnett's test to correct for the multiple comparisons	188 patients per group were required to detect a significant difference in response rates (assuming response rates of 15% for the placebo group and 30% for the prucalopride group), with a 90% statistical power of and a 2.5% two-sided type I error rate Assuming that 5% of patients would provide insufficient diary data, 198 patients were required per group	The last 7 diary days with data were used to fill missing diary days for patients who did not complete the diary through day 84 but had ≥ 7 non-missing diary days after week 1. No imputation was carried out for patients with < 7 non-missing diary days after Week 1 and average frequencies were set to missing. The weekly average frequency of bowel movements was calculated from the imputed/expanded dataset

Abbreviations: ANCOVA, Analysis of Covariance; CMH, Cochran-Mantel-Haenszel

Elderly subjects

Table 21: Statistical analyses in the RCT in elderly subjects (PRU-INT-12) (24)

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PRU-INT-12	To compare the percentage of patients reaching ≥ 3 SCBM/week	CMH test with Holm's procedure to correct for the multiple pairwise comparisons	64 patients per group were required to detect a difference of 15% and 40% response for placebo and prucalopride, respectively (assuming response rates of 15%, 30% and 50% for the placebo, prucalopride 2 mg and 4 mg, respectively) with a 80% statistical power and a 1.67% two-sided type I error rate	As per pivotal trials

Abbreviations: CMH, Cochran-Mantel-Haenszel

Opioid-induced constipation

Table 22: Statistical analyses in the RCT in subjects with opioid-induced constipation (PRU-INT-8) (25)

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PRU-INT-8	To compare the percentage of patients with an increase from baseline to 4-week double-blind period of ≥ 1 SCBM/week	CMH test with Holm's procedure to correct for the multiple pairwise comparisons	Assuming 20% of patients would have insufficient diary data, 60 randomised subjects per treatment group were required (80% power and 2.5% level of significance)	As per pivotal trials

Abbreviations: CMH, Cochran-Mantel-Haenszel

Retreatment study

Table 23: Statistical analyses in the retreatment study (PRU-USA-28) (26)

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PRU-USA-28	To compare the percentage of patients reaching ≥ 3 SCBM/week	CMH test for between-group comparisons ANCOVA for continuous data Van Elteren test, pairwise t-test and Wilcoxon signed rank test also used.	To detect a difference from placebo of 15%, for a 30% response rate for prucalopride 4 mg, with a power of 90% and 2-sided type I error rate of 5%, 159 randomised patients per treatment group with data in the second treatment period was required. Considering the expected rates of discontinuations, requalifications for the second treatment period and screening failure, 626 patients needed to be recruited in total	As per pivotal trials

Abbreviations: ANCOVA, Analysis of Covariance; CMH, Cochran-Mantel-Haenszel

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

No subgroup analyses were untaken on the individual pivotal studies however subgroup analyses were performed on the pooled data from the 3 pivotal RCTs.

In addition to the analysis of the total population from these 3 pivotal studies, a comprehensive set of subgroup analyses were carried out to assess both the robustness of the primary efficacy data and to establish whether any particular baseline characteristic is associated with response. The key points to emerge from these analyses were:

- Female patients show optimal efficacy, compared to placebo, at the recommended dose of prucalopride 2 mg. As confirmed by epidemiology data and as seen in other studies with other products in this indication, the majority of the patients were women and less than 15% of the enrolled patients were men. Although results with the 4 mg dose were similar in men when compared to women, data on efficacy in men with the 2 mg dose were less consistent. This is most likely related to the rather small number of male patients and the more severe constipation at baseline in the 2 mg group in males when compared to the other treatment groups. There is no pharmacokinetic/pharmacodynamic rationale (time to first bowel movement and colonic transit data are not different between genders) for men to respond differently to prucalopride. However, as prucalopride is indicated for female patients these results do not affect the clinical evidence supporting this submission.

- In the analysis of the pooled data, there was no clinically relevant effect of age, but patient numbers were rather small. Specific studies in elderly patients (≥ 65 years of age) indicate that prucalopride is already effective at 1 mg o.d.

- Analyses to assess impact of severity of baseline disease indicated that even the patients with the most severe and chronic disease showed a statistically and clinically significant response to prucalopride treatment.

- Most patients who responded in the first 4 weeks maintained their response, while non-responders in this time period generally remained non-responders.

5.3.7 Participant flow

CONSORT flow charts showing the details of the numbers of patients who were eligible to enter the relevant RCTs, and were randomised and allocated to each treatment are presented below.

Pivotal Studies

Figure 1: Participant flow in PRU-INT-6 (18)

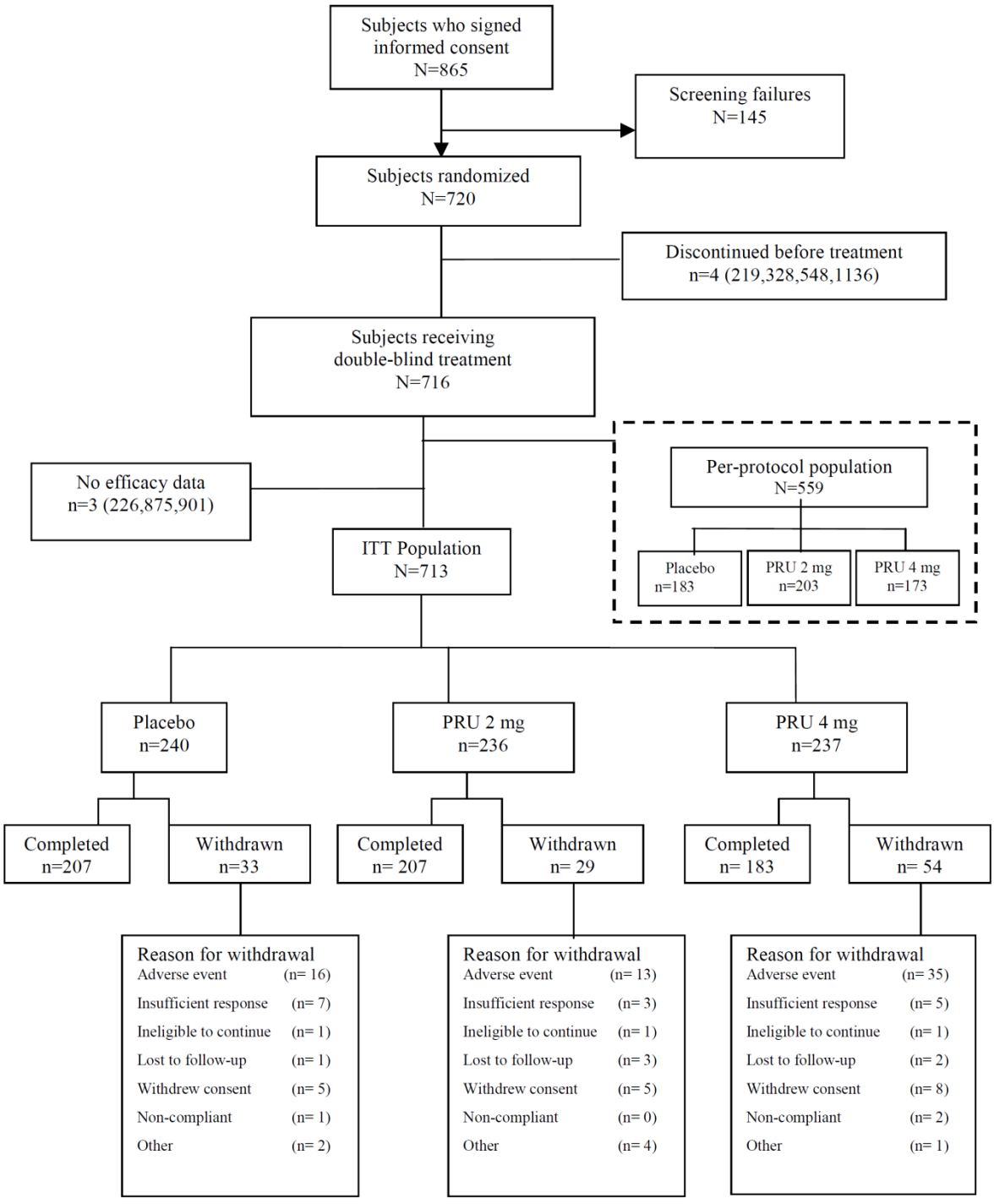


Figure 2: Participant flow in PRU-USA-11 (20)

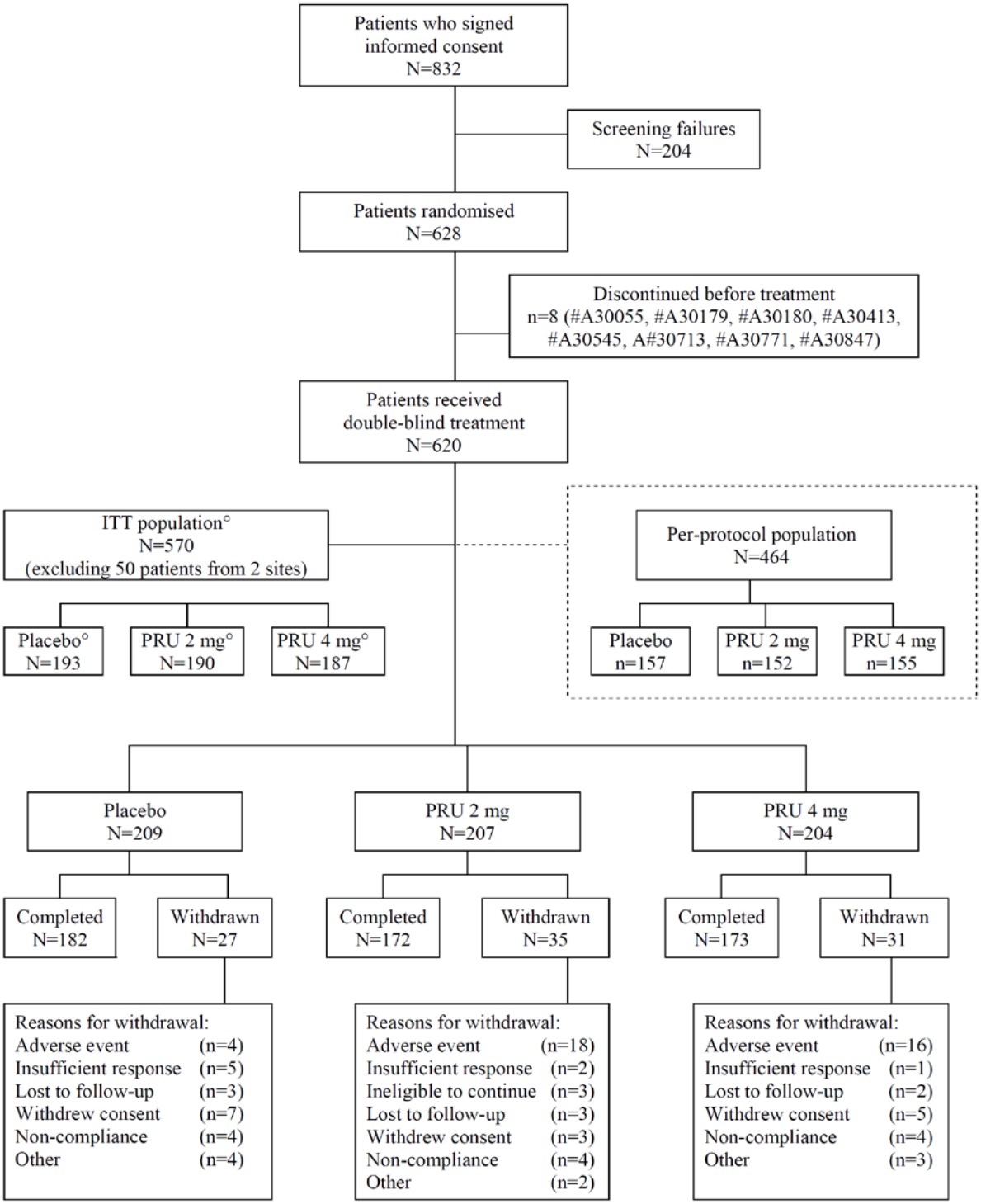
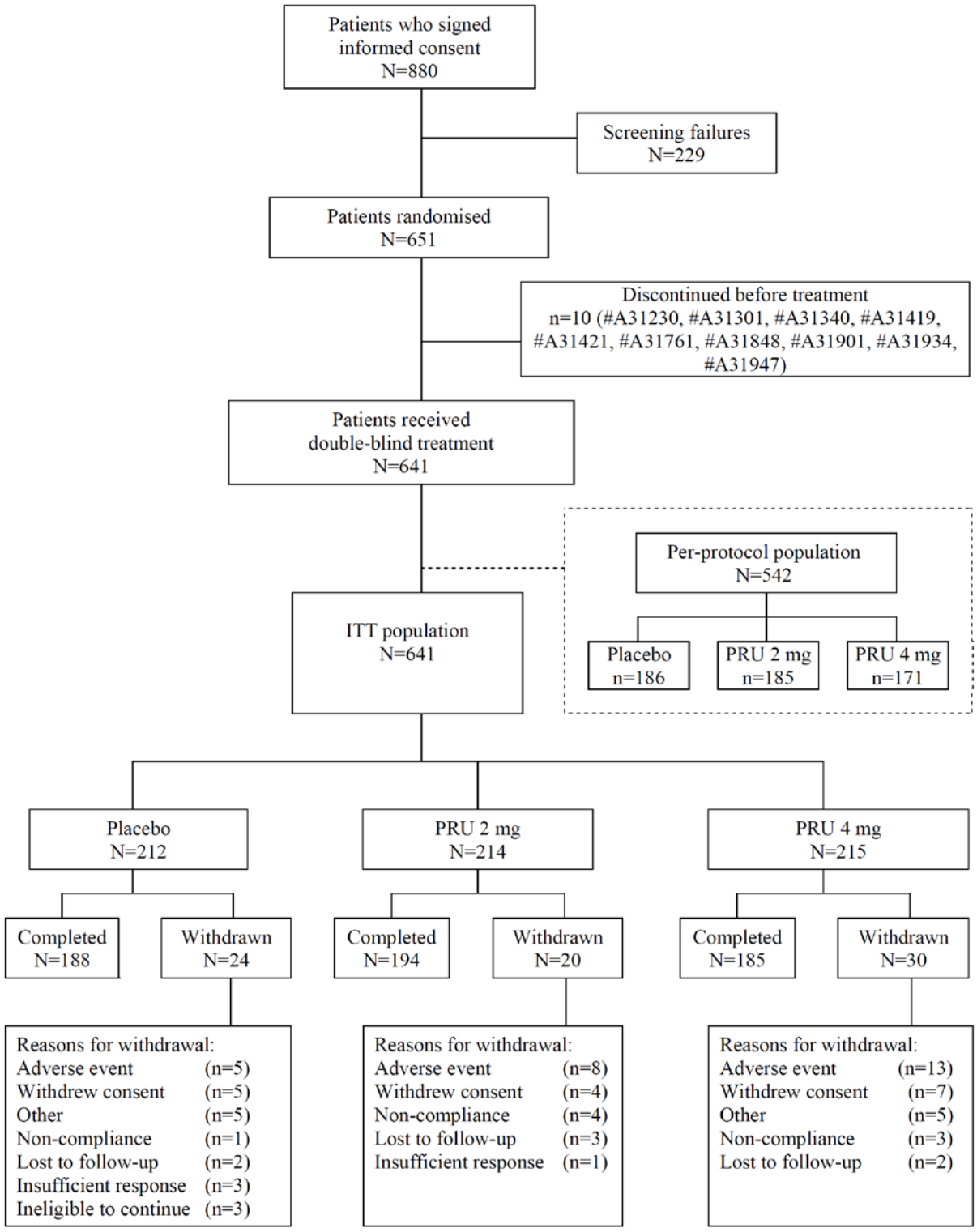
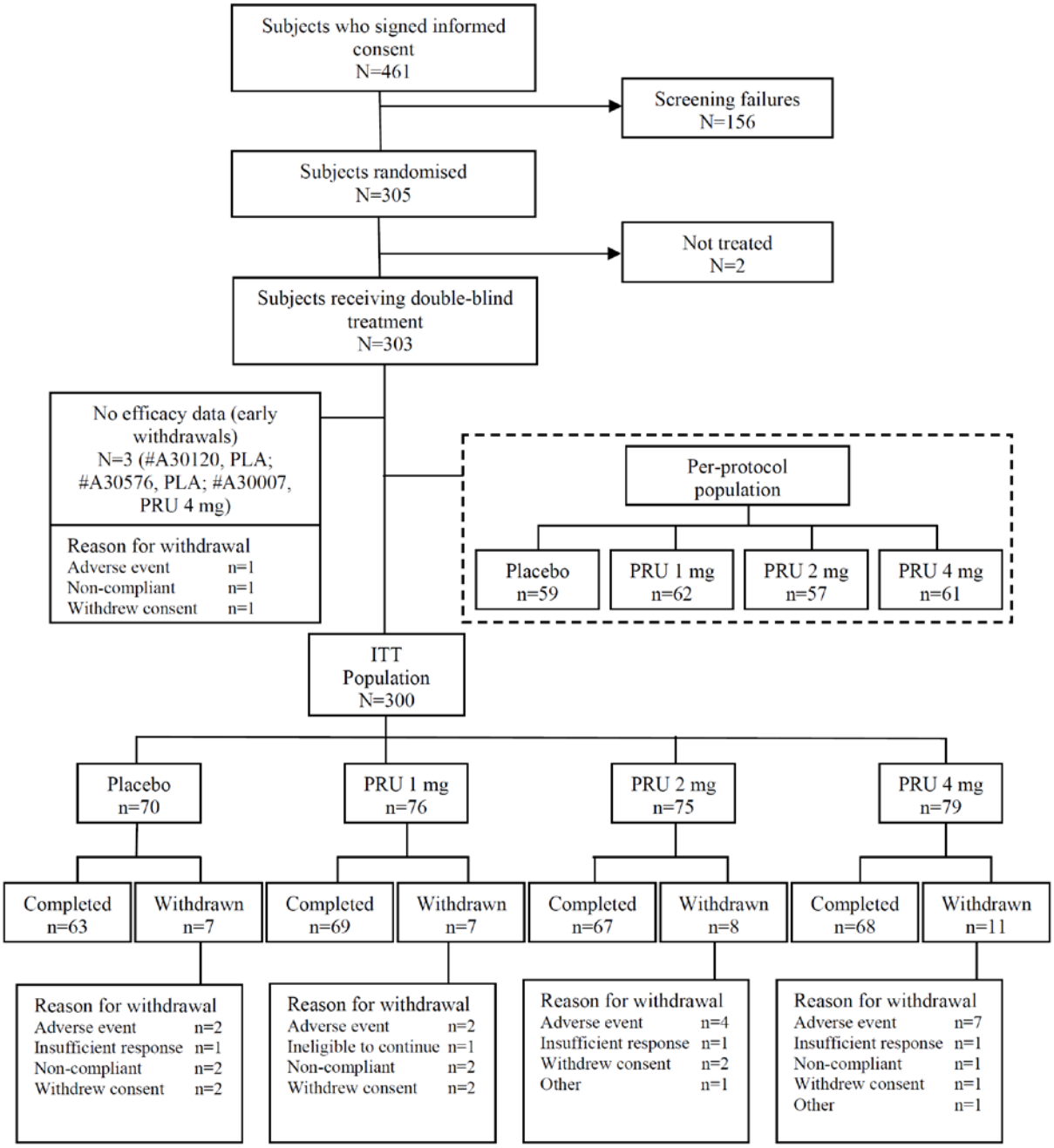


Figure 3: Participant flow in PRU-USA-13 (22)



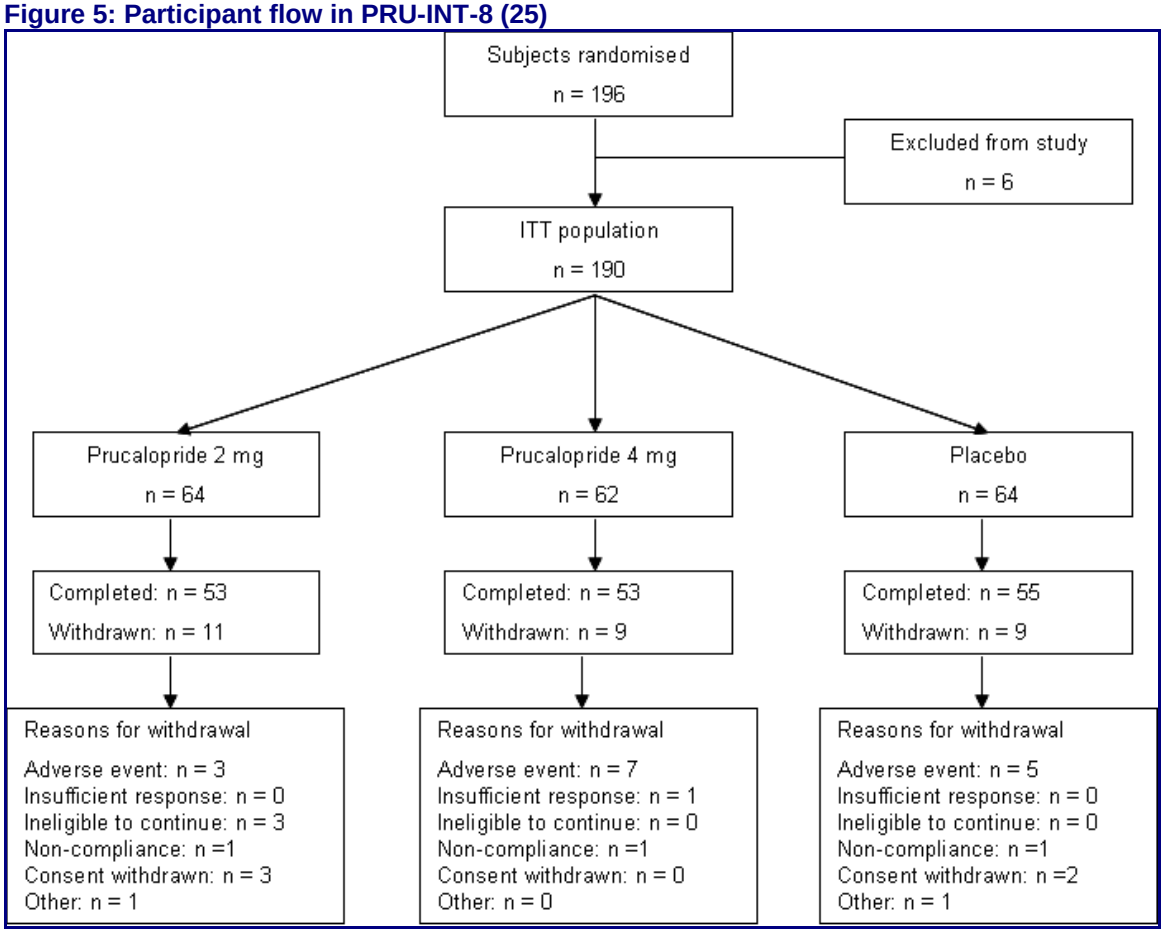
Elderly subjects

Figure 4: Participant flow in PRU-INT-12 (24)



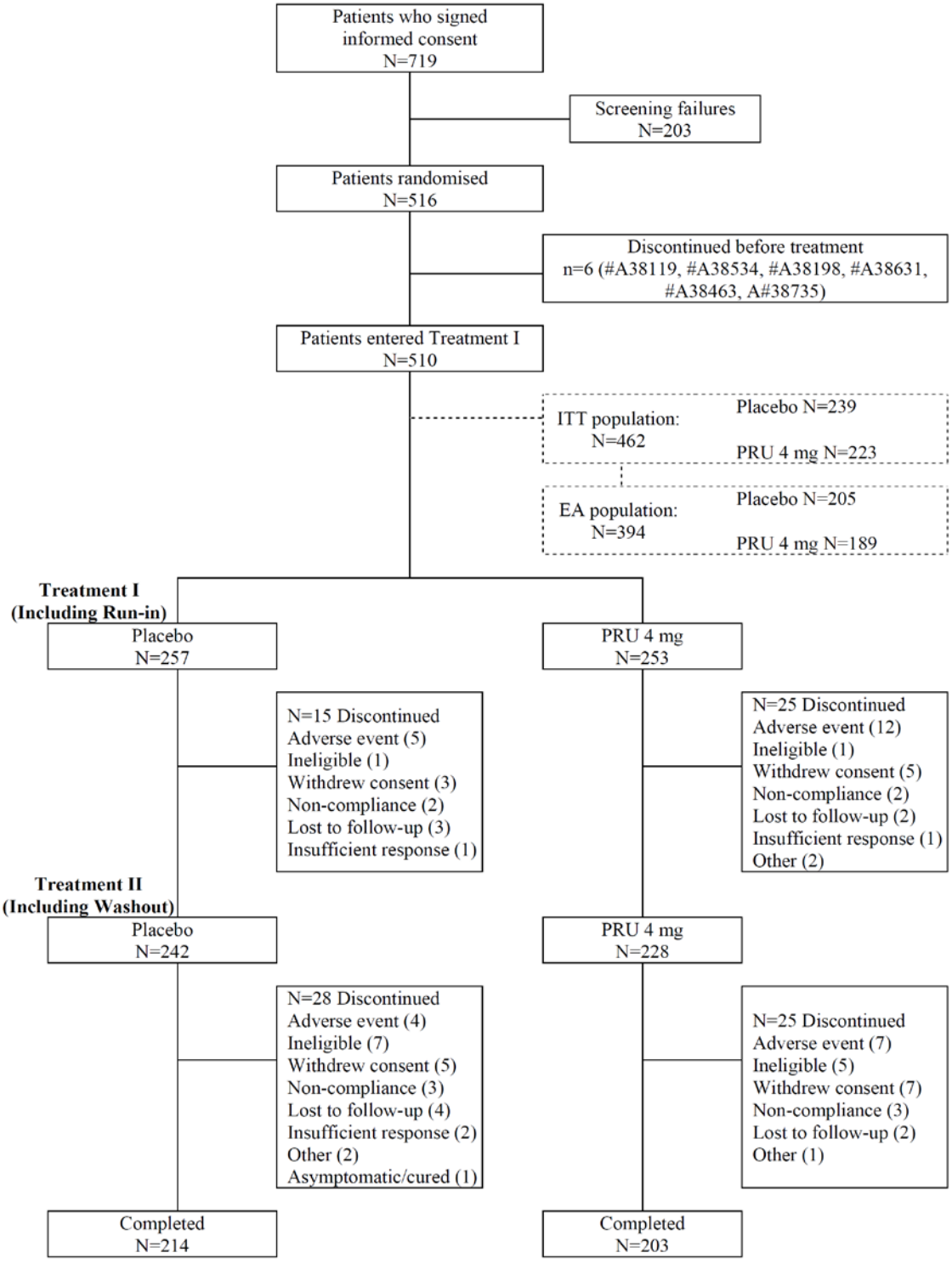
Opioid-induced constipation

Figure 5: Participant flow in PRU-INT-8 (25)



Retreatment study

Figure 6: Participant flow in PRU-USA-28 (26)



5.4 Critical appraisal of relevant RCTs

A critical appraisal of the pivotal RCTs is presented in Table 24.

Table 24: Quality assessment of pivotal RCTs (PRU-INT-6, PRU-USA-11, PRU-USA-13)(18-23)

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	A randomisation code was used to randomly allocate patients to the 3 treatment groups, with balancing per centre to obtain approximately equal numbers per group.	Yes
Was the concealment of treatment allocation adequate?	Tablets were identical in appearance, taste and smell. Containers were identical in appearance	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The three treatment arms were demographically similar and had similar baseline disease 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?	Drop-outs were accounted for and the expected higher dropout rate in the prucalopride group was mainly driven by the more frequent occurrence of AEs leading to discontinuation	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes appear to have been 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 study population for the analysis of efficacy and health-related quality-of-life variables comprised patients who received at least one dose of trial medication and had at least one post-baseline diary assessment The last 7 diary days with data were used to fill the missing diary days for patients who did not complete the diary through day 84 but had ≥ 7 non-missing diary days after week 1	Yes

† Identical methodology

5.5 Results of the relevant RCTs

Pivotal studies

PRU-INT-6 (18, 19), PRU-USA-11 (20, 21), PRU-USA-13 (22, 23)

Summary

- The primary efficacy endpoint of ≥ 3 SCBMs/week (normalisation of bowel movements) was achieved in a statistically significantly greater proportion of patients treated with prucalopride 2 mg versus placebo (P ≤ 0.01 in all studies for weeks 1-4 and weeks 1-12)
- The key secondary endpoint of an average increase of ≥ 1 SCBMs/week was achieved in a statistically significantly greater proportion of patients treated with prucalopride 2 mg versus placebo (P ≤ 0.01 in all studies for weeks 1-4 and weeks 1-12)
- In all 3 pivotal studies prucalopride 2 mg was superior to placebo and yielded a consistent and clinically relevant effect on secondary endpoints including bowel movements frequency, symptoms evaluation, and patients' quality of life and satisfaction with treatment

Summary of analysis of pooled efficacy data from the pivotal studies

- In a chronic constipation population who were not adequately relieved by laxatives and who during the run-in had a mean of ≤ 0.5 SCBM per week, 23.6% of patients achieved a normal bowel movement pattern after 12 weeks of treatment with 2 mg prucalopride o.d. compared with 11.3% of placebo patients
- 43.1% of patients that received 2 mg prucalopride compared with 24.6% of placebo-treated patients had an increase of at least 1 SCBM per week. This endpoint is an accepted clinical criterion for meaningful benefit in this population
- It is evident from the data that a SCBM, which by definition is associated with a sense of complete evaluation, is also usually associated with normal stool consistency and little or no straining. So, an increase in SCBM frequency also results in an improvement in these 2 parameters, irrespective of treatment
- When all bowel movements are considered, prucalopride decreased stool hardness and severe straining, without increasing the number of watery stools
- The improvements in SCBMs were also accompanied by positive effects on the disease symptoms with approximately one third of patients seeing a one point improvement in the overall symptom score on the PAC-SYM questionnaire. Prucalopride also provides an improvement on a variety of frequent abdominal symptoms
- Importantly, the improvements seen in the quantitative endpoints and the disease symptoms are reflected in the quality of life results which showed that 44.6% of patients on 2 mg prucalopride had a clinically meaningful improvement in the key PAC-QOL satisfaction scale compared with 19.8% of placebo patients

Datasets analysed

Analyses of efficacy and quality of life (QoL) data were based on the intent-to-treat (ITT) population, defined as all randomised patients who took at least one dose of double-blind study medication and who provided any follow-up data for one or more key efficacy variables. All randomised patients who took at least one dose of double-blind study medication were included in the analysis of safety, demographic, and baseline characteristic data (all-treated population).

The ITT population of PRU-USA-11 (20, 21) excludes 50 patients (15 patients were excluded due to an improperly constituted Institutional Review Board and 35 patients were excluded due to data quality issues). The effect of excluding these 50 patients was investigated by performing an analysis on the available data from all treated patients, as reported by Camilleri et al (2008) (20). The analysis of the data from all treated patients revealed no important differences when compared with the ITT analysis.

Efficacy data for the adult licensed dose of prucalopride (2 mg) are discussed in detail with prucalopride 4 mg presented in tables for completeness.

Primary efficacy results

Proportion of patients with ≥ 3 SCBMs/week

In studies PRU-INT-6 (18, 19), PRU-USA-11 (20, 21), PRU-USA-13 (22, 23), the primary efficacy endpoint of ≥ 3 SCBMs/week over the 12 week treatment period was achieved in a statistically significantly greater proportion of patients treated with prucalopride 2 mg versus placebo ($P \leq 0.01$ in all studies for weeks 1-4 and weeks 1-12) (Table 25).

Key secondary efficacy results

Proportion of patients with an average increase of ≥ 1 SCBMs/week

In studies PRU-INT-6 (18, 19), PRU-USA-11 (20, 21), PRU-USA-13 (22, 23), the key secondary endpoint of an average increase of ≥ 1 SCBMs/week was achieved in a statistically significantly greater proportion of patients treated with prucalopride 2 mg versus placebo ($P \leq 0.01$ in all studies for weeks 1-4 and weeks 1-12) (Table 25).

Further secondary efficacy results

In studies PRU-INT-6 (18, 19), PRU-USA-11 (20, 21), PRU-USA-13 (22, 23), prucalopride was associated with improvements versus placebo in several additional efficacy outcomes, as summarised in Table 11. A statistical significantly greater proportion of patients treated with prucalopride 2 mg versus placebo achieved a greater average number of SCBM/week and an average increase of ≥ 1 SBM/week ($P \leq 0.001$ in all studies, weeks 1-4 and weeks 1-12) (Table 25).

In all three studies (18-23), BM symptoms were improved with prucalopride versus placebo (Table 25). A statistically significantly greater percentage of BMs with normal consistency and a statistically significantly lower percentage of BMs with severe or very severe straining were reported with prucalopride 2 mg versus placebo during week 1-12 ($P \leq 0.05$ in all studies) (Table 25).

After intake of the study drug, the median time to the first SBM/SCBM was statistically significantly less with prucalopride 2 mg versus placebo ($P \leq 0.001$ in all studies) (Table 25). In each study, laxative use (or enema) during the study period was also significantly reduced with prucalopride use versus placebo ($P \leq 0.005$). Treatment was rated as ‘quite a bit’ or

'extremely effective'[1] by statistically significantly more patients treated with prucalopride 2 mg versus placebo (P ≤ 0.001 in all studies, weeks 1-12) (Table 25).

[1] According to the patient's global assessment of efficacy of treatment

Table 25: Efficacy data derived from diaries and patient global assessment questionnaires: Pivotal trials PRU-INT-6 (18, 19), PRU-USA-11 (20, 21), PRU-USA-13 (22, 23)

Outcome	PRU-INT-6			PRU-USA-11			PRU-USA-13		
	Prucalopride 2 mg†† (n = 236)	Prucalopride 4 mg (n = 237)	Placebo (n = 240)	Prucalopride 2 mg†† (n = 190)	Prucalopride 4 mg (n = 187	Placebo (n = 193)	Prucalopride 2 mg†† (n = 214)	Prucalopride 4 mg (n = 215)	Placebo (n = 212)
Primary efficacy endpoint									
Mean of ≥ 3 SCBMs/week, n (%)									
Run-in	2/236 (0.8)	3/327 (1.3)	2/239 (0.8)	2/189 (1.1)	2/187 (1.1)	0/192 (0)	1/213 (0.5)	3/215 (1.4)	2/212 (0.9)
Week 1-4	56/236 (23.7)†	63/237 (26.6)†	25/240 (10.4)	61/190 (32.1)†	70/187 (37.4)†	19/193 (9.8)	61/209 (29.2)†	59/204 (28.9)†	24/208 (11.5)
Week 1-12	46/236 (19.5)‡	56/237 (23.6)†	23/240 (9.6)	55/190 (28.9)†	54/187 (28.9)†	25/193 (13.0)	50/209 (23.9)‡	48/204 (23.5)‡	25/207 (12.1)
Key secondary efficacy endpoint									
Average increase of ≥ 1 SCBM/week, n (%)									
Week 1-4	93/227 (41.0)†	99/215 (46.0)†	49/235 (20.9)	100/177 (56.5)†	104/177 (58.8)†	46/189 (24.3)	102/209 (48.8)†	105/204 (51.5)†	53/208 (25.5)
Week 1-12	86/226 (38.1)†	94/213 (44.1)†	49/234 (20.9)	89/177 (50.3)†	90/176 (51.1)†	49/189 (25.9)	89/209 (42.6)†	95/204 (46.6)†	57/207 (27.5)
Other secondary efficacy endpoints									
Average increase of ≥ 1 SBM/week, week 1-12, n (%)									
Week 1-4	164/227 (72.2)†	162/215 (75.3)†	93/235 (39.6)	149/177 (84.2)†	142/177 (80.2)†	87/189 (46.0)	155/209 (74.2)†	167/204 (81.9)†	89/208 (42.8)
Week 1-12	145/226 (64.2)†	144/213 (67.6)†	89/234 (38.0)	132/177 (74.6)†	115/176 (65.3)†	71/189 (37.6)	131/209 (62.7)†	149/207 (73.0)†	83/207 (40.1)
Average number of SCBM/week, mean (mean change)									
Week 1-4	1.7 (1.4)†	2.0 (1.5)†	0.9 (0.5)	2.5 (2.1)†	2.8 (2.3)†	1.1 (0.7)	2.1 (1.6)†	2.4 (1.9)†	1.0 (0.6)
Week 1-12	1.6 (1.2)†	1.9 (1.4)†	1.0 (0.5)	2.3 (1.9)†	2.4 (1.9)†	1.3 (0.8)	1.9 (1.5)†	2.0 (1.5)†	1.2 (0.8)
% BMs with normal consistency, mean (mean change)									
Week 1-4	36.1 (13.4)	39.9 (15.1)‡	32.0 (10.9)	44.9 (20.3)†	45.3 (20.9)†	34.4 (11.8)	38.5 (16.4)§	45.6 (19.3)†	32.8 (9.6)
Week 1-12	40.0 (17.4)§	41.6 (16.6)‡	33.7 (12.6)	48.1 (23.5)†	47.6 (23.1)†	35.1 (12.4)	41.7 (19.5)‡	46.4 (20.1)†	35.7 (12.4)
% BMs with no straining, mean (mean change)									
Week 1-4	18.8 (3.4)‡	22.1 (3.8)†	15.0 (-3.3)	23.7 (-0.1)	24.6 (3.5)	21.9 (-1.8)	28.1 (5.4)†	28.5 (2.4)†	18.0 (-2.3)
Week 1-12	16.4 (1.0)	19.6 (1.3)§	14.8 (-3.5)	23.1 (-0.7)	26.7 (5.4)§	23.8 (0.0)	26.6 (3.9)‡	27.3 (1.2)‡	19.0 (-1.4)
% BMs with severe or very severe straining, mean (mean change)									
Week 1-4	25.3 (-14.2)†	22.8 (-14.9)†	33.9 (-4.6)	15.6 (-12.5)†	16.5 (-12.4)†	22.4 (-4.3)	15.9 (-8.3)†	18.4 (-13.3)†	27.5 (-2.9)
Week 1-12	26.6 (-13.0)†	25.1 (-12.5)†	32.6 (-5.7)	15.9 (-12.1)†	15.9 (-12.9)†	21.2 (-5.5)	17.0 (-7.3)‡	19.2 (-12.5)‡	24.3 (-6.2)
% BMs with a sensation of complete evacuation, mean (mean change)									
Week 1-4	24.6 (10.8)§	33.9 (12.6)†	22.6 (4.8)	32.6 (12.7)†	34.6 (14.0)†	26.0 (4.7)	34.5 (10.9)‡	30.7 (13.0)‡	25.7 (5.8)
Week 1-12	25.5 (11.7)§	35.7 (14.3)†	23.8 (5.9)	35.0 (15.1)§	35.5 (14.9)§	30.0 (8.8)	34.8 (11.2)	31.8 (14.2)§	28.0 (8.1)
Time to first SCBM after intake of study drug, days									
Median (days)	4.7†	2.1†	20.5	1.3†	1.0†	12.4	2.3†	1.9†	13
Number of bisacodyl tablets taken/week, mean (mean change)									

Outcome	PRU-INT-6			PRU-USA-11			PRU-USA-13		
	Prucalopride 2 mg[††] (n = 236)	Prucalopride 4 mg (n = 237)	Placebo (n = 240)	Prucalopride 2 mg[††] (n = 190)	Prucalopride 4 mg (n = 187	Placebo (n = 193)	Prucalopride 2 mg[††] (n = 214)	Prucalopride 4 mg (n = 215)	Placebo (n = 212)
Week 1-4	1.0 (-0.9)[†]	1.1 (-0.7)[†]	2.2 (-0.2)	0.9 (-1.1)[†]	0.9 (-0.9)[†]	1.9 (-0.2)	1.2 (-0.8)[†]	1.0 (-1.2)	1.8 (-0.1)
Week 1-12	1.1 (-0.8)[†]	1.1 (-0.6)[‡]	2.1 (-0.2)	0.9 (-1.1)[†]	1.1 (-0.7)[†]	2.0 (-0.0)	1.4 (-0.7)[‡]	1.2 (-1.0)	1.7 (-0.1)
Average number of days with laxative use (bisacodyl (Dulcolax) or enema)/week, mean (mean change)									
Week 1-4	0.4 (-0.4)[†]	0.4 (-0.4)[†]	0.9 (-0.1)	0.4 (-0.5)[†]	0.4 (-0.4)[†]	0.9 (-0.1)	0.5 (-0.3)†	0.4 (-0.5)[†]	0.8(-0.1)
Week 1-12	0.4 (-0.4)[†]	0.5 (-0.3)[†]	0.8 (-0.2)	0.5 (-0.5)[†]	0.5 (-0.3)[†]	0.9 (-0.0)	0.6 (-0.3)[§]	0.5 (-0.4)[†]	0.7 (-0.1)
Patient assessment of constipation severity[¶], mean (mean change)									
Week 4	1.84 (-0.82)[†]	1.87 (-0.88)[†]	2.36 (-0.39)	1.69 (-0.97)[†]	1.60 (-1.05)[†]	2.38 (-0.36)	1.94 (-0.92)[†]	1.78 (-0.93)[†]	2.34 (-0.36)
Week 12	1.90 (-0.76)[†]	1.82 (-0.92)[†]	2.39 (-0.31)	1.82 (-0.81)[†]	1.89 (-0.78)[‡]	2.26 (-0.45)	1.86 (-0.98)[†]	1.90 (-0.80)[†]	2.30 (-0.37)
Patients rating their treatment as quite a bit or extremely or extremely effective, n (%)									
Week 4	65/215 (30.2)[†]	72/209 (34.4)[†]	36/227 (15.8)	62/172 (36.0)[†]	66/172 (38.4)[†]	21/175 (12.0)	71/200 35.5)[†]	61/196 (31.1)[†]	37/184 (20.1)
Week 12	71/205 (34.6)[†]	65/180 (36.1)[†]	39/209 (18.7)	53/155 (34.2)[†]	58/159 (36.5)[†]	32/163 (19.6)	75/193 (38.9)[†]	67/181 (37.0)[†]	29/199 (14.6)

Abbreviations: BM, Bowel Movement; SBM, Spontaneous Bowel Movements; SCBM, Spontaneous, Complete Bowel Movements; [†] P ≤ 0.001; [‡] P ≤ 0.01; [§] P ≤ 0.05; [¶] None/absent = 0; mild = 1; moderate = 2; severe = 3; very severe = 4; [††] Licensed dose

Outcomes from self-rated questionnaires

Patient Assessment of Constipation – Symptoms (PAC-SYM)

A summary of the PAC-SYM scores reported in each of the pivotal Phase III studies (18-23), is provided in Table 26. It is of note that statistically significantly decreases in severity from baseline in the overall, stool and abdominal symptoms were reported in all three studies with prucalopride 2 mg versus placebo (≤ 0.05 in all studies at week 4 and 12; with the exception of stool symptoms at week 12 in PRU-USA-11 where significance was not reached[2]).

Patient Assessment of Constipation – Quality of life (PAC-QOL)

A consistent improvement in patient satisfaction with their bowel habits and their treatment was evident with prucalopride versus placebo in all three pivotal Phase III trials (18-23). Statistically significant improvements in all elements of the PAC-QOL questionnaire were reported with prucalopride 2 mg (licensed dose) versus placebo (P ≤ 0.05 in all studies at weeks 4 and 12); with the exception of the psychosocial discomfort scale in PRU-USA-13 (22, 23) (Table 27).

The PAC-QOL is a constipation-specific and validated instrument that assesses patients' HRQoL and satisfaction with bowel habits and treatments. The PAC-QOL has shown good psychometric properties in prucalopride trials. A 1-point improvement can be considered clinically meaningful and is supported by the fact that the majority of patients reaching this threshold also demonstrated improvement in other clinical parameters including the primary endpoint. In addition, the clinical meaningfulness of the PAC-QOL scores was further supported by the increase in patients' HRQoL and satisfaction observed with a decrease in the severity of constipation. The PAC-QOL scores were correlated with the efficacy of treatment, as perceived by patients.

Importantly the superior effect of prucalopride relative to placebo on quality of life at a 2 mg dose was demonstrated, irrespective of the type of analysis performed. This is confirmed by the cumulative response curves for each of the subscales. These curves show that prucalopride 2 mg and 4 gm treatment groups experienced better results than placebo for all PAC-QOL scores whatever the level of response. In other words whatever increase in quality of life is considered (0.8 point, 1 point, 1.2 points, 1.4 points etc.), there are always more patients that have this particular level of benefit on prucalopride compared with placebo

SF-36

In PRU-INT-6 (19), an improved SF-36 Physical Component Summary (PCS) score was reported at week 4 with prucalopride 2 mg (licensed dose) versus placebo (P ≤ 0.05). No further significant differences in SF-36 scores were reported in the three pivotal Phase III trials for prucalopride 2 mg (licensed dose) versus placebo (18-23). The SF-36 is a non-disease-specific quality of life (QoL) questionnaire, therefore it was expected that improvements in SF-36 scores would be less pronounced when compared with the PAC-QOL (19, 21-23) (Table 27).

[2] In the all-treated patient analysis of PRU-USA-11 (with the inclusion of an additional 50 patients) this result reaches significance at week 12 (P ≤ 0.008)

Table 26: Efficacy data derived from PAC-SYM questionnaires: Pivotal RCTs PRU-INT-6 (18, 19), PRU-USA-11 (20, 21), PRU-USA-13 (22, 23)

Outcome	PRU-INT-6			PRU-USA-11			PRU-USA-13		
	Prucalopride 2 mg†† (n = 236)	Prucalopride 4 mg (n = 237)	Placebo (n = 240)	Prucalopride 2 mg†† (n = 190)	Prucalopride 4 mg (n = 187)	Placebo (n = 193)	Prucalopride 2 mg†† (n = 214)	Prucalopride 4 mg (n = 215)	Placebo (n = 212)
PAC-SYM									
Overall PAC-SYM symptoms score, mean (mean change)									
Week 4	1.46 (-0.67)†	1.34 (-0.64)†	1.73 (-0.34)	1.26 (-0.65)†	1.22 (-0.71))†	1.57 (-0.38)	1.40 (-0.65)†	1.23 (-0.61)†	1.59 (-0.38)
Week 12	1.44 (-0.66)	1.29 (-0.71)†	1.69 (-0.37)	1.26 (-0.63)¶	1.21 (-0.70)‡	1.49 (-0.46)	1.26 (-0.78)†	1.28 (-0.56)¶	1.52 (-0.45)
Improvement ≥ 1 overall PAC-SYM score from baseline, n (%)									
Week 4	77/216 (35.6)†	61/208 (29.3)‡	41/226 (18.1)	54/172 (31.4)†	59/169 (34.9)†	26/172 (15.1)	60/199 (30.2)†	62/194 (32.0)†	31/199 (15.6)
Week 12	70/205 (34.1)‡	65/178 (36.5)†	47/208 (22.6)	48/154 (31.2)	53/158 (33.5)	37/160 (23.1)	73/192 (38.0)†	52/179 (29.1)	43/182 (23.6)
PAC-SYM Stool symptoms score, mean (mean change)									
Week 4	1.83 (-0.74)†	1.75 (-0.67)†	2.10 (-0.37)	1.69 (-0.70)†	1.73 (-0.83)†	2.14 (-0.39)	1.86 (-0.72)†	1.72 (-0.57)†	2.15 (-0.37)
Week 12	1.75 (-0.78)†	1.69 (-0.77)†	2.08 (-0.40)	1.73 (-0.63)	1.74 (-0.81)¶	1.98 (-0.54)	1.75 (-0.83)†	1.77 (-0.51)	2.07 (-0.45)
PAC-SYM Abdominal symptoms score, mean (mean change)									
Week 4	1.47 (-0.73)†	1.31 (-0.72)†	1.81 (-0.31)	1.16 (-0.75)†	1.06 (-0.75)†	1.54 (-0.38)	1.32 (-0.71)‡	1.11 (-0.82)†	1.51 (-0.46)
Week 12	1.53 (-0.66)¶	1.26 (-0.77)†	1.72 (-0.40)	1.15 (-0.74)†	0.99 (-0.78)†	1.51 (-0.44)	1.18 (-0.86)†	1.18 (-0.76)‡	1.44 (-0.53)
PAC-SYM Rectal symptoms score, mean (mean change)									
Week 4	0.84 (-0.45)§	0.69 (-0.51)‡	0.99 (-0.30)	0.71 (-0.45)	0.58 (-0.45)	0.63 (-0.37)	0.74 (-0.46)	0.58 (-0.39)	0.76 (-0.28)
Week 12	0.82 (-0.44)¶	0.67 (-0.54)†	1.01 (-0.26)	0.63 (-0.49)	0.62 (-0.39)	0.63 (-0.37)	0.58 (-0.61)¶	0.60 (-0.36)	0.72 (-0.32)

Abbreviations: PAC-SYM, Patient Assessment of Constipation Symptoms; † P ≤ 0.001; ‡ P ≤ 0.01; § ≤ 0.10; ¶ P ≤ 0.05; †† Licensed dose

Table 27: Quality of life data derived from PAC-QOL and SF-36 questionnaires: Pivotal RCTs PRU-INT-6 (18, 19), PRU-USA-11 (20, 21), PRU-USA-13 (22, 23)

Outcome	PRU-INT-6			PRU-USA-11			PRU-USA-13		
	Prucalopride 2 mg†† (n = 236)	Prucalopride 4 mg (n = 237)	Placebo (n = 240)	Prucalopride 2 mg†† (n = 190)	Prucalopride 4 mg (n = 187	Placebo (n = 193)	Prucalopride 2 mg†† (n = 214)	Prucalopride 4 mg (n = 215)	Placebo (n = 212)
PAC-QOL									
Overall PAC-QOL Satisfaction score, mean (mean change)‡‡									
Week 4	2.29 (-0.82)†	2.27 (-0.82)†	2.89 (-0.26)	2.30 (-1.11)†	2.22 (-1.16)	3.10 (-0.20)	2.51 (-0.86)†	2.42 (-0.97)†	3.06 (-0.39)
Week 12	2.34 (-0.76)†	2.22 (-0.87)†	2.85 (-0.30)	2.43 (-0.97)†	2.37 (-1.00)	2.95 (-0.32)	2.43 (-0.93)†	2.45 (-0.97)†	3.01 (-0.44)
Improvement ≥ 1 PAC-QOL Satisfaction score from baseline, n (%)									
Week 4	92/215 (42.8)†	90/202 (44.6)†	51/224 (22.8)	91/170 (53.5)†	86/168 (51.2)†	32/173 (18.5)	83/195 (42.6)†	87/194 (44.8)†	43/193 (22.3)
Week 12	94/206 (45.6)†	82/179 (45.8)†	45/206 (21.8)	73/155 (47.1)†	75/157 (47.8)†	40/159 (25.2)	83/191 (43.5)†	79/178 (44.4)†	47/181 (26.0)

Outcome	PRU-INT-6			PRU-USA-11			PRU-USA-13		
	Prucalopride 2 mg[††] (n = 236)	Prucalopride 4 mg (n = 237)	Placebo (n = 240)	Prucalopride 2 mg[††] (n = 190)	Prucalopride 4 mg (n = 187	Placebo (n = 193)	Prucalopride 2 mg[††] (n = 214)	Prucalopride 4 mg (n = 215)	Placebo (n = 212)
Overall PAC-QOL score, mean (mean change)[‡‡]									
Week 4	1.37 (-0.65)[†]	1.25 (-0.63)[†]	1.72 (-0.31)	1.28 (-0.87)[†]	1.15 (-0.87)[†]	1.83 (-0.38)	1.43 (-0.77)[†]	1.29 (-0.80)[†]	1.67 (-0.43)
Week 12	1.36 (-0.65)[†]	1.21 (-0.66)[†]	1.66 (-0.38)	1.29 (-0.84)[†]	1.19 (-0.81)[†]	1.73 (-0.47)	1.34 (-0.85)[†]	1.25 (-0.86)[†]	1.65 (-0.47)
Improvement ≥ 1 overall PAC-QOL score from baseline, n (%)									
Week 4	37/224 (16.5)	67/215 (31.1)[†]	58/205 (28.3)[‡]	72/171 (42.1)[†]	67/169 (39.6)[†]	26/174 (14.9)	76/197 (38.6)[†]	76/196 (38.8)[†]	38/199 (19.1)
Week 12	34/207 (16.4)	69/206 (33.5)[†]	53/180 (29.4)[†]	61/155 (39.4)[†]	64/158 (40.5)[†]	35/161 (21.7)	80/193 (41.5)[†]	75/182 (41.2)[†]	39/183 (21.3)
PAC-QOL Physical discomfort subscale score, mean (mean change)[‡‡]									
Week 4	1.55 (-0.89)[†]	1.41 (-0.83)[†]	1.93 (-0.44)	1.43 (-0.98)[†]	1.31 (-0.97)[†]	2.02 (-0.52)	1.61 (-0.89)[†]	1.41 (-0.94)[†]	1.92 (-0.47)
Week 12	1.55 (-0.85)[†]	1.33 (-0.90)[†]	1.86 (-0.53)	1.49 (-0.90)[†]	1.36 (-0.89)[†]	1.97 (-0.57)	1.46 (-1.02)[†]	1.44 (-0.92)[†]	1.85 (-0.55)
PAC-QOL Psychosocial discomfort subscale score, mean (mean change)[‡‡]									
Week 4	0.78 (-0.44)[†]	0.69 (-0.36)[†]	1.04 (-0.26)	0.65 (-0.57)[†]	0.54 (-0.53)[†]	0.99 (-0.37)	0.80 (-0.50)	0.62 (-0.55)[‡]	0.79 (-0.34)
Week 12	0.79 (-0.40)[§]	0.67 (-0.37)[§]	0.99 (-0.32)	0.58 (-0.60)[†]	0.53 (-0.51)[†]	0.99 (-0.37)	0.73 (-0.55)	0.59 (-0.61)[‡]	0.77 (-0.38)
PAC-QOL Worries and concerns subscale score, mean (mean change)[‡‡]									
Week 4	1.33 (-0.66)[†]	1.14 (-0.66)[†]	1.59 (-0.34)	1.23 (-0.96)[†]	1.06 (-0.94)[†]	1.80 (-0.41)	1.34 (-0.88)[†]	1.24 (-0.86)[†]	1.61 (-0.49)
Week 12	1.26 (-0.72)[†]	1.10 (-0.71)[†]	1.53 (-0.41)	1.20 (-0.95)[†]	1.08 (-0.92)[†]	1.62 (-0.58)	1.25 (-0.97)[†]	1.13 (-0.96)[†]	1.60 (-0.54)
SF-36 PCS scale score, mean (mean change)									
Week 4	46.7 (2.6)[§]	47.1 (2.2)	44.9 (1.1)	48.5 (2.3)	50.1 (3.1)[‡]	47.1 (0.9)	48.9 (2.5)	49.5 (2.3)	48.7 (1.6)
Week 12	46.3 (2.1)	47.3 (2.0)	45.6 (1.8)	49.4 (2.7)	50.2 (2.9)[§]	47.9 (1.4)	49.1 (2.7)	49.0 (2.1)	49.4 (2.5)
SF-36 MCS scale score, mean (mean change)									
Week 4	46.4 (2.2)	47.7 (2.7)[§]	45.9 (0.7)	48.8 (3.5)	49.8 (2.2)	46.7 (1.3)	47.6 (2.7)	49.1 (3.3)[§]	47.4 (1.3)
Week 12	47.6 (3.2)	48.3 (3.2)[¶]	46.1 (1.5)	48.0 (2.1)	50.6 (3.0)	47.3 (2.0)	48.6 (3.4)	49.8 (3.8)[§]	47.3 (1.4)

Abbreviations: PAC-QOL, Patient Assessment of Constipation Quality of Life; PCS, Physical Component Summary; PMS, Mental Component Summary; [†] P ≤ 0.001; [‡] P ≤ 0.01; § ≤ 0.05; [¶] P ≤ 0.10; [††] Licensed dose; [‡‡] Decreases reflect improvement

Elderly subjects

PRU-INT-12 (24)

Summary

- The primary efficacy endpoint of ≥ 3 SCBMs/week was achieved in a greater proportion of patients treated with prucalopride (all licensed doses) versus placebo during weeks 1-4
- The key secondary endpoint of an average increase of ≥ 1 SCBMs/week was achieved in a statistically significantly greater proportion of patients treated with prucalopride 1 mg and placebo (P ≤ 0.05, weeks 1-4)
- The % of patients with an improvement of ≥ 1 on the PAC-QOL satisfaction subscale was statistically significantly greater in the prucalopride 1 mg treatment group than placebo

Datasets analysed

Analyses of efficacy and QoL data were based on the ITT population, defined as all randomised patients who took ≥ 1 dose of double-blind study medication and who provided any follow-up data for one or more of the key efficacy variables. All randomised patients who took at least one dose of double-blind study medication were included in the analysis of safety, demographic, and baseline characteristic data (all-treated population).

Efficacy data for the licensed doses of prucalopride (1 mg and 2 mg) are discussed in detail with prucalopride 4 mg presented in tables for completeness.

Primary efficacy results

Proportion of patients with ≥ 3 SCBMs/week
In PRU-INT-12 (24), the primary efficacy endpoint of ≥ 3 SCBMs/week was achieved in a greater proportion of patients treated with prucalopride (all licensed doses) versus placebo during weeks 1-4, although significance was not reached (Table 28).

Key secondary efficacy results

Proportion of patients with an average increase of ≥ 1 SCBMs/week
In PRU-INT-12 (24), the key secondary endpoint of an average increase of ≥ 1 SCBMs/week was achieved in a statistically significantly greater proportion of patients treated with prucalopride 1 mg and 2 mg versus placebo (P ≤ 0.05, weeks 1-4) (Table 28).

Further secondary efficacy results

In PRU-INT-12 (24) prucalopride was associated with improvements versus placebo in several additional efficacy outcomes, as summarised in Table 28. For example, a statistically significantly greater proportion of patients treated with prucalopride 1 mg and 2 mg (versus placebo) achieved a greater average number of SCBM/week (P ≤ 0.05) (Table 28).

A statistically significantly greater percentage of BMs with normal consistency, no straining and a sensation of complete evacuation were reported with prucalopride 1 mg versus placebo (P ≤ 0.05, weeks 1-4) (Table 28).

After intake of the study drug, the median time to the first SCBM was statistically significantly less with prucalopride 1 mg and 2 mg versus placebo (P ≤ 0.05, weeks 1-4) (Table 28).

Treatment was rated as 'quite effective' or 'extremely effective'[3] by statistically significantly more patients treated with prucalopride 1 mg and 2 mg versus placebo (P < 0.05, weeks 1-4). In addition, significantly more patients treated with prucalopride 1 mg reported a decrease in the severity of constipation when compared with the placebo group.

Table 28: Efficacy data derived from diaries and patient global assessment questionnaires: PRU-INT-12 (24)

Outcome	PRU-INT-12			
	Prucalopride 1 mg§ (n = 76)	Prucalopride 2 mg§ (n = 75)	Prucalopride 4 mg (n = 79)	Placebo (n = 70)
Primary efficacy endpoint				
Mean of ≥ 3 SCBMs/week, n (%)				
Run-in	0/76	0/75	0/79	2/70 (2.9)
Week 1-4	30/76 (39.5)	24/75 (32.0)	25/79 (31.6)	14/70 (20.0)
Key secondary efficacy endpoint				
Average increase of ≥ 1 SCBM/week, n (%)				
Week 1-4	44/72 (61.1)†	41/72 (56.9)†	37/73 (50.7)†	22/65 (33.8)
Other secondary efficacy endpoints				
Average increase of ≥ 1 SBM/week, n (%)				
Week 1-4	48/72 (66.7)	41/72 (56.9)	41/73 (56.2)	29/65 (44.6)
Average increase of ≥ 1 BM/week, n (%)				
Week 1-4	45/72 (62.5)†	36/72 (50.0)	32/73 (43.8)	21/65 (32.3)
Average number of SCBM/week, mean (mean change)				
Week 1-4	2.7 (1.9)†	2.4 (1.7)†	2.4 (1.8)†	1.7 (0.6)
% BMs with normal consistency, mean (mean change)				
Week 1-4	49.4 (16.4)†	41.1 (13.7)	46.7 (9.0)	37.1 (7.3)
% BMs with no straining, mean (mean change)				
Week 1-4	26.4 (7.8)†	22.9 (-3.2)	26.7 (7.0)†	13.9 (-4.7)
% BMs with severe or very severe straining, mean (mean change)				
Week 1-4	20.6 (-11.6)	20.9 (-10.0)	17.5 (-14.6)†	26.9 (-1.4)
% BMs with a sensation of complete evacuation, mean (mean change)				
Week 1-4	48.1 (15.2)†	42.8 (14.6)	46.2 (14.9)†	36.0 (4.9)
Time to first SCBM after intake of study drug, days				
Median (days)	1.3†	1.1†	1.0†	4.1
Number of bisacodyl tablets taken/week, mean (mean change)				
Week 1-4	1.2 (-0.7)	1.2 (-1.0)	1.2 (-0.6)	1.4 (-1.0)
Average number of days with laxative use (bisacodyl (Dulcolax) or enema)/week, mean (mean change)				
Week 1-4	0.6 (-0.4)	0.6 (-0.5)	0.6 (-0.3)	0.6 (-0.4)
Patient assessment of constipation severity‡, mean (mean change)				
Week 4	1.70 (-0.52)†	1.92 (-0.51)	1.88 (-0.72)†	2.27 (-0.09)
Patients rating their treatment as quite a bit or extremely effective, n (%)				
Week 4	29/69 (42.0)†	16/66 (24.2)†	26/67 (38.8)†	10/64 (15.6)

Abbreviations: BM, Bowel Movement; SBM, Spontaneous Bowel Movements; SCBM, Spontaneous, Complete Bowel Movements; † P ≤ 0.05; ‡ None/absent = 0; mild = 1; moderate = 2; severe = 3; very severe = 4; § Licensed dose

[3] According to the patient's global assessment of efficacy of treatment

Outcomes from self-rated questionnaires

PAC-SYM

A summary of the PAC-SYM scores is provided in Table 29. A statistically significant decrease in severity from baseline in the overall PAC-SYM and stool symptoms scale is reported with prucalopride 1 mg versus placebo (≤ 0.05 at week 4).

Table 29: Efficacy data derived from PAC-SYM questionnaires: PRU-INT-12 (24)

Outcome	Prucalopride 1 mg‡ (n = 76)	Prucalopride 2 mg‡ (n = 75)	Prucalopride 4 mg (n = 79)	Placebo (n = 70)
PAC-SYM				
Overall PAC-SYM symptoms score, mean (mean change)				
Week 4	0.88 (-0.53)†	1.10 (-0.37)	0.87 (-0.55)†	1.22 (-0.23)
Improvement ≥ 1 overall PAC-SYM score from baseline, n (%)				
Week 4	12/68 (17.6)	8/64 (12.5)	13/67 (19.4)	11/64 (17.2)
PAC-SYM Stool symptoms score, mean (mean change)				
Week 4	33/68 (48.5)†	20/64 (31.3)	30/67 (44.8)†	14/64 (21.9)
PAC-SYM Abdominal symptoms score, mean (mean change)				
Week 4	12/68 (17.6)	8/63 (12.7)	12/67 (17.9)	12/64 (18.8)
PAC-SYM Rectal symptoms score, mean (mean change)				
Week 4	9/64 (14.1)	6/68 (8.8)	9/64 (14.1)	12/67 (17.9)

Abbreviations: PAC-SYM, Patient Assessment of Constipation Symptoms; † P ≤ 0.05; ‡ Licensed dose

PAC-QOL

An improvement in all PAC-QOL scores (with the exception of the psychosocial discomfort scale) was evident with prucalopride versus placebo in PRU-INT-12 (24) and reached statistical significance with prucalopride 1 mg (P ≤ 0.05 at week 4) (Table 30).

Table 30: Quality of life data derived from PAC-QOL questionnaires: PRU-INT-12 (24)

Outcome	Prucalopride 1 mg‡ (n = 76)	Prucalopride 2 mg‡ (n = 75)	Prucalopride 4 mg (n = 79)	Placebo (n = 70)
PAC-QOL				
Overall PAC-QOL satisfaction score, mean (mean change from baseline)				
Week 4	1.83 (-1.01)†	2.27 (-0.47)	2.10 (-0.65)	2.50 (-0.16)
Improvement ≥ 1 overall PAC-QOL satisfaction score from baseline, n (%)				
Week 4	33/68 (48.5)†	18/62 (29.0)	27/66 (40.9)	16/62 (25.8)
Overall PAC-QOL score, mean (mean change from baseline)				
Week 4	0.95 (-0.53)†	1.12 (-0.30)	1.05 (-0.38)	1.26 (-0.20)
Improvement ≥ 1 overall PAC-QOL score from baseline, n (%)				
Week 4	17/68 (25.0)	9/64 (14.1)	9/67 (13.4)	8/64 (12.5)
PAC-QOL Physical discomfort subscale score, mean (mean change from baseline)‡‡				
Week 4	0.91 (-0.60)†	1.19 (-0.40)	0.99 (-0.45)	1.33 (-0.21)
PAC-QOL Psychosocial discomfort subscale score, mean (mean change from baseline)‡‡				
Week 4	0.47 (-0.30)	0.49 (-0.17)	0.46 (-0.19)	0.52 (-0.28)
PAC-QOL Worries and concerns subscale score, mean (mean change from baseline)‡‡				
Week 4	0.91 (-0.46)†	1.03 (-0.30)	1.02 (-0.38)	1.23 (-0.17)

Abbreviations: PAC-QOL, Patient Assessment of Constipation Quality of Life; † P ≤ 0.05; ‡ Licensed dose

Opioid-induced constipation

PRU-INT-8 (25)

Summary

The available data from controlled and open trials in this difficult to treat opioid-induced constipation population support the efficacy and safety results obtained in the pivotal trials in the general chronic constipation population. While the trials are smaller and consequently do not always show statistical significance as consistently as the pivotal trials, the numerical superiority of the prucalopride groups are consistent with the results from the pivotal trials and suggest that there may be a role for the drug in this patient population

PRU-INT-8

- The primary efficacy endpoint of an average increase of ≥ 1 SCBMs/week was achieved in a greater proportion of patients treated with prucalopride 2 mg versus placebo and reached statistical significance at week 1
- The key secondary endpoint of ≥ 3 SCBMs/week was achieved in a greater proportion of patients treated with prucalopride 2 mg versus placebo and reached statistical significance at week 1
- Prucalopride 2 mg was associated with improvements versus placebo in PAC-SYM total, stool and abdominal scores and all elements of the PAC-QOL

Datasets analysed

Analyses of efficacy and QOL data were based on the ITT population, defined all randomised patients who took ≥ 1 dose of double-blind study medication and who provided any follow-up data for one or more of the key efficacy variables.
Efficacy data for the licensed dose of prucalopride 2 mg are discussed in detail with prucalopride 4 mg presented in tables for completeness.

Primary efficacy results

Proportion of patients with an average increase of ≥ 1 SCBMs/week

In PRU-INT-8 (25), the primary efficacy endpoint of an average increase of ≥ 1 SCBMs/week was achieved in a greater proportion of patients treated with prucalopride 2 mg versus placebo and reached significance at week 1 (P ≤ 0.05) (Table 31).

Key secondary efficacy results

Proportion of patients with ≥ 3 SCBMs/week

In PRU-INT-8 (25), the key secondary endpoint of ≥ 3 SCBMs/week was achieved in a greater proportion of patients treated with prucalopride 2 mg versus placebo and reached statistical significance at week 1 (P ≤ 0.025) (Table 31). The response rate of ≥ 3 SCBMs/week over the entire trial period was 23.4% versus 9.4% in the prucalopride 2 mg versus placebo group, respectively (uncorrected P = 0.035).

Further secondary efficacy results

In PRU-INT-8 (25) prucalopride was associated with improvements versus placebo in several additional efficacy outcomes, as summarised in Table 31. Significant increases with prucalopride 2 mg versus placebo were reported for the average number of BM/week ($P \leq 0.05$, week 1) and the percentage of SCBM and BM with hard or very hard consistency ($P \leq 0.05$, weeks 1-4) (Table 31). Significant decreases with prucalopride 2 mg versus placebo were reported for average straining/BM ($P \leq 0.05$, weeks 1-4), average number of bisacodyl tablets/week ($P \leq 0.05$, weeks 1-4) and the average number of days with laxatives/week ($P \leq 0.05$, weeks 1-4) (Table 31).

After intake of the study drug, the median time to the first SCBM, SBM and BM was statistically significantly less with prucalopride 2 mg versus placebo ($P \leq 0.05$) (Table 31). The median time to SCBM was longer in all groups versus median time to SBM or BM, which is consistent with the expected lower frequency of SCBM.

Table 31: Efficacy data derived from diaries and patient global assessment questionnaires: PRU-INT-8 (25)

Outcome	Prucalopride 2 mg[††] (n = 64)	Prucalopride 4 mg (n = 62)	Placebo (n = 64)
Primary efficacy endpoint			
Average increase of ≥ 1 SCBM/week, n (%)			
Week 1	28/64 (43.8)[†]	30/60 (50.0)[†]	15/64 (23.4)
Week 1-4	23/64 (35.9)	25/62 (40.3)	15/64 (23.4)
Key secondary efficacy endpoint			
Mean of ≥ 3 SCBMs/week, n (%)			
Run-in	2/64 (3.1)	1/62 (1.6)	0/63 (0)
Week 1	16/64 (25.0)[†]	14/60 (23.3)[†]	2/64 (3.1)
Week 1-4	15/64 (23.4)	8/62 (12.9)	6/64 (9.4)
Other secondary efficacy endpoints			
Average increase of ≥ 1 SBM/week, n (%)			
Week 1	37/64 (57.8)	45/60 (75.0)[†]	28/64 (43.8)
Week 1-4	33/61 (54.1)	37/58 (63.8)	29/60 (48.3)
Average increase of ≥ 1 BM/week, n (%)			
Week 1	28/64 (43.8)	37/60 (61.7)[†]	22/64 (34.4)
Week 1-4	22/61 (36.1)	24/58 (41.4)	15/60 (25.0)
Average number of SCBM/week, mean (mean change)			
Week 1	1.6 (1.1)	1.8 (1.5)[‡]	0.6 (0.14)
Week 1-4	1.6 (1.1)	1.4 (1.1)	0.9 (0.6)
Average number of SBM/week, mean (mean change)			
Week 1	4.5 (2.2)	6.0 (3.7)[§]	2.9 (1.4)
Week 1-4	4.5 (2.2)	4.9 (2.6)[†]	3.0 (1.4)
Average number of BM/week, mean (mean change)			
Week 1	6.3 (1.1)[†]	7.1 (2.0)[†]	4.7 (0.1)
Week 1-4	5.9 (0.7)	6.3 (1.1)	4.8 (0.1)
% SCBMs with normal consistency, mean (mean change)			
Week 1-4	51.7 (10.3)	53.2 (30.3)[§]	50.8 (-16.2)
% SCBMs with hard or very hard consistency, mean (mean change)			
Week 1-4	34.8 (24.9)	21.5 (-11.6)[†]	16.6 (-31.4)[¶]
% BMs with hard or very hard consistency, mean (mean change)			
Week 1-4	42.2 (-13.5)[†]	45.8 (-10.7)	56.1 (-2.1)
Average straining/BM (mean change)			
Week 1-4	2.1 (-0.2)[†]	2.1 (-0.2)[†]	2.5 (0.1)
% BMs with severe or very severe straining, mean (mean change)			

Outcome	Prucalopride 2 mg[††] (n = 64)	Prucalopride 4 mg (n = 62)	Placebo (n = 64)
Week 1-4	39.0 (-6.3)	37.0 (-11.7)*	54.5 (-0.8)
% BMs with a sensation of complete evacuation, mean (mean change from baseline)			
Week 1-4	31.2 (5.0)	32.6 (8.2)	31.3 (4.0)
Time to first SCBM after intake of study drug, days			
Median (days)	4.8[‡]	3.7[‡]	20.1
Time to first SBM after intake of study drug, days			
Median (days)	1.0[†]	0.3[‡]	1.8
Time to first BM after intake of study drug, days			
Median (days)	0.4[†]	0.3[‡]	1.0
Number of bisacodyl tablets taken/week, mean (mean change)			
Week 1	1.9 (-2.3)[†]	1.6 (-2.5)[‡]	3.2 (-1.3)
Week 1-4	1.9 (-2.4)[¶]	2.2 (-2.2)	2.9 (-1.4)
Average number of days with laxative use week, mean (mean change)			
Week 1	1.1 (-1.4)[†]	1.0 (-1.5)[‡]	2.0 (-0.9)
Week 1-4	1.0 (-1.4)[†]	1.2 (-1.4)[¶]	1.6 (-1.0)
Patient assessment of constipation severity, mean (mean change)			
Week 2	2.31 (-0.32)	2.02 (-0.68)[‡]	2.60 (-0.12)
Endpoint	2.22 (-0.38)	1.98 (-0.71)[†]	2.45 (-0.27)
Patient assessment of extent of being bothered by constipation, mean (mean change)			
Week 2	2.27(-0.47)	1.86 (-0.88)[†]	2.55 (-0.28)
Endpoint	2.16 (-0.56)	1.81 (-0.91[¶]	2.38 (-0.43)
Patients rating their treatment as extremely effective, n (%)			
Endpoint	4 (6.3)	6 (10.3)	2 (3.3)

Abbreviations: BM, Bowel Movement; SBM, Spontaneous Bowel Movements; SCBM, Spontaneous, Complete Bowel Movements; [†] P ≤ 0.05; [‡] P ≤ 0.01; [§] P ≤ 0.001; [¶] P ≤ 0.1; [††] Licensed dose; [‡‡] For these parameters, Holm's procedure for multiple comparison was applied. For statistical significance the smallest P-value of the two comparisons had to be < 0.025

Outcomes from self-rated questionnaires

PAC-SYM, PAC-QOL and SF-36

In PRU-INT-8 (25), prucalopride 2 mg was associated with improvements versus placebo in PAC-SYM total, stool and abdominal scores (Table 32) and all elements of the PAC-QOL (Table 33). However, statistically significant differences in PAC-SYM, PAC-QOL or SF-36 scores were not reported between the prucalopride 2 mg and placebo groups during the study (Table 32 and Table 33).

Table 32: Efficacy data derived from PAC-SYM questionnaires: PRU-INT-8 (25)

Outcome	Prucalopride 2 mg[††] (n = 64)	Prucalopride 4 mg (n = 62)	Placebo (n = 64)
PAC-SYM			
Overall PAC-SYM symptoms score, mean (mean change)			
Week 2	1.57 (-0.36)	1.65 (-0.33)	1.90 (-0.17)
Endpoint	1.49 (-0.43)	1.51 (-0.46)	1.76 (-0.33)
PAC-SYM Stool symptoms score, mean (mean change)			
Week 2	2.01 (-1.38)	2.12 (-0.36)	2.35 (-0.16)
Endpoint	1.98 (-0.40)	1.97 (-0.50)	2.24 (-0.27)
PAC-SYM Abdominal symptoms score, mean (mean change)			
Week 2	1.42 (-0.38)	1.56 (-0.24)	1.75 (-0.11)
Endpoint	1.31 (-0.47)	1.34 (-0.43)	1.54 (-0.33)
PAC-SYM Rectal symptoms score, mean (mean change)			
Week 2	1.05 (-0.27)	0.98 (-0.42)	1.37 (-0.28)
Endpoint	0.89 (-0.41)	0.97 (-0.41)	1.27 (-0.41)

Abbreviations: PAC-SYM, Patient Assessment of Constipation Symptoms; [†] P ≤ 0.001; [‡] P ≤ 0.01; [§] ≤ 0.10; [¶] P ≤ 0.05; [††] Licensed dose

Table 33: Quality of life data derived from PAC-QOL and SF-36 questionnaires: PRU-INT-8 (25)

Outcome	Prucalopride 2 mg[§] (n = 64)	Prucalopride 4 mg (n = 62)	Placebo (n = 64)
PAC-QOL			
PAC-QOL satisfaction score, mean (mean change from baseline)			
Week 4	2.5 (-0.30)	2.45 (-0.57)	2.94 (-0.14)
Endpoint	2.48 (-0.31)	2.48 (-0.53)[†]	2.97 (-0.13)
PAC-QOL total score, mean (mean change)			
Week 4	1.30 (-0.31)	1.23 (-0.41)	1.68 (-0.23)
Endpoint	1.29 (-0.33)	1.29 9-0.35)	1.72 (-0.21)
PAC-QOL Physical discomfort subscale score, mean (mean change from baseline)[¶]			
Week 4	1.46 (-0.36)	1.43 (-0.49)	1.75 (-0.29)
Endpoint	1.41 (-0.41)	1.50 (-0.42)	1.77 (-0.30)
PAC-QOL Psychosocial discomfort subscale score, mean (mean change from baseline)[¶]			
Week 4	0.70 (-0.29)	0.67 (-0.28)	1.05 (-0.20)
Endpoint	0.71 (-0.30)	0.73 (-0.23)	1.09 (-0.19)
PAC-QOL Worries and concerns subscale score, mean (mean change)[¶]			
Week 4	1.14 (-0.31)	0.99 (-0.42)	1.53 (-0.26)
Endpoint	1.14 (-0.33)	1.07 (-0.34)	1.59 (-0.24)
SF-36 PCS scale score, mean (mean change)			
Week 4	28.9 (-0.0)	29.3 (-0.7)	28.7 (-1.5)
Endpoint	29.2 (-0.2)	29.2 (-0.9)	28.8 (-1.5)
SF-36 MCS scale score, mean (mean change)			
Week 4	42.8 (-1.3)	46.3 (-0.1)	42.4 (-1.9)
Endpoint	42.5 (-1.3)	45.8 (-0.5)	41.8 (-1.5)

Abbreviations: PAC-QOL, Patient Assessment of Constipation Quality of Life; [†] P ≤ 0.1; [‡] P ≤ 0.01; [§]Licensed dose; [‡‡] Decreases reflect improvement

Retreatment study

PRU-USA-28 (26)

Summary

- The efficacy of prucalopride during the second 4-week treatment period was similar to that during the first with regard to improvements in bowel function/habit and associated symptoms
- 38.6% and 36.0% of prucalopride-treated patients in the first and second treatment periods respectively had an average of ≥ 3 SCBMs/week over the 4 weeks of treatment compared with 10.7% and 11.2% of placebo recipients ($p < 0.001$ for both comparisons)
- 60.3% and 50.8% of prucalopride-treated patients in the first and second treatment periods respectively had an average increase from baseline of ≥ 1 SCBM/week over the 4 weeks of treatment compared with 22.9% and 26.8% of placebo recipients ($p < 0.001$ for both comparisons)

Datasets analysed

Analyses of efficacy data was based on the ITT population (defined as all randomised patients who took at least one dose of double-blind study medication and who had at least 7 days of non-missing diary data in one of the 2 treatment periods) and the efficacy analyzable (EA) population (defined as all randomised patients who took at least one dose of double-blind study medication in the second treatment period and who had at least 7 days of non-missing diary data after Week 1 in each of the 2 treatment periods). The primary population for efficacy was the EA population.

Efficacy data for the licensed doses of prucalopride (1 mg and 2 mg) are discussed in detail with prucalopride 4 mg presented in tables for completeness.

The analyses of efficacy discussed below focuses on 2 main time-points: Weeks 1 through 4 of Treatment I and Weeks 1 through 4 of Treatment II.

Primary efficacy results

Proportion of patients with ≥ 3 SCBMs/week

Over Weeks 1 to 4 of Treatment I, a significantly higher proportion of patients in the prucalopride group had ≥ 3 SCBM/week as compared to the placebo group (38.6% vs. 10.7%; $P < 0.001$) (Table 34).

At each time-point during Treatment II, the percentage of placebo patients with ≥3 SCBM/week was comparable to that for Treatment I (for Weeks 1 to 4: 11.2% vs. 10.7%).

Pair wise comparison of the prucalopride group with placebo during Treatment II showed that, in the prucalopride group, the percentages of patients with ≥3 SCBM/week was significant at each weekly time-point and over Weeks 1 to 4 ($P < 0.001$). Over Weeks 1 to 4, 63.6% of placebo patients and 71.2% of prucalopride-treated patients who were responders in Treatment I had ≥ 3 SCBM/week in Treatment II (Table 28).

Key secondary efficacy results

Proportion of patients with an average increase of ≥ 1 SCBMs/week

During Treatment I, 60.3% of patients in the prucalopride group had increases in the average SCBM/week of ≥ 1 over the run-in frequency, compared to 22.9% of placebo patients. The effect of prucalopride was higher during the first week of treatment (66.7% of responders for this definition) and stabilized afterwards (55.9% to 58.7%). Pairwise comparisons of the prucalopride group with placebo were significant at each weekly interval and over the whole period of Treatment I ($P < 0.001$) (Table 34).

During Treatment II, 51.3% of patients in the prucalopride group had increases in the average SCBM/week of ≥ 1 over the washout frequency, compared to 22.0% of placebo patients. The effect of prucalopride was maintained throughout the whole treatment period, but was more pronounced during Week 1. Again, pairwise comparisons of the prucalopride group with placebo were significant at each weekly interval and over Weeks 1 to 4 ($P < 0.001$) (Table 34).

Table 34: Primary and key secondary efficacy data: PRU-USA-28 (26)

Outcome	Prucalopride 4 mg (n = 189)	Placebo (n = 205)
Primary efficacy endpoint		
Average of ≥ 3 SCBMs/week, n (%)		
Treatment I		
Run-in	1/189 (0.5)	0/205 (0)
Week 1-4	73/189 (38.6)***	22/205 (10.7)
Week 1	90/189 (47.6)***	30/205 (14.6)
Week 2	72/189 (38.1)***	33/205 (16.1)
Week 3	74/189 (39.2)***	31/205 (15.1)
Week 4	75/188 (39.9)***	35/205 (17.1)
Treatment II		
Washout	0/189 (0)	1/203 (0.5)
Week 1-4	68/189 (36.0)***	23/205 (11.2)
Week 1	81/189 (42.9)***	29/205 (14.1)
Week 2	66/189 (34.9)***	36/205 (17.6)
Week 3	68/189 (36.0)***	29/205 (14.1)
Week 4	68/189 (36.0)***	33/205 (16.1)
Key secondary efficacy endpoint		
Average increase of ≥ 1 SCBM/week, n (%)		
Treatment I		
Week 1-4†	114/189 (60.3)***	47/205 (22.9)
Week 1	126/189 (66.7)***	45/205 (22.0)
Week 2	111/189 (58.7)***	53/205 (25.9)
Week 3	109/189 (57.7)***	55/205 (26.8)
Week 4	105/188 (55.9)***	60/205 (29.3)
Treatment II		
Week 1-4†	96/189 (50.8)***	55/205 (26.8)
Week 1-4‡	97/189 (51.3)***	45/205 (22.0)
Week 1‡	110/189 (58.2)***	57/205 (27.8)
Week 2‡	93/189 (49.2)***	57/205 (27.8)
Week 3‡	101/189 (53.4)***	60/205 (29.3)
Week 4‡	92/189 (48.7)***	51/205 (24.9)

*** P ≤ 0.001 vs. placebo
† Increase from run-in values
‡ Increase from washout values

Further secondary efficacy results

The following additional secondary efficacy parameters were investigated:

- Bowel movement frequencies – the proportion of patients with an average increase of ≥ 1 SBM/week or ≥ 1 BM/week
- Average of all BMs/week – average frequency of weekly BMs
- BM symptoms – stool consistency, straining, and sensation of complete evacuation
- Time to first BM
- Laxative use
- Patient global assessment – patient assessment of treatment efficacy and severity of constipation

Statistically significant improvements were observed with prucalopride 4 mg over placebo in both treatment periods for all the above outcomes. Detailed results are presented in Table 35.

PAC-SYM

Improvements from baseline for the overall PAC-SYM score (for the stool symptoms and abdominal symptoms subscales) were significantly larger in the prucalopride groups than in the placebo group ($P < 0.001$) at all time-points in each treatment period. For rectal symptoms, the decrease in severity from baseline in the prucalopride group was significantly different from that in the placebo group at Week 2 of Treatment I and Week 4 of Treatment II ($P \leq 0.017$) (Table 35).

Table 35: Further secondary efficacy data: PRU-USA-28 (26)

Outcome	PRU-USA-28			
	Prucalopride 4 mg		Placebo	
	Treatment I (n = 189)	Treatment II (n = 189)	Treatment I (n = 205)	Treatment II (n = 205)
Average increase of ≥ 1 SBM/week, n (%)				
Week 1-4 vs. run-in	157/189 (83.1)***	129/189 (68.3)***	80/205 (39.0)	85/205 (41.5)
Week 1-4 vs. washout	–	136/189 (72.0)***	–	68/205 (33.2)
Average number of SCBM/week, mean (mean change)				
Run-in/washout	0.5 (-)	0.4 (-)	0.4 (-)	0.4 (-)
Week 1-4 vs. run-in	2.8 (2.3)***	2.5 (2.0)***	1.0 (0.6)	1.1 (0.7)
Week 1-4 vs. washout	–	2.5 (2.1)***	–	1.1 (0.6)
% BMs with normal consistency, mean (mean change)				
Run-in/washout	21.2 (-)	26.7 (-)	24.6 (-)	28.5 (-)
Week 1-4	43.5 (22.3)***	44.6 (17.9)***	34.0 (9.4)	37.8 (8.7)
% BMs with no straining, mean (mean change)				
Run-in/washout	21.6 (-)	22.0 (-)	22.2 (-)	18.2 (-)
Week 1-4	28.4 (6.8)***	24.0 (2.1)	21.5 (-0.7)	20.7 (2.7)
Time to onset of first movement, median; hh:mm				
First SCBM after Day 1 dose	22:40***	57:00***	383:00	315:00
Number of bisacodyl tablets taken/week, mean (mean change)				
Run-in/washout	1.8 (-)	2.2 (-)	1.8 (-)	2.0 (-)
Week 1-4	0.8 (-1.0)***	1.0 (-1.1)***	1.8 (0.0)	1.8 (-0.3)
Number of patients rating treatment quite a bit or extremely effective, n/N (%)				
Week 4	77/188 (41.0)***	78/186 (41.9)***	29/205 (14.1)	23/192 (12.0)
Patient assessment of constipation severity†, mean (mean change)				
Baseline I/II	2.80 (-)	2.88 (-)	2.68 (-)	2.71 (-)
Week 4	1.64 (-1.16)***	1.83 (-1.05)***	2.46 (-0.21	2.28 (-0.45)
Overall PAC-SYM score, mean (mean change)				
Baseline I/II	1.96 (-)	1.77 (-)	1.94 (-)	1.75 (-)
Week 4	1.12 (-0.83)***	1.14 (-0.64)***	1.52 (-0.41)	1.48 (-0.29)
Improvement ≥ 1 overall PAC-SYM score from baseline, n/N (%)				
Week 4	80/187 (42.8)***	64/185 (34.6)***	41/205 (20.0)	26/192 (13.5)
PAC-SYM stool symptoms score, mean (mean change)				
Baseline I/II	2.41 (-)	2.27 (-)	2.46 (-)	2.28 (-)
Week 4	1.54 (-0.87)***	1.59 (-0.68)***	2.06 (-0.40)	2.02 (-0.29)
PAC-SYM abdominal symptoms score, mean (mean change)				
Baseline I/II	1.95 (-)	1.74 (-)	1.89 (-)	1.70 (-)
Week 4	1.00 (-0.95)***	1.01 (-0.75)***	1.47 (-0.42)	1.37 (-0.35)
PAC-SYM rectal symptoms score, mean (mean change)				

Outcome	PRU-USA-28			
	Prucalopride 4 mg		Placebo	
	Treatment I (n = 189)	Treatment II (n = 189)	Treatment I (n = 205)	Treatment II (n = 205)
Baseline I/II	1.23 (-)	1.01 (-)	1.12 (-)	0.92 (-)
Week 4	0.60 (-0.62)	0.57 (-0.44)*	0.70 (-0.42)	0.74 (-0.20)

Asterisks refer to differences compared with placebo.
Abbreviations: PAC-SYM, Patient Assessment of Constipation Symptoms;
† None/absent = 0; mild = 1; moderate = 2; severe = 3; very severe = 4
* P≤ 0.05
*** P ≤ 0.001

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

A meta-analysis was not considered appropriate for this submission as there are no active comparators to prucalopride.

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

An indirect/mixed treatment comparison was not carried out because prucalopride is the only active treatment approved for patients with long term laxative refractory chronic constipation. In this case the only appropriate comparator is prucalopride plus rescue medication versus placebo plus rescue medication.

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

The non-RCT evidence considered relevant to this submission is summarised in Table 36.

Table 36: Non-RCTs relevant to the submission

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
PRU-INT-10 (27)	Prucalopride 2 mg up to 4 mg o.d.	Subjects with chronic constipation	Long-term tolerability/ safety	CSR	Long-term follow-up of PRU-INT-6/ PRU-INT-12; population relevant to decision problem
PRU-USA-22 (28)	Prucalopride 1 mg to 4 mg o.d.	Subjects with chronic constipation	Long-term tolerability, safety, patient satisfaction, pharmacokinetics and pattern of use	CSR	Long-term follow-up study including patients from pivotal trials; population relevant to decision problem
PRU-INT-17 (29)	Prucalopride 1 mg to 4 mg	Subjects with chronic pain (cancer and non-cancer pain), suffering from opioid-induced constipation	Long-term tolerability/safety and pattern of use	CSR	Long-term follow-up in population relevant to decision problem

Summary of the methodology of relevant non-RCTs

Table 37: Methodology of relevant non-RCTs (PRU-INT-10, PRU-USA-22, PRU-INT-17) (27-29)

	PRU-INT-10	PRU-USA-22	PRU-INT-17
Objectives	Evaluation of the clinical long-term safety, tolerability, patient satisfaction, PK, and pattern of use of oral prucalopride tablets	To evaluate the clinical long-term safety and the tolerability, patient satisfaction, PK, and use patterns of oral prucalopride	To evaluate the clinical long-term safety and tolerability, patient satisfaction and pattern of use of prucalopride
Location	Multinational including 21 centres in the UK	69 centres in the US	Multinational including 2 centres in the UK
Design	Phase III, open-label, long-term study	Phase III, open-label, long term study	Phase II, open-label study
Duration of study	24 months	36 months	12 months
Participants	Subjects with chronic constipation who completed PRU-INT-6 or PRU-INT-12	Subjects with chronic constipation or opioid-induced constipation who had completed one of the following studies: PRU-USA-3, PRU-USA-11, PRU2-USA-13, PRU-USA-21, PRU-USA-25, PRU-USA-27 and PRU-USA-28	Subjects with chronic pain (cancer and non-cancer), suffering from opioid-induced constipation who had completed PRU-INT-8 or PRU-INT-14
Intervention	Prucalopride 2 mg and 4 mg. Several titration cycles from 2 mg to 4 mg and back from 4 mg to 2 mg were allowed	Prucalopride 2 mg to 4 mg. Starting dose 2 mg. Thereafter patients determined their own dosage up to a maximum of 4 mg/day. Dosage interruptions were allowed	Prucalopride flexible dose regimen between 0 mg and 4 mg once daily
Outcome measures	Safety • AEs • Clinical laboratory tests • Vital signs and ECG Efficacy • Patient's satisfaction with his/her bowel function as measured by PAC-QOL • Patient's pattern of use of prucalopride Pharmacokinetics • Plasma concentrations of prucalopride	Safety • AEs • Clinical laboratory tests • Vital signs and ECG Efficacy • Patient's satisfaction with his/her bowel function as measured by PAC-QOL • Patient's pattern of use of prucalopride Pharmacokinetics • Plasma concentration of prucalopride	Safety • AEs • Clinical laboratory tests • Vital signs and ECG Efficacy • Patient's satisfaction with his/her bowel function as measured by PAC-QOL • Pattern of use of prucalopride • Patients' global evaluations of the severity of constipation, degree of being bothered by constipation and efficacy of prucalopride treatment

Abbreviations: AE, adverse event; ECG, electrocardiogram; PK, pharmacokinetic; MS, multiple sclerosis; PAC-QOL, Patients' Assessment of Constipation – Quality-of-Life; SCI, spinal cord injury;

Patient and treatment information:

PRU-INT-10 included 527 subjects from PRU-INT-6 and 166 from PRU-INT-12 of these 224 previously received placebo. PRU-USA-22 included 1,775 patients from previous studies and 656 previously received placebo. PRU-INT-17 included 73 subjects from PRU-INT-8 and 23 from PRU-INT-14 and 31 previously received placebo. Across all three studies the majority of patients discontinued early due to the decision of the previous sponsor (JRF) to stop the prucalopride developmental programme worldwide. Patient disposition over time is shown in Table 38 and all reasons for discontinuation in Table 39.

Table 38: Patient disposition over time (PRU-INT-10, PRU-USA-22, PRU-INT-17) (27-29)

Number of patients ongoing with data	PRU-INT-10		PRU-USA-22		PRU-INT-17	
	Previously on placebo (N=224)	Previously on prucalopride (N=469)	Previously on placebo (N=656)	Previously on prucalopride (N=1119)	Previously on placebo (N=31)	Previously on prucalopride (N=65)
Month 3	208 (92.9)	440 (93.8)	578 (88.1)	1007 (90.0)	29 (93.5)	60 (92.3)
Month 6	171 (76.3)	351 (74.8)	405 (61.7)	726 (64.9)	23 (74.2)	53 (81.5)
Month 9	151 (67.4)	312 (66.5)	301 (45.9)	555 (49.6)	17 (54.8)	35 (53.8)
Month 12	134 (59.8)	276 (58.8)	200 (30.5)	409 (36.6)	5 (16.1)	7 (10.8)
Month 15	105 (46.9)	199 (42.4)	161 (24.5)	339 (30.3)	0	0
Month 18	80 (35.7)	132 (28.1)	116 (17.7)	264 (23.6)	-	-
Month 21	39 (17.4)	64 (13.6)	74 (11.3)	167 (14.9)	-	-
Month 24	18 (8.0)	21 (4.5)	12 (1.8)	18 (1.6)	-	-
Month 27	0	0	-	-	-	-

Table 39: Patient demographic data and reasons for discontinuation (PRU-INT-10, PRU-USA-22, PRU-INT-17) (27-29)

	PRU-INT-10	PRU-USA-22	PRU-INT-17
Number of patients enrolled (M/F)	693 (100/593)	1775 (199/1576)	96 (33/63)
Mean age years (range)	50.8 (18-92)	47.2 (18-89)	52.4 (24-83)
Mean duration of treatment days (range)	342.2 (1-733)	231.17 (1-721)	127.32 (2-286)
Discontinuations (n[%])	658 (95)	1775 (100)	96 (100)
Insufficient response	119 (17)	316 (17.8)	12 (12.5)
Adverse event	70 (10)	140 (7.9)[†]	6 (6.3)
Withdrew consent	53 (8)	326 (18.4)	7 (7.3)
Lost to follow-up	29 (4)	209 (11.8)	1 (1.0)
Non-compliant	11 (2)	59 (3.3)	1 (1.0)
Ineligible to continue	4 (1)	17 (1.0)	-
Asymptomatic/cured	3 (<1)	13 (<1)	-
Death	1 (<1)	-	4 (4.2)
Other	368 (53)[‡]	695 (39.2)[‡]	65 (67.7)[‡]

[†]Three deaths included

[‡]Mostly discontinuation due to the decision of previous sponsor (JRF) to stop the prucalopride developmental program worldwide

Summary of efficacy results for relevant non-RCTs

Table 40: Summary of efficacy results for relevant non-RCTs (PRU-INT-10, PRU-USA-22, PRU-INT-17) (27-29)

PRU-INT-10 (27)	**PAC-QOL** • There was statistically significant improvement from baseline in total and individual PAC-QOL scores at all time-points • The mean (SE) improvement in total PAC-QOL satisfaction subscale score at month 3 was –1.14 (0.054), –1.41 (0.062) at month 12 and –1.68 (0.132) at month 21 • Mean decrease from baseline in total and individual items of PAC-QOL satisfaction subscale scores were maximal at month 21, ranging from –1.39 to –1.86 • 54.9% patients had an improvement in total PAC-QOL satisfaction subscale score ≥ 1 on a 5-point scale at month 3, this proportion increased to 65.3% at month 12 and 72.0% at month 21 • Results showed that patient's satisfaction with his/her bowel function and treatment improved over time when receiving treatment with 2 mg to 4 mg prucalopride for a long-term period **Patient's Daily Diary** • Mean daily dose of prucalopride was 2.56 mg (range 0-4 mg) during the entire study period. For the first 11 weeks of the study 2 mg was the more frequent pattern of use, from week 15 onwards 4 mg became more common • Use of laxatives decreased during prucalopride treatment, the decrease was more pronounced in patients who previously received placebo
PRU-USA-22 (28)	**PAC-QOL** • There was statistically significant improvement from baseline in total and individual PAC-QOL scores at all time-points • The mean (SE) improvement in total PAC-QOL satisfaction subscale score at month 3 was –1.04 (0.040), –1.38 (0.059) at month 12 and –1.33 (0.099) at month 21 • Mean decrease from baseline in total and individual items of PAC-QOL satisfaction subscale scores were maximal at month 15 or month 18, ranging from –1.27 to –1.61 • 50.8% patients had an improvement in total PAC-QOL satisfaction subscale score ≥ 1 on a 5-point scale at month 3, this proportion increased to 65.3% at month 12 and 61.9% at month 21 • Results showed that patient's satisfaction with his/her bowel function and treatment improved over time when receiving treatment with 2 mg to 4 mg prucalopride for a long-term period **Patient's Daily Diary** • The most frequent weekly pattern of prucalopride use was 4 mg daily for 5 days or more • Use of laxatives decreased during prucalopride treatment, generally the decrease was more pronounced in patients who previously received placebo

PRU-INT-17 (29)	**PAC-QOL** • There was improvement from baseline in total and individual PAC-QOL scores at all time-points • 45.3% patients had an improvement in total PAC-QOL satisfaction subscale score ≥ 1 on a 5-point scale at month 1, this proportion improved further throughout the study • The mean (SE) improvement in total PAC-QOL satisfaction subscale score at month 1 was –0.95 (0.134), –0.85 (0.149) at month 3 and –1.17 (0.195) at month 6 • Results showed that patient's satisfaction with his/her bowel function and treatment improved over time when receiving treatment with 1 mg to 4 mg prucalopride for a long-term period **Patient's Daily Diary** • Generally patients use of laxatives decreased during prucalopride treatment, the decrease was more pronounced in patients who previously received placebo • The proportion of patients who indicated that treatment was moderately to extremely effective was high at month 1 (69.8%) and remained high throughout the study 66.7% at month 3, 68.8% at month 6 and 90.0% at month 9 (although only a small number of patients had data at month 9) • At month 1, 39.1% of patients had no or mild constipation, 35.6% at month 3, 38.8% at month 6 and 60% at month 9, compared with 7.9% of patients at baseline • The percentage of patients that indicated they were bothered by their constipation decreased from 60.7% at baseline to 29.9% at month 1, 34.2% at month 3 and 26.5% at month 6

5.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

Summary of safety data

- Prucalopride was well tolerated in all patient groups studied
- Gastrointestinal AEs (predominantly diarrhoea, abdominal pain and nausea) are the most important AEs that are clearly linked to the pharmacodynamic action of prucalopride. They were generally considered to be mild or moderate in severity.
- The day of onset of these AEs of interest (diarrhoea, abdominal pain and nausea) was most frequently reported on Day 1 or in Week 1 of treatment.
- The incidence of SAEs was low and the majority of recorded SAEs were not considered to be treatment-related.
- The incidence of discontinuations due to AEs was generally low and balanced between treatment groups.
- Long-term treatment with prucalopride was generally well-tolerated with an adverse event profile similar to that observed during the 4-12 week trials
- There were no clinically meaningful differences between the prucalopride and placebo groups with respect to vital sign, ECG parameters, haematology, clinical chemistry and urinalysis
- There were no clinically relevant QT effects observed with prucalopride. This is supported by results from studies specifically designed to look for potential QT effects at doses up to 5-10 fold therapeutic dose, which showed that prucalopride had no effect on QT interval.
- There does not appear to be an increased frequency of cardiovascular ischaemic events with prucalopride, and case series review indicated that events occurred in patients with risk factors of medical history and age. The onset of new cases of angina pectoris, and other cardiovascular events, grouped together in this category of ischaemic-related AEs was not any higher than expected. Prucalopride does not appear to be associated with cardiovascular ischaemia and related events

Trials designed primarily to assess safety outcomes

PRU-USA-26 (1, 2)

PRU-USA-26 was a double-blind, placebo controlled trial to evaluate the safety and tolerability of prucalopride solution in constipated elderly patients living in a nursing facility. As the primary outcome of this study was safety, this trial is described in full in this section.

Summary of methodology

Table 41: Summary of methodology of PRU-USA-26 (1, 2)

Study	PRU-USA-26
Location	National multicentre – conducted at 18 sites in the USA
Design	Randomised, double-blind, placebo-controlled, parallel-group, Phase II trial
Duration of study	4 weeks
Method of randomisation	A randomisation code was used to randomly allocate patients to the 4 treatment groups. For every 4 patients randomised to active treatment, 1 was randomised to receive placebo. Patient numbers were consecutively assigned (lowest number first).
Method of blinding	Group assignment was concealed from investigators and participants. Containers were identical in appearance. In the case of an emergency, the investigator could obtain treatment details (per patient) from sealed code envelopes.
Intervention(s) (n =) and comparator(s) (n =)	Prucalopride 0.5 mg o.d. (n = 21) Prucalopride 1 mg o.d. (n = 24) Prucalopride 2 mg (n = 26) Placebo o.d. (n = 18)
Primary outcomes	Safety/tolerability of prucalopride 0.5 mg, 1 mg, 2 mg, and 4 mg in elderly, constipated patients living in a nursing facility.
Key secondary outcome	Efficacy, exploratory only (global assessment, symptom assessment, healthcare utilisation-record of constipation treatment, quality of life)
Duration of follow-up	4 weeks

Abbreviations: o.d., once daily; SCBM, Spontaneous Complete Bowel Movements

Participants

Table 42: Eligibility criteria in PRU-USA-26 (1, 2)

Study	Inclusion criteria	Exclusion criteria
PRU-USA-26	Male and female patients at least 65 years of age (no upper age limit), with a history of constipation (having received treatment in the 4 weeks preceding study entry). Patients also had to live in a nursing facility, be clinically stable, be mostly continent of their bowels and be able to take oral medications.	HIV/AIDS patients Patients treated with cisapride or cancer chemotherapy Significantly impaired renal function Patients who had received an investigational drug in the 30 days preceding the study or either R093877 or R108512

Patient characteristics at baseline

Table 43: Characteristics of participants in PRU-USA-26 (1, 2)

Baseline characteristic	Prucalopride 0.5 mg (n = 21)	Prucalopride 1 mg (n = 24)	Prucalopride 2 mg (n = 26)	Placebo (n = 18)
Mean age, years (SE)	84.4 (1.46)	82.6 (1.72)	81.7 (1.65)	85.4 (1.77)
Sex, n (%)				
Male	3 (14.3)	7 (29.2)	9 (34.6	24 (27.0)
Female	18 (85.7)	17 (70.8)	17 (65.4	65 (73.0)
Race, n (%)				
Caucasian	19 (90.5)	24 (100.0)	25 (96.2	18 (100.0)
Black	2 (9.5)	0	0	0
Hispanic	0	0	1 (3.8)	0
Height (cm), mean ± SE	160.9 (3.62)	162.5 (2.52)	164.6 (2.92)	160.6 (2.84)
Weight (kg), mean ± SE	72.7 (3.01)	61.7 (2.9)	71.6 (4.9)	63.5 (3.63)
Age groupings				
[65, 75)	0	6 (25.0)	5 (19.2)	2 (11.1)
[75, 85)	12 (57.1)	7 (29.2)	9 (34.6)	7 (38.9)
≥ 85	9 (42.9)	11 (45.8)	12 (46.2)	9 (50.0)
Patients actively treated for a cardiovascular condition (%)	15 (71.4)	19 (79.2)	20 (76.9)	15 (83.3)

Abbreviations: SE, Standard Error;

Primary and secondary outcomes

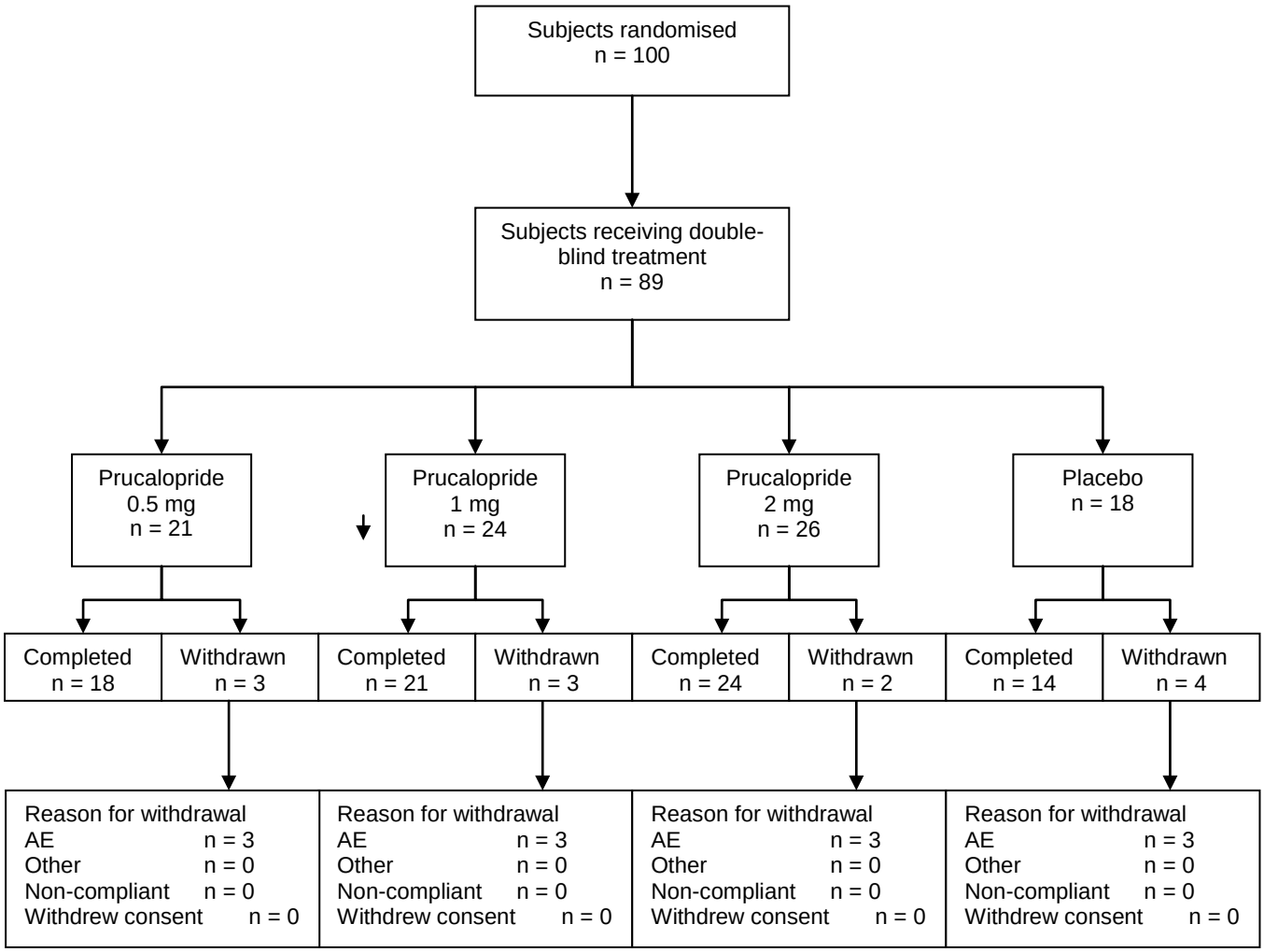
Table 44: Primary and secondary outcomes of PRU-USA-26 (1, 2)

Study	Primary outcome(s) and measures	Secondary outcome(s) and measures	Other outcomes and measures	Reliability/validity/ current use in clinical practice
PRU-USA-26	Safety/tolerability	• Patient global assessment of severity of constipation and efficacy of treatment • PAC-SYM • PAC-QOL • Healthcare utilisation –record of constipation treatment	• Clinical laboratory parameters (haematology, clinical chemistry and urinalysis parameters) • Cardiovascular parameters (vital signs, ECG, Holter monitoring)	• The PAC-SYM has been previously validated in patients with opioid-induced constipation (30) and was shown to be a 'reliable, valid and responsive measure of the presence and severity of constipation-related symptoms' (30) • The PAC-QOL is described as 'a brief but comprehensive assessment of the burden of constipation on patients' everyday functioning and well-being' and has been demonstrated via multinational studies to be 'internally consistent, reproducible, valid, and responsive to improvements over time' (31)

Abbreviations: PAC-SYM, Patient Assessment of Constipation Symptoms; PAC-QOL, Patient Assessment of Constipation Quality of Life; SCBM, spontaneous, complete bowel movement

Participant flow

Figure 7: Participant flow in the Phase II RCT PRU-USA-26 (1, 2)



Quality assessment

Table 45: Quality assessment of PRU-USA-26 (1, 2)

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	A randomisation code was used to randomly allocate patients to the 4 treatment groups.	Yes
Was the concealment of treatment allocation adequate?	Containers were identical in appearance	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The 4 treatment arms were demographically similar and had similar baseline disease 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?	Drop-outs were accounted for and there was no imbalance in drop-outs between groups.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes appear to have been 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 safety analysis was based on all patients treated. The secondary outcome of efficacy was analysed in the ITT population (defined as all randomised patients who took at least 1 dose of double-blind study medication and who provided any follow-up data for 1 or more of the efficacy variables)	Yes

[†]While it is not explicitly stated that investigators were blinded to treatment allocation, this is strongly implied by the statement that investigators were provided with sealed envelopes, containing treatment information, only to be opened in case of emergency

Safety Results

Where not specified, AE refers to treatment-emergent AE (TEAE) throughout.

PRU-USA-26 (1, 2)

Datasets analysed

All randomised patients who received at least 1 dose of study medication were included in the all-(treated) patients population. The ITT population (defined as all randomised patients who took at least 1 dose of double-blind study medication and who provided any follow-up data for 1 or more of the efficacy variables) comprised 89 patients. None of the patients were excluded. As a consequence, the populations that are used for the safety and efficacy analysis are the same.

It should be noted that this was an elderly population of which 80% had a history of cardiovascular disease, making this a sensitive population in which to detect CV related events.

Key Safety Results

One or more adverse events (AEs) were reported by 9 (50.0%) patients treated with placebo, 18 (85.7%) patients treated with prucalopride 0.5 mg, 17 (70.8%) patients treated with prucalopride 1 mg, and 18 (69.2%) patients treated with prucalopride 2 mg. Treatment-emergent AEs (TEAEs) that occurred in ≥ 5% of patients in either prucalopride treatment arm are listed in Table 48. The most commonly reported AEs were gastrointestinal and urinary system disorders. There were no cases of diarrhoea in the placebo group, and the incidence of diarrhoea tended to increase the increasing prucalopride dose. While headache was also observed more frequently in the active treatment groups than in the placebo group, there was no evidence of a dose response.

The only AEs reported to be at least possibly treatment-related in more than one patient were diarrhoea and abdominal pain. Most TEAEs were considered by the investigator to be mild or moderate in severity. Severe AEs were reported by two patients each in the placebo and prucalopride 0.5 mg and 1 mg groups and one patient in the prucalopride 2 mg group. Two AEs were reported to be severe by more than one patient: constipation (reported by one patient on placebo and by one patient on prucalopride 1 mg) and tachycardia (reported by two patients on prucalopride 1 mg).

Two patients died during the study, one in the prucalopride 1 mg group, and one in the prucalopride 2 mg group. Neither death was considered related to study medication by the investigator. Both patients reporting one or more serious AEs (SAEs) were in the prucalopride 0.5 mg arm. These SAEs were melaena, colitis, diverticulitis, which were considered possibly related to the study medication, as well as urinary tract infection and skin ulceration, both of which were assessed as not related to prucalopride.

Three patients discontinued prucalopride due to AEs. In addition to the two patients experiencing SAEs (described above), one patient, also in the prucalopride 0.5 mg arm, discontinued prucalopride due to ventricular tachycardia, which was considered to be possibly related to the study drug.

Table 46: TEAEs occurring in ≥ 5% of patients in any PRU treatment arm

System organ/ class/adverse events	Study PRU-USA-26 (1, 2)			
	Prucalopride 0.5 mg (n = 21)	Prucalopride 1 mg (n = 24)	Prucalopride 2 mg (n = 26)	Placebo (n = 18)
No of patients with AE, n (%)	18 (85.7)	17 (70.8)	18 (69.2)	9 (50.0)
No of patients with serious AE, n (%)	2 (9.5)	0	0	0
No of discontinuations due to AE, n (%)	3 (14)	0	0	0
No of deaths	0	1 (4.2)	1 (3.8)	0
Gastrointestinal system disorders				
Total	6 (28.6)	8 (33.3)	9 (34.6)	5 (27.8)
Diarrhoea	1 (4.8)	3 (12.5)	4 (15.4)	0
Nausea	2 (9.5)	2 (8.3)	2 (7.7)	0
Vomiting	1 (4.8)	2 (8.3)	2 (7.7)	1 (5.6)
Melaena	1 (4.8)	1 (4.2)	2 (7.7)	1 (5.6)
Flatulence	0	0	2 (7.7)	0
Abdominal pain	0	2 (8.3)	0	2 (11.1)
Dyspepsia	2 (9.5)	0	0	0
Haemorrhoids	0	0	2 (7.7)	0
Urinary system disorders				
Total	8 (38.1)	4 (16.7)	3 (11.5)	3 (16.7)
Urinary tract infection	7 (33.3)	1 (4.2)	1 (3.8)	3 (16.7)
Pyuria	0	0	2 (7.7)	0
General disorders				
Total	3 (14.3)	6 (25.0)	1 (3.8)	2 (11.1)
Injury	1 (4.8)	4 (16.7)	0	1 (5.6)
Back pain	–	–	–	–
Nervous system disorders				
Total	5 (23.8)	1 (4.2)	3 (11.5)	1 (5.6)
Headache	3 (14.3)	0	1 (3.8)	0
Dizziness	–	–	–	–
Respiratory system disorders				
Total	1 (4.8)	4 (16.7)	3 (11.5)	2 (11.1)
Rhinitis	1 (4.8)	2 (8.3)	1 (3.8)	0
Coughing	0	2 (8.3)	1 (3.8)	1 (5.6)
Bronchitis	0	2 (8.3)	1 (3.8)	0
Metabolic and nutritional disorders				
Total	0	2 (8.3)	5 (19.2)	1 (5.6%)
Cachexia	0	1 (4.2)	2 (7.7)	0
Prealbumin decreased	0	0	2 (7.7)	0
Skin and appendages disorders				
Total	2 (9.5)	4 (16.7)	1 (3.8)	0
Skin ulceration	2 (9.5)	1 (4.2)	0	0
Psychiatric disorders				
Total	0	5 (20.8)	1 (3.8)	2 (11.1%)
Confusion	0	2 (8.3)	0	0
HR and rhythm disorders				
Total	1 (4.8%)	3 (12.5)	1 (3.8)	0
Tachycardia	0	2 (8.3)	1 (3.8)	0
Platelet, bleeding & clotting disorders				
Total	3 (14.3)	1 (4.2)	1 (3.8)	1 (5.6)
Secondary terms				
Fall	1 (4.8)	3 (12.5)	1 (3.8)	1 (5.6)
Red blood cell disorders				
Anaemia	0	0	0	4 (15.4)

Abbreviations: AE, Adverse events; No, number; TEAE, treatment-emergent adverse event

Clinical laboratory parameters

No clinically relevant changes or dose-related effects in time were evident in the summary statistics for the haematology, clinical chemistry and urinalysis parameters. For a total of 13 patients, at least one laboratory abnormality was reported as an AE during the treatment period. The most commonly reported treatment-emergent laboratory-related AE was anaemia, which occurred in four patients of the prucalopride 2 mg group. All laboratory-related AEs were considered to be not or doubtfully related to the prucalopride treatment.

No relevant changes over time or differences between treatments were observed with regard to supine pulse rate and systolic and diastolic blood pressure, based on vital sign measurement.

Cardiovascular safety

ECG measurements: QT related events

ECG measurements showed an increase in median heart rate 3 hours after treatment administration in both the placebo and the prucalopride groups. No relevant differences between active and placebo treatment were noted, and no dose-relationship was observed. No consistent or clinically relevant treatment-related differences were noted in PR, QT, QTcB, QTcF, QTlc or QTdisp time intervals.

ECG evaluations: ischaemic cardiac events

The majority of all ECG evaluations in the study were abnormal, including at baseline. The percentage of patients for which the ECG abnormalities deteriorated compared to baseline was higher in the placebo group (varying from 5.6% to 30.8% at different time-points) than in the prucalopride groups (varying from 0-14.3%, 0-16.7% and 0-16.0% at different time-points for the prucalopride 0.5 mg, 1 mg and 2 mg groups, respectively). No increase was detected in the percentage of patient with clinically relevant abnormalities when compared to baseline in any of the treatment groups.

Holter monitoring: atrial and ventricular arrhythmias

Holter monitoring was performed to detect for proarrhythmic effects using strict criteria. In addition, the presence or absence of each of the following was determined at each time-point: atrial fibrillation, SVT, non-sustained SVT, ventricular fibrillation or torsade de pointes. The presence or absence of any run of SVT of at least 5 beats and any run of SVT of at least 10 beats was determined.

The only statistically significant difference between any prucalopride group and placebo was the prucalopride 2 mg vs. placebo comparison of non-sustained ventricular tachycardia at Day 7, with a higher incidence in the placebo group (30.8%) when compared to the prucalopride 2 mg group (0%). There were no events of sustained ventricular tachycardia, ventricular fibrillation, or torsade de pointes.

The change from baseline for average supraventricular premature beats per hour was not significantly different between placebo and any prucalopride group.

There were also no statistically significant differences between placebo and any prucalopride group in the incidence of runs of SVT (HR≥100).

Key Efficacy Results

The efficacy parameters measured in this trial are for exploratory purposes only.

On Days 14 and 28, in all prucalopride treatment groups, more patients rated their constipation during the past week as mild or absent than placebo patients did.

The prucalopride groups rated the effectiveness of their treatment better than the placebo group.

At Days 14 and 28, the median changes from baseline were similar among the placebo, prucalopride 0.5 mg, and prucalopride 2 mg groups for each PAC-SYM scale. At Days 14 and 28, none of the patients in the placebo group had an improvement of ≥ 1 point for the overall PAC-SYM symptoms score, while this percentage amounted 5.6% and 9.5% for the prucalopride 0.5 mg group, 33.3% and 47.6 % for the prucalopride 1 mg group, and 18.2% and 25.0% for the prucalopride 2 mg group.

The great majority of patients had no enemas, suppositories, or disimpactions administered to them either during the month prior to screening or during the study, with no differences between treatment groups. The number of patients with changes in use over time never exceeded 3 in any treatment group.

On both Days 14 and 28, more prucalopride-treated patients than placebo-treated patients had an improvement in the satisfaction subscale of ≥ 1 point.

5.9.1 Safety Results from other relevant RCTs

The safety results from the other relevant RCTs are discussed in this section.
Where not specified, AE refers to treatment-emergent AE (TEAE) throughout.

Pivotal studies

Study PRU-INT-6 (18, 19)

Study PRU-INT-6 was performed in adults (18 years and older), including male and non-pregnant, non-breast-feeding female outpatients with a history of constipation.

The majority of TEAEs were mild or moderate, demonstrating that prucalopride was generally well tolerated. TEAEs that occurred in ≥ 5% of patients in either prucalopride treatment arm are listed in Table 47. Considering all AEs, 66.0% to 80.8% of patients reported at least one AE, the incidence being slightly higher in the treatment arms than in the placebo arm (80.8% and 75.8% versus 66.0%). The most frequently reported AEs (>10% in the prucalopride and placebo groups) included headache, nausea, and abdominal pain. The incidence of diarrhoea was 2 to 3 times higher in the prucalopride 2 and 4 mg groups (13.0% and 12.6%, respectively) when compared with the placebo group (5.4%).

The frequency distribution of onset day and duration were investigated for the four most frequently reported AEs, abdominal pain, nausea, diarrhoea, and headache. In both prucalopride groups, the onset of these AEs of interest was most frequently reported on day one. The duration of these AEs was short. When day one is excluded from the analysis, the incidence of these AEs is comparable between the treatment groups.

There were no deaths during the study. Serious AEs were experienced by 2.1% and 2.5% of patients in the active treatment arms, compared with 2.1% of patients in the placebo group. The SAEs during the double-blind treatment phase included anxiety, bronchitis, infection viral, neoplasm NOS, pneumonia, stridor, suicide attempt, uterine haemorrhage (in the prucalopride 2 mg group), abrasion NOS, back pain, cardiac failure, dizziness, fibrillation atrial, headache, hypertension aggravated, MS aggravated, pulmonary oedema, upper respiratory infection (in the prucalopride 4 mg group), abdominal pain, anaemia, epistaxis, ileus, injury, migraine aggravated, unintended pregnancy, and syncope (in the placebo group). The majority of SAEs were considered not or doubtfully related to the study medication by the investigator.

Discontinuations due to AEs were higher in the prucalopride 4 mg group (15.1%) compared with the prucalopride 2 mg or the placebo group (5.9% and 6.3%, respectively). The incidence of headache, abdominal pain, nausea, diarrhoea and vomiting leading to discontinuation was higher in the prucalopride 4 mg group than in the prucalopride 2 mg and placebo groups.

Other safety results

No clinically relevant changes over time were observed in haematology, clinical chemistry or urinalysis parameters. There were no important differences in the incidence of treatment-emergent laboratory abnormalities between the treatment groups. The proportion of patients with laboratory-related AEs was 8.4% and 10.9% in the prucalopride 2 and 4 mg groups, and 4.6% in the placebo group.

Cardiovascular parameters also did not change over time in a clinically significant way. The overall incidence of patients with prolonged (M: >450, F: >470 ms) corrected QT intervals post-baseline was low and comparable between the treatment groups.

Physical examination, including body weight, revealed no meaningful between-group differences.

Study PRU-USA-11 (20, 21)

Patient selection criteria for study PRU-USA-11 were the same as for study PRU-USA-6, including male and non-pregnant, non-breast-feeding female adult (≥ 18 years old) patients with a history of constipation.

The majority of treatment-emergent adverse events (TEAEs) were mild or moderate, demonstrating that prucalopride was generally well tolerated. TEAEs that occurred in ≥ 5% of patients in either prucalopride treatment arm are listed in Table 47. Considering all AEs, 71.3% to 80.2% of patients reported at least one adverse event (AE), the incidence being slightly higher in the treatment arms than in the placebo arm (80.2% and 78.4% versus 71.3%). The most frequently reported AEs (>10% in any prucalopride group) included headache, nausea, abdominal pain, diarrhoea, and flatulence. These AEs were also frequently reported in the placebo group. The incidence of diarrhoea was 2 to 3 times higher in the prucalopride 2 and 4 mg groups (13.5% and 18.6%) when compared with the placebo group (5.3%).

The frequency distribution of onset day and duration were investigated for the four most frequently reported AEs, abdominal pain, nausea, diarrhoea, and headache. In both prucalopride groups, the onset of these AEs of interest was most frequently reported on day one. The duration of these AEs was short. When day one is excluded from the analysis, the incidence of these AEs is comparable between the treatment groups.

There were no deaths during the study. The percentages of patients experiencing SAEs were 1.4 and 3.4 in the 2 mg and 4 mg prucalopride arms and 3.8 in the placebo groups. SAEs during the study included surgical intervention (7 patients), abdominal pain, arthropathy, chest pain, ovarian cyst and pain (each 2 patients), anuria, anxiety, back pain, blood pressure fluctuation, constipation, fever, gastritis, heart valve disorders, hypokalaemia, increased sweating, infection, infection fungal, muscle weakness, palpitation, pneumonia, skeletal pain, tachycardia supraventricular and vertigo (1 patient each). The majority of SAEs were considered not or doubtfully related to the study medication by the investigator.

The number of patients who discontinued the study medication was higher in the prucalopride 2 and 4 mg groups (8.2% and 7.8%, respectively) than in the placebo group (1.9%). Discontinuations were predominantly due to gastrointestinal system- and nervous system disorders. The incidence of diarrhoea leading to permanent discontinuation was slightly higher in the prucalopride 4 mg group (4.4%) than in the prucalopride 2 mg group (1.5%).

Other safety results

No clinically relevant changes over time were observed in haematology, clinical chemistry or urinalysis parameters. There were no important differences in the incidence of treatment-emergent laboratory abnormalities between the treatment groups. The proportion of patients with laboratory-related AEs was 12.1% and 11.3% in the prucalopride 2 and 4 mg groups, and 12.9% in the placebo group.

There were no clinically relevant changes over time in vital signs or ECG parameters. The overall incidence of patients with prolonged (M: >450, F: >470 ms) corrected QT intervals post-baseline was low with no important differences between the treatment groups. The proportion of patients with a prolonged QTcB interval at Week 12 (and normal at baseline) was slightly higher in the prucalopride 4 mg group (4.0%) when compared with the prucalopride 2 mg (1.3%) and placebo (0%) groups.

Physical examination, including body weight, revealed no meaningful between-group differences.

Study PRU-USA-13 (22, 23)

Patient selection criteria for study PRU-USA-13 were the same as for study PRU-USA-6, including male and non-pregnant, non-breast-feeding female adult (≥ 18 years old) patients with a history of constipation.

The majority of treatment-emergent adverse events (TEAEs) were mild or moderate, demonstrating that prucalopride was generally well tolerated. TEAEs that occurred in ≥ 5% of patients in either prucalopride treatment arm are listed in Table 47. Considering all AEs, 67.1% to 74.8% of patients reported at least one adverse event (AE), the incidence being slightly higher in the treatment arms than in the placebo arm (71.4% and 74.8% versus 67.1%). The most frequently reported AEs (>10% in any prucalopride group) included headache, abdominal pain, nausea, diarrhoea and flatulence. The incidence of severe diarrhoea was only slightly higher in the prucalopride 4 mg group (3.3%) when compared with the prucalopride 2 mg (0.5%) and placebo (0.9%) groups.

The frequency distribution of onset day and duration were investigated for the four most frequently reported AEs, abdominal pain, nausea, diarrhoea, and headache. In both prucalopride groups, the onset of these AEs of interest was most frequently reported on day one. The duration of these AEs was short. When day one is excluded from the analysis, the incidence of these AEs is comparable between the treatment groups.

There were no deaths during the study. A total of 14 patients reported 22 treatment-emergent SAEs during this study: 4 (1.9%) and 5 (2.3%) patients in the prucalopride 2 and 4 mg groups, respectively, and 5 (2.4%) patients in the placebo group. The SAEs during the double-blind treatment phase included bronchitis, ovarian cyst, chest pain, abdominal pain (in the prucalopride 2 mg group), surgical intervention (2 patients), gastroenteritis, abdominal pain, angina pectoris (1 patient each; in the prucalopride 4 mg group), nausea, syncope (2 patients each), surgical intervention, pregnancy unintended, back pain, vomiting, arrhythmia, chest pain, hypertension, hypotension, and dizziness (one patient each in the placebo group).

The incidence of patients who discontinued the study medication was slightly higher in the prucalopride 4 mg group (5.6%) than in the prucalopride 2 mg and placebo groups (3.7% and 2.4%, respectively). Discontinuations were predominantly due to gastrointestinal system- and nervous system disorders. The incidence of abdominal pain and nausea leading to discontinuation was slightly higher in the prucalopride 4 mg group than in the prucalopride 2 mg and placebo groups.

Other safety results

No clinically relevant changes over time were observed in haematology, clinical chemistry or urinalysis parameters. There were no important differences in the incidence of treatment-emergent laboratory abnormalities between the treatment groups. The proportion of patients

with laboratory-related AEs was 9.3% and 6.5% in the prucalopride 2 and 4 mg groups, and 5.2% in the placebo group.

There were no clinically relevant changes over time in vital signs or ECG parameters. The overall incidence of patients with prolonged (M: >450, F: >470 ms) corrected QT intervals post-baseline was low and comparable between the treatment groups.

Physical examination, including body weight, revealed no meaningful between-group differences.

Table 47: TEAEs occurring in ≥ 5% of patients in any PRU treatment arm

System organ/ class/adverse events	Study PRU-INT-6 (19)			Study PRU-USA-11 (21)			Study PRU-USA-13 (23)		
	Prucalopride 2 mg (n = 238)	Prucalopride 4 mg (n = 238)	Placebo (n = 240)	Prucalopride 2 mg (n = 207)	Prucalopride 4 mg (n = 204)	Placebo (n = 209)	Prucalopride 2 mg (n = 214)	Prucalopride 4 mg (n = 215)	Placebo (n = 212)
No of patients with AE, n (%)	170 (71.4)	178 (74.8)	161 (67.1)	166 (80.2)	160 (78.4)	149 (71.3)	173 (80.8)	163 (75.8)	140 (66.0)
No of patients with serious AE, n (%)	5 (2.1%)	6 (2.5%)	5 (2.1%)	3 (1.4)	7 (3.4)	8 (3.8)	4 (1.9)	5 (2.3)	5 (2.4)
No of discontinuations due to AE, n (%)	14 (5.9)	36 (15.1)	15 (6.3)	17 (8.2)	16 (7.8)	4 (1.9)	8 (3.7)	12 (5.6)	5 (2.4)
Gastrointestinal system disorders									
Nausea	57 (23.9)	56 (23.5)	34 (14.2)	46 (22.2)	44 (21.6)	17 (8.1)	26 (12.1)	44 (20.5)	16 (7.5)
Abdominal pain	55 (23.1)	44 (18.5)	41 (17.1)	40 (19.3)	46 (22.5)	40 (19.1)	38 (17.8)	35 (16.3)	23 (10.8)
Diarrhoea	31 (13.0)	30 (12.6)	13 (5.4)	28 (13.5)	38 (18.6)	11 (5.3)	25 (11.7)	28 (13.0)	7 (3.3)
Flatulence	21 (8.8)	18 (7.6)	18 (7.5)	23 (11.1)	17 (8.3)	18 (8.6)	24 (11.2)	19 (8.8)	11 (5.2)
Vomiting	11 (4.6)	17 (7.1)	11 (4.6)	14 (6.8)	10 (4.9)	4 (1.9)	–	–	–
Dyspepsia	–	–	–	10 (4.8)	12 (5.9)	7 (3.3)	–	–	–
Resistance mechanism disorders									
Viral infection	21 (8.8)	14 (5.9)	28 (11.7)	12 (5.8)	9 (4.4)	8 (3.8)	14 (6.5)	10 (4.7)	11 (5.2)
Nervous system disorders									
Headache	62 (26.1)	71 (29.8)	40 (16.7)	55 (26.6)	60 (29.4)	25 (12.0)	54 (25.2)	54 (25.1)	32 (15.1)
Dizziness	12 (5.0)	11 (4.6)	4 (1.7)	17 (8.2)	14 (6.9)	6 (2.9)	–	–	–
General disorders									
Fatigue	12 (5.0)	14 (5.9)	6 (2.5)	–	–	–	–	–	–
Influenza-like symptoms	–	–	–	6 (2.9)	11 (5.4)	7 (3.3)	–	–	–
Back pain	–	–	–	13 (6.3)	5 (2.5)	10 (4.8)	–	–	–
Respiratory system disorders									
Sinusitis	–	–	–	10 (4.8)	19 (9.2)	15 (7.4)	16 (7.5)	15 (7.0)	17 (7.9)
Upper respiratory tract infection	–	–	–	–	–	–	5 (2.4)	15 (7.0)	13 (6.0)

AE, Adverse events; No, number; TEAE, treatment-emergent adverse event

Elderly subjects

Study PRU-INT-12 (24)

Study PRU-INT-12 included patients ≥ 65 years of age, with a history of constipation.

The majority of TEAEs were considered by the investigator to be mild or moderate in severity. TEAEs that occurred in ≥ 5% of patients in either prucalopride treatment arm are listed in Table 48. The incidence of patients with treatment-emergent AEs in the prucalopride 1 mg (37 patients, 48.7%), prucalopride 2 mg (29 patients, 38.7%) and prucalopride 4 mg groups (38 patients, 47.5%) was similar when compared with the placebo group (32 patients, 44.4%).

The frequency distribution of onset day and duration were investigated for four AEs of interest, abdominal pain, nausea, diarrhoea, and headache. In the prucalopride groups, the onset of these AEs of interest was most frequently reported on day one or two, with no difference in onset in the placebo group (with the exception of nausea and abdominal pain in the prucalopride 2 mg group).

One patient in the placebo group died due to arrhythmia and myocardial infarction. Additional treatment-emergent SAEs were reported by one (1.3%) patient in the prucalopride 1 mg group and one (1.3%) patient in the prucalopride 4 mg group. These events were an increased dose of the study drug (3 mg) and a fracture, neither of which was considered related to the study treatment.

Discontinuations due to AEs occurred in two (2.6%), four (5.3%) and seven (8.8%) patients in the prucalopride 1, 2 and 4 mg groups, respectively, and in three (4.2%) patients in the placebo group. Most of the AEs leading to discontinuation were due to gastrointestinal- or nervous system disorders.

Other safety results

No clinically relevant changes over time were observed in haematology, clinical chemistry or urinalysis parameters. There were no important differences in the incidence of treatment-emergent laboratory abnormalities between the treatment groups.

There were no clinically relevant changes over time in vital signs or ECG parameters. The overall incidence of patients with prolonged (M: >450, F: >470 ms) corrected QT intervals post-baseline was comparable between the treatment groups.

Physical examination, including body weight, revealed no meaningful between-group differences.

Table 48: TEAEs occurring in ≥ 5% of patients in any PRU treatment arm

System organ/ class/adverse events	Study PRU-INT-12 (24)			
	Prucalopride 1 mg (n = 76)	Prucalopride 2 mg (n = 75)	Prucalopride 4 mg (n = 80)	Placebo (n = 72)
No of patients with AE, n (%)	37 (48.7)	29 (38.7)	38 (47.5)	32 (44.4)
No of patients with serious AE, n (%)	1 (1.3)	0	1 (1.3)	1 (1.4)
No of discontinuations due to AE, n (%)	2 (2.6)	4 (5.3)	7 (8.8)	3 (4.2)
No of deaths	0	0	0	1 (1.4)
Gastrointestinal system disorders				
Diarrhoea	5 (6.6)	1 (1.3)	5 (6.3)	0
Nausea	4 (5.3)	1 (1.3)	4 (5.0)	2 (2.8)
Abdominal pain	7 (9.2)	3 (4.0)	9 (11.3)	4 (5.6)
General disorders				

Back pain	2 (2.6)	4 (5.3)	3 (3.8)	2 (2.8)
Nervous system disorders				
Headache	5 (6.6)	4 (5.3)	7 (8.8)	3 (4.2)
Dizziness	0	0	4 (5.0)	1 (1.4)

AE, Adverse events; No, number; TEAE, treatment-emergent adverse event

Opioid-induced constipation

Study PRU-INT-8 (25)

Study PRU-INT-8 was performed in adults (18 years and older), including male and non-pregnant, non-breast-feeding female outpatients suffering from opioid-induced constipation, with no history of chronic constipation prior to instigation of opioid therapy. The reason for the opioid therapy had to be chronic pain (of any aetiology other than cancer).

In total, about half the subjects reported a TEAE. The incidence was distributed evenly between the placebo (32 subjects, 48.5%), prucalopride 2 mg (38 subjects, 57.6%) and prucalopride 4 mg (32 subjects, 50%) groups. TEAEs that occurred in ≥ 5% of patients in either prucalopride treatment arm are listed in Table 49. Severe AEs accounted for approximately a third of recorded AEs. Gastrointestinal disorders (particularly abdominal pain) and headache were most frequently reported as severe.

The frequency distribution of onset day and duration were investigated for four AEs of interest, abdominal pain, nausea, diarrhoea, and headache. In all categories, the largest number of complaints occurred on the first day of dosing in the prucalopride groups.

There were no deaths in the course of this study. A total of ten patients reported SAEs during this trial: five in the placebo group, four in the prucalopride 2 mg group and one in the prucalopride 4 mg group. Of these SAEs, one occurred during the run-in period in the placebo group, eight during the treatment period in placebo (four subjects) and prucalopride 2 mg (four subjects) groups and one post-treatment in the prucalopride 4 mg group. Apart from abdominal pain, which was recorded twice (two different patients), no SAE occurred more than once.

Of the 17 TEAEs that led to discontinuation (in 15 patients), seven (10.6% were in the placebo group, three (4.5%) in the prucalopride 2 mg group and five (7.8%) in the prucalopride 4 mg group. Abdominal pain was the most frequent reason for discontinuation (eight events), followed by nausea (five events) and diarrhoea (four events).

Other safety results

The numbers of subjects with treatment-emergent abnormal values in mean haematology, clinical chemistry or urinalysis were small.. One subject in the placebo group, three in the prucalopride 2 mg group and one in the prucalopride 4 mg group had laboratory abnormalities that were reported as an adverse event. None of these was considered to be related to trial medication by the investigator.

There were no statistically significant differences at Week 4 of treatment between either of the prucalopride groups and the placebo group in pulse, systolic and diastolic blood pressures and weight. The only within-group changes from baseline occurred in the placebo group for diastolic blood pressure.

The mean heart rate increased from baseline in both prucalopride-treated groups but this was only statistically significant for the 2 mg group at Week 4 (3.14 beats/min, P = 0.006). The heart rate of the prucalopride 2 mg group was also significantly higher than placebo at Week 4. As a consequence of the increased heart rate there was a slight increase in QT_CB

from baseline, which was significant at Week 4 for prucalopride 2 mg subjects (P = 0.047). When the correction formula QT_CF was applied, the increase was small and not statistically significant. Changes from baseline in QT_CB and QT_CF were always less than 60 ms, but changes in QT_CF did appear to increase in a dose-dependent manner. The values for these two different parameters were not statistically significantly different between prucalopride and placebo.

Table 49: TEAEs occurring in ≥ 5% of patients

System organ/ class/adverse events	Study PRU-INT-8 (25)		
	Prucalopride 2 mg (n = 66)	Prucalopride 4 mg (n = 64)	Placebo (n = 66)
No of patients with AE, n (%)	38 (57.6)	32 (50.0)	32 (48.5)
No of patients with serious AE, n (%)	4 (6.1)	0	4 (6.1)
No of discontinuations due to AE, n (%)	3 (4.5)	5 (7.8)	7 (10.6)
Gastrointestinal system disorders			
Total	15 (22.7)	20 (31.3)	17 (25.8)
Abdominal pain	8 (12.1)	16 (25.0)	6 (9.1)
Diarrhoea	0	4 (6.3)	2 (3.0)
Nausea	7 (10.6)	3 (4.7)	6 (9.1)
Vomiting	3 (4.5)	2 (3.1)	4 (6.1)
Flatulence			
General disorders			
Total	13 (19.7)	11 (17.2)	13 (19.7)
Pain	4 (6.1)	2 (3.1)	3 (4.5)
Peripheral oedema			
Nervous system disorders			
Total	7 (10.6)	8 (12.5)	6 (9.1)
Headache	4 (6.1)	5 (7.8)	3 (4.5)
Dizziness			
Skin and appendages disorders			
Total	5 (7.6)	5 (7.8)	3 (4.5)
Respiratory system disorders			
Total	3 (4.5)	0	4 (6.1)

AE, Adverse events; No, number; TEAE, treatment-emergent adverse even

Retreatment study

Study PRU-USA-28 (26)

Study PRU-USA-28 was performed in adults (18 years and older), including male and non-pregnant, non-breast-feeding female outpatients with a history of constipation.

For both treatment periods, the incidence of patients with treatment-emergent AEs in the prucalopride group (Treatment I: 67.2%; Treatment II: 44.9%) was higher than in the placebo group (Treatment I: 50.2%; Treatment II: 38.1%) TEAEs that occurred in ≥ 5% of patients in either prucalopride treatment arm are listed in Table 50.

The onset of the AEs of interest (abdominal pain, nausea, diarrhoea, and headache) in the prucalopride group was most frequently reported on Day 1 of each treatment period. For placebo, the frequency of these AEs was less than 30% on Day 1 of both treatment periods.

There were no deaths during the study. A total of eight patients reported ten treatment-emergent SAEs during this study: four (1.6%) patients in the prucalopride group (two patients during Treatment I, three during Treatment II) and four (1.6%) patients in the

placebo group (all during Treatment I). The SAEs included varicella, supraventricular tachycardia, unintended pregnancy, vaginal haemorrhage, abortion, menstrual disorder, hypokalaemia and abdominal pain, surgical intervention, uterine disorders NOS, uterovaginal prolapse, neuropathy and allergic reaction (in the placebo group).

The study medication was discontinued by four patients due to AEs: two patients in the prucalopride group (unintended pregnancy, vaginal haemorrhage and abortion, and hypokalaemia and abdominal pain, respectively) and two patients in the placebo group (neuropathy and allergic reaction, respectively)

Other safety results

No clinically relevant changes over time were observed in haematology, clinical chemistry or urinalysis parameters. There were no important differences in the incidence of treatment-emergent laboratory abnormalities between the treatment groups. The proportion of patients with treatment-emergent laboratory-related AEs during treatments I and II was 5.1% and 6.3% in the prucalopride group, compared with 6.6% and 4.5% in the placebo group, respectively.

There were no clinically relevant changes over time in vital signs or ECG parameters. The incidence of abnormal values for vital signs and ECG parameters was low and comparable between the treatment groups.

Physical examination, including body weight, revealed no meaningful between-group differences.

Table 50: TEAEs occurring in ≥ 5% of patients in any PRU treatment arm

System organ/ class/adverse events	Study PRU-USA-28 (26)			
	Prucalopride		Placebo	
	Tx1 (n = 253)	Tx2 (n = 205)	Tx1 (n = 257)	Tx2 (n = 223)
No of patients with AE, n (%)	170 (67.2)	92 (44.9)	129 (50.2)	85 (38.1)
No of patients with serious AE, n (%)	2 (0.8)	3 (1.5)	4 (1.6)	0
No of discontinuations due to AE, n (%)	17 (6.7)	1 (0.4)	5 (1.9)	4 (1.8)
Gastrointestinal system disorders				
Abdominal pain	38 (15.0)	13 (6.3)	20 (7.8)	11 (4.9)
Nausea	54 (21.3)	13 (6.3)	17 (6.6)	4 (1.8)
Diarrhoea	35 (13.8)	8 (3.9)	4 (1.6)	2 (0.9)
Flatulence	18 (7.1)	4 (2.0)	15 (5.8)	7 (3.1)
Dyspepsia	14 (5.5)	5 (2.4)	3 (1.2)	3 (1.3)
Vomiting	14 (5.5)	5 (2.4)	3 (1.2)	2 (0.9)
Nervous system disorders				
Headache	64 (25.3)	20 (9.8)	15 (5.8)	10 (4.5)

AE, Adverse events; No, number; TEAE, treatment-emergent adverse event

5.9.2 Safety Results from relevant non-RCTs

Summary of adverse events for PRU-INT-10, PRU-USA-22 and PRU-INT-17 (27-29)

AEs were analysed according to the treatment-emergent principle, i.e., an event was only reported after first occurrence or worsening in at least severity, relation, seriousness, or action taken towards study medication. AEs reported in previous studies and that were still ongoing at the start of this study were not considered treatment-emergent, except when they worsened in severity.

A summary of treatment-emergent AEs in all studies is presented in Table 51

Table 51: Summary of incidence and most frequently reported treatment related adverse events (PRU-INT-10, PRU-USA-22 and PRU-INT-17) (27-29)

Adverse events	Treatment-emergent adverse events reported by:		
	≥ 5% of patients	> 5% of patients	≥ 4% of patients
	PRU-INT-10	PRU-USA-22	PRU-INT-17
No. (%) with 1 or more AE	524 (75.6)	1433 (80.7)	70 (72.9)
No. (%) with 1 or more SAE	91 (13.1)	113 (6.4)	13 (13.5)
No. (%) of deaths	2 (0.3)	2 (0.1)	4 (4.2)
No. (%) with discontinuation due to AE	66 (9.5)	131 (7.4)	9 (9.4)
Most frequently reported AEs, n (%)			
Abdominal pain	110 (15.9)	428 (24.1)	4 (4.2)
Headache	78 (11.3)	553 (31.2)	4 (4.2)
Diarrhoea	63 (9.1)	361 (20.3)	-
Influenza-like symptoms	60 (8.7)	-	-
Nausea	54 (7.8)	266 (15.0)	7 (7.3)
Back pain	53 (7.6)	122 (6.9)	-
Sinusitis	45 (6.5)	192 (10.8)	-
Infection viral	44 (6.3)	136 (7.7)	-
Surgical intervention	38 (5.5)	146 (8.2)	6 (6.3)
Flatulence	37 (5.3)	285 (16.1)	4 (4.2)
Dizziness	36 (5.2)	-	5 (5.2)
Dyspepsia	-	120 (6.8)	-
Injury	-	115 (6.5)	5 (5.2)
Upper respiratory tract infection	-	98 (5.5)	-
Pain	-	-	7 (7.3)
Constipation	-	-	4 (4.2)
Insomnia	-	-	4 (4.2)
Fall	-	-	4 (4.2)

PRU-INT-10 (27)

Adverse events:
During the treatment period 524/693 (75.6%) patients were reported to have ≥ 1 AE (Table 51). The majority of AEs were mild or moderate in intensity.

Two deaths were reported. One patient died due to myocardial infarction 67 days after treatment stop, another due to pneumonia 4 days after treatment stop. Both events were considered not related to study medication. Non-fatal SAEs were reported in 91 patients (13.1%) during the long-term treatment period. The most common non-fatal SAE was surgical intervention reported in 17 patients (2.5%). All other non-fatal SAEs were reported in less than 10 patients.

Twenty-one patients experienced a non-fatal SAE leading to permanent discontinuation of the study. The majority of non-fatal SAEs were considered to be severe (61/91 patients) and not or doubtfully related to the study medication by the investigator. Nine patients experienced non-fatal SAEs considered possibly related to study medication. For 1 patient, severe arrhythmia was noted on an ECG taken 182 days after treatment start. This AE was considered very likely related to study medication by the investigator and was reported as SAE. No relevant changes were noted at the ECG taken at the next visit, 11 days later.

Treatment-emergent AEs leading to permanent study discontinuation were reported in 66 patients (9.5%) during long-term treatment with prucalopride. The most common AE leading to permanent discontinuation from the study were the gastro-intestinal disorders diarrhoea (14 patients, 2.0%) and abdominal pain (11 patients, 1.6%) and unintended pregnancy reported in 10 patients (1.4%). All other AEs for which study medication was permanently stopped were reported in less than 10 patients.

No differences in terms of incidence, severity, drug-relatedness, seriousness, or discontinuations of AEs were observed between patients previously treated with either prucalopride or placebo.

Clinical Laboratory:
The incidence of AEs related to laboratory abnormalities was low (< 1% - 3%). The most frequent laboratory abnormalities reported as an AE were creatine phosphokinase (CPK) increased in 18 patients (2.6%), anaemia in 17 patients (2.5%), haematuria in 12 patients (1.7%), hypertriglyceridaemia in 11 patients (1.6%), hypercholesterolaemia in 10 patients (1.4%), and hyperglycaemia in 9 patients (1.3%).

Vital Signs:
Mean changes from baseline in vital signs parameters were generally small and no trend became apparent over time. These mean changes in vital signs parameters were rarely statistically significant and were not considered clinically relevant. The incidence of AEs related to vital signs abnormalities was low (at most 1.4%). The most frequent (≥ 1% of patients) vital signs abnormalities reported as an AE were hypertension in 10 patients (1.4%) and weight decrease in 8 patients (1.2%).

ECG and Corrected QT Intervals:
Generally, mean changes from baseline in ECG parameters (HR, QT, QTc, PR, and QRS) were small and considered not clinically relevant during long-term prucalopride treatment. Incidence of individual patient changes in ECG parameters considered as clinically significant abnormalities by the investigator was low, i.e., in 0% to 5% of patients. ECG abnormal was reported in 9 (1.3%) patients as an AE.

PRU-USA-22 (28)

Adverse events:
During the treatment period 1433/1775 (80.7%) patients were reported to have ≥ 1 AE (Table 51). The majority of AEs were mild or moderate in intensity.

Three deaths were reported. One patient died during treatment (myocardial infarction), and two patients outside the treatment period (1 severe asphyxia and 1 gunshot wound), no treatment information was available for the patient with the gunshot wound, but the other two deaths were considered unrelated to study medication. SAEs were reported in 115 patients (6.5%), including 2 deaths (myocardial infarction and injury) during the long-term treatment period. The most common SAE was surgical intervention reported in 58 patients (3.3%). All other SAEs were reported in less than 0.5% of the patients.

The most common AE leading to premature discontinuation from the study were abdominal pain (27 patients, 1.5%) and headache (26 patients, 1.5%). All other AEs for which study medication was permanently stopped were reported in less than 1% of the patients.

No differences in terms of incidence, severity, drug-relatedness, seriousness, or discontinuations of AEs were observed between patients previously treated with either prucalopride or placebo, except for headache (27.6% of the patients previously treated with prucalopride versus 37.2% of the patients previously treated with placebo).

Clinical Laboratory Safety:
No notable mean changes from baseline in any of the laboratory parameters were observed throughout the study. There were no clinically relevant findings for the shifts from below, within or above normal range compared to the reference time-point. Overall, the incidence of AEs related to laboratory abnormalities was low (< 1 - 2%), indicating that the majority of treatment-emergent laboratory abnormalities are not clinically significant.

Vital Signs:
Mean changes from baseline in weight and vital signs parameters were generally small and no trend over time was apparent. These mean changes in vital signs parameters were not considered clinically relevant. The percentage of patients with treatment-emergent abnormal (high or low) vital signs values was low. The most common vital signs abnormality was abnormally low pulse, reported in 93 (6.9%) patients. The incidence of vital signs-related AEs was low. Tachycardia, hypertension, hypotension, weight increase or decrease, and obesity were the most frequently reported clinically relevant vital-signs related AEs and were reported by at most 1.5% of the patients.

Cardiovascular Safety:
Mean changes from baseline in ECG parameters were generally small and no trend over time was apparent. The percentage of patients that had a shift from normal PR or QRS values at baseline to abnormal (high or low) PR or QRS values during treatment was low (< 2% of patients). Shifts from normal to abnormally low heart rate (HR) on the other hand, were slightly more frequent, i.e., reported in 180 (16.3%) patients. Small increases in HR and accompanying decreases in uncorrected QT intervals were observed compared to baseline but were not considered clinically relevant. Correction of QT intervals for HR resulted in less pronounced changes especially for QTcF values.

PRU-INT-17 (29)

Adverse events:
During this long-term treatment study, 70/96 (72.9%) patients were reported to have at least on AE (Table 51). The majority of AEs were mild or moderate in severity.

AEs led to death for 4 patients. All 4 patients previously participated in the PRU-INT-14 study and had a history of cancer. One patient had convulsions 10 days after treatment start, fell into coma 6 days later and died the following day (5 days after study medication stop). One patient died from progression of breast cancer (22 days after discontinuation of study medication), one from sarcoma (5 days after the last intake of study medication), and one from aggravated condition (reported as SAE 11 days after treatment start). None of these death causes were considered related to the study medication by the investigator. One additional patient died during the study; death (unknown cause) was indicated as reason for study discontinuation but was not reported as an AE. SAEs other than death were reported by 13.5% patients. All SAEs were assessed as at most doubtfully related to the study medication, by the investigator except moderate tachycardia, reported 83 days after start of prucalopride treatment in one patient, which was considered possibly related to the study medication.

AEs leading to premature study discontinuation were reported in 9 (9.4%) patients.

No differences in terms of incidence, severity, drug-relatedness, seriousness, or discontinuations of AEs were observed between patients treated with either prucalopride or placebo in the preceding studies.

Clinical Laboratory:
The incidence of AEs related to laboratory abnormalities was low, i.e., 11 (11.5%) patients had in total 24 treatment-emergent laboratory-related AEs. The most commonly reported were hypercholesterolaemia, hypertriglyceridaemia, γGT increased and creatine phosphokinase increased. All others were reported in at most 1 patient during the treatment period of this long-term follow-up study.

Cardiovascular Safety:
Mean changes from baseline in vital signs parameters were generally small and no trend over time became apparent. These mean changes in vital signs parameters were rarely statistically significant and were not considered clinically relevant. The incidence of patients with vital signs-related AEs was low, i.e., 7 vital signs-related abnormalities were reported as AE in 6 (6.3%) patients. Mean changes from baseline in ECG parameters were generally small and not considered clinically relevant. Changes in ECG parameters were considered clinically significant for 1 (1.2%) patient. Abnormal ECG assessment was reported as an AE for this patient. No other ECG abnormalities were reported as AE. Shifts in QTcB from normal at baseline to prolonged during treatment were occasionally seen. No shifts from normal at baseline to prolonged at any time-point during treatment were reported for QTcF. None of the patients had a QTcB or QTcF interval that exceeded 500 ms at any time-point after baseline and for none of the patients QTcB or QTcF increases were larger than 60 ms.

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The safety data that is presented within this section clearly demonstrates that prucalopride is well tolerated in all patient groups studied.

Key results of the safety analyses are summarised below:

- Gastrointestinal AEs (predominantly diarrhoea, abdominal pain and nausea) are the most important AEs that are clearly linked to the pharmacodynamic action of prucalopride. They were generally considered to be mild or moderate in severity. Diarrhoea was not associated with clinically significant consequences such as dehydration or hypokaleaemia.
- The gastrointestinal AEs (such as diarrhoea and nausea) and headache were most frequently reported on Day 1 or in Week 1 of treatment. The incidence as of day two was not different from placebo for these most common AEs.
- SAEs were rare to very rare and the majority of recorded SAEs were not considered to be treatment-related. The overall incidence of SAEs with prucalopride in the double-blind pivotal trials was low (2.1%) and comparable to that observed with placebo (1.9%), and there was no apparent dose relationship
- The incidence of discontinuations due to AEs was low. Across all phase II/III double-blind placebo-controlled studies in chronic constipation (and all other studies) the most commonly reported AEs leading to discontinuation were within the system organ class of GI disorders (reported by 5.0% of prucalopride-treated patients and 1.5% in the placebo group) and headache (2.3% and 0.4%, respectively).
- Long-term treatment with prucalopride was generally well-tolerated with an adverse event profile similar to that observed during the 4-12 week trials
- An in depth analysis of the AE profile by gender or age did not reveal any differences
- There were no clinically meaningful differences between the prucalopride and placebo groups with respect to vital sign, ECG parameters, haematology, clinical chemistry and urinalysis
- There were no clinically relevant QT effects observed with prucalopride. This is supported by results from three studies specifically designed to look for potential QT effects at doses up to 5-10 fold therapeutic dose, which showed that prucalopride had no effect on QT interval.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Consistent results in the phase III pivotal trials showed a statistically significant improvement in the primary endpoint (≥ 3 SCBM per week or normalisation) at the recommended dose of 2 mg/day (licensed dose for adults) and positive effects across the wide range of secondary endpoints, including the symptom scores and overall patient and treatment satisfaction as measured by the PAC-QOL. Prucalopride normalised bowel habits (≥ 3 SCBM) in 23.6% of patients and provided a clinically meaningful benefit (based on increase in SCBM frequency and patient satisfaction) in an additional 30-35% of patients in the pooled population (3 pivotal studies). The positive effect of treatment was evident over the first 4 weeks and was maintained over the 12 weeks double blind phase of the study. It should be noted that the patients included in the studies had a high degree of severity of constipation; they had a long standing history of chronic constipation of a mean of 20 years and > 85 % had used and were dissatisfied with available treatment (laxatives). The mean number of SCBMs per week prior to entry into the trials was 0.5, approximately 57% had no SCBM and quality of life was low.

Specific trials performed in elderly patients confirmed the efficacy of prucalopride in this patient group. In the elderly, a daily dose of 1 mg appeared as effective as the 2 mg dose, using the same efficacy criteria as in the pivotal trials. This can, at least in part, by explained by reduced renal clearance in this population.

The phase III pivotal trials demonstrated that treatment with prucalopride 2 mg/day and 4 mg/day for 4-12 weeks was generally well tolerated in patients with chronic constipation. The most frequent treatment-related adverse events were headache, nausea, diarrhoea and abdominal pain. These adverse events were more frequent in prucalopride than placebo treated subjects, but primarily on the first day of treatment. Following the first day, the frequency of these adverse events was similar between treatment groups and placebo. Most adverse events were mild to moderate in severity and were transient. In the elderly studies, the tolerability profile of prucalopride was similar to that observed in the pivotal trials.

A long-term follow-up programme in chronic constipation was conducted. The total patient exposure in these open trials exceeded 2000 patient-years and 1490 patients were treated for 6 months and longer. During this long-term treatment, the efficacy, as measured by the patient satisfaction scale (PAC-QOL), was maintained, with the reported drop-out rate due to lack of efficacy being low (< 5%). In addition, data from a retreatment trial (PRU-USA-28) demonstrated that if a patient was taken off treatment (after 4 weeks) and then restarted after a break of at least 2 weeks, the response level in the second treatment period was at a similar level to that seen in the first period. The majority (approximately 70%) of patients who responded on the first treatment period (≥ 3 SCBM/week) also responded in the second period. In between treatment periods, endpoints tended to revert to baseline values. This data together with available preclinical data support a lack of tachyphylaxis.

Long-term treatment with prucalopride was generally well-tolerated with an adverse event profile similar to that observed in the phase III pivotal trials.

The available data from the opioid-induced constipation population support the results obtained in the pivotal studies for chronic constipation. While the studies are smaller and consequently do not all show statistical significance, the numerical superiority of the prucalopride groups is consistent with the results from the pivotal studies and suggests a role for the drug in this patient population.

Additional studies were also conducted in other specific populations with difficult-to-treat constipation; a small double-blind placebo-controlled study of patients with multiple sclerosis, another of patients with spinal cord injury, and an open-label, long-term study of both populations. Data from the trials suggest that prucalopride is well tolerated in these patient groups. The trials were too small to draw conclusions on efficacy, however similar absolute improvements in bowel frequency and other parameters were observed, supporting a positive effect of prucalopride in these populations.

Cardiovascular effects have been a concern with nonselective 5-HT_4 receptor agonists. Extensive safety data has been accumulated from human studies on prucalopride. ECG data was collected throughout the Phase II/III clinical program. Overall, there were no clinically relevant changes over time for mean heart rate and corrected QT values (QTcB, QTcF). There were also no clinically relevant differences between prucalopride and placebo, and there was no apparent effect of dose. Furthermore, three QT studies, two placebo controlled and one active controlled, specifically designed to look for any potential QT effects at doses up to 5-10 fold therapeutic dose, showed no evidence of drug-induced QT related prolongation.

The Phase I, double-blind, randomised, placebo- and positive (moxifloxacin)-controlled, parallel group/crossover thorough QT/QTc study to evaluate the effect of therapeutic and supratherapeutic multiple doses of prucalopride on cardiac repolarisation in healthy male and female volunteers.

The primary objective of the study was:

- to assess whether treatment with therapeutic (2 mg) or supratherapeutic (10 mg) doses of prucalopride in healthy male and female volunteers does not increase QTc interval compared to placebo.

The secondary objectives of the study were:

- to demonstrate assay sensitivity by showing that the active control (moxifloxacin 400 mg) treatment,corrected for placebo, produces a QTc change >5 ms;
- to assess prucalopride pharmacokinetic (PK) parameters and perform a pharmacokinetic/Pharmacodynamic (PK/PD) assessment; and,
- to assess safety and tolerability of prucalopride.

120 subjects were included in the safety analysis set and ECG analysis set.

Primary endpoint:
For both the therapeutic prucalopride dose of 2 mg and for the supratherapeutic dose of 10 mg, the upper limit of the confidence interval (CI) for the difference in time-matched QTcSS change from baseline between prucalopride and placebo, was below the non-inferiority margin of 10 ms at all time points, confirming the absence of any clinically relevant effect of prucalopride on cardiac repolarisation.

Secondary endpoints:

- For moxifloxacin, the lower limit of the CI derived from the average QTcSS interval for the mean of two time points 1 and 2 hours post-dose was above 5 ms. This was also true for the mean of 1, 2 and 3 hours, the mean of 2 and 3 hours post-dose and for all individual time points studied except 1 hour post-dose, confirming assay sensitivity.
- QTcF values and derived estimates were comparable with the QTcSS values, indicating that the study specific QT correction has a high resemblance to the Fridericia corrections.

- For both genders studied, there were no QTcSS outlying values > 450 ms at any time point following either of the treatments prucalopride (2 mg or 10 mg).
- With regard to QTcSS increases from baseline between 30 and 60 ms, the total number of occurrences over a 24 hour period post-dose in all subjects was very low and comparible for prucalopride and placebo.The number was higher following moxifloxacin treatment. There were only isolated occurrences of increases greater than 60 ms; the number did not exceed 2 for either prucalopride, placebo or moxifloxacin. None of the subjects had QTcSS > 450 ms, and no subject had an increase > 60 ms that resulted in QTcSS > 500 ms, the parameters of usual regulatory concern.
- For prucalopride (2 and 10 mg), a small increase in heart rate (HR) relative to placebo was observed but this did not exceed 6 bpm at any time point. The small increase in HR due to prucalopride is a known effect which is not clinically relevant.
- On 24-hour Holter recordings, morphological analysis showed very similar numbers following each treatment over a comparable time interval. No significant differences were seen between prucalopride and placebo in ECG morphologic changes or arrythmias.
- Pharmacokinetic/pharmacodynamic correlations showed no significant correlations based on predicting QTc prolongation (and its upper 95% CI) at the mean C_{max} of both the 2 mg and 10 mg dose levels (separate and combined).

Prucalopride, at doses both 2 and 10 mg daily, had no statistically significant and clinically relevant effect on cardiac repolarisation based on procedures described in ICH E14 Guidance on Clinical Evaluation of QT/QTc Interval Prolongation. No subject has a QTcSS increase of >60 ms that resulted in QTcSS > 500 ms, the parameter of usual regulatory concern. At 2 mg, an increase in HR was seen, which was similar to the increase at 10 mg dose. No significant differences were seen between prucalopride and placebo in ECG morphologic changes or arrhythmias and observed abnormalities were not considered to be of clinical relevance. Treatment with prucalopride in up-titrating doses up to 10 mg once daily was safe and well tolerated from Day 2 onwards. The higher incidence of AEs such as headache, nausea and vomiting on Day 1 are known and considered due to the PD effects of the drug.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The Phase II/III program for prucalopride is the most extensive program to date in this indication comprising 25 Phase II and 10 Phase III studies with over 2,600 patient years of data. The studies discussed in this submission correspond to the key studies that support the evidence for a clinically meaningful effect and maintenance of that effect during long-term treatment (>12 months) in the proposed indication.

The results from the pivotal studies show consistently in all studies that prucalopride 2 mg is statistically significantly effective in patients with chronic constipation, the vast majority of whom were dissatisfied with their previous laxative treatment. The pivotal studies each individually showed a statistically significant improvement in the primary efficacy endpoint (≥ 3 SCBMs per week) for 12 weeks. This primary efficacy endpoint is clinically relevant as it is considered a normalisation of bowel movement. As most patients had no SCBM at entry it is also a stringent clinical endpoint rather than a pure statistical endpoint.
Prucalopride not only improves bowel function but also has significant effects on a broad range of distressing constipation symptoms. The data support that symptoms like bloating,

distension, abdominal discomfort and pain, which are not always well treated by current laxative medications, tend to respond well to prucalopride.

Long term studies indicate that efficacy is maintained. Across all open-label studies the withdrawal rate due to lack of efficacy was 19.5%. However sub-analysis of the data showed that of the 19% who withdrew, 16% were non-responders during the double-blind phase. Consequently, only 3% of patients who respond during the first three months of treatment are likely to discontinue (and stop treatment) due to lack of response during the course of two and a half years of treatment.

Across all studies, validated questionnaires for assessing effects on constipation symptoms (Patient Assessment of Constipation – Symptoms [PAC-SYM]) and quality of life (Patient Assessment of Constipation – Symptoms [PAC-QOL]) were used.The PAC-QOL was specifically and uniquely developed to assess the HRQL and satisfaction of patients with chronic constipation. The psychometric properties of the final version of the PAC-QOL, including reliability, validity and responsiveness, were assessed in a specific and large validation study. The PAC-QOL offers the opportunity to capture, in one consistent endpoint, the individual symptomatology of the disease and measure satisfaction with treatment through a validated tool independent of the predominant complaint which may be different between patients. The PAC-QOL results correlate well with both primary and secondary endpoints in the studies.

The patients included in the clinical study programme had a substantial clinical need; with a history of on average 20 years of constipation, a high degree of general dissatisfaction with their bowel habits, a high degree of dissatisfaction with previous laxative treatment and a low quality of life. The label was further and voluntarily restricted to those not adequately resonding to laxatives at baseline to focus on the area of highest medical need.

The pivotal studies comprised a large percentage of Caucasian women, consequently prucalopride may not have been sufficiently evaluated in men. However, pharmacokinetic, pharmacodynamic and safety data demonstrate that the effect of prucalopride is similar in men and women compared with placebo. The small number of male subjects in the double blind studies may explain the lack of statistical significance observed with the 2 mg dose, which is further compounded by the higher proportion of male patients with more severe constipation at baseline in this dosing group (more patients with 0 SCBM at entry). This is a limitation of the studies, but does not impact on the current submission as the licensed indication is for women with chronic constipation. An extra trial in males will be started in 2010.

There are missing data for relevant populations, such as paediatric patients, pregnant women and patients with impaired hepatic function. These has been addressed in the EMEA Risk Management Plan; routine pharmacovigilance for paediatric, pregnancy and hepatic impairment, targeted follow-up of all pregnancy cases and a hepatic impairment study. Additional studies in pediatric patients and patients with impaired hepatic function will start in 2010.

5.10.3 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.

The primary efficacy endpoint used throughout the clinical program was the percentage of patients with a mean of ≥3 SCBMs per week. This endpoint combines both a measurable endpoint (number of spontaneous stools) and a qualitative measure of each bowel movement based on the patients' assessment of the completeness of evacuation. In addition, input from clinical experts and established criteria for diagnosis of chronic constipation indicates that a patient with ≥ 3 SCBM per week has a normal bowel habit and is no longer considered constipated. Given that in the patient population studied, the mean number of SCBMs per week was only around 0.5, and 57% had no SCBM per week during the run-in period, meeting the primary endpoint represented a stringent and clinically relevant improvement in their constipation. This endpoint (i.e. ≥ 3 SCBM per week) was discussed and agreed with EMEA and FDA as an acceptable and clinically meaningful endpoint for Phase III registration studies.

The secondary endpoints used were considered equally clinically relevant both from the treating physician and patient perspectives. These endpoints included improvement of 1 SCBM per week, increase to 3 SBM, improvement of a broad range of bowel and stool symptoms (straining, bloating, abdominal discomfort, pain, sense of incomplete evacuation etc.) and overall satisfaction with treatment which are likely to be considered relevant efficacy measures by patients.

Patients' perspectives are viewed as increasingly important in studies of medical treatment effectiveness and outcomes. Symptoms are best assessed by the patient, and in the clinical studies the Patient-Assessment of Constipation (PAC) was used to measure patients' experience of constipation over time. The PAC is a self-report and validated instrument composed of two complementary components, the Symptom questionnaire (PAC-SYM) and the Quality of Life questionnaire (PAC-QOL), which can be used separately or together.

Treatment response was measured at 4 and 12 weeks in the double blind clinical studies. This is relevant to clinical practice as data suggest that responders can be easily identified after 4 weeks or one pack of prucalopride. Consequently treatment can be reviewed and stopped after 4 weeks in those patients not responding.

Treatment response was followed after the 12 week double blind trials – using the satisfaction scale of the PAC-QOL – during open label long term follow-up studies to measure and demonstrate the long term efficacy and safety of the drug. These efficacy measurements are considered relevant as the PAC-QOL has shown to have clear correlation with a range of primary and secondary endpoints in the phase III studies.

5.10.4 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?

The use of prucalopride in the clinical studies reflects its intended use in clinical practice, it was administered at the licensed frequency and dose. The recommended dose is 2 mg in adults and 1 mg in the elderly. The pivotal phase III studies used 2 and 4 mg. Both doses were efficacious and safety was comparable. The minimally efficacious dose was chosen as 2 mg. Elderly dosing is based on the pharmacokinetics of prucalopride, and reflects a low renal clearance due to decreased glomerular filtration rate in the elderly. The dose can be adjusted upwards up to 2 mg in the elderly if needed.

Patients in the Phase II/III program in chronic constipation were predominantly women of Caucasian origin, with a mean age of around 50 years. Based upon referral patterns, the current laxative usage (IMS Health) and available epidemiology data this reflects the patient population seen in routine clinical practice (i.e 85 % females).

Patients in the trials had long standing disease with a history of on average 20 years of constipation, a high degree of general dissatisfaction with their bowel habits and previous treatment, and a low quality of life. Furthermore, the average frequency of SCBMs prior to study entry was 3 or less for the vast majority of patients (97.8% and 98.6% of all prucalopride and placebo-treated patients respectively), and approximately 57% had no SCBM, supporting the medical need in this population.

Over 85 % of patients included in the studies were dissatisfied with available treatment (laxatives), and the indication was voluntarily restricted to this group. The patients in which prucalopride was studied/is indicated can be identified in clinical practice using the general inclusion criteria of the pivotal trials: at least 6 months of history of chronic constipation (consistent with Rome III criteria), having used at least one laxative before and symptomatic relief under previous laxative treatment was deemed inadequate by both patient and doctor.

The clinical evidence also supports the use of prucalopride in the elderly and in patients with opioid induced constipation, multiple sclerosis and spinal cord injury.

In the clinical studies short term contact laxative treatment (bisacodyl) was permitted as a rescue medication. This product is not indicated for chronic use. Placebo-treated subjects used an average of two bisacodyl tablets (10 mg) per week, which is representative of clinical practice (IMS). This may indicate that the placebo arm is a valid representation of or represent clinical practice in patients with chronic constipation that are inadequately relieved by laxatives.

Studies described in the evidence base include the doses given in the SPC.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 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 9.10, appendix 10.

A comprehensive review of the literature was undertaken to identify any existing cost-effectiveness studies in the field of long term chronic constipation. Although a limited number of (non-UK) cost analyses were identified no previous economic evaluations were identified for the patient population being targeted by prucalopride. A search was undertaken on PubMed to identify published EQ-5D utility scores for constipation. A total of 25 citations were identified and reviewed. After reviewing all 25 articles it was found that none provided EQ-5D for the laxative refractory long term chronically constipated target population. Given that it was not possible to apply EQ-5D utility values identified in the literature to prucalopride data and EQ-5D data were not collected directly in the prucalopride trials it became necessary to 'map' from the SF-36 and Patient Assessment of Constipation quality of life (PAC-QOL) and symptom (PAC SYM) data to generate the necessary EQ-5D utility scores for inclusion into the economic model.

The search terms used and consequent results are listed below:

Item	Searches	Results
1	chronic.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	717,421
2	constipat*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	14,128
3	cost.mp. [mp=title, original title, abstract, name of substance word, subject heading word	225,631
4	cost*.mp. [mp=title, original title, abstract, name of substance word, subject heading word	304,415
5	1 and 2	2,950
6	3 or 4	304,415
7	5 and 6	69
8	from 7 keep 1-69	69

Description of identified studies

6.1.2 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.

No relevant studies relating to the cost effectiveness of treatment in population being targeted by prucalopride (laxative refractory chronic constipation) were identified in the systematic search.

As such a de novo economic evaluation of the cost effectiveness of prucalopride (plus rescue medication) versus placebo (plus rescue medication) was undertaken in female patients suffering from long term chronic constipation.

6.1.3 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)[4] or Philips et al. (2004)[5]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

As no cost-effectiveness studies were identified that had relevance in the patient population appropriate to prucalopride no such quality assessment was required.

6.2 De novo analysis

Patients

6.2.1 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 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the

[4] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[5] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

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 and included in the trials.

The patient group incorporated in the economic evaluation are taken from the clinical trial programme undertaken for prucalopride. As such the patients analysed in the economic model accurately reflect the patients evaluated in the clinical trials of prucalopride. The license for prucalopride is restricted to females, therefore the economic analysis isolates the costs and benefits associated with female patients and is fully in line with the obtained indication.

As there is a higher prevalence of chronic constipation in the elderly population, two clinical trials were undertaken specifically in patients aged 65+ years (PRU-USA-26 AND PRU-INT-12). For the elderly population a dose of 1 mg was used (as opposed to 2 mg for adults 18-65 years) in line with recommendations in the SPC. As such, the economic model was designed to evaluate the cost effectiveness of treatment with prucalopride in two separate populations; adults (18-65 years) and elderly (65+ years). Firstly all available clinical trial data relating to the comparative effectiveness of treating adult (18-65) female patients with a 2 mg dosage of prucalopride were identified from the clinical trials. Secondly all available clinical trial data relating to the comparative effectiveness of treating elderly (65+) female patients with a 1 mg dosage of prucalopride were identified in the trials. In both groups the comparator was placebo plus rescue medication (which is the current standard of care in patients in whom laxatives do not provide adequate relief).

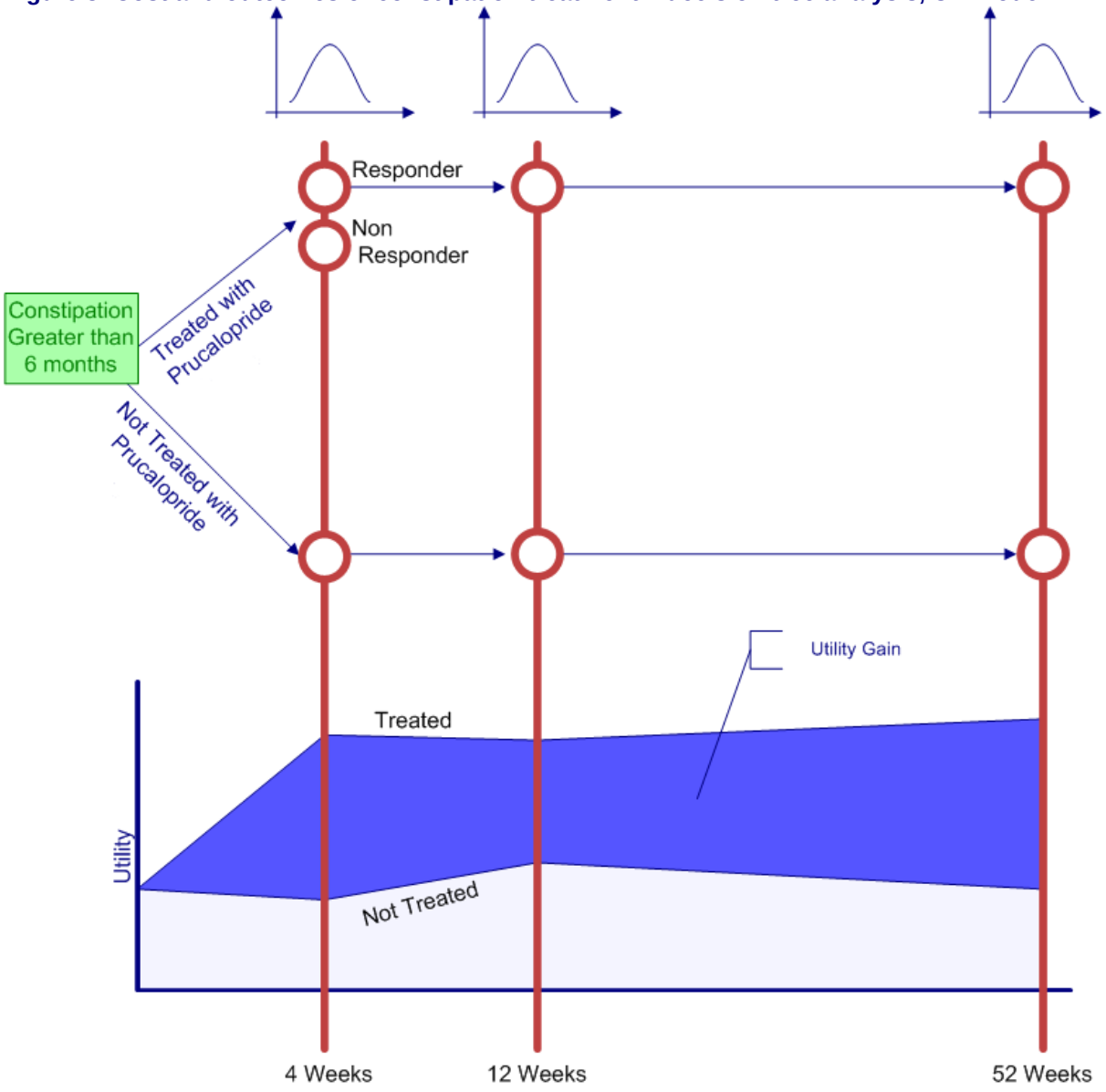
The justification for use of placebo (with rescue medication as required) as a comparator was that the majority of the patients analysed in the trials underpinning the economic model had been previously treated with laxatives over a long time period. In these studies over 80% of patients stated that laxative treatment was inadequate in relieving their symptoms. The majority of the female patients incorporated in the prucalopride trials were experiencing long term laxative refractory chronic constipation.

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

A decision analytical framework was used to develop the economic model of prucalopride versus standard care in the treatment of chronic constipation. The structure of the economic model follows the structure of the clinical algorithm that will underpin the use of prucalopride in mainstream clinical practice. A simplified version of the economic model is outlined below.

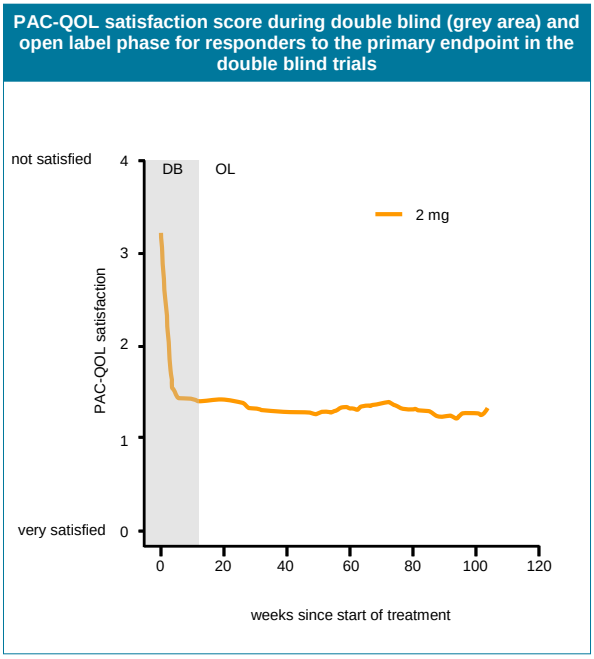
Figure 8: Cost and outcomes of constipation treatment – decision tree analysis, UK model



Following detailed discussion with clinical experts a structure was identified for the economic model which facilitated the use of the extensive evidence concerning the comparative clinical efficacy of prucalopride data that had been collected in the prucalopride trials.

For the first 12 weeks of the economic model for adults an analysis of individual patient level data is undertaken for all female patients treated with 2 mg dose of prucalopride. Observational trial data collected in adult female patients for an additional 40 weeks beyond the initial trial period emphasised that patient satisfaction with prucalopride therapy was maintained over the initial year (52 weeks) of prucalopride therapy in adult female patients (Figure 9). The model did not go beyond 52 weeks in order to keep it simple and avoid issues associated with discounting and the effect of discounting on QALYs which brings them back to the same value. This 52-week period can also be supported with solid clinical data and is a sufficient time span to address the main adverse events and complications.

Figure 9: PAC-QOL satisfaction scores in the open label phase



Note: In open label studies efficacy was assessed by the PAC-QOL at 3 month intervals

The clinical trials of prucalopride in elderly female patients only covered a four week period of analysis. As such the economic model in elderly patients used an analysis of individual patient level data for all female patients treated with the 1 mg dose of prucalopride. Again observational data was utilised to extend the analysis out to one year. In the case of elderly patients patient satisfaction with prucalopride actually appeared to further improve over this initial one year period of treatment.

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The structure of the economic model is consistent with the pivotal clinical trials for prucalopride; for example, inclusion of 4-week, 12-week and 52-week timepoints. The pivotal trials are in line with the care pathway for female patients with laxative-refractory chronic constipation.

6.2.4 Please define what the health states in the model are meant to capture.

Health states are not relevant to this model because it is based on individual patient data.

The patient reported outcomes included in the model reflect the comparative quality of life (QoL) being experienced by the patient population at any point in the analysis.

6.2.5 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.

Treatment outcome in chronic constipation is evaluated in the first instance in terms of the frequency of spontaneous complete bowel movement (SCBM). A patient experiencing 3 or more SCBMs in one week is defined as having achieved normalised bowel movements and hence is categorised as being a ‘responder’. Achieving this target was the primary efficacy endpoint in the prucalopride trials and is used to distinguish between ’responders’ and ‘non-responders’ to prucalopride for the purpose of the economic model. An SCBM is defined as a non-laxative induced bowel movement (spontaneous), with a sense of complete evacuation. The number and nature of SCBMs are derived from diary data collected during the trials.

Treatment outcomes are also evaluated in terms of the patient reported outcomes of symptom relief and health-related quality of life, measured directly in the prucalopride trials using a range of validated measures.

Given the available evidence from the clinical trials a patient level decision analytical model structure (Weinstein MC & Fineberg HV, 1999) provided the most appropriate framework for the economic model comparing prucalopride versus standard care in the treatment of chronic constipation.

Chronic constipation is not a progressive disease, so disease progression was not built into the model.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 52: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	52 weeks	Chronic disease that is not progressive	See section 6.2.2 Guide to the methods of technology appraisal
Cycle length	1mg and 2mg - 4 weeks, 2mg - 12 weeks Both doses - up to 52 weeks	Availability and best fit to data and clinical practice	Guide to the methods of technology appraisal
Half-cycle correction	0	Time horizon and cycle length too short to require correction.	Guide to the methods of technology appraisal
Were health effects measured in QALYs; if not, what was used?	Yes	Mapping method is a widely accepted method for translating disease specific into EQ-5D data.	Guide to the methods of technology appraisal
Discount of 3.5% for utilities and costs	Same	Analysis undertaken of costs and benefits over a one year time frame.	Guide to the methods of technology appraisal
Perspective (NHS/PSS)	NHS costs. Patient reported outcomes	Best practice	Guide to the methods of technology appraisal
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 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 economic evaluation analyses the costs and benefits associated with the use of prucalopride as per the clinical trials. Thus two separate analyses are undertaken. The first population consists of female adult patients (18-65) who are laxative refractory and suffering from long term chronic constipation and who are treated with prucalopride 2 mg. The second population are elderly female patients (65+) who are laxative refractory and suffering from long term chronic constipation and who are treated with prucalopride 1 mg. This is entirely consistent with the licensed indication for prucalopride. Prucalopride treatment consists of continuous oral once daily dosing which replaces laxative therapy which has been identified as being ineffective in this patient group. The duration of prucalopride use varies for each

patient depending on the time spent responding to treatment. In order to optimise the clinical and cost effectiveness of treatment with prucalopride a treatment continuation rule has been identified (and included in the SmPC) to ensure that treatment is focussed entirely on patients who are responding to treatment (returned to 'normal' bowel movements). Details of this continuation rule are provided in the section below.

6.2.8 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.

The development of a treatment continuation rule for prucalopride is facilitated by two important characteristics of the drug, firstly the speed of the clinical response to prucalopride and secondly the visibility and ease of assessment of the physical response to prucalopride.

Prucalopride has a particularly rapid speed of action and the vast majority of patients that are likely to respond to the drug in any particular episode of treatment are likely to have responded and stabilised within a four week treatment period. As such the treatment continuation rule suggests reassessment of the patient after four weeks by a general practitioner and discontinuation of treatment for patients who fail to achieve 3 or more spontaneous (i.e. not laxative generated) and complete bowel movements (SCBMs). In addition it is suggested that patients who have achieved 'normality' in bowel movements are reassessed after 12 weeks to fully ensure that treatment effectiveness is sustained. Again in

patients who do not maintain the target treatment response of 3 or more SCBMs treatment is discontinued. In addition to these continuation rules patients should be informed to discontinue treatment and visit their GP for reassessment should the effectiveness of prucalopride treatment fall below this target level. It is considered most likely then that the patient does not suffer from a general impairment of bowel motility and careful examinations may be warranted.

The additional monitoring and costs associated with this treatment continuation rule is negligible and effective treatment for long term chronic constipation is likely to reduce the numbers of (particularly elderly) 'revolving door' patients frequenting GP surgeries in an effort to obtain satisfactory relief from their chronic constipation. The fact that treatment will be confined to patients in whom the benefit is greatest will also maximise the benefits obtained per unit of resource.

The endpoint chosen is easily and readily measured and apparent to both patients and GPs. The timing of response aims to limit the amount of drug wasted on non-responders (4 week assessment) and ensure that the drug is only continued if there is a measurable and sustained patient benefit (12 weeks). It is expected to also result in less frequent and more effective use of more expensive diagnostic procedures. For the purposes of the economic model these time points also coincide with the timings of patient responses undertaken in the clinical trials of prucalopride and hence the impacts of applying the continuation rules were readily assessable from the clinical trial data.

The continuation rule is therefore easily applied in clinical practice and ensures that patients are not subjected to drug therapy from which they are receiving too little benefit to justify the cost. In terms of equity considerations patients who fail to respond adequately to prucalopride at any particular are rapidly and easily identified in order to discontinue therapy and explore alternative (and perhaps more life threatening) potential causes of their chronic constipation. In addition subsequent to any necessary reassessment the reapplication of prucalopride may be clinically indicated in such patients.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

The structure of the economic model was entirely derived from the regression analysis on clinical data collected in the prucalopride trials. As such the primary source of information used to develop the structure of the model was a detailed analysis of the individual patient data derived from the randomised controlled trials of prucalopride plus rescue medication versus placebo plus rescue medication (see Table 53). This informed the starting patient

population and disease state and the disease progression pathway adopted in the first 12 weeks of the economic analysis.

Table 53: Clinical trial data incorporated in the model

	Group			
TRIAL	**Placebo**	**Prucalopride 1 mg**	**Prucalopride 2 mg**	**Total**
FRA-1	12	11	14	37
GBR-4	36	39	0	75
INT-1	44	43	39	126
INT-12	72	76	75	75
INT-2	63	66	62	191
INT-6	239	0	238	477
USA-11	209	0	207	416
USA-13	212	0	214	426
USA-26	18	24	26	68
USA-3	46	48	48	142
Totals	879	231	923	2033

The results obtained in the short term (12 week) clinical trials was supported by longer term (additional 40 weeks) observational studies to assess patient satisfaction with prucalopride treatment (PRU-INT-10 [extension of INT-6 and INT-12], PRU-INT-17 and PRU-USA-22 [extension of USA-11 and USA-13]). The aim of this longer term analysis was to assess the extent to which patient satisfaction with the effectiveness of prucalopride treatment was sustained over the first year of treatment. The results of this observational trial emphasised that levels of patient satisfaction experienced with prucalopride (measured at 12 weeks) were sustained over the next 40 weeks thus indicating a continued effectiveness of treatment and sustained treatment outcomes. Very low drop-out rates confirm this long term effect.

6.3.2 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.

For both the prucalopride and comparator arm observed pooled patient data from the clinical trial programme was used to calculate the transitional probabilities from long term chronic constipation (the disease state experienced by all patients entering the trials) to ‘normal’ bowel function as defined by patients achieving 3 or more SCBMs. Patients who achieved normality in bowel function were defined as responders and continued on therapy whilst those who failed to achieve this target level were defined as non-responders and had therapy withdrawn. On the basis of observational data emphasising that satisfaction with prucalopride therapy at 52 weeks was equivalent to satisfaction with therapy at 12 weeks the effectiveness of prucalopride therapy in responders was assumed to be maintained over this time period.

6.3.3 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.

There is no evidence that transitional probabilities vary over time. The only available evidence (the post trial 40 week observational data) indicates that the impact of prucalopride on patient symptoms is sustained over time and hence transitional parameters would appear to be stable over time. The low drop out rate in the long term studies due to lack of efficacy (< 5 %) support the stable response of the drug.

6.3.4 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?

The primary efficacy endpoint in the clinical trials of prucalopride was increasing the number of spontaneous and complete bowel movements (SCBM). An SCBM is defined as a non-laxative induced bowel movement which leaves the patient with a sense of complete evacuation. The number of SCBMs was derived from diary data collected from patients during the trials. Achieving 3 or more SCBMs in one week was defined as achieving normalised bowel function and the patient became defined as being a 'responder' for the purposes of the economic model.

The true final outcome associated with the treatment of chronic constipation is the achievement of an improvement in the quality of life of patients with changes in the number of bowel movements simply being a physical manifestation of symptomatology. As such the economic model concentrated on evaluating the impact of treatment with prucalopride on this aspect of patient outcome.

Quality of life was measured in the prucalopride trials using the Patient Assessment of Constipation outcome measures. This consisted of two disease specific validated questionnaires PAC-SYM (patient assessment of constipation- symptom questionnaire) and PAC-QOL (patient assessment of constipation-quality of life). Both questionnaires were developed among community-dwelling adults under age 65. The PAC questionnaires are also easily administered and well understood by older adult residents in long-term care (32).

PAC-SYM is a 12 item self reported instrument that has been previously validated for assessing patients with constipation (30, 33).

Each of the 12 symptoms of chronic constipation is rated on an inverse scale from 0 (absent) to 4 (very severe). PAC-QOL is a constipation specific health related quality of life measure that also has been validated for assessing patients with constipation (31, 34).This questionnaire provides greater sensitivity to constipation specific quality of life factors than generic measures but obviously cannot be used for comparisons across therapeutic boundaries. It consists of a 28 item question made up of 4 sub-scales (physical discomfort, worries and concerns, psychosocial discomfort and satisfaction). PAC-QOL data were collected for all patients included in the clinical trials of prucalopride and hence an extensive dataset is available concerning the change in quality of life arising as a consequence of treatment with prucalopride utilizing this disease specific quality of life measure.

The short form 36 (SF36) questionnaire was the only generic measure collected in the prucalopride trials however given that the questionnaire was applied at multiple time periods details are available concerning the patterns of patient responses for both adult and elderly female patients. Unfortunately the prucalopride trials did not collect data using the EQ-5D questionnaire. This represented a serious shortcoming in the evidence base underpinning prucalopride as being a preference based index, EQ-5D can be used to compare across therapeutic boundaries. Given this fact it became essential to 'map' as accurately as possible EQ-5D in relation to the quality of life questionnaires that were directly measured in the trials to facilitate and inform a Quality Adjusted Life Year (QALY) analysis for the purpose of calculating the Incremental Cost Effectiveness Ratio (ICER) that is associated with prucalopride treatment in this target patient population. Regression methods (described in detail elsewhere) were used to provide a scaled measure of change in quality of life derived from the quality of life measures directly utilised in the prucalopride trials. This was achieved by first estimating an EQ-5D score for each SF36 sample using GLS(3) (35). Given that SF-36 had been directly measured in the prucalopride trials alongside the Patient Assessment of Constipation questionnaires (PAC-QOL and PAC-SYM) the relationship established between SF-36 and the PAC questionnaires could then be extrapolated to EQ-5D.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- 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).

[6] 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 in order to understand patient pathways and standards of care; however their input was not required for the development of the algorithms in the economic model.

Summary of selected values

6.3.6 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. Please present in a table, as suggested below.

The only resource/cost incorporated into the economic model is the acquisition cost of prucalopride (see Section 6.5.2/6.5.5). This was done in line with the underlying rationale for the modelling, which was to minimise the number of assumptions. The clinical trials for prucalopride did not collect data on resources used.

The question asked is less relevant to the model because individual patient-level data are used. The table below shows how EQ-5D scores are derived for individual patients rather than health states. The patient profiles to which these scores are applied are sourced from ONS UK population data (see Section 7).

Table 54[7] shows how QALYs are calculated for individual patients at each time point. For example, a responding patient at 4 weeks aged 50, with a baseline EQ-5D of 60 would have an EQ-5D gain of 0.0338 (the fact they are a responder) + 0.0835 (the fact they have been treated) -0.0542 (baseline adjustment) = increased QALY of 0.0631.

[7] This table includes data to 6 decimal places because PAC-QOL provides greater sensitivity to constipation related symptoms and their impact on quality of life compared with generic measures such as SF36 or EQ-5D. The reason is that the latter questionnaires are insensitive to small changes in health state. The lack of sensitivity in EQ-5D and SF36 presents a problem when trying to quantify patient benefits, that are relevant to the patient in terms of health change.
For example, with SF36, when considering a treatment which is expected to have a 0.1 overall improvement in a physical component; SF36 can, for example only record discrete value increments of around 0.04 (e.g. 49.72671, 49.75688 and 49.80622), assuming the domain of this component is adequately covered in the questionnaire. This means that patients who start with a value of 49.74, and improve to 49.77 will register no change on the SF36 scale, whereas other patients, with less of a change may register the full 0.04 shift, by virtue of moving between bands within subscales. This noise around small changes makes typical non-specific measures unsuitable for treatments which would not be expected to show large changes in quality of life, and can be expected to contribute significantly to the minimal important difference (MID).

Table 54: Summary of variables applied in the economic model

Responder defined as achieving 3 SCBM per week, with baseline constipation severity related treatment effect				
Week 4 EQ-5D 2mg treatment (responder analysis)				
variable	**coefficient**	**Std. Err.**	**95% Confidence interval**	
treated baseline adj.	-0.090283	0.037125	-0.127408	-0.053158
Baseline EQ-5D	0.572695	0.026129	0.546566	0.598824
Age	0.104711	0.063344	0.041367	0.168055
Age^2	-0.000902	0.000607	0.000000	0.000000
Treatment 2	8.355882	2.897850	5.458032	11.253732
Male	0.153064	0.783298	-0.630234	0.936362
Treated Male	-1.040007	1.080983	-2.120990	0.040976
Responder	3.377139	0.587876	2.789263	3.965015
Constant	34.757660	2.452340	32.305320	37.210000
Week 12 EQ-5D 2mg treatment (responder analysis)				
variable	**coefficient**	**Std. Err.**	**95% Confidence interval**	
treated baseline adj.	-0.082869	0.041043	-0.123912	-0.041827
Baseline EQ-5D	0.542449	0.029018	0.513431	0.571466
Age	0.171991	0.077677	0.094314	0.249668
Age^2	-0.001862	0.000790	-0.002652	-0.001072
Treatment 2	7.847982	3.190501	4.657481	11.038483
Male	-0.332919	0.964966	-1.297886	0.632047
Treated Male	0.037163	1.316199	-1.279036	1.353362
Responder	2.612715	0.653666	1.959049	3.266381
Constant	36.515310	2.761544	33.753766	39.276854
Week 4 EQ-5D 1mg treatment (responder analysis)				
variable	**coefficient**	**Std. Err.**	**95% Confidence interval**	
treated baseline adj.	-0.062863	0.120306	-0.183169	0.057443
Baseline EQ-5D	0.566438	0.026064	0.540374	0.592502
Age	0.033836	0.016821	0.017015	0.050657
Treatment 1	4.644709	10.059340	-5.414631	14.704049
Male	-0.264189	0.777943	-1.042132	0.513754
Treated Male	0.745725	1.989900	-1.244175	2.735625
Responder	3.453895	1.626776	1.827119	5.080671
Constant	36.388780	2.014719	34.374061	38.403499

Responder defined as achieving 3 SCBM per week, with baseline constipation severity related treatment effect				
Week 4 EQ-5D 2mg treatment (responder analysis)				
variable	**coefficient**	**Std. Err.**	**95% Confidence interval**	
treated baseline adj.	-0.090283	0.037125	-0.127408	-0.053158
Week 4 EQ-5D 2mg treatment (ignoring responder analysis)				
variable	**coefficient**	**Std. Err.**	**95% Confidence interval**	
treated baseline adj.	-0.085740	0.037318	-0.123057	-0.048422
Baseline EQ-5D	0.586643	0.026379	0.560264	0.613022
Age	0.111073	0.064007	0.047066	0.175081
Age^2	-0.000919	0.000613	-0.001532	-0.000306
Treatment 2	8.936207	2.924161	6.012046	11.860368
Male	0.124337	0.797379	-0.673042	0.921717
Treated Male	-1.499189	1.090278	-2.589467	-0.408911
Constant	33.342760	2.479545	30.863215	35.822305
Week 12 EQ-5D 2mg treatment (ignoring responder analysis)				
variable	**coefficient**	**Std. Err.**	**95% Confidence interval**	
treated baseline adj.	-0.088931	0.041094	-0.130025	-0.047837
Baseline EQ-5D	0.559231	0.029135	0.530096	0.588367
Age	0.164641	0.078160	0.086482	0.242801
Age^2	-0.001757	0.000794	-0.002551	-0.000962
Treatment 2	9.026382	3.202756	5.823626	12.229138
Male	-0.311122	0.978012	-1.289134	0.666890
Treated Male	-0.495040	1.321484	-1.816524	0.826444
Constant	35.231070	2.778175	32.452895	38.009245
Week 4 EQ-5D 1mg treatment (ignoring responder analysis)				
variable	**coefficient**	**Std. Err.**	**95% Confidence interval**	
treated baseline adj.	-0.030533	0.118399	-0.148932	0.087866
Baseline EQ-5D	0.581804	0.026112	0.555692	0.607916
Age	0.033445	0.016868	0.016577	0.050313
Treatment 1	3.506121	10.037080	-6.530959	13.543201
Male	-0.230907	0.784905	-1.015812	0.553998
Treated Male	0.277307	1.993936	-1.716629	2.271243
Constant	35.135910	2.011930	33.123980	37.147840

Treated baseline adj. = baseline constipation-severity-related treatment effect
Treatment 1 = treated with 1mg prucalopride
Treatment 2 = treated with 2mg prucalopride

One other variable is not included in the table: baseline EQ-5D constipation severity: estimated from the clinical trials and had a mean value of 82.22 (SD 10.17).

6.3.7 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.

As previously emphasised the majority of patients included in the short term clinical trials (12 weeks) of prucalopride were followed up in an observational trial covering an additional 40 weeks to assess their long term satisfaction with treatment. The results emphasised that there was no significant difference between measured levels of patient satisfaction with prucalopride treatment at 12 weeks and at 52 weeks. Patient drop out due to lack of efficacy was low (< 5 %). On this basis the costs and outcomes directly measured at 12 weeks were carried over the following 40 weeks. There was therefore no extrapolation beyond the trial follow up period.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

The following key assumptions underpin the economic model:

- Placebo data from the prucalopride clinical trial were taken as an approximation for the efficacy of response for patients on laxatives. This assumption was necessary as evidence concerning the efficacy of laxatives in this defined patient population was unavailable. In addition, the target patient population for prucalopride had already failed on laxatives and subsequently expressed their dissatisfaction with laxatives
- The probability of adverse events to both prucalopride and standard care are taken from the prucalopride clinical trials. Adverse events are not anticipated as being a major problem for prucalopride given its side-effect profile being similar to that of placebo. Again, as a consequence of the limited clinical trial evidence, the adverse event profile for laxatives was assumed to equate to that of placebo

Additional assumptions were made for the responder model:

- Patients who are prescribed a new medication for treatment of constipation (either prucalopride or laxatives) will have at least 4 weeks of receiving this medication. At the end of this 4-week initial trial, patients who do not respond adequately will be withdrawn from treatment
- Patients who respond to prucalopride at 4 weeks (defined as achieving three or more SCBMs) will remain on prucalopride for an additional 8 weeks. Patients will then be reassessed to determine whether the response identified at 4 weeks has been maintained at 12 weeks. In cases where response has not been maintained at 12 weeks, the patient is defined as a non-responder and withdrawn from treatment with prucalopride

The perspective chosen for the analysis aimed to ensure consistency with evidence-based medicine by ensuring that any assumptions or ‘leaps of faith’ underlying the analysis were kept to a minimum. In all important elements, the data underpinning the economic model

were based on information generated within the clinical trials programme developed for prucalopride. Where assumptions had to be made, the most conservative assumption was chosen.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Quality of life in constipated patients appears to be most affected by the constipation symptomatology, with subjects reporting more severe constipation symptoms also experiencing lower quality of life.

Chronic constipation symptoms include several abdominal-, stool-, and rectal symptoms. Low frequency of bowel movements is only one of the symptoms. Data support that bloating, straining, hard stool, abdominal discomfort, low number of bowel movements and sensation of incomplete evacuation are particularly bothersome (17).

The psychological distress and altered physical functioning associated with chronic constipation symptoms can be substantial (6, 36, 37). For example, the negative impact of constipation in the individual QOL has been observed in long-term survivors of colorectal or anal carcinoma. Constipation symptoms are frequently reported by these patients and are perceived as one of the factors that has the most negative impact on their QOL (38).

The constipation related symptoms severity and their impact on health related quality of life were measured through patient-reported outcomes, utilising the validated PAC-SYM and PAC-QOL questionnaires. The conceptual framework of the PAC instruments is based on the Wilson and Cleary model of health outcomes linking biological and physiological factors with patient-based symptoms, functioning, general health perceptions and overall quality of life (39).

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Patients with long-standing laxative refractory chronic constipation have failed to adequately respond to changes in diet and lifestyle, and will also have failed to achieve adequate relief with laxatives. The quality of life of these patients is impaired by the continous and distressing symptoms they suffer from.

This a small proportion of patients with constipation; these chronic patients have a reduced quality of life as a consequence of their unmet medical need. This can be and was quantified with the PAC-QOL and PAC-SYM questionnaires as used in the prucalopride clinical trials. If left untreated, patients will be maintained with impaired quality of life.

Some patients with severe chronic constipation will develop complications and/or will be admitted under emergency admission with faecal impaction. A small proportion of these severe patients will require surgical intervention as a last resort.

In contrast, a significant body of evidence has been generated in different clinical trials and clinical practice to support the rapid and sustained efficacy of prucalopride in this target population of dissatisfied patients resulting in a demonstrated improvement in HRQL.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (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.

The clinical trials used as the basis for the economic model are presented in Table 53. The related quality of life data collected in the pivotal clinical trials of prucalopride are outlined in the clinical sections. A number of previously validated Quality of life measures were employed (SF-36, PAC-QOL, PAC-SYM) to directly measure HRQOL in the clinical trials of prucalopride. Measurements were undertaken at frequent intervals throughout the trials thus providing numerous data points relating to changes in the comparative QOL being experienced by each patient during the trial period.

Unfortunately EQ-5D data were not collected in the clinical trials and therefore in order to facilitate cost-effectiveness analysis and coincide with the reference case a detailed

mapping exercise was undertaken to link the HRQOL data collected in the trial with EQ-5D. Full details of this mapping exercise are provided in section 6.4.4.

Table 55: Mean utility scores

	Mean scores	SD
Summary of baseline EQ-5D		
PLACEBO	78.003222	10.184318
PRU 1mg	85.104505	6.8157887
PRU 2mg	77.916173	9.7492345
Summary of week4 EQ-5D		
PLACEBO	82.160975	9.0813219
PRU 1mg	87.776692	6.0004481
PRU 2mg	84.056248	8.2969906
Summary of week12 EQ-5D		
PLACEBO	82.152392	9.1466806
PRU 2mg	83.974575	8.4466835

These results are summary estimated EQ-5D scores at each point in time, which are potentially misleading because of baseline differences between the groups.

Regression analysis was used to correct for these imbalances.

Mapping

6.4.4 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.

Mapping was used to transform PAC-QoL and PAC-SYM into EQ-5D via SF36. The process undertaken in the mapping is illustrated in Figure 10.

The approach uses all available data and combines it in a statistical inference to the utility-based measure. The inclusion of additional variables is particularly valuable as the available condition-specific measures are targeted on a limited range of dimensions or severity of therapeutic outcomes which are not adequately reflected in the generic measure. The inclusion of additional variables improves quality and nature of the inference to the generic outcome measure.

Mapping onto generic measures allows different interventions to be evaluated and compared across therapeutic boundaries. For this reason it becomes necessary to translate disease specific outcome measures into generic utility values. The results obtained in the utility analysis emphasise both the quality of life and utility loss being experienced by patients suffering from chronic constipation.

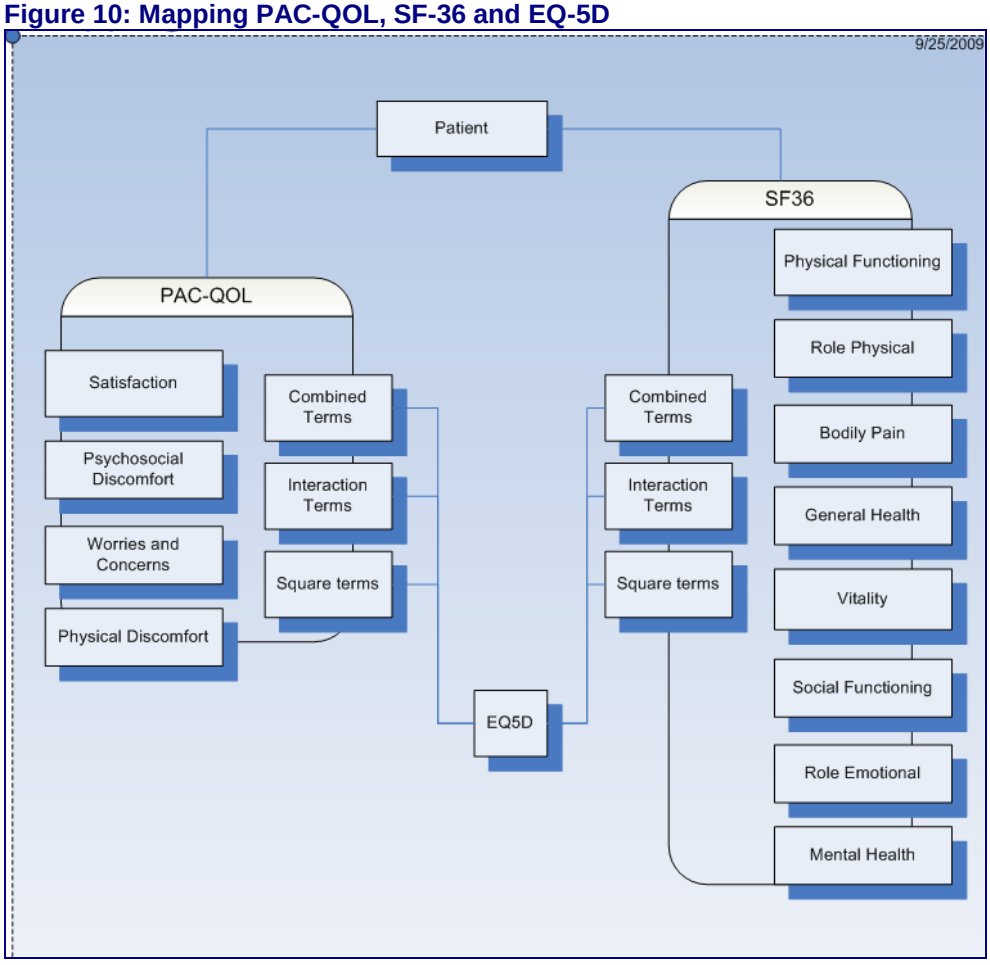
The mapping of PAC-QOL and PAC-SYM to EQ-5D generated a robust and reliable relationship between these measures. For full details of the mapping analysis, please see the manuscript accepted for publication in *Pharmacoeconomics* (Appendix 14:

For example, an estimated equation for deriving EQ-5D from PAC-QOL was:-

EQ-5D = 97.7 – 9.8 (PAC-QOL)

Thus, for every one in four point change in PAC-QOL overall score there is an 9.8/100 change in EQ-5D.This gives a non-preference, non-ordinal comparison between a PAC-QOL score and a QALY as measured by EQ-5D.

Figure 10: Mapping PAC-QOL, SF-36 and EQ-5D



HRQL studies

6.4.5 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 9.12, appendix 12.

A search was undertaken in PubMed in an attempt to identify published EQ-5D utility scores for constipation. A total of 25 citations were identified and reviewed. After reviewing all 25 articles it was found that none provided EQ-5D for the laxative refractory long term chronically constipated target population being addressed by prucalopride. Given that it was not possible to apply EQ-FD utility values identified in the literature to prucalopride data and EQ-5D data were not collected directly in the prucalopride trials it became necessary to 'map' from the SF-36 and PAC quality of life and symptom data to generate the necessary EQ-5D utility scores for inclusion into the economic model.

6.4.6 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.

None of the studies identified reported EQ-5D derived utilities.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not relevant.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

The adverse events associated with the prucalopride treatment arm in the clinical trials were identified as being insignificantly different from the adverse events associated with the placebo arm. Adverse events would be adequately captured by PAC-QOL. For a detailed review of safety data see Section 5.9

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

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

The sample table is not relevant to this analysis. Quality of life was individually determined for each patient analysed in the pooled prucalopride trials. As such, the comparative quality of life being experienced on prucalopride and standard care was directly evaluated for each patient rather than being arbitrarily allocated to broad and discrete patient states. In cases where broad categories (e.g. age 18-65 and 65+) are analysed they are derived from the summary of the individual patient data for relevant patients. Please see section 6.3.6 for discussion of the values included in the model.

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[8]:

- 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

[8] 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 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).

All health related quality of life data were collected directly from patients in the clinical trials of prucalopride and hence resort to expert opinion was not required.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Each patient's experience of chronic constipation will be different in terms of both the range and severity of symptoms suffered and their impact on the patient's health related quality of life. In general the impact on QOL will increase as the severity of symptoms get worse. The target group for prucalopride treatment are the patients with unmet medical needs who are failing to achieve adequate relief with laxatives. Chronic constipation is not a progressive disease, so health related quality of life can be expected to stabilise at a low level.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No relevant health effects were excluded from the analysis.

6.4.13 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?

Baseline health-related quality of life was assumed to be the same profile of that measured and experienced in the clinical trials.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Each patient's experience of chronic constipation will be different in terms of both the range and severity of symptoms suffered and their impact on the patient's health related quality of life. In general the impact on QOL will increase as the severity of symptoms get worse. The target group for prucalopride treatment are the patients with unmet medical needs who are

failing to achieve adequate relief with laxatives. Chronic constipation is not a progressive disease, so health related quality of life can be expected to stabilise at a low level.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Health-related quality of life data used in the development of the model were patient reported outcomes from the prucalopride clinical trials. No changes were made.

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 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.

Chronic constipation is normally managed in primary care. Chronic constipation patients are typically 'revolving door' patients who have suffered from the disorder for more than one decade (average duration of constipation suffered by patients in the prucalopride trials varied from 17.5 to 22 years). Thus, the resource saving associated with normalised bowel movements (≥ 3 SCBM) would be likely to significantly offset the acquisition cost of prucalopride. However given that no resource data had been generated in any of the clinical trials underpinning the economic model two options were available.

Firstly the analysis could generate 'hypothetical' costs to reflect the cost savings that would be likely to arise as a consequence of the use of prucalopride. Alternatively the cost analysis could be restricted simply to address the resource data that is certain-the physical use and acquisition cost of prucalopride. In line with the highly conservative approach adopted in this submission which aims to ensure that as much of the modelling as possible is evidence based and the most conservative or least favourable case is presented, it was decided that the resource analysis should simply include the direct acquisition cost of prucalopride.

Although the additional clinical efficacy of prucalopride will undoubtedly lead to significant ongoing savings in healthcare resources (particularly in laxative use, GP consultations and hospital referrals and possibly reduced rate of complications), the inclusion of a wider set of costs would have introduced an element of uncertainty into the cost estimates. As such, it was decided that any such broader cost estimates should be avoided in the base case analysis.

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Current standard care for patients with chronic constipation who are not adequately treated with laxatives involves referral to secondary care which has an HRG4 tarrif of £164 per visit for a new patient with a follow up fee of £60 per visit. The majority of patients with long-term chronic constipation will also have undergone sigmoidoscopy with a tariff of £410. A smaller proportion will be referred with faecal impaction; tariff for this depends on length of stay. The use of prucalopride in this target population will reduce secondary care referrals and associated tariffs, improving healthcare resource utilisation.

The acquisition costs incorporated into the model reflected the full list price of prucalopride to the NHS. Prucalopride is priced at £2.13 for a 2 mg tablet, equating to £59.52 for a 28 day course. Continuous use of the 2 mg tablet would cost £777 per year. The 1 mg tablet costs £1.38 equating to £38.69 for a 28 day course or £503 for continuous use per year. The long term prucalopride trial data suggests that in real world clinical practice the average duration of use of prucalopride is 220 days per year which would equate to an annual cost of £468 for the 2 mg tablet and £303 for the 1 mg tablet. Current laxative usage varies between 30-150 days (IMS).

Aggregated data from three phase III trials suggest that approximately one third of patients will not satisfactorily respond to enterokinetic therapy and will cease medication after one pack of prucalopride (28 tablets). These patients are expected not to have a bowel motility disorder and other causes should be suspected. A further one third of patients will have a clinically meaningful benefit (as supported by QOL data) and are expected to use the medication for an average 150 days out of 365 (comparable to the group of long term laxative drug users in this indication). In this sub set it is anticipated that patients will not take medication when they are free of symptoms, recommencing their medication only when symptoms return. Approximately one third of patients will experience normalization of disease (primary endpoint in the trials) and are expected to use medication almost continuously (treatment duration in open long term follow-up trials in responders was in excess of 200 days). The high number of days of treatment, in contrast to current laxative usage, is consistent with the conservative and evidenced based approach taken in this application.

Patients, who respond to initial treatment with prucalopride but cease treatment, will respond to medication if restarted.

Changes to lifestyle such as improved diet, increased exercise, and weight loss may result in reduced need for therapy.

Resource identification, measurement and valuation studies

6.5.3 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 9.13, 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.

The only resource cost incorporated into the economic model relates to the (fixed) NHS acquisition cost for the drug. Ideally all resource changes that arise from the introduction of prucalopride should be assessed to identify the net resource cost that would underlie the introduction of prucalopride into the NHS. Unfortunately no resource data were collected in the clinical trials of prucalopride and hence the only resource data available related to the acquisition costs of prucalopride.

However it is unlikely that any additional significant costs would be imposed on the NHS as a consequence of the introduction of prucalopride. The condition is self evident, the selection of prucalopride patients is based upon symptoms/response to laxative treatment and the condition is largely managed in primary care so no new diagnostic/management costs would be incurred. In addition given that the adverse event profile for prucalopride was found in the clinical trials to be insignificantly different from Placebo it is unlikely that any significant additional costs will be imposed on the NHS as a consequence of serious side effects.

As such any additional resource changes that result from the introduction of prucalopride (reduced use of laxatives, reduced primary care consultations and specialist referrals or potentially less hospitalisations for acute constipation) will undoubtedly lead to an improved resource position from the perspective of the NHS.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[9]:

- 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

[9] 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).

No clinical experts were utilised to estimate any of the amounts or values of resources incorporated into the economic model.

Intervention and comparators' costs

6.5.5 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 6.2.2.

Table 56: Unit costs associated with the technology in the economic model

Items	Intervention (confidence interval)	Dose	Cost/ tablet	Annual price (365 days)	Ref. in submission	Comparator 1 (confidence interval)
Technology cost	Acquisition cost of prucalopride	1 mg 2 mg	£1.38 £2.13	£503 £777	6.5.2	N/A
Mean cost of technology treatment	Acquisition cost of prucalopride	(80% compliance) 1 mg annual £402 2 mg annual £622			-	N/A
Administration cost	None				NA	N/A
Monitoring cost	None				NA	N/A
Tests	None				NA	N/A

Health-state costs

6.5.6 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 6.2.4.

There is one health state: being a patient with chronic constipation not adequately treated with laxatives. There are two costs associated with this state: the acquisition cost of either 1mg or 2mg prucalopride (Section 6.5.2).

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. 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 6.2.2.

Not applicable.
The adverse event profile of prucalopride is equivalent to that of placebo and hence no additional serious adverse events associated with prucalopride treatment are anticipated.

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 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.

Yes. The issue is with the reliability of SF-36. The main structural uncertainty exists around the mapping from PAC QoL via SF-36 to EQ-5D. The areas of uncertainty are at the extremes of the SF36 scores. The mapping process accommodated these structural uncertainties via a detailed analysis of factors underlying the quality of this process was undertaken and compared with results obtained from mapping SF-36 to SF-6D using the

Brazier algorithm. Another structural uncertainty is the way the treatment effects were modelled as specified by the patient-level regression analysis. To this end a range of possible mappings and treatment effect specifications were investigated, choosing the most conservative mapping equation (little to no EQ-5D gain for patients relieved from mild chronic constipation) and a range of possible treatment effect models presented.
Four different approaches to deriving EQ-5D treatment effect for patients treated with prucalopride were investigated.

1. 'Responder' was defined as achieving ≥ 3 SCBMs per week with an equation with a baseline constipation-severity-related treatment effect. This means that within this group, variation is allowed for baseline 0-2 SCBMs per week.
2. 'Responder' was defined as achieving an increase of ≥ 1 SCBM per week
3. Leaving out the SCBM-defined variation from the equation (no variation between achieving or not achieving primary endpoint). This pools the effect between responders and non-responders.
4. The above three analyses were repeated using different combinations of the definitions of responder with or without SCBM-defined variation

Having this rigorous assessment showed very little difference between these scenarios; therefore the level of uncertainty is inconsequential. The scenario that best represents clinical practice was chosen for the analysis presented.

6.6.2 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 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

All individual parameters (as listed in section 6.3.6) were tested in the sensitivity analysis. Based on the rationale of an individual patient-level model, variables were more suitable to probabilistic sensitivity analysis than deterministic sensitivity analysis. The specifications used to derive these variables were altered structurally to provide a range of feasible means and distributions.

6.6.3 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 6.3.6, 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).

Yes. As stated above, all parameters, their means and distributions are sourced from individual patient data made available from the clinical trials. No parameters were omitted.

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), 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.

This question is not relevant to the decision problem as chronic constipation is not a progressive disease and is not directly associated with mortality.

6.7.2 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.

Not applicable.

6.7.3 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.

Given that the analysis is based on patient level data the quality of life changes experienced by each patient is individually measured and accrued. These grouped individual experiences are converted based on the mapping of their measured quality of life changes onto EQ-5D. See Figure 10.

6.7.4 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. For example:

The short term variability in the nature of the underlying disease process and the fact that rescue medication was available to bring short term relief complicates the interpretation of the relationship between model outputs and clinical outcomes. As the analysis was undertaken at individual patient level the grouping and aggregating of outcomes as above is inappropriate.

6.7.5 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.

Please see Table 54 in section 6.3.6

Base-case analysis

6.7.6 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.

As there is only a single intervention compared to placebo (equivalent to standard care) the ICERs and CEACs represent a simple comparison between treatment with and without prucalopride.

The SmPC base case is all female patients excluding those who are non-responders by the 4-week stopping rule. This best represents clinical practice and conforms to the recommendations in the SmPC.

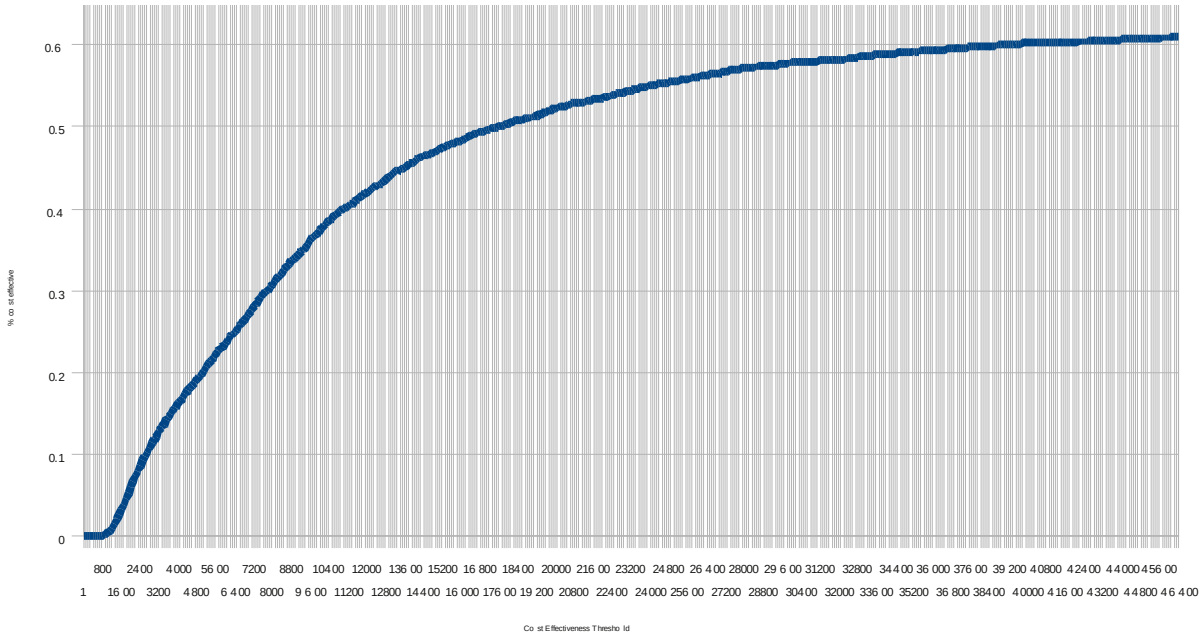
Table 57: Cost and QALY data for SmPC Base Case (treatment compliance 80%)

Treatment	Average incremental cost/year (SD)	Average QALY gained per year (SD)	Average cost/QALY (SD)
Prucalopride	£498.01 (108)	0.0316 (0.1124)	£15,700 (961)
Current standard care	—	—	—

This case is associated with an ICER of £15,700 per QALY; this represents the 50% cumulative probability of prucalopride being cost-effective compared to standard care.

The CEAC graph for base case is Figure 11.

Figure 11: CEAC for all female patients



Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

A tornado analysis was not undertaken as all clinical data were directly obtained from clinical trials and the only cost data utilised in the base case analysis related to the (fixed) acquisition cost of prucalopride. As such very little uncertainty exists relating to the parameter values underpinning the estimates of both costs and benefits.

A range of results are generated depending on the patient group being addressed (female adults [SmPC base case], elderly and combined) and the clinical 4-week stopping decision rule being applied.

It conforms to the SmPC to identify at 4 weeks patients who are non-responders and discontinue treatment with prucalopride. Data for non-responders are therefore not presented here.

A range of options are included in the model; the following are presented here:

- A full (or complete) response is defined as patients who achieve **'normalisation' of bowel function** as defined by the achievement of the primary trial outcome measure of achieving 3 or more SCBMs per week. As this is our 'base case' analysis the results for this patient group are provided below for all patients and separately for adult and elderly patients. Cost/QALY results for this analysis are in Table 58.

Table 58: Cost and QALY data for ≥3 SCBM responders (primary clinical endpoint)

≥3 SCBM responders	Average incremental cost/year (SD)	Average QALY gained per year (SD)	Average cost/QALY (SD)
All females	£498.01 (108)	0.0316 (0.1124)	£15,700 (961)
Adult females	£622.00 (0)	0.0369 (0.0450)	£16,800 (—)
Elderly females	£403 (0)	0.0342 (0.1495)	£11,700 (—)

The CEAC graphs for these groups are in Figure 11, Figure 12 and Figure 13.

Figure 12: CEAC for all adult patients (18-65 years)

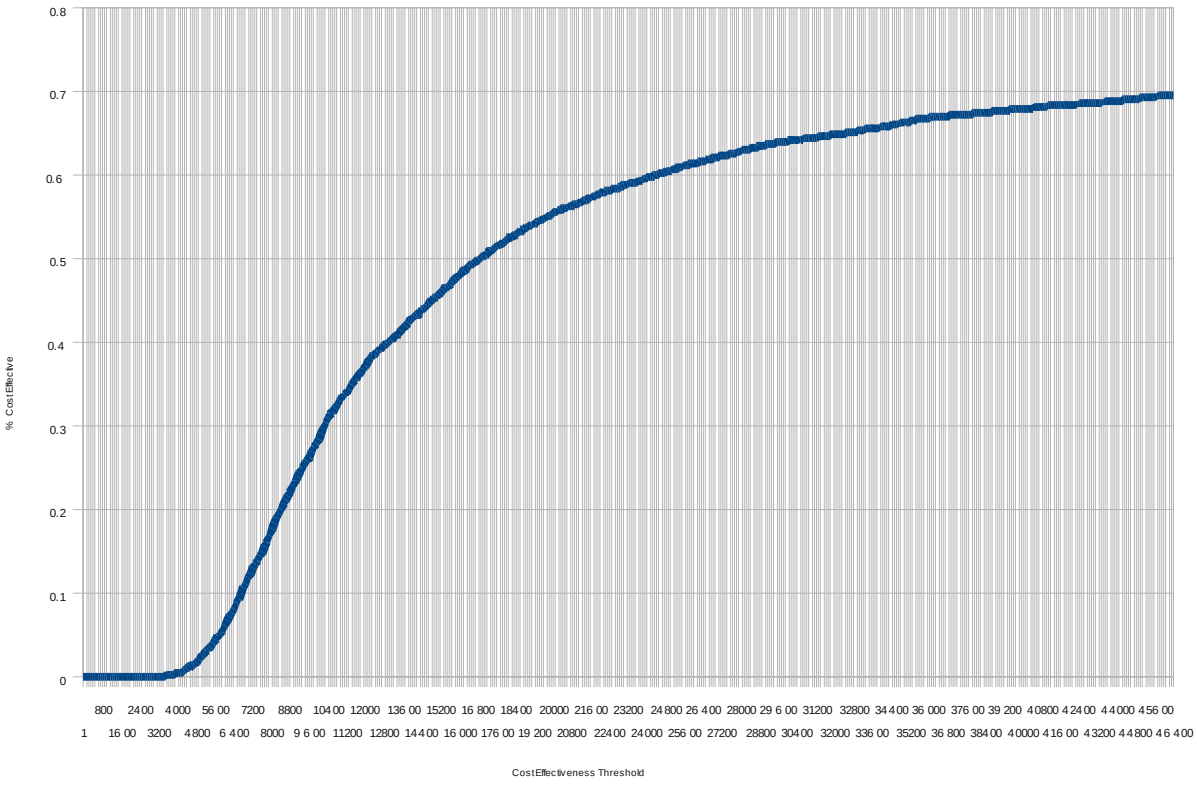
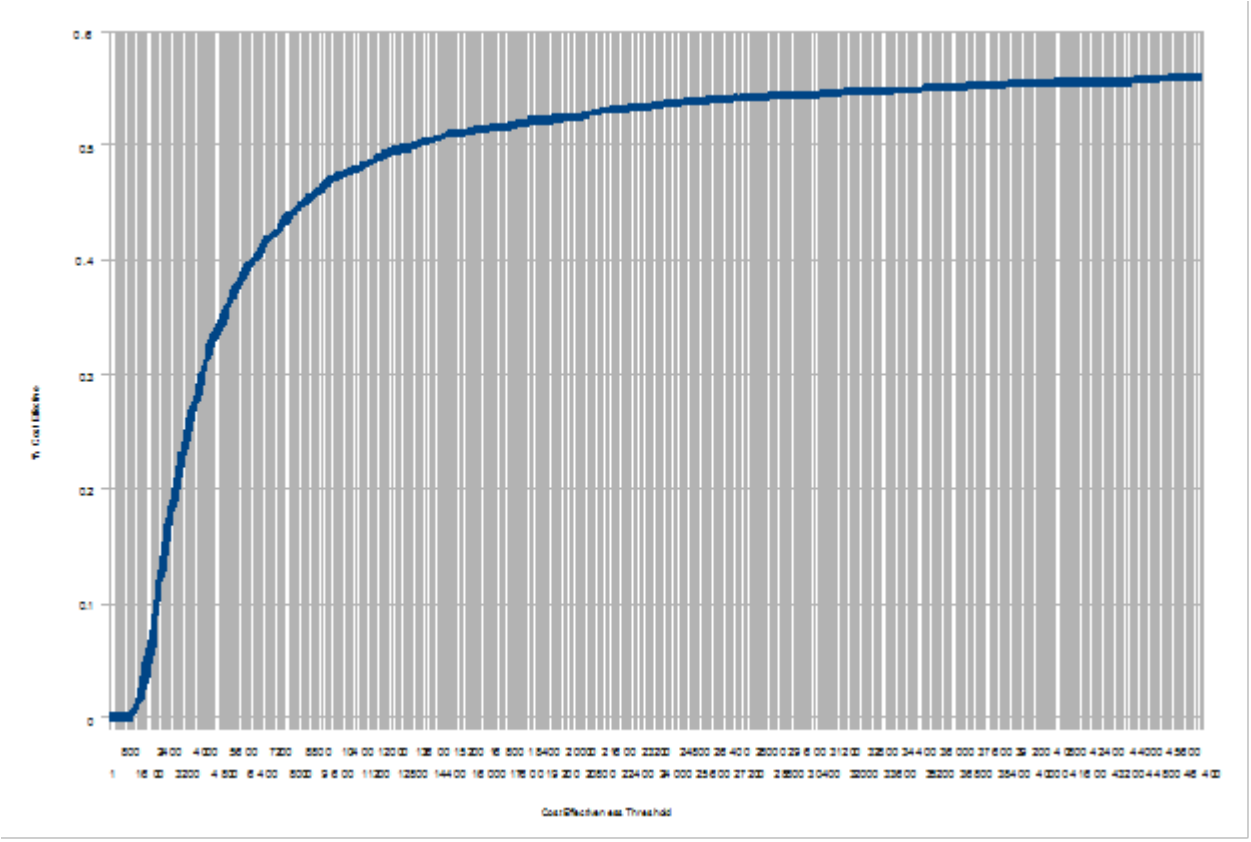


Figure 13: CEAC for elderly patients (>65 years)



- All patients who achieved an additional bowel movement per week were designated as **partial responders** and the cost-effectiveness of treating all such patients was analysed. Analysis of the relationship between PROMs and this partial outcome measure emphasises that patients who achieve an additional SCBM per week also experience significant improvements in PROMs. Cost and QALY data are in Table 59.

Table 59: Cost and QALY data for partial responders (≥1 improvement in SCBM responders = secondary clinical endpoint)

≥1 SCBM responders	Average incremental cost/year (SD)	Average QALY gained per year (SD)	Average cost/QALY (SD)
All females	£498 (108)	0.0277 (0.1133)	£18,000 (934)
Adult females	£622 (0)	0.0342 (0.0430)	£18,000 (—)
Elderly females	£403 (0)	0.0255 (0.1466)	£15,815 (—)

Both of the cases analysed (≥3 and ≥1improvement in SCBMs/week) emphasise the cost-effectiveness of prucalopride in treating patients who are assessed as achieving three or more SCBMs after the initial four weeks of therapy.

The sensitivity/scenario analysis provided below emphasizes the robustness of these baseline analyses and assesses the ICERs in other target patient populations.

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The use of scatter plots was inappropriate as the analysis only addressed two cost variables: the acquisition cost of prucalopride at 1mg and 2mg dosage.

The CEAC graphs for all females, adults and elderly patients are shown above as Figure 11, Figure 12 and Figure 13.

The probabilistic analysis is presented in Table 60.

One of the assumptions made in the model is that treatement effect is dependent on how severe the constipation is at baseline.

At one extreme is the assumption that treatment effect varies depending on baseline severity. Table 60 shows the proportion of patients who are not cost-effectively treated based on this assumption.

Table 60: CEACs for patients achieving ≥3 SCBMs – baseline adjusted

	All females	Adult	Elderly
Prob > 20k/QALY	44.85 %	44.00 %	47.38 %
Prob > 30k/QALY	40.03 %	35.53 %	45.28 %

At the other extreme, if this assumption is changed to assume that treatment effect is the same regardless of baseline severity, then the number of patients who are not cost-effectively treated reduces significantly. This is demonstrated by the low percentages in Table 61 below.

Table 61: CEACs for patients achieving ≥3 SCBMs – without baseline constipation-severity-related treatment effect

	All females	Adult	Elderly
Prob > 20k/QALY	24.80 %	10.45 %	35.95 %
Prob > 30k/QALY	14.73 %	0.30 %	25.35 %

The difference between Table 60 and Table 61 can be explained by the better median EQ-5D score than the average EQ-5D score at baseline. This dilutes treatment effect due to the non-linear nature of the mapping.

6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Results of the following scenarios and structural analyses have been presented above:

- Treatment compliance
- Effect of constipation severity at baseline on treatment effect
- Patient groups by age (all female, adults, elderly patients)
- Mapping PAC-QOL to EQ-5D

6.7.10 What were the main findings of each of the sensitivity analyses?

The main finding of the sensitivity analysis is that all the results are robust.

Prucalopride remains cost-effective in the target population despite the reasonable variations incorporated into the sensitivity analysis (e.g. baseline severity, age, selection of endpoint).

For example, the Cost/QALY for all females (SmPC base case) is £15,700 using the stringent primary endpoint of normalisation (≥ 3 SCBMs/week) and £18,000 using the secondary endpoint of ≥1 improvement in SCBM/week (Table 58 and Table 59).

6.7.11 What are the key drivers of the cost-effectiveness results?

The key drivers of cost-effectiveness are:

- clinical effectiveness of prucalopride
- ability to identify non-responders at a very early stage of treatment
- prucalopride acquisition cost
- robustness of the mapping process

In order to not jeopardise the robustness of the model, healthcare resource use was not captured. This potentially loses valuable health gains and resource savings associated with effective treatment of chronic constipation (e.g. reduction adverse events associated with being chronically constipated, less hospitalisation for impaction, less GP and specialist visits by more satisfied patients etc…). Therefore the cost-effectiveness estimates included here almost certainly represent the most conservative figures.

6.8 Validation

6.8.1 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.

Given the importance of the economic model in evaluating the cost-effectiveness of prucalopride, every effort has been made to ensure the validity of the analysis undertaken and the transparency of the underlying assumptions and methodology.

As there is limited theoretical guidance with regard to ‘good mapping practice; the mapping process undertaken was extensively reviewed by a health economic colleague at the University of Liverpool Management School:Dr Antonieta Medina Lara (Senior Research Fellow). Dr Lara has extensive experience in qualty of life analysis and mapping procedures. The mapping analysis was subsequently adapated in line with suggested improvements from Dr Medina Lara.

The final stage of the quality assurance process related to an external validation process undertaken with Professor John Brazier from SCHARR (University of Sheffield). Professor Brazier has written extensively on mapping and is one of the foremost experts on this topics in the UK. During a 3 hr meeting, the inputs, process and outcomes of the mapping process were discussed in detail with Professor Brazier who expressed his support for the theoretical

and practical approach that underpinned the mapping analysis undertaken. However, Professor Brazier suggested a few comparatively minor improvements which were subsequently incorporated in to the final version of the mapping analysis.

The approach, analysis and results presented here have been peer reviewed and accepted for publication in the journal *Pharmacoeconomics*. Authors of the paper are Mark Parker (ESRC Doctoral Student), Dr Alan Haycox (Reader in Health Economics) and Dr Antonieta Medina Lara. Draft copies of this paper are available as (Appendix 14:)

Design of the economic model focused on keeping the structure as simple as possible, providing a structure which aligned as closely with real world clinical practice as possible. The first step in the process was to identify the effect of treatment upon a patient's quality of life, and how this compared with current practice. One particular issue was the lack of any specific evidence relating to the treatment of chronic constipation. Whilst laxative use is widespread, readily available over the counter and inexpensive, the inclusion criteria for the evaluation of prucalopride defines patients who are both unresponsive to current medication and who have suffered from constipation for longer than six months.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 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 due to known,

biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

The economic model is based on a detailed analysis of individual patient data and hence can be sub-divided to analyse any sub-group of the patient population (ethnicity, age, gender). However, the SmPC basecase analysis presents data for females (the licensed indication), sub-divided between adult patients (2mg) and elderly patients (1mg).

The estimate of the potential numbers of patients that can benefit from prucalopride was again derived from UK data. The overall prevalence of chronic constipation in the UK population has been estimated at 7.7% (average of several European epidemiology papers using the validated Rome criteria) with 10% of patients being refractory to laxatives. Although different publications and IMS data supports that only 60-70 % of patients with chronic constipation will visit their physician in the UK, we have conservatively assumed that all patients are accessible to prucalopride.

Given these assumptions it is estimated that approximately 191,000 female patients could benefit from treatment with prucalopride of which 108,000 of these are expected to be over 65. This greater number of elderly patients occurs due to the increased prevalence of chronic constipation in the elderly female population (20% in comparison to 4.3% in adult female patients).

Race was considered as a subgroup; initial analysis showed there was no difference and there is also no clinical reason to consider this group further.

Males are another possible subgroup but they are not included here because the licensed indication is for females only.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

The patients participating in the prucalopride trials accurately reflect the typical patients that are likely to present in actual clinical practice in the NHS. The patients in the trials were community-based patients who had suffered from chronic constipation for at least six months (and for the majority of patients, considerably longer) and who were ‘dissatisfied’ with laxative treatment. Trials in specific sub-groups of patients with specific needs (e.g. opiate dependent patients) were excluded from the database underlying the model and analysed separately. In addition, given that the EMEA licence is currently restricted to the treatment in females, the base case analysis generated in the economic model is similarly restricted to female patients.

The base case economic model for prucalopride was developed for two separate female patient populations:

- Adult Patients (18-65 years)
- Elderly Patients (65+ years)

For both female populations, in order for patients to be included in the model, they must have had a prior history of treatment with laxatives for at least 6 months and be not

adequately treated by laxatives. The entry criteria for the model therefore entirely coincide with the female populations defined in the licensed indication for prucalopride.

6.9.3 Please describe how the statistical analysis was undertaken.

Probabalistic sensitivity analysis was used to evaluate differences between subgroups.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

The results for the SmPC base case and the adult and elderly patient subgroups are presented in Table 62.

Table 62: Cost and QALY data for ≥3 SCBM responders (primary clinical endpoint)

≥3 SCBM responders	Average incremental cost/year (SD)	Average QALY gained per year (SD)	Average cost/QALY (SD)
All females	£498.01 (108)	0.0316 (0.1124)	£15,700 (961)
Adult females	£622.00 (0)	0.0369 (0.0450)	£16,800 (—)
Elderly females	£403 (0)	0.0342 (0.1495)	£11,700 (—)

6.9.5 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 4.

Please see answer to section 6.9.1.

6.10 Interpretation of economic evidence

6.10.1 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 results for this specific target group (female patients with laxative refractory chronic constipation) mapping to EQ-5D effects were available from the published literature.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Yes.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The economic model developed evaluated the costs and outcomes of using prucalopride in targeted patients with laxative refractory chronic constipation compared to usual care. All aspects of the model kept as closely as possible to the requirements of evidence-based medicine to ensure that it provided a robust and reliable basis for healthcare decision making. Such an aim inherently represents a very conservative approach particularly with regard to the evaluation of the savings in overall healthcare consumption that would be expected to arise through the use of prucalopride in comparison to current resource use in standard care.

Clinical database
The clinical trial data which support the structure of the initial 12 weeks of the model does not necessarily exhibit a high degree of external validity as the results may be affected by the trial setting. However, the robust clinical trial evidence generated in support of prucalopride far exceeds the much more limited evidence supporting the efficacy of laxatives in this target patient group. In this manner, the strength of the clinical trial data generated in support of prucalopride provides a firm evidence base to support the efficacy of prucalopride both in terms of its beneficial impact on physical outcomes (achieving three or more complete and spontaneous bowel movements) and on patient reported outcomes (PAC-QOL and PAC-SYM). The evidence base upon which the 12-week model is extrapolated to a 52-week timeframe is more limited as it is based solely on the observational and open long term data collected in the period following the trials. As such, the longer term data should be interpreted with caution. The number of patients in the prucalopride 1mg arm is a potential weakness compared with the larger numbers in the 2mg arm.

The cost-effectiveness model
A strength of the model is that it is based on individual patient results. The model is discussed further in Section 6.2.2.

Placebo response as comparator
One of the key assumptions underlying the analysis equates to the efficiency of laxatives with placebo response in the clinical trials. Such an assumption requires further examination and justification. Obviously such an assumption would be inappropriate for a less severe patient population suffering from short-term or easily reversible constipation. In such a patient population, laxatives represent an efficacious method of treating less severe acute constipation. However, this assumption would appear to be more appropriate in the context of the specific patient population being targeted by prucalopride. In this specific target population (patients who have suffered long-term chronic constipation and who are laxative refractory), the equating of laxative response with placebo response for both efficacy and side-and side-effects appears to be sustainable. This target population has experience

chronic constipation that has not been relieved by laxatives over a significant period of time and hence equating this lack of efficacy with placebo response would appear to be appropriate. However, should evidence become available that justifies a move away from this assumption then the model is sufficiently flexible to incorporate any additional evidence concerning the impact of laxative use in this patient group.

Comparators
The comparator used in the clinical trials programme which formed the basis for the economic model was placebo supported by bisacodyl (Dulcolax) as rescue medication used over the short term to obtain some patient relief. Given the proven lack of long-term efficacy provided by laxatives to the target population analysed in the prucalopride trials it is argued that currently no effective long term standard of care is currently available for severe chronic constipation.

Other healthcare resources
The clinical uncertainty exhibited by clinicians with regard to identifying effective treatment options for this patient group is evidenced by the wide range of clinical practice provided to this patient group. In particular a broad range of different forms of laxatives are prescribed in a wide variety of dosages and combinations by clinicians engaged in an increasingly fruitless search to identify an effective therapeutic option. Given such uncertainty in therapeutic interventions it becomes difficult to identify in detail the range and nature of treatments that will be displaced by prucalopride in normal clinical practice. A strength of the model is that it does not include additional resources; however this is a potential weakness in the interpretation of the cost effectiveness data.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The quality and size of the clinical trials undertaken in support of prucalopride and the quality of the economic analysis undertaken provides robust evidence concerning the clinical and cost effectiveness of prucalopride in this licensed indication.

Additional analyses could include other healthcare resources and costs.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 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.

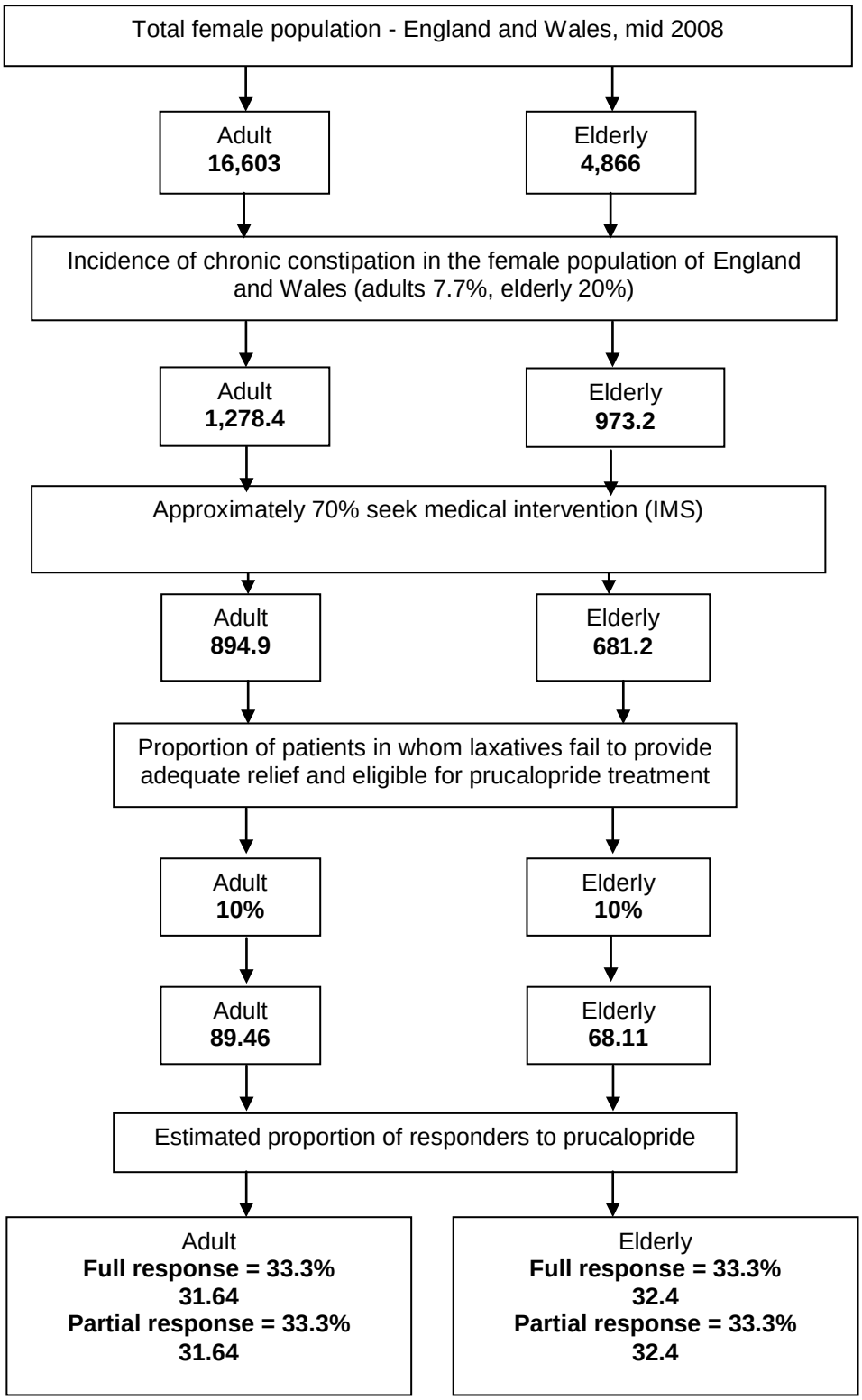
The licensed indication for prucalopride is symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. Obviously there remains significant variation in clinical interpretation of what constitutes 'adequate relief' but the best estimates are provided within this section.

The total female population figures for England and Wales are outlined in Table 63. The estimated adult (18-65) population in England and Wales is 16.6 million and the estimated elderly (65+) population is 4.9 million. Figure 14 defines the patient population that could be eligible for prucalopride treatment.

Table 63: Female population England and Wales (000's) - mid-2008 estimated population (40)

Females (18-65)	Females (65+)
16,603	4,866

Figure 14: Prucalopride patient population estimate (000's)



7.2 What assumption(s) were made about current treatment options and uptake of technologies?

In England and Wales, long term chronic constipation patients who are laxative refractory in the absence of prucalopride receive treatment in primary care. This treatment includes laxative switches and combinations (that have previously been identified as being of limited long term value). All of these patients will at some time be referred to secondary care for second opinion and reinforcement of dietary and lifestyle advice. Secondary care clinicians frequently make tertary referrals of patients with severe chronic constipation to a limited number of specialist centres. A significant proportion of these patients will go on to have many follow-up consultations in secondary care, notwithstanding the fact that prior to prucalopride becoming available the secondary care clinician has no addition medical intervention to offer over and above that available to the patients primary care clinican.

It is common practice for these laxative refractory patients to be investigated with sigmoidoscopy and or colonoscopy, these investigations generally reassure the patient that there is no sinister reason for their chronic constipation, as they do not discover a cause for the chronic constipation. Standard care for patients with chronic constipation includes the use of stimulant rescue laxatives or enemas, elderly patients may require the support of community nurses for these interventions. In some severe chronic constipation the patient will become impacted and will require admitting to hospital for bowel evacuation. *Please see table 56.*

There currently exists a 'stock' of patients who are being largely treated with interventions that provide short term relief but do not address the long term causality underlying the disease. This stock of patients is addressed in the estimated patient population provided. It is unlikely that this 'stock' of patients will vary significantly over the first five years in which prucalopride is made available.

7.3 What assumption(s) were made about market share (when relevant)?

Prucaloride will be the first and initially the only medication in ATC subgroup class (A03AE04) it will have 100% market share in this group, this is meaningless as an estimate of up-take. The rate limiting factor for use of prucalopride will be NHS formulary restrictions.

It is assumed that until clinican experience with prucalopride is widespread prucalopride prescriptions will be initiated by secondary care clinicans only, with the mantence prescriptions being written by GPs. The conservative nature of the majority of GPs and the restriction placed on GPs through formulary based prescribing policy will mean that there will be a slow up-take of prucalopride in the target patient population.

The process of prucalopride achieving formulary listings takes between two and six months per formulary (depending on frequency of drug and therapeutic committee meetings and available agenda slots at these meetings). It is anticpated that the tertary referral centres will be the first hospitals to list prucalopride on formulary, the precedent set by the tertary referral centres will then slowly spread across teaching hospitals and eventually district general hospitals.

Acceptance of prucalopride on to joint hospital / PCT formularies of prucalopride will eventually allow GPs to initiate treatment for patients with chronic constipation this will increase the frequency of prescribing. It is assumed that it will take three years from launch for prucalopride to be listed on 70% of joint formularies, and five years to be listed on all formularies.

7.4 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).

No additional costs are expected to be associated with treatment with prucalopride.

7.5 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 of prucalopride applied in the budget impact estimates are based on the acquisition cost of the drug to the NHS.

7.6 Were there any estimates of resource savings? If so, what were they?

Lack of effective treatments in this patient group leads to significant additional expenditure at both primary and secondary care level in attempts to bring short term relief to patients. The use of prucalopride in patients whose chronic constipation responds to treatment is therefore likely to lead to significant savings in laxative use, primary care consultations and secondary care referrals. A brief examination of some of these resource savings and the evidence supporting them is provided below.

Analysis of the available published literature on healthcare resource use (American data) emphasises the high level of resource use associated with chronic constipation. The most recent analysis estimated the total cost per patient with chronic constipation at $7522 (41) in the context of the American health sector.

Resource data for the UK health system are severely limited. However even a brief overview of the 'map of medicine' (produced by NHS evidence) associated with severe chronic constipation (http://nhsevidence.mapofmedicine.com/evidence/map/constipation5.html) emphasises the potential for significant NHS savings resulting from effective treatment of this patient group. Savings in primary care consultations (a GP consultation in the surgery costs on average £35-PSSRU cost database) and specialist referrals (the day case tariff for a Sigmoidoscopy is £410 - NHS reference cost database) are likely to significantly offset the cost of introducing prucalopride into the NHS.

Payment by Results (PbR) Tariffs

Patients with chronic constipation may be referred into secondary care to undergo a sigmoidoscopy. All procedures within the PbR tariff are grouped into sets of similar procedures known as Healthcare Resource Groups (HRGs).

Sigmoidoscopy falls into the HRG4 code FZ26A "Endoscopic or Intermediate Large Intestine Procedures 19 and over". The planned same day tariff i.e. a day case for a sigmoidoscopy is charged at £410.

After diagnostic tests further care and treatment may be required. The ICD-10 code for "Other impaction of intestine" is K56.4 which will include faecal impaction. ICD-10 code K56.4 in included in the following three HRG4 codes:

FZ35A – General Abdominal Disorders with Major CC
FZ35B – General Abdominal Disorders with Intermediate CC
FZ35C – General Abdominal Disorders without CC

Table 64: National tariffs and other associated NHS costs

HRG Code	HRG Description	Planned same day tariff (£)	Elective spell tariff (£)	Elective spell long stay trimpoint (days)	Non-elective spell tariff (£)	Non-elective long stay trimpoint (days)	Per day long stay payment for days exceeding trimpoint (£)
FZ35A	General Abdominal Disorders with Major CC	491	2,595	16	2,185	19	199
FZ35B	General Abdominal Disorders with Intermediate CC	555	2,004	9	1,392	9	202
FZ35C	General Abdominal Disorders without CC	551	1,619	6	997	5	205
FZ26A	"Endoscopic or Intermediate Large Intestine Procedures	410					
CN301AF	District nursing services: Adult: Face to Face	38					
301m	Referrals to secondary care first referral	168					
301m	Referrals to secondary care follow-up referral	51					

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table 65 estimates, based on the manufacturers market forecast, the anticipated budget impact of introducing prucalopride use in England and Wales over a 5-year period. The budget impact estimate is based on the acquisition cost at current NHS tariff price of prucalopride.

The cost per day of prucalopride for adults (2 mg) is £2.13 and for the elderly (1 mg) £1.38)

Table 65: Cumulative budget impact over 5 years (£000)

Year	All Female
2010	£2,002
2011	£5,421
2012	£7,047
2013	£9,161
2014	£11,909

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

As discussed in detail in this submission it is likely that a wide range of opportunities for significant resource savings are likely to arise enabling redirection of resources both at the primary and secondary care level. In particular a large number of laxative refractory patients are likely to be kept out of GPs as prucalopride will prove to be an effective resolution.

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9 Appendices

9.1 Appendix 1 – Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Resolor 1 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg prucalopride (as prucalopride succinate).

Excipients: Each film-coated tablet contains 150 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

White to off-white, round, biconvex tablets marked “PRU 1” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Resolor is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.

4.2 Posology and method of administration

Posology

Adults: 2 mg once daily.

Elderly (>65 years): Start with one 1 mg once daily (see section 5.2); if needed the dose can be increased to 2 mg once daily.

Children and adolescents: Resolor is not recommended in children and adolescents younger than 18 years until further data become available. Currently available data are described in section 5.2.

Patients with renal impairment: The dose for patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2) is 1 mg once daily (see sections 4.3 and 5.2). No dose adjustment is required for patients with mild to moderate renal impairment.

Patients with hepatic impairment: The dose for patients with severe hepatic impairment (Child-Pugh class C) is 1 mg once daily (see sections 4.4 and 5.2). No dose adjustment is required for patients with mild to moderate hepatic impairment.

Due to the specific mode of action of prucalopride (stimulation of propulsive motility) exceeding the daily dose of 2 mg is not expected to increase efficacy.
If the intake of once daily prucalopride is not effective after 4 weeks of treatment, the patient should be re-examined and the benefit of continuing treatment reconsidered.

The efficacy of prucalopride has been established in double blind placebo controlled studies for up to 3 months. In case of prolonged treatment the benefit should be reassessed at regular intervals.

Method of administration
Resolor film-coated tablets are for oral use and can be taken with or without food, at any time of the day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Renal impairment requiring dialysis.
- Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease, and ulcerative colitis and toxic megacolon/megarectum.

4.4 Special warnings and precautions for use

Renal excretion is the main route of elimination of prucalopride (see section 5.2). A dose of 1 mg is recommended in subjects with severe renal impairment (see section 4.2).

Patients with severe and clinically unstable concomitant disease (e.g. liver, cardiovascular or lung disease, neurological or psychiatric disorders, cancer or AIDS and other endocrine disorders) have not been studied. Caution should be exercised when prescribing Resolor to patients with these conditions. In particular Resolor should be used with caution in patients with a history of arrhythmias or ischaemic cardiovascular disease.

In case of severe diarrhoea, the efficacy of oral contraceptives may be reduced and the use of an additional contraceptive method is recommended to prevent possible failure of oral contraception (see the prescribing information of the oral contraceptive).

It is unlikely that hepatic impairment will affect prucalopride metabolism and exposure in man to a clinically relevant extent. No data are available in patients with mild, moderate or severe hepatic impairment, and therefore a lower dose is recommended for patients with severe hepatic impairment (see section 4.2).

The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption must not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that prucalopride has a low interaction potential, and therapeutic concentrations of prucalopride are not expected to affect the CYP-mediated metabolism of co-medicated medicinal products. Although prucalopride may be a weak substrate for P-glycoprotein (P-gp), it is not an inhibitor of P-gp at clinically relevant concentrations.

Ketoconazole (200 mg b.i.d.), a potent inhibitor of CYP3A4 and of P-gp, increased the area under the curve (AUC) of prucalopride by approximately 40%. This effect is too small to be clinically relevant and is likely attributable to inhibition of P-gp mediated renal transport. Interactions of similar magnitude as observed with ketoconazole may also occur with other potent inhibitors of P-gp such as verapamil, cyclosporine A and quinidine. Prucalopride is likely also secreted via another renal transporter(s). Inhibition of all transporters involved in the active secretion of prucalopride (including P-gp) may theoretically increase the exposure by up to 75%.

Studies in healthy subjects showed that there were no clinically relevant effects of prucalopride on the pharmacokinetics of warfarin, digoxin, alcohol and paroxetine. A 30% increase in the plasma concentrations of erythromycin was found during prucalopride co-treatment. The mechanism for this interaction is not fully known, but the available data support that this is the consequence of the high intrinsic variability in erythromycin kinetics, rather than a direct effect of prucalopride.

Therapeutic doses of probenecid, cimetidine, erythromycin and paroxetine did not affect the pharmacokinetics of prucalopride.

Resolor should be used with caution in patients receiving concomitant drugs known to cause QTc prolongation.

Because of the mechanism of action, the use of atropine-like substances may reduce the 5-HT_4 receptor mediated effects of prucalopride.

Interactions with food have not been observed.

4.6 Pregnancy and lactation

Pregnancy

Experience with prucalopride during pregnancy is limited. Cases of spontaneous abortion have been observed during clinical studies, although, in the presence of other risk factors, the relationship to prucalopride is unknown. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Resolor is not

recommended during pregnancy. Women of childbearing potential should use effective contraception during treatment with prucalopride.

Lactation

Prucalopride is excreted in breast milk. However, at therapeutic doses of Resolor no effects on the breastfed newborns/infants are anticipated. In the absence of human data, it is not recommended to use Resolor during breast-feeding.

Fertility

Animal studies indicate that there is no effect on male or female fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of prucalopride on the ability to drive and use machines have been performed. Resolor has been associated with dizziness and fatigue particularly during the first day of treatment which may have an effect on driving and using machines (see section 4.8).

4.8 Undesirable effects

Resolor has been given orally to approximately 2,700 patients with chronic constipation in controlled clinical studies. Of these patients, almost 1,000 patients received Resolor at the recommended dose of 2 mg per day, while about 1,300 patients were treated with 4 mg prucalopride daily. Total exposure in the clinical development plan exceeded 2,600 patient years. The most frequently reported adverse reactions associated with Resolor therapy are headache and gastrointestinal symptoms (abdominal pain, nausea or diarrhoea) occurring in approximately 20% of patients each. The adverse reactions occur predominantly at the start of therapy and usually disappear within a few days with continued treatment. Other adverse reactions have been reported occasionally. The majority of adverse events were mild to moderate in intensity.

The following adverse reactions were reported in controlled clinical studies at the recommended dose of 2 mg with frequencies corresponding to Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (> 1/1,000 to < 1/100), Rare (> 1/10,000 to < 1/1,000) and Very rare (≤ 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are calculated based on the placebo-controlled clinical study data.

Metabolism and nutrition disorders
Uncommon: anorexia

Nervous system disorders
Very common: headache
Common: dizziness
Uncommon: tremors

Cardiac disorders
Uncommon: palpitations

Gastrointestinal disorders
Very common: nausea, diarrhoea, abdominal pain
Common: vomiting, dyspepsia, rectal haemorrhage, flatulence, abnormal bowel sounds

Renal and urinary disorders
Common: pollakiuria

General disorders and administration site conditions
Common: fatigue
Uncommon: fever, malaise

After the first day of treatment, the most common adverse reactions were reported in similar frequencies (incidence less than 1% different between prucalopride and placebo) during Resolor therapy as during placebo, with the exception of nausea and diarrhoea that still occurred more frequently during Resolor therapy, but less pronounced (difference in incidence between prucalopride and placebo between 1 and 3%).

Palpitations were reported in 0.7% of the placebo patients, 1.0% of the 1 mg prucalopride patients, 0.7% of the 2 mg prucalopride patients and 1.9% of the 4 mg prucalopride patients. The majority of patients continued using prucalopride. As with any new symptom, patients should discuss the new onset of palpitations with their physician.

4.9 Overdose

In a study in healthy volunteers treatment with prucalopride was well tolerated when given in an up-titrating scheme up to 20 mg once daily (10 times the recommended therapeutic dose). An overdose may result in symptoms resulting from an exaggeration of the medicinal product’s known pharmacodynamic effects and include headache, nausea and diarrhoea. Specific treatment is not available for Resolor overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Extensive fluid loss by diarrhoea or vomiting may require correction of electrolyte disturbances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs acting on serotonin receptors, ATC code: A03AE04.

Mechanism of action
Prucalopride is a dihydrobenzofurancarboxamide with enterokinetic activities. Prucalopride is a selective, high affinity serotonin (5-HT_4) receptor agonist, which is likely to explain its enterokinetic effects. *In vitro*, only at concentrations exceeding its 5-HT_4 receptor affinity by at least 150-fold, affinity for other receptors was detected. In rats prucalopride *in vivo* at doses above 5 mg/kg (at and above 30-70 times the clinical exposure) induced hyperprolactinaemia caused by an antagonistic action at the D2 receptor.

In dogs, prucalopride alters colonic motility patterns via serotonin 5-HT_4 receptor stimulation: it stimulates proximal colonic motility, enhances gastroduodenal motility and accelerates delayed gastric emptying. Furthermore, giant migrating contractions are induced by prucalopride. These are equivalent to the colonic mass movements in humans, and provide the main propulsive force to defecation. In dogs, the effects observed in the gastrointestinal tract are sensitive to blockade with selective 5-HT_4 receptor antagonists illustrating that the observed effects are exerted via selective action on 5-HT_4 receptors.

Clinical experience
The efficacy of prucalopride was established in three multicentre, randomised, double-blind, 12-week placebo-controlled studies in subjects with chronic constipation (n=1,279 on prucalopride, 1,124 females, 155 males). The prucalopride doses studied in each of these three studies included 2 mg and 4 mg once daily. The primary efficacy endpoint was the proportion (%) of subjects that reached normalisation of bowel movements defined as an average of three or more spontaneous, complete bowel movements (SCBM) per week over the 12-week treatment period. Both doses were statistically superior ($p<0.001$) to placebo at the primary endpoint in each of the three studies, with no incremental benefit of the 4 mg over the 2 mg dose. The proportion of patients treated with the recommended dose of 2 mg prucalopride that reached an average of ≥ 3 SCBM per week was 27.8% (week 4) and 23.6% (week 12), versus 10.5% (week 4) and 11.3% (week 12) on placebo. A clinically meaningful improvement of ≥ 1 SCBM per week, the most important secondary efficacy endpoint, was achieved in 48.1% (week 4) and 43.1% (week 12) of patients treated with 2 mg prucalopride versus 23.4% (week 4) and 24.6% (week 12) of placebo patients.

In all three studies, treatment with prucalopride also resulted in significant improvements in a validated and disease specific set of symptom measures (PAC SYM), including abdominal, stool and rectal symptoms, determined at week 4 and week 12. A significant benefit on a number of Quality of Life measures, such as degree of satisfaction with treatment and with bowel habits, physical and

psychosocial discomfort and worries and concerns, was also observed at both the 4 and 12 week assessment time points.

Prucalopride has been shown not to cause rebound phenomena, nor to induce dependency.

A thorough QT study was performed to evaluate the effects of prucalopride on the QT interval at therapeutic (2 mg) and supratherapeutic doses (10 mg) and compared with the effects of placebo and a positive control. This study did not show significant differences between prucalopride and placebo at either dose, based on mean QT measurements and outlier analysis. This confirmed the results of two placebo controlled QT studies. In double blind clinical studies, the incidence of QT-related adverse events and ventricular arrhythmias was low and comparable to placebo.

Data from open label studies up to 2.6 years offer some evidence for longer-term safety and efficacy; however, no placebo controlled efficacy data for treatments longer than 12 weeks duration are available.

5.2 Pharmacokinetic properties

Absorption
Prucalopride is rapidly absorbed; after a single oral dose of 2 mg C_{max} was attained in 2-3 hours. The absolute oral bioavailability is >90%. Concomitant intake of food does not influence the oral bioavailability of prucalopride.

Distribution
Prucalopride is extensively distributed, and has a steady-state volume of distribution (Vd_{ss}) of 567 litre. The plasma protein binding of prucalopride is about 30%.

Metabolism
Metabolism is not the major route of elimination of prucalopride. *In vitro*, human liver metabolism is very slow and only minor amounts of metabolites are found. In an oral dose study with radiolabelled prucalopride in man small amounts of eight metabolites were recovered in urine and faeces. The major metabolite (R107504, formed by O-demethylation and oxidation of the resulting alcohol function to a carboxylic acid) accounted for less than 4% of the dose. Unchanged active substance made up about 85% of the total radioactivity in plasma and only R107504 was a minor plasma metabolite.

Elimination
A large fraction of the active substance is excreted unchanged (about 60% of the administered dose in urine and at least 6% in faeces). Renal excretion of unchanged prucalopride involves both passive filtration and active secretion. The plasma clearance of prucalopride averages 317 ml/min. Its terminal half-life is about one day. Steady-state is reached within three to four days. On once daily treatment with 2 mg prucalopride steady-state plasma concentrations fluctuate between trough and peak values of 2.5 and 7 ng/ml, respectively. The accumulation ratio after once daily dosing ranged from 1.9 to 2.3. The pharmacokinetics of prucalopride is dose-

proportional within and beyond the therapeutic range (tested up to 20 mg). Prucalopride o.d. displays time-independent kinetics during prolonged treatment.

Special populations

Population pharmacokinetics

A population pharmacokinetic analysis showed that the apparent total clearance of prucalopride was correlated with creatinine clearance, but that age, body weight, sex or race had no influence.

Elderly

After once daily dosing of 1 mg, peak plasma concentrations and AUC of prucalopride in elderly subjects were 26% to 28% higher than in young adults. This effect can be attributed to a diminished renal function in elderly.

Renal impairment

Compared to subjects with normal renal function, plasma concentrations of prucalopride after a single 2 mg dose were on average 25% and 51% higher in subjects with mild (Cl_{CR} 50-79 ml/min) and moderate (Cl_{CR} 25-49 ml/min) renal impairment, respectively. In subjects with severe renal impairment (Cl_{CR} ≤ 24 ml/min), plasma concentrations were 2.3 times the levels in healthy subjects (see section 4.2 and 4.4).

Hepatic impairment

Non-renal elimination contributes to about 35% of total elimination, and hepatic impairment is unlikely to affect the pharmacokinetics of prucalopride to a clinically relevant extent (see section 4.2 and 4.4).

Paediatric population

After a single oral dose of 0.03 mg/kg in paediatric patients aged between 4 and 12 years, C_{max} of prucalopride was comparable to the C_{max} in adults after a single 2 mg dose, while unbound AUC was 30-40% lower than after 2 mg in adults. Unbound exposure was similar over the whole age-range (4-12 years).The average terminal half life in the paediatric subjects was about 19 hours (range 11.6 to 26.8 hours) (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. An extended series of safety pharmacology studies with special emphasis on cardiovascular parameters showed no relevant changes in haemodynamic and ECG derived parameters (QTc) with the exception of a modest increase in heart rate and blood pressure observed in anaesthesized pigs after intravenous administration, and an increase in blood pressure in conscious dogs after bolus intravenous administration, which was not observed either in anaesthetized dogs or after oral administration in dogs reaching similar plasma levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate

Coating
Hypromellose
Lactose monohydrate
Triacetin
Titanium dioxide (E171)
Macrogol 3000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original blister in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/aluminium perforated unit dose blisters (calendar marked) containing 7 tablets. Each pack contains 28 x 1 film-coated tablet.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Movetis NV
Veedijk 58
B-2300 Turnhout
Belgium
E-mail: info@movetis.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/581/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/10/09

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Resolor 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2 mg prucalopride (as prucalopride succinate).

Excipients: Each film-coated tablet contains 165 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pink, round, biconvex tablets marked “PRU 2” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Resolor is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.

4.2 Posology and method of administration

Posology

Adults: 2 mg once daily.

Elderly (>65 years): Start with one 1 mg once daily (see section 5.2); if needed the dose can be increased to 2 mg once daily.

Children and adolescents: Resolor is not recommended in children and adolescents younger than 18 years until further data become available. Currently available data are described in section 5.2.

Patients with renal impairment: The dose for patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2) is 1 mg once daily (see sections 4.3 and 5.2). No dose adjustment is required for patients with mild to moderate renal impairment.

Patients with hepatic impairment: The dose for patients with severe hepatic impairment (Child-Pugh class C) is 1 mg once daily (see sections 4.4 and 5.2). No dose adjustment is required for patients with mild to moderate hepatic impairment.

Due to the specific mode of action of prucalopride (stimulation of propulsive motility) exceeding the daily dose of 2 mg is not expected to increase efficacy.
If the intake of once daily prucalopride is not effective after 4 weeks of treatment, the patient should be re-examined and the benefit of continuing treatment reconsidered.

The efficacy of prucalopride has been established in double blind placebo controlled studies for up to 3 months. In case of prolonged treatment the benefit should be reassessed at regular intervals.

Method of administration
Resolor film-coated tablets are for oral use and can be taken with or without food, at any time of the day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Renal impairment requiring dialysis.
- Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease, and ulcerative colitis and toxic megacolon/megarectum.

4.4 Special warnings and precautions for use

Renal excretion is the main route of elimination of prucalopride (see section 5.2). A dose of 1 mg is recommended in subjects with severe renal impairment (see section 4.2).

Patients with severe and clinically unstable concomitant disease (e.g. liver, cardiovascular or lung disease, neurological or psychiatric disorders, cancer or AIDS and other endocrine disorders) have not been studied. Caution should be exercised when prescribing Resolor to patients with these conditions. In particular Resolor should be used with caution in patients with a history of arrhythmias or ischaemic cardiovascular disease.

In case of severe diarrhoea, the efficacy of oral contraceptives may be reduced and the use of an additional contraceptive method is recommended to prevent possible failure of oral contraception (see the prescribing information of the oral contraceptive).

It is unlikely that hepatic impairment will affect prucalopride metabolism and exposure in man to a clinically relevant extent. No data are available in patients with mild, moderate or severe hepatic impairment, and therefore a lower dose is recommended for patients with severe hepatic impairment (see section 4.2).

The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption must not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that prucalopride has a low interaction potential, and therapeutic concentrations of prucalopride are not expected to affect the CYP-mediated metabolism of co-medicated medicinal products. Although prucalopride may be a weak substrate for P-glycoprotein (P-gp), it is not an inhibitor of P-gp at clinically relevant concentrations.

Ketoconazole (200 mg b.i.d.), a potent inhibitor of CYP3A4 and of P-gp, increased the area under the curve (AUC) of prucalopride by approximately 40%. This effect is too small to be clinically relevant and is likely attributable to inhibition of P-gp mediated renal transport. Interactions of similar magnitude as observed with ketoconazole may also occur with other potent inhibitors of P-gp such as verapamil, cyclosporine A and quinidine. Prucalopride is likely also secreted via another renal transporter(s). Inhibition of all transporters involved in the active secretion of prucalopride (including P-gp) may theoretically increase the exposure by up to 75%.

Studies in healthy subjects showed that there were no clinically relevant effects of prucalopride on the pharmacokinetics of warfarin, digoxin, alcohol and paroxetine. A 30% increase in the plasma concentrations of erythromycin was found during prucalopride co-treatment. The mechanism for this interaction is not fully known, but the available data support that this is the consequence of the high intrinsic variability in erythromycin kinetics, rather than a direct effect of prucalopride.

Therapeutic doses of probenecid, cimetidine, erythromycin and paroxetine did not affect the pharmacokinetics of prucalopride.

Resolor should be used with caution in patients receiving concomitant drugs known to cause QTc prolongation.

Because of the mechanism of action, the use of atropine-like substances may reduce the 5-HT_4 receptor mediated effects of prucalopride.

Interactions with food have not been observed.

4.6 Pregnancy and lactation

Pregnancy

Experience with prucalopride during pregnancy is limited. Cases of spontaneous abortion have been observed during clinical studies, although, in the presence of other risk factors, the relationship to prucalopride is unknown. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Resolor is not recommended during pregnancy. Women of childbearing potential should use effective contraception during treatment with prucalopride.

Lactation

Prucalopride is excreted in breast milk. However, at therapeutic doses of Resolor no effects on the breastfed newborns/infants are anticipated. In the absence of human data, it is not recommended to use Resolor during breast-feeding.

Fertility

Animal studies indicate that there is no effect on male or female fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of prucalopride on the ability to drive and use machines have been performed. Resolor has been associated with dizziness and fatigue particularly during the first day of treatment which may have an effect on driving and using machines (see section 4.8).

4.8 Undesirable effects

Resolor has been given orally to approximately 2,700 patients with chronic constipation in controlled clinical studies. Of these patients, almost 1,000 patients received Resolor at the recommended dose of 2 mg per day, while about 1,300 patients were treated with 4 mg prucalopride daily. Total exposure in the clinical development plan exceeded 2,600 patient years. The most frequently reported adverse reactions associated with Resolor therapy are headache and gastrointestinal symptoms (abdominal pain, nausea or diarrhoea) occurring in approximately 20% of patients each. The adverse reactions occur predominantly at the start of therapy and usually disappear within a few days with continued treatment. Other adverse reactions have been reported occasionally. The majority of adverse events were mild to moderate in intensity.

The following adverse reactions were reported in controlled clinical studies at the recommended dose of 2 mg with frequencies corresponding to Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (> 1/1,000 to < 1/100), Rare (> 1/10,000 to < 1/1,000) and Very rare (≤ 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are calculated based on the placebo-controlled clinical study data.

Metabolism and nutrition disorders
Uncommon: anorexia

Nervous system disorders
Very common: headache
Common: dizziness
Uncommon: tremors

Cardiac disorders
Uncommon: palpitations

Gastrointestinal disorders
Very common: nausea, diarrhoea, abdominal pain
Common: vomiting, dyspepsia, rectal haemorrhage, flatulence, abnormal bowel sounds

Renal and urinary disorders
Common: pollakiuria
General disorders and administration site conditions

Common: fatigue
Uncommon: fever, malaise

After the first day of treatment, the most common adverse reactions were reported in similar frequencies (incidence less than 1% different between prucalopride and placebo) during Resolor therapy as during placebo, with the exception of nausea and diarrhoea that still occurred more frequently during Resolor therapy, but less pronounced (difference in incidence between prucalopride and placebo between 1 and 3%).

Palpitations were reported in 0.7% of the placebo patients, 1.0% of the 1 mg prucalopride patients, 0.7% of the 2 mg prucalopride patients and 1.9% of the 4 mg prucalopride patients. The majority of patients continued using prucalopride. As with any new symptom, patients should discuss the new onset of palpitations with their physician.

4.9 Overdose

In a study in healthy volunteers treatment with prucalopride was well tolerated when given in an up-titrating scheme up to 20 mg once daily (10 times the recommended therapeutic dose). An overdose may result in symptoms resulting from an exaggeration of the medicinal product’s known pharmacodynamic effects and include headache, nausea and diarrhoea. Specific treatment is not available for Resolor overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Extensive fluid loss by diarrhoea or vomiting may require correction of electrolyte disturbances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs acting on serotonin receptors, ATC code: A03AE04.

Mechanism of action
Prucalopride is a dihydrobenzofurancarboxamide with enterokinetic activities. Prucalopride is a selective, high affinity serotonin (5-HT_4) receptor agonist, which is likely to explain its enterokinetic effects. *In vitro*, only at concentrations exceeding its 5-HT_4 receptor affinity by at least 150-fold, affinity for other receptors was detected. In rats prucalopride *in vivo* at doses above 5 mg/kg (at and above 30-70 times the clinical exposure) induced hyperprolactinaemia caused by an antagonistic action at the D2 receptor.

In dogs, prucalopride alters colonic motility patterns via serotonin 5-HT_4 receptor stimulation: it stimulates proximal colonic motility, enhances gastroduodenal motility and accelerates delayed gastric emptying. Furthermore, giant migrating contractions are induced by prucalopride. These are equivalent to the colonic mass movements in humans, and provide the main propulsive force to defecation. In dogs, the effects observed in the gastrointestinal tract are sensitive to blockade with selective 5-HT_4 receptor antagonists illustrating that the observed effects are exerted via selective action on 5-HT_4 receptors.

Clinical experience
The efficacy of prucalopride was established in three multicentre, randomised, double-blind, 12-week placebo-controlled studies in subjects with chronic constipation (n=1,279 on prucalopride, 1,124 females, 155 males). The prucalopride doses studied in each of these three studies included 2 mg and 4 mg once daily. The primary efficacy endpoint was the proportion (%) of subjects that reached normalisation of bowel movements defined as an average of three or more spontaneous, complete bowel movements (SCBM) per week over the 12-week treatment period. Both doses were statistically superior ($p<0.001$) to placebo at the primary endpoint in each of the three studies, with no incremental benefit of the 4 mg over the 2 mg dose. The proportion of patients treated with the recommended dose of 2 mg prucalopride that reached an average of ≥ 3 SCBM per week was 27.8% (week 4) and 23.6% (week 12), versus 10.5% (week 4) and 11.3% (week 12) on placebo. A clinically meaningful improvement of ≥ 1 SCBM per week, the most important secondary efficacy endpoint, was achieved in 48.1% (week 4) and 43.1% (week 12) of patients treated with 2 mg prucalopride versus 23.4% (week 4) and 24.6% (week 12) of placebo patients.

In all three studies, treatment with prucalopride also resulted in significant improvements in a validated and disease specific set of symptom measures (PAC SYM), including abdominal, stool and rectal symptoms, determined at week 4 and week 12. A significant benefit on a number of Quality of Life measures, such as degree of satisfaction with treatment and with bowel habits, physical and

psychosocial discomfort and worries and concerns, was also observed at both the 4 and 12 week assessment time points.

Prucalopride has been shown not to cause rebound phenomena, nor to induce dependency.

A thorough QT study was performed to evaluate the effects of prucalopride on the QT interval at therapeutic (2 mg) and supratherapeutic doses (10 mg) and compared with the effects of placebo and a positive control. This study did not show significant differences between prucalopride and placebo at either dose, based on mean QT measurements and outlier analysis. This confirmed the results of two placebo controlled QT studies. In double blind clinical studies, the incidence of QT-related adverse events and ventricular arrhythmias was low and comparable to placebo.

Data from open label studies up to 2.6 years offer some evidence for longer-term safety and efficacy; however, no placebo controlled efficacy data for treatments longer than 12 weeks duration are available.

5.2 Pharmacokinetic properties

Absorption
Prucalopride is rapidly absorbed; after a single oral dose of 2 mg C_{max} was attained in 2-3 hours. The absolute oral bioavailability is >90%. Concomitant intake of food does not influence the oral bioavailability of prucalopride.

Distribution
Prucalopride is extensively distributed, and has a steady-state volume of distribution (Vd_{ss}) of 567 litre. The plasma protein binding of prucalopride is about 30%.

Metabolism
Metabolism is not the major route of elimination of prucalopride. *In vitro*, human liver metabolism is very slow and only minor amounts of metabolites are found. In an oral dose study with radiolabelled prucalopride in man small amounts of eight metabolites were recovered in urine and faeces. The major metabolite (R107504, formed by O-demethylation and oxidation of the resulting alcohol function to a carboxylic acid) accounted for less than 4% of the dose. Unchanged active substance made up about 85% of the total radioactivity in plasma and only R107504 was a minor plasma metabolite.

Elimination
A large fraction of the active substance is excreted unchanged (about 60% of the administered dose in urine and at least 6% in faeces). Renal excretion of unchanged prucalopride involves both passive filtration and active secretion. The plasma clearance of prucalopride averages 317 ml/min. Its terminal half-life is about one day. Steady-state is reached within three to four days. On once daily treatment with 2 mg prucalopride steady-state plasma concentrations fluctuate between trough and peak values of 2.5 and 7 ng/ml, respectively. The accumulation ratio after once daily dosing ranged from 1.9 to 2.3. The pharmacokinetics of prucalopride is dose-

proportional within and beyond the therapeutic range (tested up to 20 mg). Prucalopride o.d. displays time-independent kinetics during prolonged treatment.

Special populations

Population pharmacokinetics

A population pharmacokinetic analysis showed that the apparent total clearance of prucalopride was correlated with creatinine clearance, but that age, body weight, sex or race had no influence.

Elderly

After once daily dosing of 1 mg, peak plasma concentrations and AUC of prucalopride in elderly subjects were 26% to 28% higher than in young adults. This effect can be attributed to a diminished renal function in elderly.

Renal impairment

Compared to subjects with normal renal function, plasma concentrations of prucalopride after a single 2 mg dose were on average 25% and 51% higher in subjects with mild (Cl_{CR} 50-79 ml/min) and moderate (Cl_{CR} 25-49 ml/min) renal impairment, respectively. In subjects with severe renal impairment (Cl_{CR} ≤ 24 ml/min), plasma concentrations were 2.3 times the levels in healthy subjects (see section 4.2 and 4.4).

Hepatic impairment

Non-renal elimination contributes to about 35% of total elimination, and hepatic impairment is unlikely to affect the pharmacokinetics of prucalopride to a clinically relevant extent (see section 4.2 and 4.4).

Paediatric population

After a single oral dose of 0.03 mg/kg in paediatric patients aged between 4 and 12 years, C_{max} of prucalopride was comparable to the C_{max} in adults after a single 2 mg dose, while unbound AUC was 30-40% lower than after 2 mg in adults. Unbound exposure was similar over the whole age-range (4-12 years).The average terminal half life in the paediatric subjects was about 19 hours (range 11.6 to 26.8 hours) (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. An extended series of safety pharmacology studies with special emphasis on cardiovascular parameters showed no relevant changes in haemodynamic and ECG derived parameters (QTc) with the exception of a modest increase in heart rate and blood pressure observed in anaesthesized pigs after intravenous administration, and an increase in blood pressure in conscious dogs after bolus intravenous administration, which was not observed either in anaesthetized dogs or after oral administration in dogs reaching similar plasma levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate

Coating
Hypromellose
Lactose monohydrate
Triacetin
Titanium dioxide (E171)
Macrogol
Iron oxide red (E172)
Iron oxide yellow (E172)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original blister in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/aluminium perforated unit dose blisters (calendar marked) containing 7 tablets. Each pack contains 28 x 1 film-coated tablet.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Movetis NV
Veedijk 58
B-2300 Turnhout
Belgium
E-mail: info@movetis.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/581/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/10/09

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Sanico N.V.
Veedijk 59
B-2300 Turnhout
Belgium

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 3.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Resolor 1 mg film-coated tablets
Prucalopride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1 mg prucalopride (as prucalopride succinate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 x 1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in the original blister in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Movetis NV
Veedijk 58 (1004)
B-2300 Turnhout, Belgium
info@movetis.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/581/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Resolor 1 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Resolor 2 mg film-coated tablets
Prucalopride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 2 mg prucalopride (as prucalopride succinate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 x 1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in the original blister in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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info@movetis.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/581/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Resolor 2 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Resolor 1 mg tablets
Prucalopride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Movetis

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

Mon Tue Wed Thu Fri Sat Sun

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Resolor 2 mg tablets
Prucalopride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Movetis

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

Mon Tue Wed Thu Fri Sat Sun

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Resolor 1 mg film-coated tablets
Resolor 2 mg film-coated tablets
prucalopride

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Resolor is and what it is used for
2. Before you take Resolor
3. How to take Resolor
4. Possible side effects
5. How to store Resolor
6. Further information

1. WHAT RESOLOR IS AND WHAT IT IS USED FOR

Resolor belongs to a group of gut motility enhancing medicines (enterokinetics). It acts on the muscle wall of the gut, helping to restore the normal functioning of the bowel. The tablets are used for the treatment of chronic constipation in women in whom laxatives do not work well enough.

2. BEFORE YOU TAKE RESOLOR

Do not take Resolor if you:
- are allergic (hypersensitive) to prucalopride or any of the other ingredients of Resolor,
- are on renal dialysis,
- suffer from perforation or obstruction of the gut wall, severe inflammation of the intestinal tract, such as Crohn’s disease, ulcerative colitis or toxic megacolon/megarectum.

Take special care with Resolor if you:
- suffer from severe kidney disease,
- suffer from severe liver disease,
- are currently under supervision by your doctor for a serious medical problem such as lung or heart disease, cancer or AIDS.

If you have very bad diarrhoea, the contraceptive pill may not work properly and the use of an extra method of contraception is recommended. See the instructions in the patient leaflet of the contraceptive pill you are taking.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Resolor with food and drink
Resolor can be taken with or without food and drinks, at any time of the day.

Pregnancy and breast-feeding
Do not take Resolor if you are pregnant or if you intend to become pregnant unless your doctor advises you to do so.

When breast-feeding, prucalopride can pass into breast milk. Do not use Resolor while breastfeeding unless your doctor advises you to do so.

Ask your doctor for advice before taking any medicine.

Driving and using machines
Resolor is unlikely to affect your ability to drive or use machines. However, sometimes Resolor may cause dizziness and tiredness, especially on the first day of treatment, and this may have an effect on driving and use of machines.

Important information about some of the ingredients of Resolor
Resolor contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE RESOLOR

Always take Resolor exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. You must take Resolor every day for as long as your doctor prescribes it.

The doctor may want to reassess your condition and the benefit of continued treatment after the first 4 weeks and thereafter at regular intervals.

The usual dose of Resolor for most patients is one 2 mg tablet once a day.

If you are older than 65 years, the starting dose is one 1 mg tablet once a day, which your doctor may increase to 2 mg once a day if needed.

Your doctor may also recommend a lower dose of one 1 mg tablet daily if you have severe kidney or liver disease.

Taking a higher dose than recommended will not make the product work better.

Resolor is only for adult women and should not be taken by children and adolescents up to 18 years.

If you take more Resolor than you should
It is important to keep to the dose as prescribed by your doctor. If you have taken more Resolor than you should, it is possible that you will get diarrhoea, headache and/or nausea. In case of diarrhoea, make sure that you drink enough water.

If you forget to take Resolor
Do not take a double dose to make up for a forgotten tablet.

If you stop taking Resolor
If you stop taking Resolor, your constipation symptoms may come back again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Resolor can cause side effects, although not everybody gets them. The side effects mostly occur at the start of treatment and usually disappear within a few days with continued treatment.

The frequency of possible side effects listed below is defined using the following convention:
- very common (affects more than 1 user in 10)
- common (affects 1 to 10 users in 100)
- uncommon (affects 1 to 10 users in 1,000)
- rare (affects 1 to 10 users in 10,000)
- very rare (affects less than 1 user in 10,000)
- not known (frequency cannot be estimated from the available data).

The following side effects have been reported very commonly: headache, feeling sick, diarrhoea and abdominal pain.

The following side effects have been reported commonly: dizziness, vomiting, disturbed digestion (dyspepsia), rectal bleeding, windiness, abnormal bowel sounds, increase in frequency of passing urine (pollakiuria), tiredness.

The following uncommon side effects have also been seen: loss of appetite, tremors, pounding heart, fever and weakness. If pounding heart occurs, please tell your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE RESOLOR

Keep out of the reach and sight of children.

Do not use Resolor after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

Store in the original blister package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Resolor contains
The active substance is prucalopride.

One film-coated tablet of Resolor 1 mg contains 1 mg prucalopride (as prucalopride succinate).
One film-coated tablet of Resolor 2 mg contains 2 mg prucalopride (as prucalopride succinate).

The other ingredients are:
Lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, hypromellose, triacetin, titanium dioxide (E171), macrogol 3000. The 2 mg tablet also contains iron oxide red (E172), iron oxide yellow (E172), indigo carmine aluminium lake (E132).

What Resolor looks like and contents of the pack
Resolor 1 mg film-coated tablets are white to off-white, biconvex, round shaped tablets marked “PRU 1” on one side.
Resolor 2 mg film-coated tablets are pink, biconvex, round shaped tablets marked “PRU 2” on one side.

Resolor is provided in aluminium/aluminium perforated unit dose blister (calendar marked) containing 7 tablets. Each pack contains 28x1 film-coated tablet.

Marketing authorisation holder
Movetis NV
Veedijk 58
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Belgium
E-mail: info@movetis.com

Manufacturer
Sanico NV
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Belgium

This leaflet was last approved in 10/2009.

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

A systematic review was not performed as part of this submission.

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

Quality assessments of the relevant RCTs are presented in Table 24 (section 5.4) and Table 45 (section 5.9).

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

Indirect and mixed treatment comparisons were not conducted.

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

Not applicable.

9.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

This was not performed as part of this submission.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

This was not performed as part of this submission.

9.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

This was not performed as part of this submission.

9.9 Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

This was not performed as part of this submission.

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.10.1 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
- EconLIT
- NHS EED.

9.10.2 The date on which the search was conducted.

9.10.3 The date span of the search.

9.10.4 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).

Item	Searches	Results
1	chronic.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	717,421
2	constipat*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	14,128
3	cost.mp. [mp=title, original title, abstract, name of substance word, subject heading word	225,631
4	cost*.mp. [mp=title, original title, abstract, name of substance word, subject	304,415

	heading word	
5	1 and 2	2,950
6	3 or 4	304,415
7	5 and 6	69
8	from 7 keep 1-69	69

Articles returned

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9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

9.10.6 The inclusion and exclusion criteria.

9.10.7 The data abstraction strategy.

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

No cost-effectiveness studies were identified.

9.12 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.12.1 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
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

The search was performed on PubMed and covers Medline, which includes also Cochrane.

9.12.2 The date on which the search was conducted.

19 March, 2010

9.12.3 The date span of the search.

1990/01/01 to 2010/03/19

9.12.4 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).

Item	Searches	Results
1	((EQ-5D[All Fields] OR euro-qol[All Fields]) OR cost-utility[All Fields]) OR ("cost-benefit analysis"[MeSH Terms] OR ("cost-benefit"[All Fields] AND "analysis"[All Fields]) OR "cost-benefit analysis"[All Fields] OR ("cost"[All Fields] AND "effectiveness"[All Fields]) OR "cost effectiveness"[All Fields])) OR ("quality-adjusted life years"[MeSH Terms] OR ("quality-adjusted"[All Fields] AND "life"[All Fields] AND "years"[All Fields]) OR "quality-adjusted life years"[All Fields] OR ("quality"[All Fields] AND "adjusted"[All Fields] AND "life"[All Fields] AND "years"[All Fields]) OR "quality adjusted life years"[All Fields]) AND ("humans"[MeSH Terms] AND English[lang] AND medline[sb] AND "adult"[MeSH Terms] AND ("1990/01/01"[PDAT] : "2010/03/19"[PDAT]))	16697
2	"Constipation"[Mesh] AND ("humans"[MeSH Terms] AND English[lang] AND medline[sb] AND "adult"[MeSH Terms] AND ("1990/01/01"[PDAT] : "2010/03/19"[PDAT]))	2385
3	#1 AND #2 AND ("humans"[MeSH Terms] AND English[lang] AND medline[sb] AND "adult"[MeSH Terms] AND ("1990/01/01"[PDAT] : "2010/03/19"[PDAT])	25

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9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None

9.12.6 The inclusion and exclusion criteria.

Limited to adult (> 18 years), humans
Limited to English language
Exploded MeSH terms:

- no specific Mesh terms for functional or chronic constipation

- no specific Mesh terms for instrument, inventory, scale, assessment

Exclusion criteria:
1. EQ-5D or quality of life not mentioned in title or abstract,
2. constipation not major focus

9.12.7 The data abstraction strategy.

Abstracts of all 25 articles were reviewed. After applying the exclusion criteria, 17 articles were excluded on the basis of exclusion criterion 1, and 6 on the basis of exclusion criterion 2. Two articles were retained for review of the full paper.

9.13 Appendix 13: Resource identification, measurement and valuation (section 6.5)

A comprehensive literature search was undertaken to identify economic literature that may be relevant to this therapeutic area. The search strategy utilised and literature identified are outlined at the end of this section.

9.13.1 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
- NHS EED
- EconLIT.

Not applicable – resource use data are not available for prucalopride so no search was undertaken.

9.13.2 The date on which the search was conducted.

Not applicable – resource use data are not available for prucalopride so no search was undertaken.

9.13.3 The date span of the search.

Not applicable – resource use data are not available for prucalopride so no search was undertaken.

9.13.4 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).

Not applicable – resource use data are not available for prucalopride so no search was undertaken.

9.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable – resource use data are not available for prucalopride so no search was undertaken.

9.13.6 The inclusion and exclusion criteria.

Not applicable – resource use data are not available for prucalopride so no search was undertaken.

9.13.7 The data abstraction strategy.

Not applicable – resource use data are not available for prucalopride so no search was undertaken.

9.14 Appendix 14: Publication in Pharmacoeconomics

Title: Health Related Quality of Life Mapping – Its Role in Theory and Practice

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Conflict of Interest Statement

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INTRODUCTION

At a time of increasing economic constraints, it is crucial that healthcare systems optimise their resources use to ensure that they generate the maximum possible health gain from their available resources. In order to achieve this, it is necessary for healthcare interventions to be evaluated and compared across therapeutic boundaries. Undertaking such evaluations requires interventions from each disease area to be compared using a generic utility based measure that is specifically designed to undertake comparisons across therapeutic boundaries. The importance of such utility based outcome comparisons in generating information that is of value to policy-makers is widely acknowledged. For example, the National Institute of Health and Clinical Excellence (NICE) requires all sponsors of drugs being evaluated to provide generic utility assessments which enable NICE to assess the extent to which health gains per unit of resource generated by the intervention being evaluated compares with other therapeutic areas. At the heart of such evaluations is the concept of opportunity cost which attains greater importance as resource constraints in the NHS continue to tighten. This concept emphasises that the true cost of investing in cost-effective health services is measured in terms of the greater benefit lost as a consequence of the crowding out of more effective interventions. Accepting such sub-optimal decision-making would damage the health of the population being served just as significantly as the funding of interventions which actively damage patients.

The methodological guidance produced by NICE[1] unambiguously emphasises that the primary measure of health effects that they require is the Quality Adjusted Life Year (QALY). However, many trials currently reporting were designed before QALY analyses were as pre-eminent and hence were not routinely incorporated into their research protocols. As such, both sponsors and regulators are confronted by the potential current mismatch between the information that is required by the regulator to evaluate a new intervention and the information that has been generated in the clinical trials. However all clinical trials will have generated information related to disease specific measures to facilitate comparisons with standard care. Whilst it is always preferable to directly incorporate generic utility measures into clinical trials in the absence of such measures it becomes necessary to ‘map’ disease-specific quality of life measures on to a generic utility-based measure which facilitates comparisons across therapeutic boundaries. Such mapping analyses are routinely incorporated into regulatory submissions in cases where direct measurement of QALYs was not available. However, this in itself presents problems in relation to the reliance that can be placed on the mapping process undertaken. The need to ‘quality assure’ such mapping processes is important given that they will inevitably be based on a large number of assumptions which imply the presence of uncertainty in the estimates generated. As such a detailed quality assessment is required to assess the strength of the relationship between the outcome measures being linked and assess the impact of uncertainty on the robustness and reliability of the mapping process being presented in support of the new healthcare intervention.

EVALUATING QUALITY OF LIFE USING DISEASE-SPECIFIC AND GENERIC MEASURES

It is widely recognised that evaluating the impact of health-related quality of life represents a crucial element in evaluating healthcare outcomes. Comparing quality of life improvements between the new intervention and standard care represents a crucial step in estimating the clinical and cost effectiveness arising from any intervention. Disease-specific measures will capture more sensitively changes in quality of life as they are specifically focussed on characteristics that will alter in the population being studied. Thus, from a clinical perspective, disease-specific measures are more likely to capture in a sensitive manner the clinical benefits arising from a new intervention. However policymakers and regulators have different requirements from quality of life data as they need to compare QoL benefits that arise in different therapeutic areas. To achieve this requires generic QoL measurement that by its nature will be less sensitive to subtle disease-specific changes but is equally applicable across all therapeutic areas. The need for comparability and consistency in QoL evaluations therefore requires that the evaluations of all new healthcare interventions must generate generic data that can be used to measure and value health-related quality of life.

Generic health measures are inherently difficult to apply in areas where the nature and extent of the health benefits to each individual patient may be difficult to capture in a non-specific health measure. It is also important to acknowledge that all generic measures will have both strengths and weaknesses that may make them particularly appropriate/problematic for use in particular therapeutic areas. A number of generic utility-based measures are available and it is important to assess which has the best psychometric properties to use in any particular mapping process. However, from a UK perspective, there is no doubt that currently the dominant generic measure is the EQ-5D which produces utility scores which capture the preferences for individuals for particular health states. The five dimensions assessed are: mobility; self-care; usual activity; pain/discomfort and anxiety/depression and each dimension has three levels: no problems, some problems and extreme problems. Each individual health state has been valued[2]. The EQ-5D has been criticised as showing poor sensitivity to clinical change, particularly in the most severe health states, with Brazier and colleagues emphasising the potential for ceiling effects[3].

One potential alternative generic outcome measure that could be utilised is the medical outcomes study short form (SF-36). This is a health profile measure consisting of 36 items with a score of zero to 100. Outcomes are broken down into eight dimensions: physical functioning; role – physical; bodily pain; general health; vitality; social functioning; role – emotional and mental health. However, the scores generated from the SF-36 are not based on individual preferences and therefore they cannot directly be used to generate QALYs.

However, it is also important to recognise that QALYs are of much more limited interest outside the UK particularly in America where the SF-36 is far more dominant. For this reason, even in trials that are currently being designed, the collection of EQ-5D data may still not be routinely incorporated in such trials if they are largely aimed at the dominant US market. Regression analysis has been used to examine the relationship between EQ-5D utility scores and the SF-36 health domains[4].

MAPPING FROM DISEASE-SPECIFIC TO GENERIC MEASURES

The different possible specifications for any mapping function are numerous; however, two general approaches exist for mapping disease-specific to generic QoL measures. The first approach relies on the judgement of clinical experts to link and weight individual elements from a disease specific measure to individual elements in the generic measure. The major problem with this approach is its essential subjectivity leading to the likelihood that different evaluators/experts would link the two measures using a different structural framework. The alternative (and, for our purposes, preferred) approach is to undertake the mapping empirically using statistical methods to inform the inference between the disease-specific and generic QoL measures. The aim of the empirical analysis is to calculate 'exchange rates' between the disease-specific and the generic measure in order to predict one measure from the other. As such any statistical linkage that improves the 'quality' of this relationship should be incorporated into the analysis.

Inevitably it is necessary to make a range of assumptions concerning both the structure and parameter values underpinning any mapping analysis. The structural assumptions underlying the mapping should be clearly documented and the nature and extent of structural uncertainty on the mapping process should be explored and validated. However very limited theoretical guidance is available to optimise the structural assumptions underpinning the mapping or to assess the level of uncertainty associated with the mapping structure.

All parameters underlying the mapping analysis will be estimated with a certain (and perhaps unknown) degree of imprecision. As such in order to assess the robustness and reliability of the parameter estimates such uncertainty should be comprehensively explored through sensitivity analyses preferably using probabilistic methods. In assessing the quality of any mapping process both the methods and results of quality assurance and mapping validation should be outlined in detail.

Mapping functions utilise statistical methods to assess the extent to which changes in generic quality of life can be 'explained' by more condition-specific measures[5]. In this regard, it is important to acknowledge that the use of a mapping function always represents a second best solution to direct incorporation of a generic measure into the clinical trial. However in circumstances where such measures have not been incorporated into the trial, mapping can be used to estimate generic utility data from disease-specific health-related quality of life measures. In addition it is widely recognised that generic outcome measures may be too insensitive to capture the comparatively small but clinically meaningful changes that arise in certain therapeutic areas. Thus, it is possible that mapping can also be used to enhance the sensitivity of generic measures by linking them to more sensitive disease-specific measures. By using mapping from a disease-specific measure it may be possible to sub-divide and hence 'fine tune' the generic measure to enable it to better capture small but clinically significant changes that whilst important would not move a patient between the broad generic categories and hence would not be valued within the QALY framework[6].

In order for decision makers to have confidence in this process a high quality relationship must be established and validated between the disease-specific and generic outcome measure[5]. To achieve this, the mapping process must be based on empirically derived data and the statistical properties of the mapping function should be explored to assess the quality and robustness of the relationship being derived. The 'quality' of any mapping process is

therefore in large part dependent on the degree to which the structure and content of the disease-specific and generic QoL measure cover similar 'dimensions'. It is largely dependent on the internal validity and comprehensiveness of the disease-specific measure that is utilised in the clinical trials and the extent to which the generic measure covers all important aspects of QoL experienced by patients in the therapeutic area under evaluation. In cases where important dimensions of patients QoL are excluded from either the disease specific or generic outcome measures then this is likely to severely limit the quality of the mapping process. Even in cases where all dimensions are incorporated in both measures a mismatch may occur in the severity range covered for the given health dimensions. The EQ-5D pain dimension for example broadly categorises a wide range of pain severity in a small number of categories. In comparison patients in many therapeutic areas are unlikely to suffer extreme pain as a consequence of their condition and hence any measure of pain (or discomfort) is likely to be far more sensitive in the disease specific measure at distinguishing between different levels of mild pain and yet ignore completely moderate to severe pain. As such disease-specific pain measures might map only to a limited part of the pain scale of the generic measure. In cases where there is a systematic tendency for one measure to be restricted to a limited spectrum of the other measure then the quality of the mapping may be limited[7]. In this regard, transparency in the mapping process is essential and therefore full details and justification of all assumptions underlying the mapping should be provided.

The quality of the mapping process can be assessed in a number of ways. Ultimately, the aim is to predict values in the mapping process. This requires an examination of the difference between the predicted and observed value in some manner. However, the first step in the process is to identify the disease-specific measure which best captures patient reported outcomes and use this as the basis for the mapping process. The statistical approach utilises all relevant disease-specific data and combines it through statistical inference to the generic utility-based measure. Although this could be seen as 'data dredging', it has the benefit that all available evidence is incorporated into the mapping process to derive the best possible fit between the disease-specific and generic measures. In this manner a range of disease-specific measures may be linked to a single generic measure or physical outcome or demographic data can be incorporated into the mapping analysis if they improve the 'goodness of fit' between the matched variables. The inclusion of additional variables is likely to be particularly valuable in therapeutic areas where condition-specific measures are targeted on a limited range of dimensions or severity of therapeutic outcomes which do not adequately cover the broad spectrum of outcomes included in the generic measure. In such circumstances the inclusion of additional variables may improve the quality and nature of the linkage to the generic outcome measure.

The application of generic measures such as SF-36 and EQ-5D is problematic due to the comparative insensitivity of the measures. For example, with SF-36, when considering a treatment which is expected to have a 0.1 overall improvement in a physical component; SF-36 can, for example only record discrete value increments of around 0.04 (e.g. 49.72671, 49.75688 and 49.80622), assuming the domain of this component is adequately covered in the questionnaire. This means, for example, that patients who start with a value of 49.74, and improve to 49.77 will register no change on the SF-36 scale, whereas other patients, with less of a change may register the full 0.4 shift, simply by virtue of moving between bands. This noise around small changes makes typical non specific measures difficult to apply to treatments which would not be expected to show large swings in quality of life. This is even more pronounced in the EQ-5D questionnaire, which has an even more limited range of

health states

CASE STUDY – MAPPING IN CHRONIC CONSTIPATION

The primary therapeutic objective in treating chronic constipation is to improve the quality of life being experienced by the patient. It is important when evaluating quality of life in any therapeutic area that a disease-specific tool is chosen for use that has been validated and its psychometric properties have been established. The self-reported impact of therapy upon the patient captured through patient-reported outcome measures (PROMs) is also becoming increasingly influential in regulatory decision-making. A number of quality of life indicators have been developed for use in chronic constipation and the ones evaluated in the Prucalopride trials were derived from the PAC index. The PAC-SYM is one of two components of the patient assessment of constipation index. The second component is the PAC-QOL, which is a constipation-specific measure of quality of life. The PAC index is the only constipation-specific instrument that measures both quality of life and symptoms and whose psychometric reliability and validity have been evaluated and confirmed in constipated adults[8,9]. Full details of the disease specific measures utilised in this analysis are provided in Appendix 1. In addition, patient satisfaction with treatment was evaluated, both within the clinical trials and in observational data up to a period of 12 months.

PAC-QOL and PAC-SYM have both been validated for use in the context of quality of life measurement for patients suffering from chronic constipation[10]. Unfortunately, neither of these measures can be directly incorporated into assessments of cost utility using a cost per quality adjusted life year (QALY) framework. Given that the preference-based measure preferred by NICE (EQ-5D) was not directly measured in the clinical trials, it became necessary to apply a mapping function to convert the available disease-specific data into a generic preference-based measure. However, this will only represent a valid and legitimate approach if the relationship identified accurately and reliably links the available disease-specific measures with the required generic utility measure. The reliability that can be placed on such mapping depends upon the size and nature of the data sets being mapped and the appropriateness and accuracy of the modelling procedure utilised to undertake the mapping.

The modelling procedure utilised followed a well-established statistical procedure which identified an accurate and reliable mapping between SF-36 and EQ-5D[4]. However, one limitation of PAC-QOL is the absence of questions relating to the more severe pain covered in EQ-5D. The only place where a patients experience of pain would be captured is in the physical discomfort sub-scale which by its' very nature does not capture more severe manifestations of pain. The procedure followed identified that the relationship between SF-36 and EQ-5D was generally good except in the case of more severe health states. In the case of such severe health states, the 'floor effect' of the SF-36 limited the ability to map to the broader range of health states contained in the EQ-5D. The fact that the mapping was found to be less reliable for these extreme health states should not prove a problem for evaluation in the field of chronic constipation as none of the patients included in the clinical trials would map to the most severe health states of EQ-5D.

METHODOLOGY

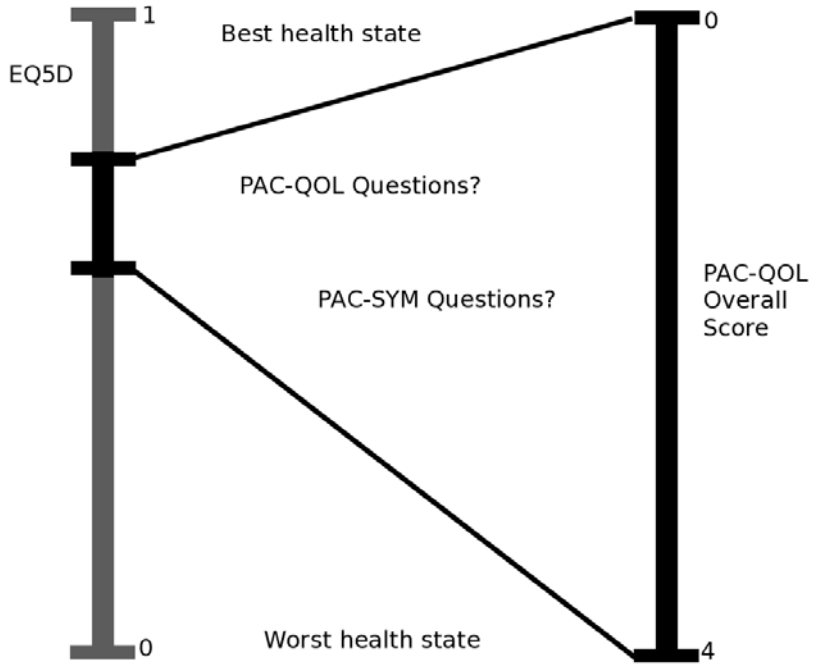
The absence of direct measurement of the EQ-5D generic outcome measure required a

mapping process to be developed to relate the outcome measures evaluated in the clinical trials to EQ-5D. The approach taken was to use statistical methods to identify the optimum method for translating PAC-QOL data into utilities to translate the health benefits into terms that could be interpreted as utility improvements.

The mapping relationship between the disease-specific and generic quality of life measures was therefore estimated using a range of techniques and statistical specifications[11].

A large quantity of PAC-QOL related data is available from the various clinical trials conducted for Prucalopride, with full data available for up to 3 months of treatment and longer term data on satisfaction over longer term trials. PAC-QOL therefore serves as the main measure of quality of life for the economic evaluation of Prucalopride (see Appendix 2).

Figure 1. Mapping Patient Assessed Constipation onto EQ-5D

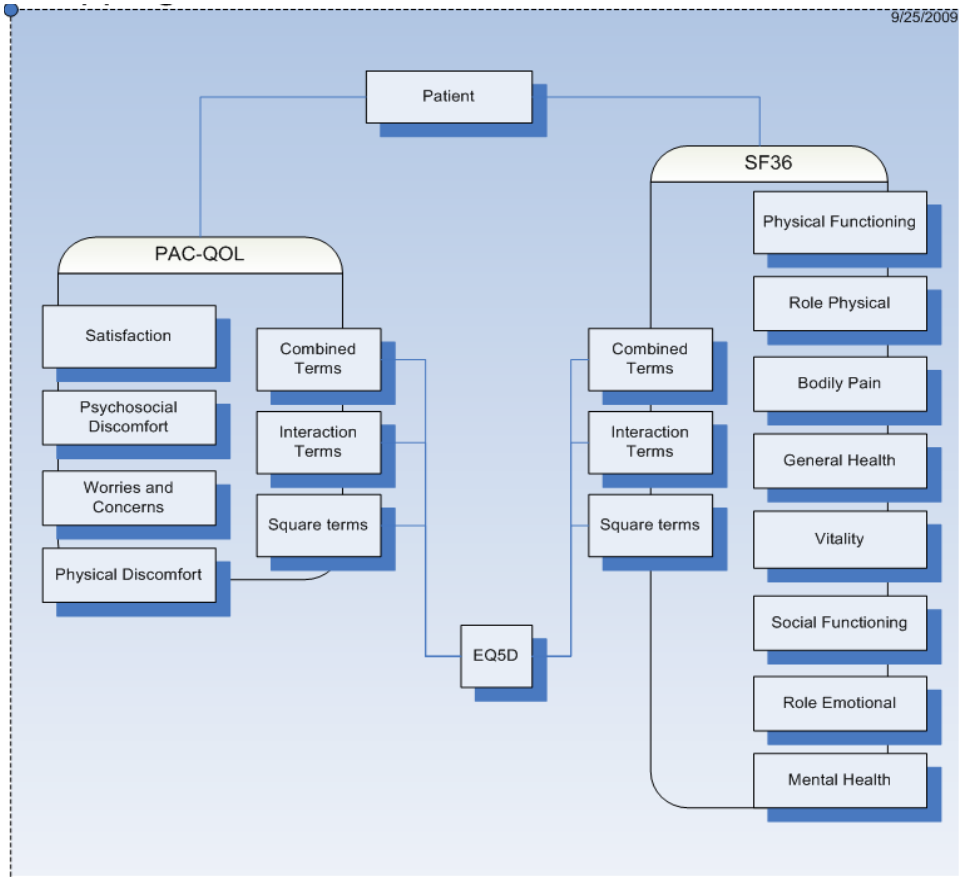


The clinical trials contained a large sample of individual responses to both SF-36 and PAC-QOL, since each patient responded at multiple time periods at the same time to both questionnaires. As such sufficient data was generated (5488 observations) to estimate the effect of changes of PAC-QOL scores as a preference weighted quality of life measure. This process is illustrated graphically in Figure 1. This allows for the scale of the treatment effect measured with PAC-QOL to be mapped on to EQ-5D by utilising the established relationship between SF-36 and EQ-5D. EQ-5D was estimated for each SF-36 observation, using the values of the predicted model previously published[4].

Two possible methods for mapping this relationship were available. Firstly the PAQ-QOL score could be directly converted to an EQ-5D score or alternatively, PAC-QOL could be

interpreted as being an additive sub-scale of EQ-5D. This second approach in effect would assess how an EQ-5D score would be affected if answers to the PAC-QOL questions were included in the calculation of the EQ-5D score.

Figure 2. Mapping PAC-QOL, SF-36 and EQ-5D



RESULTS

Regression analysis was used to provide a scaled measure of change in quality of life based on the constipation specific measures available (see Figure 2). This was achieved by first estimating an EQ-5D score for each SF-36 sample using GLS (3) (SF-36 to EQ-5D). The results of this analysis are provided in Table 1.

Table 1. Calculation of EQ-5D from SF-36 subscales

Physical functioning (PF) x 0.559	**+Role physical (RP) x -0.146**	**+Bodily pain (BP) x 0.715**
+General health (GH) x 0.407	**+Vitality (VIT) x 0.017**	**+Social functioning (SF) x 0.293**
+Role-emotional (RE) x 0.067	**+Mental health (MH) x 0.483**	**$(PF)^2$ x -0.227**
+$(RP)^2$ x 0.001	**+$(BP)^2$ x -0.330**	**+$(GH)^2$ x 0.032**
+$(VIT)^2$ x 0.012	**+$(SF)^2$ x -0.163**	**+$(RE)^2$ x 0.034**
+$(MH)^2$ x -0.242	**+PF x RP x 0.022**	**+PF x BP x -0.032**
+PF x GH x 0.073	**+PF x VIT x -0.132**	**+PF x SF x -0.023**
+PF x RE x 0.047	**+PF x MH x -0.014**	**+RP x BP x 0.019**
+RP x GH x 0.068	**+RP x VIT x 0.050**	**+RP x SF x 0.067**
+RP x RE x -0.012	**+RP x MH x 0.022**	**+BP x GH x -0.217**
+BP x VIT x -0.002	**+BP x SF x 0.055**	**+BP x RE x -0.038**
+BP x MH x 0.131	**+GH x VIT x -0.066**	**+GH x SF x -0.157**
+GP x RE x -0.033	**+GH x MH x -0.084**	**+VIT x SF x 0.143**
+VIT x RE x -0.020	**+VIT x MH x 0.023**	**+SF x RE x -0.023**
+SF x MH x -0.065	**+RE x MH x -0.048**	**-0.256**

The summary of linked measures derived from the mapping process is provided in Table 2. The mapping of PAC-QOL to EQ-5D generated a robust and reliable relationship between these two measures.

The estimated equation for deriving EQ-5D from PAC-QOL was:-

EQ-5D = 97.7 – 9.8 (PAC-QOL)

This mapping provides a non-preference, non ordinal comparison between a PAC-QOL score and EQ-5D and illustrates how a PAC-QOL improvement would translate into an improvement in a generic utility-based quality of life measure. The PAC-QOL is an inverse measure from 1 (mild symptoms) to 4 (severe symptoms). As such, a patient suffering from severe chronic constipation (4) would map onto an EQ-5D score of 0.585 (on the zero to 1 EQ-5D scale). This partial mapping onto the higher score of EQ-5D emphasises that, although chronic constipation exerts a significant influence over the quality of life of sufferers, it is obviously not the sole influence (other factors such as sensory deprivation would have an additional impact in combination).

CAPTURING PREFERENCES

Once scale and general location of the mapped quality of life as measured by a disease specific measure have been established, the most important step is to establish the preference between states as would be captured by an actual EQ5D scoring.

This is the role the squared and interaction terms play in the mapping process, they allow for a more accurate inference of the preference between the states captured by the disease specific measure. Not including square and interaction terms in the mapping equation will tend to ignore these preferences. The difference between mapping from PAC-QOL to EQ5D with and without squared and interaction terms are presented in Appendix 3, the three most obvious differences being, firstly, that there is not a significant improvement in quality of life moving from a PAC-QOL score of 1 to 0 (PAC-QOL is an inverse scale with 4 being the worst health state, and 0 being the best), which is not accurately represented without the square and interaction terms. Secondly, that excluding the interaction terms tends to underestimate the detriment in quality of life for severely chronically constipated patients, and thirdly a tendency to exaggerate the quality of life of patients with a good PAC-QOL score.

Equation 2

*eq5d = Dissatisfaction * 0.0276081 +Physical Discomfort*0.0027602+Psychosocial Discomfort*-0.0470309+Worries and Concerns*-0.043229+Pacsym_overall_score*-0.0594403+0.9385863*
Number of observations = 5421
Adjusted R-squared = 0.3087

Table 2. 95% Confidence Intervals for Equation 2

Variable	95% Confidence interval
Dissatisfaction:	0.0226575<->0 .0325588
Physical Discomfort	-0.0046802<->0.0102006
Psychosocial Discomfort:	-0.0538426<->-0.0402192
Worries and Concerns:	-0.0499174<->-0.0365406
PacSym overall score:	-0.0675207<->-0.05136
Constant:	0.9272804<->0.9498921

Equation 3

eq5d=Dissatisfaction(PD)-0.0108734 +Physical Discomfort(PPD)*0.0062618 +Psychosocial Discomfort(PSD)*-.0257802 +Worries and Concerns(WC)*-0.0378959 +Pacsym overall score(PS)* -0.0088172 +PD²*0.004867 +PPD²*0.0003386 +PSD²*-0.000529 +WC²*-0.0124099 +PS²*-0.0156052 +PD*PPD*-0.0050104 +PD*PSD*0.0016543 +PD*PW*0.0166514 +PPD*PSD*0.0012205 +PPD*PWC*-0.0069619 +PSD*PWC*-0.0010802 +PS*PD*-0.0023178 +PS*PPD*0.0100286 +PS*PSD*-0.0105971 +PS*PWC*0.0018687+0.9345446*

Number of observations = 5421
Adjusted R-squared = 0.3195

Table 3. 95% Confidence Intervals for Equation 3

Variable	95% Confidence interval
Dissatisfaction (PD):	*-0.0297088<->0.007962*
Physical Discomfort (PPD):	*-0.0223797<->0.0349032*
Psychosocial Discomfort(PSD):	*-0.0568675<->0.0053072*
Worries and Concerns(WC):	*-0.0663592<->-0.0094326*
Pacsym overall score (PS):	*-0.0416361<->0.0240016*
PD²:	*-0.0001815<->0.0099154*
PPD²:	*-0.0090533<->0.0097305*
PSD²:	*-0.0082486<->0.0071907*
PWC²:	*-0.0200935<->-0.0047262*
PS²:	*-0.0265191<->-0.0046913*
PD*PPD:	*-0.0149056<->0.0048848*
PD*PSD:	*-0.0086078<->0.0119164*
PD*PWC:	*0.006998<->0.0263048*
PPD*PSD:	*-0.0114086<->0.0138496*
PPD*PWC:	*-0.019118<->0.0051942*
PSD*PWC:	*-0.0123025<->0.010142*
PS*PD:	*-0.0127807<->0.0081451*
PS*PPD:	*-0.0050323<->0.0250894*
PS*PSD:	*-0.0232334<->0.0020392*
PS*PWC:	*-0.0105231<->0.0142605*
Constant:	*0.9141693<->0.9549198*

Table 4. Summary of linked measures

Variable	Observations	Mean	Std. Dev	Min	Max
EQ-5D estimated from SF-36	5492	0.812517	.1754299	-0.2525	0.999
EQ-5D estimated by full mapping Eq. 3	5456	0.812355	0.099643	0.328434	0.972314
EQ-5D estimated by mapping without square and interaction terms	5456	0.812140	0.093344	0.501540	0.995843
EQ-5D estimated by Equation 1.	5488	0.812411	0.084857	0.582156	0.977254
Sex (female=1)	5492	.8889294	.3142482	0	1
Age	5491	46.39519	14.12912	17	95
SF-36 Physical functioning	5492	82.22814	22.52976	0	100
SF-36 Role - physical	5492	71.44331	37.79174	0	100
SF-36 Bodily pain	5492	62.3496	25.41944	0	100
SF-36 General health	5492	68.22053	22.23483	0	100
SF-36 Vitality	5492	50.47056	23.52581	0	100
SF-36 Social functioning	5492	77.35115	25.2428	0	100
SF-36 Role – emotional	5492	73.49781	37.64823	0	100
SF-36 Mental health	5492	70.22087	19.96932	0	100
SF-36 Mental scale	5492	46.93843	11.22477	2.180166	69.94523
SF-36 Physical scale	5492	47.18955	9.561877	10.4304	73.03338
PAC-QOL overall score	5488	1.668165	.8584525	0	4
PAC-QOL Satisfaction	5473	2.829024	1.093626	0	4
PAC-QOL Physical Discomfort	5484	1.894724	1.031429	0	4
PAC-QOL Psychosocial Discomfort	5481	.9226994	.8631427	0	4
PAC-QOL Worries and Concerns	5483	1.605082	1.030692	0	4

DISCUSSION AND CONCLUSION

The mapping analysis presented here analysed the quality of the mapping undertaken to link disease-specific to generic measures in the area of chronic constipation. As in most clinical trials outcome measures were identified in two dimensions: Firstly ‘physical outcomes’ were evaluated in terms of the increase in bowel movements and secondly a range of patient reported outcome measures (PROMs) were measured to evaluate the impact of this increase in bowel movement on the patients quality of life. The PROMs analysed consisted of PAC-QOL (patient assessed quality of life) PAC-SYM (patient assessed symptoms) and a summary measure of patient satisfaction with treatment. Data on these diseases specific PROMs were ‘mapped’ on to EQ-5D to generate utilities. A detailed analysis of factors underlying the quality of this process was undertaken and compared with results obtained from mapping SF-36 to SF-6D using the Brazier algorithm. The results emphasize the importance of undertaking such quality assessments if decision makers are to base resource prioritization decisions on analyses of this nature.

Although quality of life studies have clearly indicated an ‘association’ between constipation and poor quality of life, their study design, makes it difficult to assess causality rather than mere association. Most of the studies are cross-sectional studies of small samples of patients and the fact that constipation tends to be co-morbid with a range of other diseases makes it difficult to isolate the impact of constipation alone from other confounders potentially limiting quality of life. This histograms in Figures 7 and 8 show how patients in the Prucalopride trials with SF36 data are allocated into EQ5D and PacQoL summary scores, The confidence intervals for Equation 3 highlight the fact that the PacQoL measure of physical discomfort does appear to have any real noticeable effect on overall Quality of life, but this is somewhat to be expected since the questions asked in the PacQoL questionnaire relating to physical discomfort cover a very narrow range of physical discomfort; studying mostly bloating and a feeling of heaviness.

Mapping to SF6D produces significantly different results, compressing the mapping into a narrower range of quality of life, and showing a more linear relationship across the scale – with SF6D a PacQoL change from 1 to 0 gives a similar quality of life change to a PacQoL change from 4 to 3, whereas with the EQ5D mapping the former shows a much smaller improvement in Quality of Life.

This appears to be explained by the difference in allocation of overall Quality of Life for each patient. SF6D appears to not just have a "floor" effect[12] when allocating patient QALYs, but also a ceiling effect, not capturing changes in patient quality of life for patients that are otherwise healthy, except for less debilitating ailments such as constipation.

As emphasised in this paper mapping from disease-specific to generic QoL measures is an area where empiricism rules. The relationship between the disease-specific and the utility-based measures has to be context and individual specific. The nature of the relationship (linear quadratic or some other functional form) has to be empirically determined depending on the 'goodness of fit' arising from the different functional forms. A range of potential statistical tests are available to assess the quality of linkage between disease-specific and utility-based measures. However, none of the measures have been definitively shown to be better than any of the others. Evaluators frequently fall back on a visualisation of the mapping process to assess its quality. In this regard, mapping is not a precise science and it is always better to directly measure EQ-5D if this is possible and appropriate in the therapeutic context being studied.

Mapping allows different interventions to be evaluated and compared across therapeutic boundaries in a manner that enables policy makers to make a more informed decision with regard to the optimisation of scarce healthcare resources. For this reason it becomes necessary to translate disease-specific outcome measures into generic utility values. The results obtained in the utility analysis emphasise both the quality of life and utility loss being experienced by patients suffering from chronic constipation.

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APPENDIX 1 - THE PATIENT ASSESSMENT OF CONSTIPATION (PAC) EVALUATION PACKAGE

PAC-SYM is a 12 item self-reported questionnaire which concentrates purely on the symptoms of chronic constipation (see Appendix 1). It is an inverse scale of symptoms ranging from 0 meaning absent to 4 meaning very severe. In this sense, while it is an excellent measure for assessing response to treatment for constipation, it is less useful as an outcome measure for the economic evaluation. This is because it is not possible to 'map' from PAC-SYM to the broader based 'utility' measures required to estimate QALYs in this therapeutic area. Such a mapping would require these symptoms to be placed into the wider context as the severity of constipation symptoms do not necessarily reflect the effect of such symptoms on the broader aspects of people's day to day lives.

Stool symptoms:

- Straining
- Too hard
- Incomplete evacuation
- False alarm

Abdominal Symptoms:

- Discomfort
- Pain
- Cramping
- Bloating

Rectal Symptoms:

- Painful bowel movement
- Burning
- Bleeding and tearing

APPENDIX 2 – PAC-QOL

PAC-QOL is a 28 item questionnaire made up of four sub scales: Physical Discomfort, worries and concerns, Psychosocial Discomfort and satisfaction. It is a constipation specific Health Related Quality of Life tool which captures the impact of constipation-related symptoms on overall quality of life. In comparison to more generic measures such as SF-36, PAC-QOL is more sensitive to small changes in health state that are likely to specifically impact upon patients suffering from chronic constipation and can therefore capture the smaller levels of change related to those symptoms. This questionnaire is very sensitive to constipation related symptoms, but significantly less so to wider health implications.

Figure 3. EQ5D Patient mappings without square and interaction terms (Equation 2)

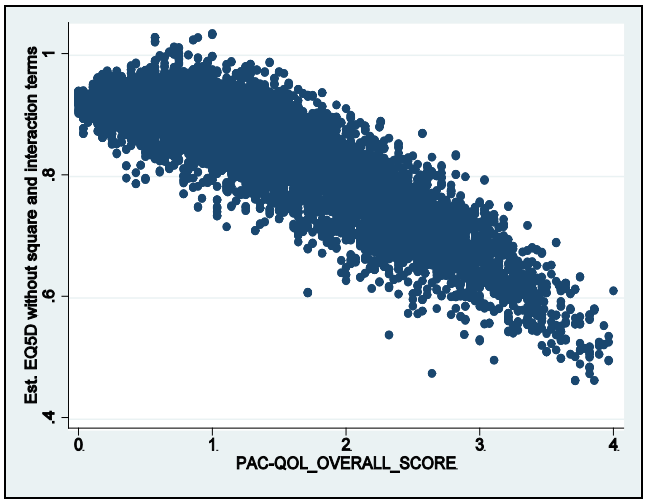


Figure 4. EQ5D Patient mappings with square terms

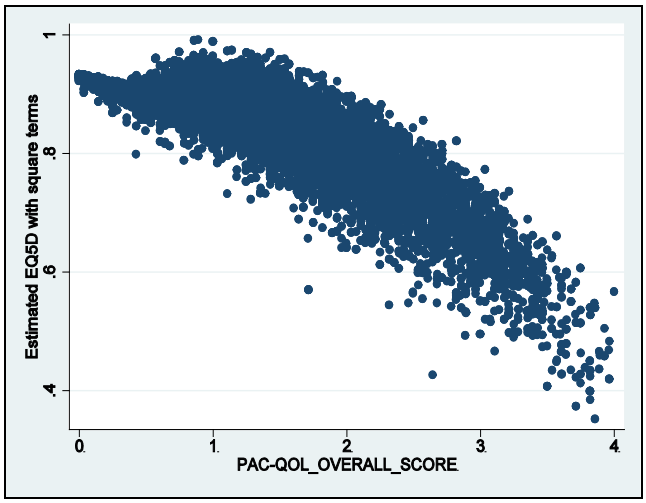


Figure 5. EQ5D Patient mappings with square and interaction terms (Equation 3)

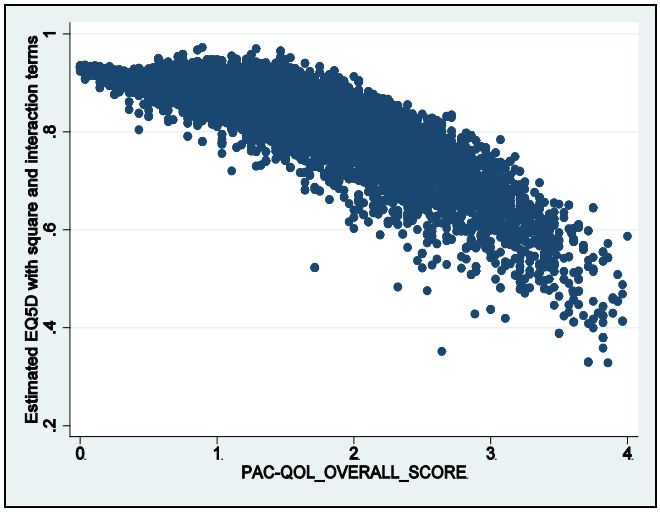


Figure 6. SF6D Patient mappings with square and interaction terms

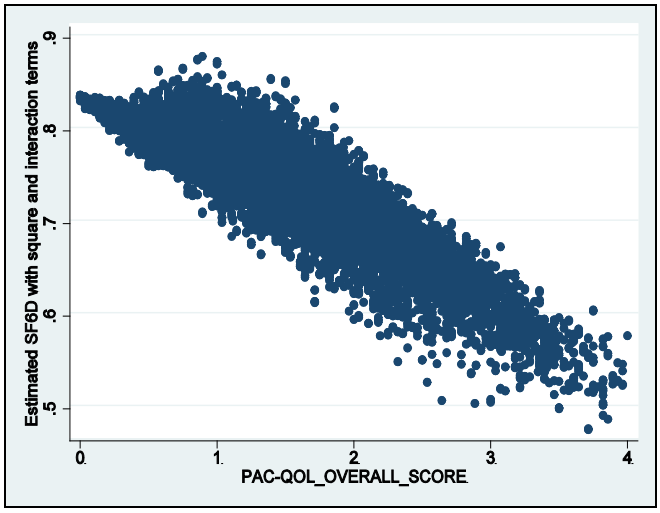


Figure 7. Histogram of EQ5D patient score allocations

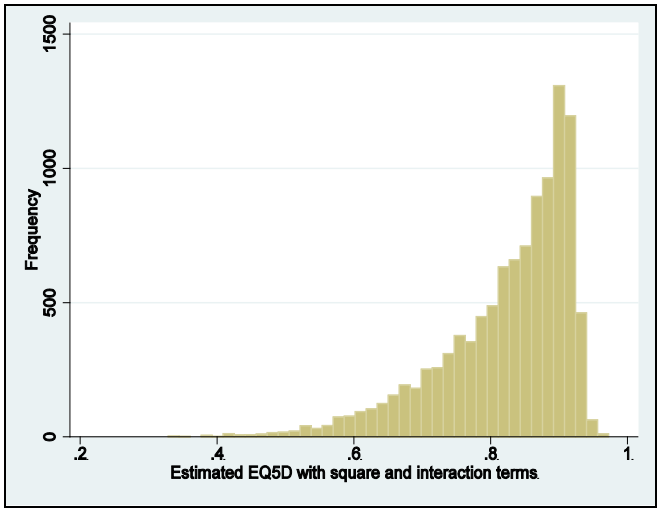


Figure 8. Histogram of PacQol patient score allocations

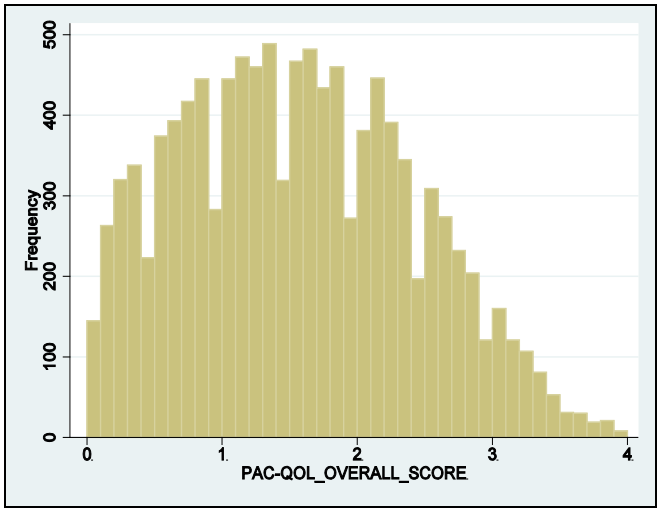
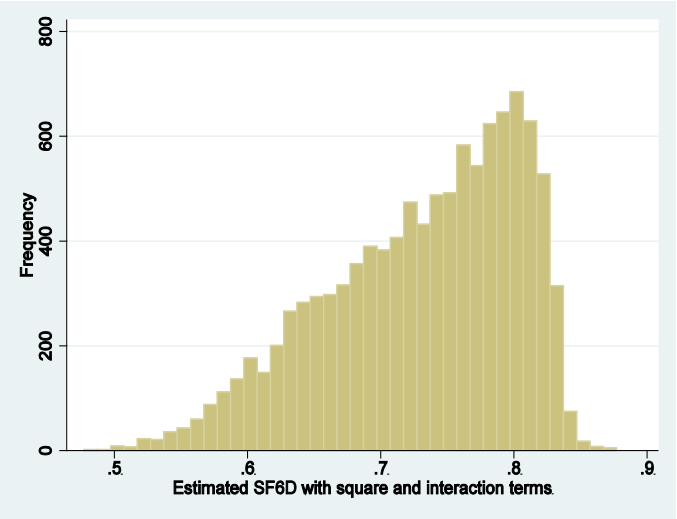


Figure 9. Histogram of SF6D patient score allocations



10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will

be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in red and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all

consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

10.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).