## Section A: Clarification on effectiveness data

### Literature searching

A1. In appendix 2 (page 204), the submission states that a systematic review for clinical effectiveness studies was not conducted. Please provide details of how clinical effectiveness literature searches were done, the dates and databases searched. Please clarify if any searches of ongoing trials registers were conducted and whether any company databases were searched.

The 'Prucalopride' Clinical Development Database of Movetis includes the clinical studies conducted under the sponsorship of Johnson & Johnson from 1999 to 2003.

This database was searched for phase II-III double-blind, placebo-controlled studies in adult and elderly patients with chronic constipation not adequately relieved by laxatives or in patients with chronic non-cancer pain, suffering from opioid-induced constipation. The non-randomized controlled trials on the long-term efficacy & safety of prucalopride were selected. Dose finding studies were excluded.

No additional trials were identified via searches on Medline (keyword: prucalopride, limited to clinical or randomized controlled trials) or ClinTrials.Gov (keyword: prucalopride).

A2. In appendix 10 Section 9.10 (page 205), please supply the date on which the cost effectiveness search was conducted, the date span of the search and clarify which databases were searched (if only MEDLINE was searched, please state).

A detailed search of **Medline** and **Embase** was undertaken from 2000 to Dec 2009 to identify whether any cost effectiveness analyses had been undertaken in the specific target group (patients suffering from long term chronic constipation) that would be appropriate to Prucalopride. No such analyses were identified in the search. We also searched the abstracts in **NHS HEED** and again no analyses were identified that provided any evidence regarding the cost effectiveness of treatment in the specific patient group being targeted by Prucalopride.

A3. In appendix 13 Section 9.13 (page 214) the introductory text of this section states that searches are outlined at the end of the section but no searches appear to be included. Please provide the searches completed to identify resource use.

Resource identification measurement and valuation

A detailed search was undertaken of Medline and Embase from 2000 onwards to identify potential changes in resource use that would result from the effective control of the symptoms of chronic constipation. The resource analysis emphasised that patients who suffer from chronic constipation that is ineffectively treated impose significant costs on the NHS at both the primary and secondary level.

Such patients represent a significant proportion of 'revolving door' patients who continually revisit GPs in an attempt to obtain effective relief of their symptoms.

Unfortunately the Prucalopride trials did not collect resource data and hence direct evidence from the trials was unavailable to support such resource savings from the use of Prucalopride. Therefore a very conservative assumption was made that no such savings would result from effectively controlling the symptoms of chronic constipation through the use of Prucalopride and hence the resource analysis was entirely confined to addressing the acquisition costs related to treatment with Prucalopride.

## Clinical trials

A4. Page 36 of the submission states that in the pivotal studies, laxatives were not allowed but a rescue therapy (bisacodyl (a type of laxative) or enema) could be given.

- Please define the laxatives used in trials for banned medication

In the pivotal trials, the intake of banned laxatives was limited as can be derived from table 1 below. Most of these medications were used by less than 0.5 % of the patients; only 2 medications were taken by more than 2 % of the patients i.e. golytely (3.6% for all prucalopride groups vs 3.9 for placebo) and magnesium citrate (3.5 vs 4.4 % for prucalopride and placebo respectively)

| LAXATIVE | PLACEBO NO. SUBJECTS (%) | PRU 2mg NO. SUBJECTS (%) | PRU 4mg NO. SUBJECTS (%) | ALL PRU NO. SUBJECTS (%) |
|---|---|---|---|---|
| TOTAL NUMBER OF SUBJECTS | 661 | 659 | 657 | 1316 |
| AGAROL | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| CAPSUVAC | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| COLOXYL WITH DANTHRON | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.1) |
| DOCUSATE | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.1) |
| DOCUSATE CALCIUM | 2 ( 0.3) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.1) |
| DOCUSATE SODIUM | 8 ( 1.2) | 2 ( 0.3) | 2 ( 0.3) | 4 ( 0.3) |
| DORBANEX | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.1) |
| DOXIDAN | 1 ( 0.2) | 2 ( 0.3) | 0 ( 0.0) | 2 ( 0.2) |
| EMTIX | 2 ( 0.3) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.1) |
| GLYCEROL | 3 ( 0.5) | 3 ( 0.5) | 7 ( 1.1) | 10 ( 0.8) |
| GOLYTELY | 26 ( 3.9) | 24 ( 3.6) | 24 ( 3.7) | 48 ( 3.6) |
| LACTITOL | 1 ( 0.2) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.1) |
| LACTULOSE | 9 ( 1.4) | 3 ( 0.5) | 7 ( 1.1) | 10 ( 0.8) |
| MAGNESIUM CITRATE | 29 ( 4.4) | 19 ( 2.9) | 27 ( 4.1) | 46 ( 3.5) |
| MAGNESIUM OXIDE | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.1) |
| MAGNESIUM SULFATE | 1 ( 0.2) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.1) |
| METHYLCELLULOSE | 7 ( 1.1) | 1 ( 0.2) | 4 ( 0.6) | 5 ( 0.4) |
| MICROLAX | 2 ( 0.3) | 2 ( 0.3) | 1 ( 0.2) | 3 ( 0.2) |
| MINERAL OIL | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| NULYTELY | 11 ( 1.7) | 11 ( 1.7) | 12 ( 1.8) | 23 ( 1.7) |
| PERDIEM | 10 ( 1.5) | 5 ( 0.8) | 6 ( 0.9) | 11 ( 0.8) |
| PERI-COLACE | 4 ( 0.6) | 1 ( 0.2) | 2 ( 0.3) | 3 ( 0.2) |
| PHENOLPHTHALEIN | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.2) | 2 ( 0.2) |
| PHILLIPS LAXCAPS | 9 ( 1.4) | 18 ( 2.7) | 13 ( 2.0) | 31 ( 2.4) |
| POLYCARBOPHIL CALCIUM | 1 ( 0.2) | 2 ( 0.3) | 12 ( 1.8) | 14 ( 1.1) |
| PRODIEM | 0 ( 0.0) | 2 ( 0.3) | 0 ( 0.0) | 2 ( 0.2) |
| PSYLLIUM HYDROPHILIC MUCILLOID | 0 ( 0.0) | 1 ( 0.2) | 1 ( 0.2) | 2 ( 0.2) |
| SALINE | 2 ( 0.3) | 0 ( 0.0) | 3 ( 0.5) | 3 ( 0.2) |
| SENNOSIDE A+B | 2 ( 0.3) | 1 ( 0.2) | 2 ( 0.3) | 3 ( 0.2) |
| SODIUM CHLORIDE | 5 ( 0.8) | 2 ( 0.3) | 4 ( 0.6) | 6 ( 0.5) |
| SODIUM PHOSPHATE (32 P) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| SODIUM PICOSULFATE | 1 ( 0.2) | 5 ( 0.8) | 1 ( 0.2) | 6 ( 0.5) |

- Please describe the criteria for allowing rescue therapy and the process by which patients could receive that therapy

Laxatives were not allowed. However, if the subject did not have a bowel movement for three or more consecutive days throughout the trial, he/she was allowed bisacodyl (Dulcolax®) as rescue medication. A maximum single dose of 15 mg (3 tablets) of bisacodyl was prescribed. If this standard dose was insufficient, an increase in the dose was allowed, but only after the subject had contacted the investigator. If no bowel movements were passed after an increase in the amount of Dulcolax®, an enema could be administered. The use had to be documented in the subject's diary.

No Dulcolax® could be taken or enemas used within 48 hours prior to the start of double-blind treatment (visit 2) and 48 hours following the start of double-blind treatment.

The marketed tablet of bisacodyl (Dulcolax®) was supplied by the sponsor as a rescue medication (5 mg tablets)

A5. Please clarify

1. what medications were allowed during the run-in period and

2. whether in the run-in period spontaneous complete bowel movements (SCBM) were classed only as those >24 hours after the use of laxative.

**1. Medications allowed during the run-in period**

During the whole study period **(including the run-in period**) the same rules for concomitant medications were applied:

Medications that were disallowed during the conduct of the trial were the following:

- Agents that influence the bowel habit could not be taken by, or administered to the subject during the trial; i.e., anticholinergics (not including antihistamines), opioids, spasmolytics, prokinetics, and tricyclic antidepressants. Intake of these medications had to be stopped at the start of the run-in period and was disallowed during the entire trial.

- Laxatives were not allowed. However, if the subject did not have a bowel movement for three or more consecutive days throughout the trial, he/she was allowed bisacodyl (Dulcolax®) as rescue medication (see above answer to A4)

If subjects were receiving $Ca^{2+}$ blockers, treatment had to be continued at the same dose.

**2 Definition of Spontaneous complete bowel movements (SCBM) during the run-in period.**

During the run-in period SCBMs were indeed classed only as those not preceded within a period of 24 hours by the intake of a laxative agent or by the use of an enema.

A6. In tables 12, 13 and 15 (pages 41-4) combined data for patients' previous laxative and enema use are provided. Please provide separate data for previous laxative use and enemas that patients used before they took part in the pivotal. Please provide data for the pivotal, elderly and retreatment populations for each study arm separately.

The following question was asked at the screening visit "Have you been treated for your constipation during the previous 6 months?"

- Diet: yes/no
- Bulk forming agents: yes/no
- Laxatives/enemas: yes/no

More detailed information on the type of laxatives used in previous 6 months was not collected. Thus more detailed information as presented in tables 12, 13 and 15 (pages 41-4) is not available.

A7. Pages 45-48 of the submission present results in terms of spontaneous bowel movements so that all bowel movements occurring due to the comparator treatment (biscodyl) are discounted. Please provide data for the total number of bowel movements (spontaneous and non-spontaneous) in each arm of pivotal, elderly and retreatment trials

Figure 1 and Tables 2, 3 and 4, below present results for all type of bowel movements i.e. SCBMs, SBMs and all BMs. The difference between the average BM and average SBM represents the average NON-spontaneous BM.

For the pivotal trials, the mean number of non-spontaneous BM in the placebo group was 1.9 during run-in and 1.7 during week 1-4 and week 1-12. A similar value was seen during the run-in with both prucalopride groups (1.8). The number of non-spontaneous BM decreased to 1.1 and 1.0 in both prucalopride groups at week 1-4 and 1-12 respectively

For the elderly trial, the mean number of non-spontaneous BM in the placebo group was 1.0 during run-in and 0.8 to 0.9 during week1-4 after treatment with prucalopride 1 to 4 mg.

For the retreatment trial, the mean number of non-spontaneous BM in the placebo group was 1.5 during both the run-in and wash-out period and was reduced to ≤ 1 after treatment with prucalopride (for both treatment periods).

In conclusion, overall an increase in spontaneous BM and a decrease in non-spontaneous BM was seen after treatment with prucalopride.

*Figure 1: Average number of SCBM, SBM and BM per treatment group during run-in and during 12 weeks of treatment for combined pivotal trials. The total bar represents average number of all BM, including both SBM and SCBM. The black coloured part represents the part of all BM that were non-spontaneous.*

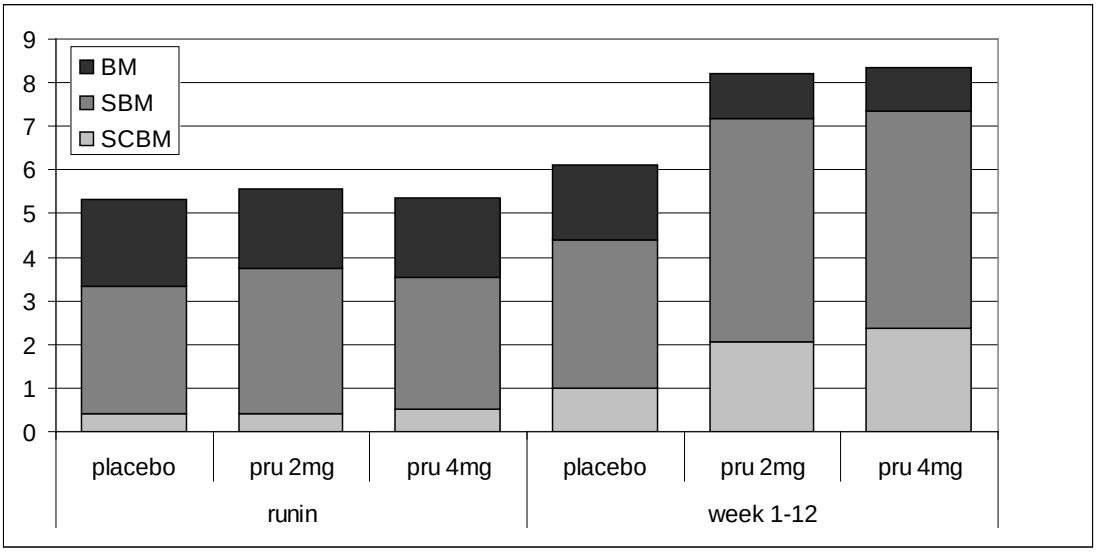



*Table 2: Average number of SCBM, SBM and BM per treatment group during run-in and during 4 and 12 weeks of treatment for combined pivotal trials*

| Pivotal trials | PLA | | | | | | PRU 2 mg | | | PRU 4 mg | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | Mean change | | | | N | Mean | Mean change | N | Mean | Mean change |
| *Average SCBM/week* | | | | | | | | | | | | |
| *Run-in* | 643 | 0.42 | | | | | 638 | 0.42 | | 639 | 0.53 | |
| *Weeks 1-4* | 630 | 1.11 | 0.69 | | | | 612 | 1.89 | 1.49 | 593 | 2.07 | 1.58 |
| *Weeks 1-12* | 632 | 1.01 | 0.58 | | | | 613 | 2.06 | 1.67 | 596 | 2.36 | 1.87 |
| *Average SBM/week* | | | | | | | | | | | | |
| *Run-in* | 643 | 3.34 | | | | | 638 | 3.73 | | 639 | 3.54 | |
| *Weeks 1-4* | 630 | 4.21 | 0.86 | | | | 612 | 6.25 | 2.57 | 593 | 6.34 | 2.91 |
| *Weeks 1-12* | 632 | 4.38 | 1.04 | | | | 613 | 7.17 | 3.48 | 596 | 7.36 | 3.92 |
| *Average BM/week* | | | | | | | | | | | | |
| *Run-in* | 643 | 5.31 | | | | | 638 | 5.56 | | 639 | 5.35 | |
| *Weeks 1-4* | 630 | 5.97 | 0.64 | | | | 612 | 7.37 | 1.84 | 593 | 7.47 | 2.22 |
| *Weeks 1-12* | 632 | 6.12 | 0.8 | | | | 613 | 8.2 | 2.67 | 596 | 8.35 | 3.09 |

*Table 3 Average number of SCBM, SBM and BM per treatment group during run- in and during 4 weeks of treatment for the elderly trial*

| INT 12 | PLA | | | PRU 1 mg | | | PRU 2 mg | | | PRU 4 mg | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | Mean change | N | Mean | Mean change | N | Mean | Mean change | N | Mean | Mean change |
| *Average SCBM/week* | | | | | | | | | | | | |
| *Run-in* | 70 | 1.1 | | 76 | 0.8 | | 75 | 0.7 | | 79 | 0.7 | |
| *Weeks 1-4* | 65 | 1.7 | 0.6 | 72 | 2.7 | 1.9* | 72 | 2.4 | 1.7* | 73 | 2.4 | 1.8* |
| *Average SBM/week* | | | | | | | | | | | | |
| *Run-in* | 70 | 4.2 | | 76 | 4.5 | | 75 | 4.1 | | 79 | 4.3 | |
| *Weeks 1-4* | 65 | 5.1 | 1.0 | 72 | 6.9 | 2.4* | 72 | 6.0 | 1.9 | 73 | 6.2 | 2.0 |
| *Average BM/week* | | | | | | | | | | | | |
| *Run-in* | 70 | 6.1 | | 76 | 5.7 | | 75 | 5.7 | | 79 | 5.7 | |
| *Weeks 1-4* | 65 | 6.1 | 0.2 | 72 | 7.7 | 2.0* | 72 | 6.9 | 1.2 | 73 | 7.1 | 1.4* |

*Table 4 Average number of SCBM, SBM and BM per treatment group during run-in and during 4 weeks of treatment and retreatment*

| USA 28 | PLA | | | PRU 4 mg | | |
|---|---|---|---|---|---|---|
| | N | Mean | Mean change[1] | N | Mean | Mean change[1] |
| Average SCBM/week | | | | | | |
| Treatment Period I | | | | | | |
| Run-in | 205 | 0.4±0.04 | - | 189 | 0.5±0.06 | - |
| Weeks 1-4 | 205 | 1.0±0.10 | 0.6±0.10 | 189 | 2.8±0.20 | 2.3±0.19*** |
| Treatment Period II | | | | | | |
| Washout II | 203 | 0.4±0.05 | - | 189 | 0.4±0.04 | - |
| Weeks 1-4 | 205 | 1.1±0.11 | 0.6±0.09 | 189 | 2.5±0.21 | 2.1±0.20*** |
| Average SBM/week | | | | | | |
| Treatment Period I | | | | | | |
| Run-in | 205 | 3.4±0.25 | - | 189 | 2.8±0.20* | - |
| Weeks 1-4 | 205 | 4.3±0.27 | 0.9±0.21 | 189 | 6.9±0.29 | 4.1±0.27*** |
| Treatment Period II | | | | | | |
| Washout II | 203 | 3.2±0.25 | - | 189 | 2.5±0.18** | - |
| Weeks 1-4 | 205 | 3.9±0.25 | 0.7±0.15 | 189 | 5.7±0.29 | 3.2±0.23*** |
| Average BM/week | | | | | | |
| Treatment Period I | | | | | | |
| Run-in | 205 | 5.0±0.23 | - | 189 | 4.4±0.20* | - |
| Weeks 1-4 | 205 | 5.8±0.24 | 0.8±0.18 | 189 | 7.7±0.27 | 3.3±0.21*** |
| Treatment Period II | | | | | | |
| Washout II | 203 | 4.9±0.22 | - | 189 | 4.5±0.18□ | - |
| Weeks 1-4 | 205 | 5.4±0.22 | 0.4±0.15 | 189 | 6.7±0.26 | 2.2±0.20*** |

A8. Page 58 of the submission states that data from the last 7 diary days were used to fill in missing diary days.

- Please provide a full description of how this was done
- Please provide data for the number of days that patients filled in their diaries in the different treatment arms for the pivotal, elderly and retreatment studies.

(1) The methods of imputations were pre-specified in the statistical analyses plans. To evaluate the impact of these imputations several additional sensitivity analyses were performed for the pivotal trials. These were described in the individual reports and all gave similar results.

The following section is taken from the analysis plan of the pivotal trials.

***Imputations for diary data***

***Imputation primary period***

***Periods Week 1-4, Week 5-8, Week 9-12 and All DB period (week 1-12)***

*For subjects who did not complete the diary up to day 84, but with at least 7 non-missing diary days after week 1, the last 7 diary days were used to impute the missing diary information after the last diary day up to day 84. No imputation was carried out for subjects with less than 7 non-missing diary days after week 1 and average frequencies were set to missing.*

*The weekly average frequency of bowel movements for each 4-week period (weeks 1-4, 5-8, 9-12) and the entire double blind period (weeks 1-12) was calculated from the expanded dataset.*

*The primary analyses was based on weekly frequencies and scores calculated using this method.*

*(2) Distribution number of days with diary data.*

Pivotal trials

The distribution of number of days with diary data for the 3 combined pivotal trials is presented in figure 2 and table 5 below. As can be seen more than 80% of the patients have more than 80 days with diary data. From Table 5 it is clear that there is no difference between placebo and PRU 2mg group in this distribution.

For patients with less than 14 days of diary data (4.5%), no imputations were performed and patients were considered non-responder for the primary endpoint (and excluded from other analyses).

*Figure 2: cumulative distribution of number of days with diary data in pooled pivotal trials (n=1921 patients).*

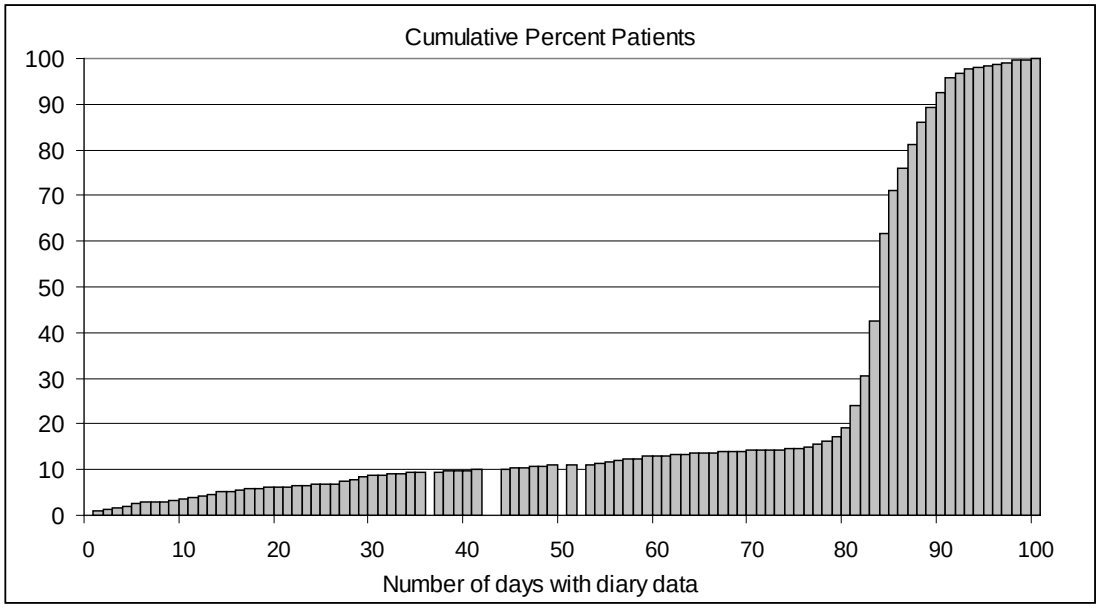



*Table 5: categorized distribution of number of days with diary data for pooled pivotal trials: total and splitted per treatment group.*

| ***Days with diary data*** | ***Number of patients*** | ***Percent*** | ***Cumulative Percent*** |
|---|---|---|---|
| ***ALL PATIENTS*** | | | |
| *<= 20 days* | *118* | *6.14* | *6.14* |
| *<= 40 days* | *70* | *3.64* | *9.79* |
| *<= 60 days* | *63* | *3.28* | *13.07* |
| *<= 80 days* | *117* | *6.09* | *19.16* |
| *> 80 days* | *1553* | *80.84* | *100.00* |
| ***PLACEBO*** | | | |
| *<= 20 days* | *27* | *4.19* | *4.19* |
| *<= 40 days* | *29* | *4.50* | *8.68* |
| *<= 60 days* | *21* | *3.26* | *11.94* |
| *<= 80 days* | *41* | *6.36* | *18.29* |
| *> 80 days* | *527* | *81.71* | *100.00* |
| ***PRU 2MG*** | | | |
| *<= 20 days* | *33* | *5.17* | *5.17* |
| *<= 40 days* | *20* | *3.13* | *8.31* |
| *<= 60 days* | *18* | *2.82* | *11.13* |
| *<= 80 days* | *40* | *6.27* | *17.40* |
| *> 80 days* | *527* | *82.60* | *100.00* |
| ***PRU 4MG*** | | | |
| *<= 20 days* | *58* | *9.09* | *9.09* |
| *<= 40 days* | *21* | *3.29* | *12.38* |
| *<= 60 days* | *24* | *3.76* | *16.14* |
| *<= 80 days* | *36* | *5.64* | *21.79* |
| *> 80 days* | *499* | *78.21* | *100.00* |

Elderly trial (INT-12)

The same results as presented for the pivotal trials are shown below for the elderly trial (table 6, figure 3): only 11.7% of the patients have less than 21 days with diary data and no differences were seen in distribution between the different treatment groups

*Figure 3: cumulative distribution of number of days with diary data in elderly trial (n=300 patients).*

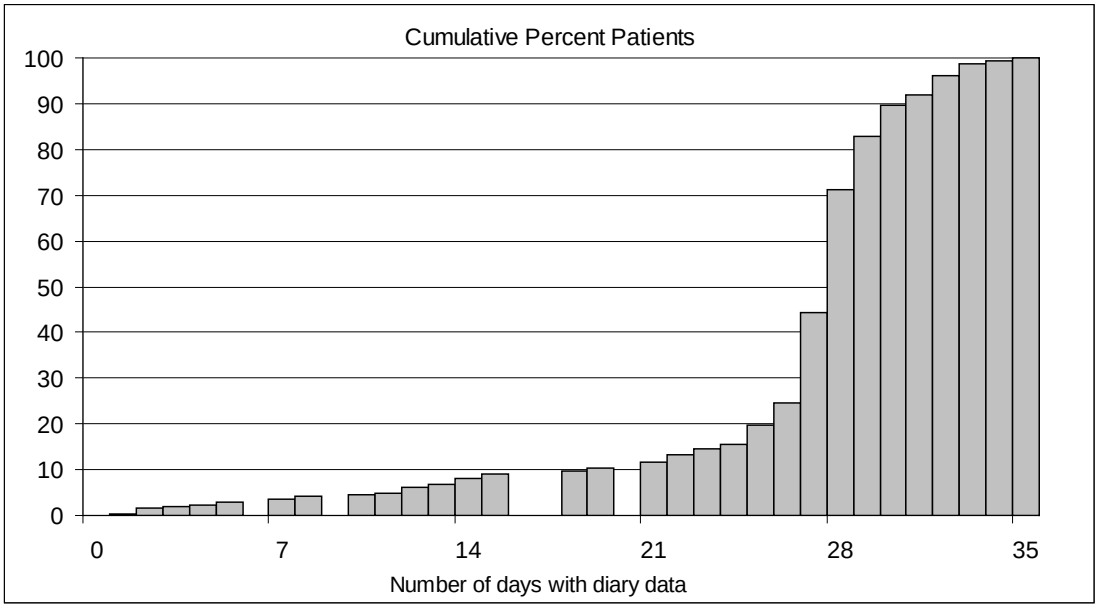



*Table 6: categorized distribution of number of days with diary data for elderly trial.*

| ***Days with diary data*** | ***Number of patients*** | ***Percent*** | ***Cumulative Percent*** |
|---|---|---|---|
| ***ALL PATIENTS*** | | | |
| *<= 7 days* | *11* | *3.7* | *3.7* |
| *<= 14 days* | *13* | *4.3* | *8.0* |
| *<= 21 days* | *11* | *3.7* | *11.7* |
| *<= 28 days* | *179* | *59.7* | *71.3* |
| *> 28 days* | *86* | *28.7* | *100.0* |
| **PLACEBO** | | | |
| <= 7 days | 2 | 2.9 | 2.9 |
| <= 14 days | 4 | 5.7 | 8.6 |
| <= 28 days | 46 | 65.7 | 74.3 |
| > 28 days | 18 | 25.7 | 100.0 |
| **PRU 1MG** | | | |
| <= 7 days | 2 | 2.6 | 2.6 |
| <= 14 days | 4 | 5.3 | 7.9 |
| <= 21 days | 2 | 2.6 | 10.5 |
| <= 28 days | 47 | 61.8 | 72.4 |
| > 28 days | 21 | 27.6 | 100.0 |
| **PRU 2MG** | | | |
| <= 7 days | 2 | 2.7 | 2.7 |
| <= 14 days | 2 | 2.7 | 5.3 |

| | | | |
|---|---|---|---|
| <= 21 days | 5 | 6.7 | 12.0 |
| <= 28 days | 45 | 60.0 | 72.0 |
| > 28 days | 21 | 28.0 | 100.0 |
| **PRU 4MG** | | | |
| <= 7 days | 5 | 6.3 | 6.3 |
| <= 14 days | 3 | 3.8 | 10.1 |
| <= 21 days | 4 | 5.1 | 15.2 |
| <= 28 days | 41 | 51.9 | 67.1 |
| > 28 days | 26 | 32.9 | 100.0 |

Retreatment trial (USA-28)

Distribution of the number of days with diary data during the first and second period of treatment in USA-28 are similar. In both periods less than 4% of patients had less than 21 days with diary data with no difference in distribution between the two treatment periods.

*Figure 4: cumulative distribution of number of days with diary data for period 1in retreatment trial (n=462 patients).*

*Treatment period 1*

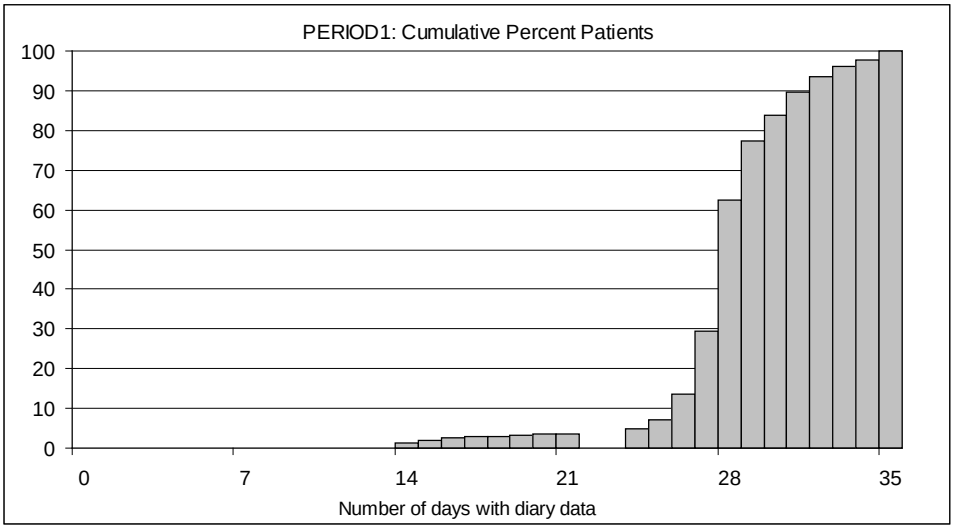



*Table 7: categorized distribution of number of days with diary data for retreatment trial period 1.*

| ***Days with diary data*** | ***Number of patients*** | ***Percent*** | ***Cumulative Percent*** |
|---|---|---|---|
| ***ALL PATIENTS*** | | | |
| *<= 7 days* | *0* | *0* | *0* |
| *<= 14 days* | *6* | *1.3* | *1.3* |
| *<= 21 days* | *11* | *2.4* | *3.7* |
| *<= 28 days* | *271* | *58.7* | *62.3* |
| *> 28 days* | *174* | *37.7* | *100.0* |
| ***PLACEBO*** | | | |
| *<= 7 days* | *0* | *0.0* | *0.0* |
| *<= 14 days* | *4* | *1.7* | *1.7* |
| *<= 21 days* | *5* | *2.1* | *3.8* |
| *<= 28 days* | *137* | *57.3* | *61.1* |

| | | | |
|---|---|---|---|
| *> 28 days* | *93* | *38.9* | *100.0* |
| ***PRU 4MG*** | | | |
| *<= 7 days* | *0* | *0.0* | *0.0* |
| *<= 14 days* | *2* | *0.9* | *0.9* |
| *<= 21 days* | *6* | *2.7* | *3.6* |
| *<= 28 days* | *134* | *60.1* | *63.7* |
| *> 28 days* | *81* | *36.3* | *100.0* |

## *Treatment period 2*

*Figure 5: cumulative distribution of number of days with diary data for period 2 in retreatment trial (n=398 patients).*

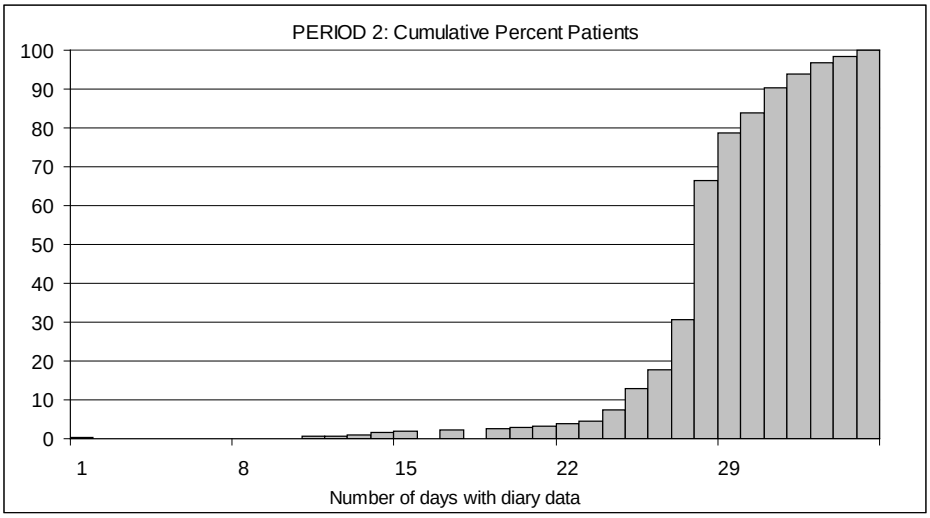



*Table 8: categorized distribution of number of days with diary data for retreatment trial period 2.*

| ***Days with diary data*** | ***Number of patients*** | ***Percent*** | ***Cumulative Percent*** |
|---|---|---|---|
| ***ALL PATIENTS*** | | | |
| *<= 7 days* | *1* | *0.25* | *0.25* |
| *<= 14 days* | *5* | *1.26* | *1.51* |
| *<= 21 days* | *7* | *1.76* | *3.27* |
| *<= 28 days* | *252* | *63.32* | *66.58* |
| *> 28 days* | *133* | *33.42* | *100.00* |
| ***PLACEBO*** | ***0*** | ***0.0*** | ***0.0*** |
| *<= 7 days* | *1* | *0.5* | *0.5* |
| *<= 14 days* | *3* | *1.4* | *1.9* |
| *<= 21 days* | *6* | *2.9* | *4.8* |
| *<= 28 days* | *129* | *62.0* | *66.8* |
| *> 28 days* | *69* | *33.2* | *100.0* |
| ***PRU 4MG*** | | | |
| *<= 7 days* | *0* | *0.0* | *0.0* |
| *<= 14 days* | *2* | *1.1* | *1.1* |
| *<= 21 days* | *1* | *0.5* | *1.6* |
| *<= 28 days* | *123* | *64.7* | *66.3* |
| *> 28 days* | *64* | *33.7* | *100.0* |

A9. It is stated on page 79 that meta-analysis was not conducted. However, pooled results are described in the summary of section 5.5 and elsewhere in the submission. Please provide details of the methods used to pool results from the three pivotal trials.

If the pooling of clinical trial data as required for regulatory submissions is considered as meta-analyses, we indeed performed meta-analyses. The pooling of all different kinds of data (adverse events data, ECG data, diary data, data phase I trials etc.) are described in statistical analysis plans (separated for safety and efficacy).

The original SAS data sets were the basis of the pooled data, which are also available as SAS data sets. For phase III trials and most phase II trials the structure of these data sets were similar, such that pooling (combining) was straightforward.

During this process continuous checking was performed to guarantee that pooled data was identical to the original data.

A10. It is stated in page 60 that 50 patients were excluded from PRU-USA-11 trial (Camilleri 2008) for the pooled efficacy pivotal trial results.

- Please explain why these patients appear to be excluded from the analysis of pivotal trials (table 25, page 62) but included in the economic modelling (table 53, page 124)
- Please provide details and results of the additional analysis referred to on page 60.

The exclusion of the centers was specified in the statistical analyses plan of the corresponding trial as well as in the SAP for the summary of efficacy.

The ITT population consisted of all randomized patients who took at least 1 dose of double-blind study medication and who provided any follow-up data for one or more key efficacy variables. A total of 628 patients were randomized: 8 patients did not use any treatment.

In the trial report, 15 patients were excluded from one site (Dr Ohning) due to an improperly constituted IRB and 35 patients were excluded from another site (Dr. Krumholz) due to data quality issues.

The effect of excluding 50 patients from the ITT analysis was investigated by performing the same analyses including the available data from all treated patients (N=620, including the 50 patients).These analyses revealed no meaningful differences when compared to the analysis excluding the 50 patients. For all treated patients, the proportion of patients with ≥3 SCBM/week over the 12-week treatment period was 30.9% in the prucalopride 2 mg group and 28.4% in the prucalopride 4 mg group, compared to 12.0% in the placebo group ($p<0.001$). These findings are in line when excluding the 50 patients (28.9% in each prucalopride group vs. 13.0% in the placebo group;

Thus, as the results of analyses with and without the centres did not result in meaningful differences and because safety analyses was also based on all patients, data from these patients were added to the efficacy analyses for the publication (Camilleri, 2009) and were also used for the economic modelling.

*Original analyses excluding the 50 patients*

| | *PLA* | *PRU 2 mg* | *PRU 4 mg* |
|---|---|---|---|
| *Number of subjects with an average ≥3 SCBM per week, n/N (%)* | | | |
| *Run-in* | *0/192 (0)* | *2/189 (1.1)* | *2/187 (1.1)* |
| *Weeks 1-12* | *25/193 (13.0)* | *55/190 (28.9)* | *54/187 (28.9)* |
| *Weeks 1-4* | *19/193 (9.8)* | *61/190 (32.1)* | *70/187 (37.4)* |
| *Number of subjects with an average increase ≥1 SCBM per week, n/N (%)* | | | |

| | | | |
|---|---|---|---|
| *Weeks 1-12* | *49/189 (25.9)* | *89/177 (50.3)* | *90/176 (51.1)* |
| *Weeks 1-4* | *46/189 (24.3)* | *100/177 (56.5)* | *104/177 (58.8)* |
| *Average SCBM per week, mean (mean change)* | | | |
| *Run-in* | *0.4 (-)* | *0.5 (-)* | *0.5 (-)* |
| *Weeks 1-12* | *1.3 (0.8)* | *2.3 (1.9)* | *2.4 (1.9)* |
| *Weeks 1-4* | *1.1 (0.7)* | *2.5 (2.1)* | *2.8 (2.3)* |

*Analyses including the 50 patients*

| | *PLA* | *PRU 2 mg* | *PRU 4 mg* |
|---|---|---|---|
| *Number of subjects with an average ≥3 SCBM per week, n/N (%)* | | | |
| *Run-in* | *0/209 (0)* | *2/207 (1.0)* | *2/204 (1.0)* |
| *Weeks 1-12* | *25/209 (12.0)* | *64/207 (30.9)* | *57/204 (28.4)* |
| *Weeks 1-4* | *21/209 (10.1)* | *70/207 (33.8)* | *74/204 (36.3)* |
| *Number of subjects with an average increase ≥1 SCBM per week, n/N (%)* | | | |
| *Weeks 1-12* | *54/204 (26.5)* | *98/193 (50.8)* | *95/190 (50.0)* |
| *Weeks 1-4* | *49/205 (23.9)* | *111/193 (57.5)* | *111/191 (58.1)* |
| *Average SCBM per week, mean (mean change)* | | | |
| *Run-in* | *0.4 (-)* | *0.5 (-)* | *0.5 (-)* |
| *Weeks 1-12* | *1.2 (0.8)* | *2.3 (1.9)* | *2.4 (1.9)* |
| *Weeks 1-4* | *1.1 (0.7)* | *2.5 (2.1)* | *2.7(2.2)* |

A11. On pages 62-63, all data for the three pivotal clinical trials appear to have informed the analysis of pooled efficacy. Please clarify whether male patients and those who had not previously taken laxatives were included in the pooled analysis of pivotal trials.

Yes these results included all original ITT patients. However during the pooled analyses a large number of subgroup analyses were performed. All efficacy endpoints were basically analyses by ITT and by our 'Target' population, i.e only those patients from the ITT population that rated their previous laxative therapy (in 6 months before start of trial) as inadequate.

For both populations analyses were performed in subgroups of sex. So results of the females in the target population are available and are summarized for the parameters ≥3 SCBM and an increase of ≥1 SCBM in the tables 9 a and b below

*Table 9*

*a. Number (%) of female patients who not adequately relieved on laxatives with ≥3 SCBM per week*

| | **Placebo** | | **PRU 2 mg** | | **PRU 4 mg** | |
|---|---|---|---|---|---|---|
| **Time-point** | **N** | **n (%)** | **N** | **n (%)** | **N** | **n (%)** |
| Female n (%) | | | | | | |
| Run-in | 466 | 2 (0.4) | 451 | 4 (0.9) | 452 | 6 (1.3) |
| Weeks 1-12 | 468 | 44 (9.4) | 452 | 109 (24.1) | 452 | 110 (24.3) |
| Weeks-1-4 | 468 | 39 (8.3) | 452 | 138 (30.5) | 452 | 134 (29.6) |

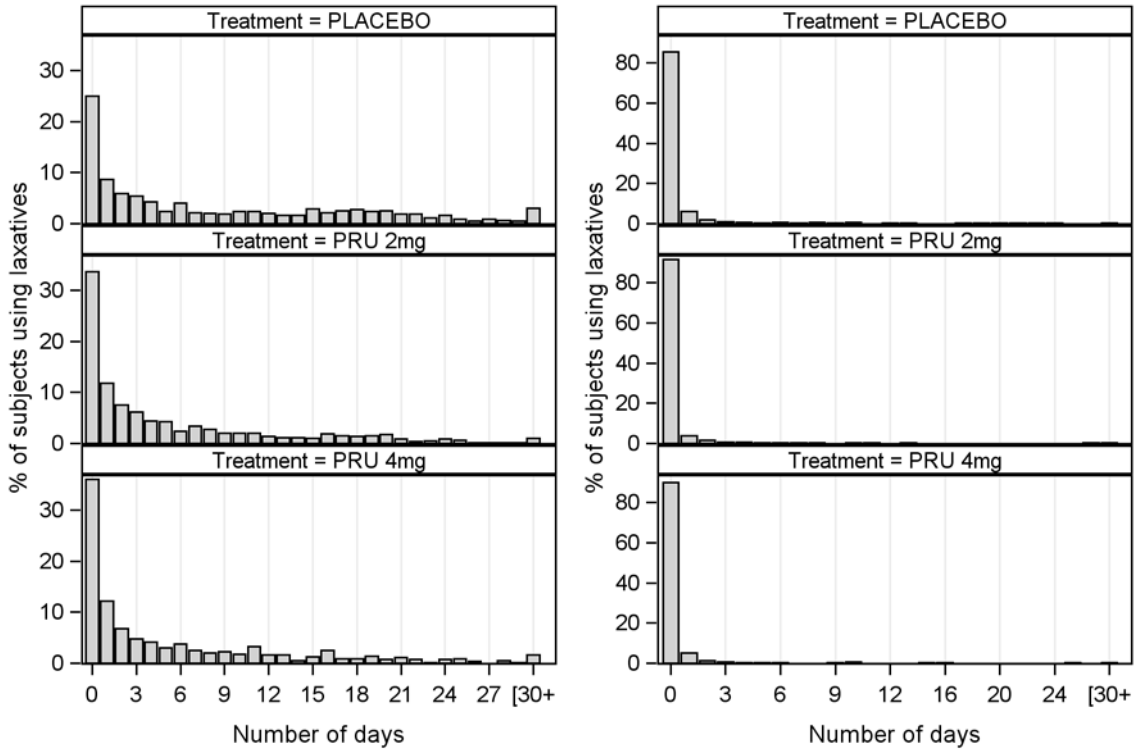
*b Number (%) of female patients not adequately relieved on laxatives with an increase of ≥1 SCBM*

| | **Placebo** | | **PRU 2 mg** | | **PRU 4 mg** | |
|---|---|---|---|---|---|---|
| **Time-point** | **N** | **n (%)** | **N** | **n (%)** | **N** | **n (%)** |
| Female n (%) | | | | | | |
| Weeks 1-12 | 455 | 101 (22.2) | 433 | 190 (43.9) | 420 | 195 (46.4) |
| Weeks 1-4 | 456 | 98 (21.5) | 433 | 220 (50.8) | 423 | 215 (50.8) |

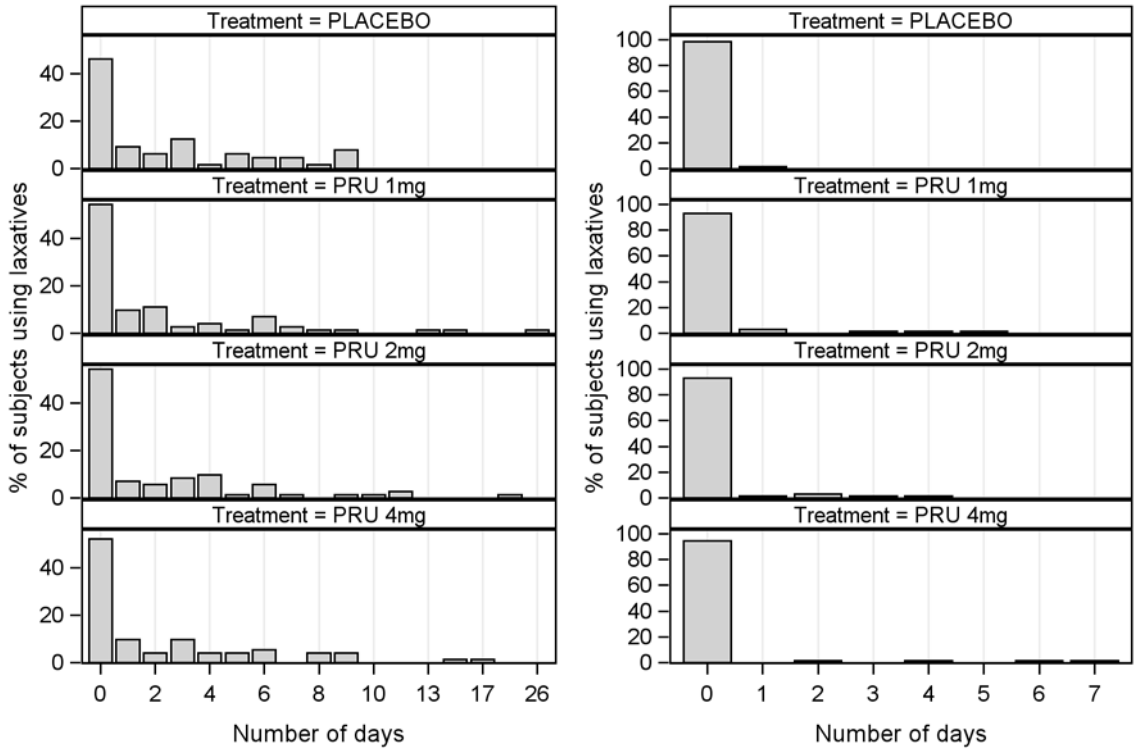
A12. Section 5.5 of the submission (pages 62-68) provides combined data for laxative and enema use during the clinical trial. Please provide separate data for the number of days with bisacodyl use and days with enemas in the pivotal, elderly and retreatment trials in each study arm.

*Figures 6 below present the distribution of the number of days with bisacodyl use and with enema use. Use of rescue medication was low. As can be derived from the figures, 30 to 40% of the patients did not take bisacodyl and 85% to 90% of the patients did not have enemas during the whole trial period.*

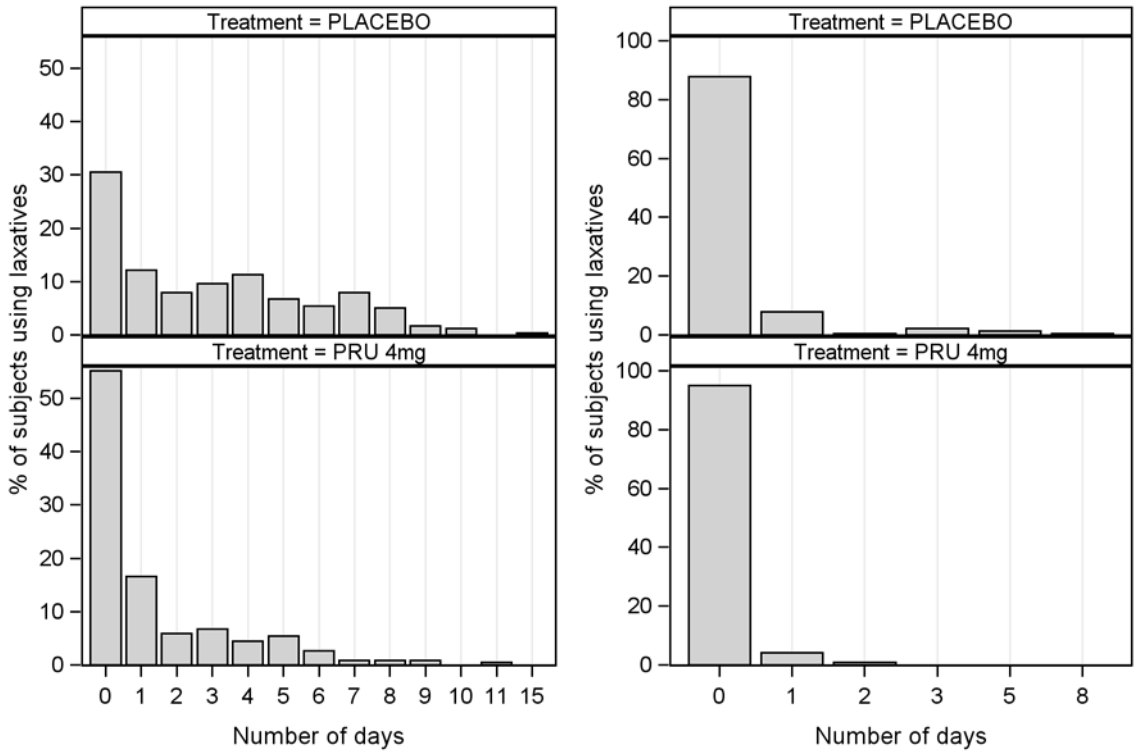
*Pivotals: bisacodyl (left) and enema(right)*



*Elderly trial (INT 12) : bisacodyl (left) and enema(right)*




*Retreatment trial (USA 28): bisacodyl (left) and enema(right)*



A13. On page 62 of the submission, the change between run in and week 4 for the primary efficacy endpoint (% patients with > 3 SCBMs/week) in the placebo arm rises in the three pivotal trials, for example, for PRU-INT-6 the increase is from 0.8% to 10.4%. This appears counterintuitive for a situation in which laxative availability has been withdrawn and only “rescue therapy” is available. Please provide a discussion and explanation for the increases observed.

It is a known effect that an inactive substance can improve a patient's condition simply because the person has the expectation that it will be helpful. Expectation plays a potent role in the placebo effect; the more a person believes he/she is going to benefit from a treatment, the more likely that a benefit will be experienced.

A placebo arm is added in clinical trials to separate out this power of positive thinking and some other variables from a drug's true medical benefits

It has been shown that placebos have measurable physiological effects. Treatment with placebo tends to speed up pulse rate, increase blood pressure, and improve reaction speeds, for example, when participants are told they have taken a stimulant (Placebo effects: understanding the mechanism in health and disease F Benedetti, 2009. Oxford University Press Inc. NY)

The placebo response can be particulary high in functional gastrointestinal (GI) disorders, which can make it more difficult to show superiority of a new treatment over placebo. In functional GI disorders (functional dyspepsia) the placebo response has varied from 13 to 73% (Veldhyuzen van Zanten S et al., Drug treatment of functional dyspepsia: a systemic analysis of trial methodology with recommendations for design of future trials; Am J Gastroenterol, 1996 91, 660-671) while for IBS the reported range has been up to 70% (Klein KB. Controlled treatment trials in IBS: a critique. Gastroenterology 1988; 95: 232-241). Thus the placebo response observed in our clinical trials was not unexpected and the placebo response observed was very similar to other trials in constipation using a similar endpoint (Kamm et al, Am J Gastroenterol, 2005; 100: 362-37. Tegaserod for the treatment of chronic constipation: a randomized, double blind placebo controlled multinational study)

A14. Table 25 (page 63), describes patients' rating of their treatment. Please clarify whether patients were asked to rate only the study intervention part of their treatment that is, prucalopride or placebo, or whether this rating also included the rescue therapy.

Patients were asked to rate the efficacy of the study intervention on the CRF based on the following question

Please rate how effective your trial medication was by ticking one of the following (from not effective to very effective). Thus, patients were clearly asked to rate the effect of treatment with either prucalopride or placebo

A15. Adverse events are only given for those occurring in≥5% of patients (pages 99-103). Please provide full data for adverse events for each study arm in the pivotal, elderly and retreatment trials.

*A compiled list with all reported adverse event per trial is presented in attachment table DSAF 1.1.1.C per trial.*

## Section B: Clarification on cost-effectiveness data

1. Please clarify whether data for a comparator group are included in the economic model. Further, please confirm whether the estimates of NET_COST and EQ5D change in columns F and J of the spreadsheets are intended to represent differences between the results with and without prucalopride

The comparator group is included in the model; the placebo control group is standard care for laxative refractory patients. Standard care for patients with laxative refractory chronic constipation is, on a PRN basis, to use short-term stimulant laxatives as rescue medication, therefore the trials did compare prucalopride plus PRN rescue medication versus standard of care (placebo plus PRN rescue medication) for laxative refractory patients.

*Please see; page 156 of the submission dossier inserted below.* *

Estimates of net cost and eq5d changes are both included in the model. Estimates of NET_COST and EQ5D change in columns F and J of the spreadsheets are intended to represent differences between the results with and without prucalopride.

### *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

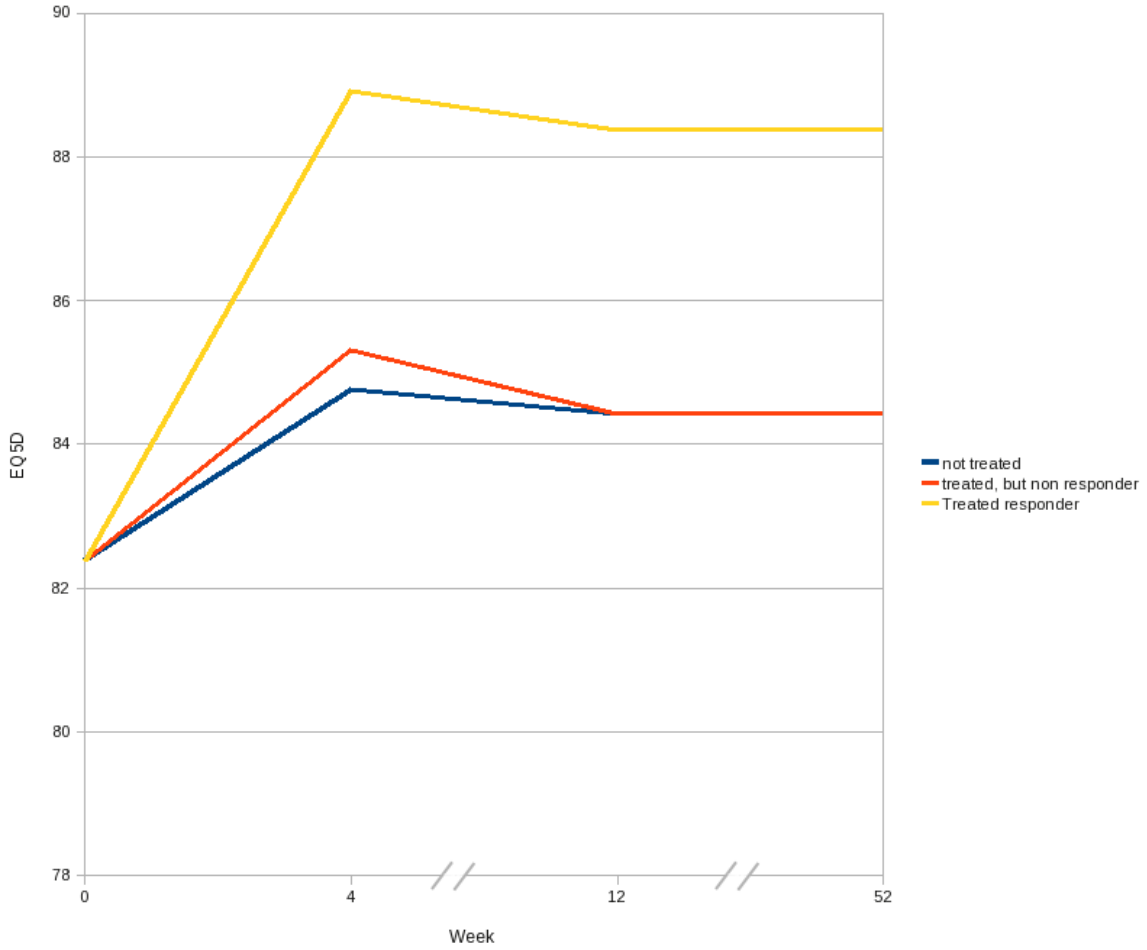
side-effects appears to be sustainable. This target population has experience chronic constipation that has not been relieved by laxatives over a significant period of time and hence equating this lack of efficacy with placebo response would appear to be appropriate. However, should evidence become available 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 a laxative induced bowel movement. 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 care is currently available for patients with chronic constipation.

2. Please clarify whether figure 8 (page 118) is purely illustrative of utility profiles for the two compared groups. If so, please supply a corresponding graph that is generated by the model in the base case situation (after any model changes following from clarification) with utility quantified on the vertical axis.

Yes, Figure 8 is illustrative. Both groups start at same utility level with a mean index score of 82.22 (.8222) the group of patients not treated with prucalopride do get slightly better between 0 to 12 weeks, this is typical of a placebo effect, and all patients in the studies receive lifestyle and dietary advice,. A revised illustrative graph with actual utility score on the vertical axis is now included.



The prucalopride group start at the same level and have a mean increase in their utility score, this mean change shows an increase in utility score between day zero and the end of week 12 and is sustained to week 52.

The sub-group of elderly patients were assessed at week 4 and 52, but not week 12, the elderly patients at week 52 showed a sustained and improved utility score at week 52 compared to week 4.

The adult group were assessed at week 4, 12 and 52, the improvement between week four and week 12 in the adult group was shown to be sustained to week 52.

3. Please clarify what items of PAC Q are represented in figure 9 (page 119). If this graph is based on the dissatisfaction subscale please clarify stability of other scale values between 12 and 52 weeks.

The graph in Fig.9 is based on the PAC-QOL 5-item dissatisfaction subscale scores.

1. fewer bowel movements than you would like
2. satisfied with how often you open your bowels
3. satisfied with the regularity with which you open your bowels
4. satisfied with your bowel function
5. satisfied with your treatment

This PAC-QOL subscale that was used in the long-term continuation studies was selected to avoid excessive patient burden when completing the questionnaires. The study protocols only required completion of the 5-items satisfaction subscale, (the pre-defined primary outcome measure of the PAC-QOL in the pivotal trials). It should also be noted that the primary objective of these long-term open label continuation trials was to establish safety and tolerability of prucalopride, rather than efficacy, negating the need for the complete set of PAC QOL subscales in the questionnaire

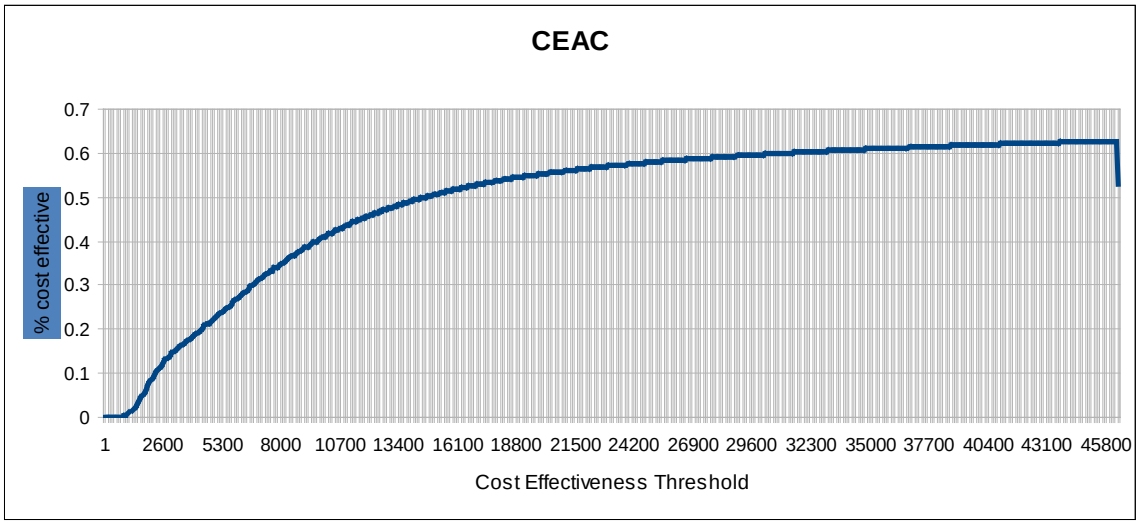
No other subscales of the PAC QOL questionnaire were used with these 12 and 52 week patient cohorts. There is no issue with stability of other scores and scales as none were used.

4. Please confirm whether the CEAC curves in figures 11-13 (pages 148-150) represent variability between individual patient or uncertainty around parameters?

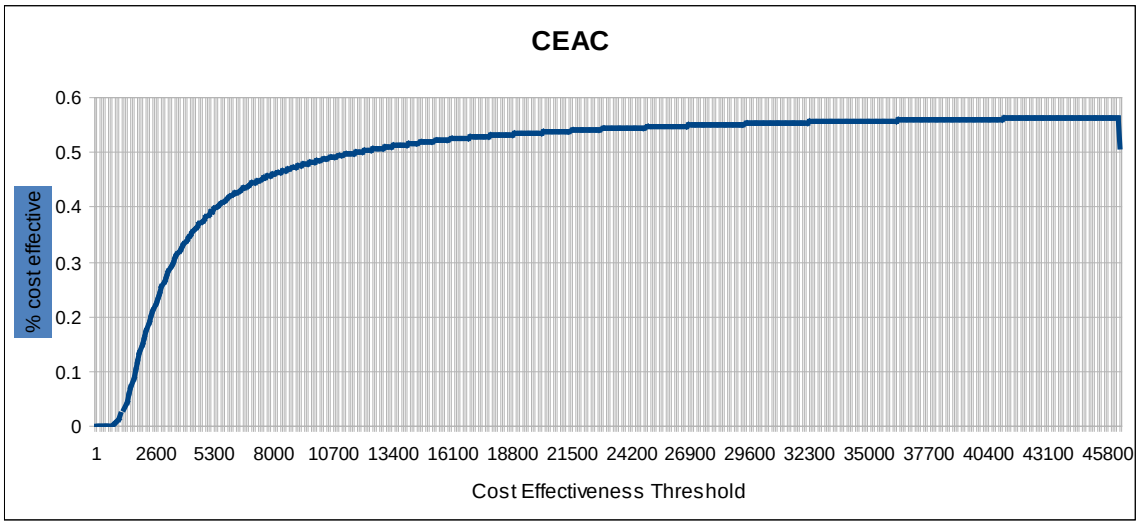
The CEAC curves represent variability between individual patients; the costs are constant and are limited to drug acquisition costs, no other costs are included, therefore there is no uncertainty around these cost parameters. For the other parameters the probabilistic model addresses uncertainty.

The performance of the Health Economic model has been improved; please see the latest version included with this response, and shown below are CEAC curves taken from this new version of the model

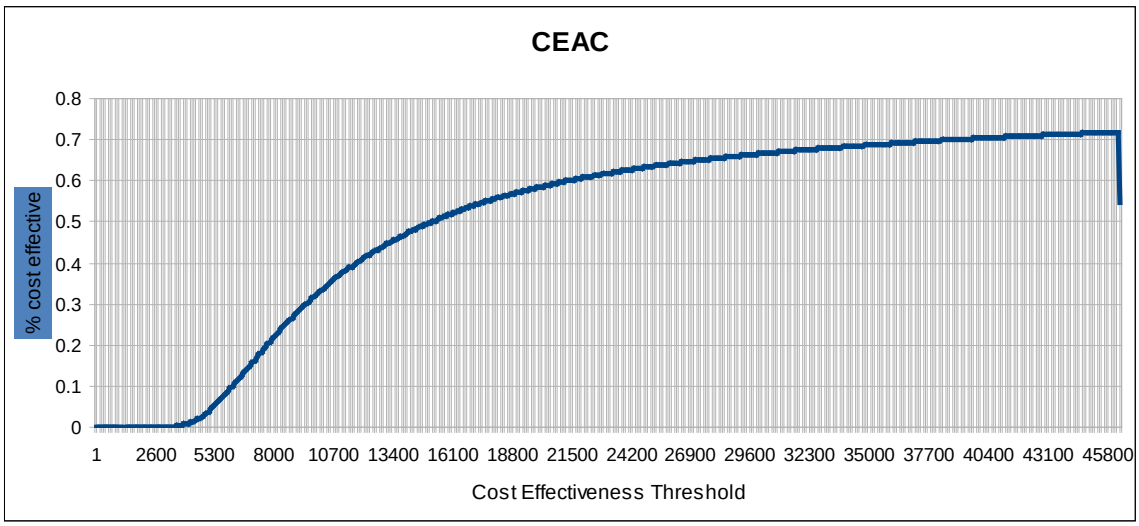
CEAC scenario one Responder defined as achieving 3 SCBM per week, adjusted for baseline disease severity




Scenario two Responder defined as achieving >1 improvement in SCBM per week, adjusted for baseline disease severity




Scenario three Responder defined as >1 improvement in weekly SCBM, without baseline constipation severity related treatment effect




5. On each spreadsheet, please clarify whether columns: B (=Age), C (=Gender), D (=Baseline) represent individual patient data? In addition please clarify the source of the values used in the spreadsheet? In particular, please clarify what is driving the number of rows in each sheet

This Health Economic model is an individual patient(s) model, each row representing individual patient data.

The number of variables assessed per patient drive the number of rows of data in the spreadsheet, there is a row for each variable per patient and at each of the time points , baseline, week four, week twelve and week 52.

In the latest version of the model the number of rows has been reduced because a macro is now used to calculate the values. The Visual Basic Script used to run the macro is available in the Microsoft Visual Basic editor in Excel.

6. Please clarify how the stopping rule (that is, patients who after 4 weeks do not continue the therapy or patients who experienced free symptoms period and taking it only when they needed) is incorporated into the model and how non-responders are included in the model.

The stopping rule is for patients who are non-responders and therefore cease treatment at four weeks. Costs for these patients are incorporated in the model via the compliance assumption.

Ideally patient compliance would be 100% as per the indication, clinical trial experience shows that this is unrealistic as the open label long-term extensions showed that responder patient compliance was 57% (210 days). The compliance figure used in the latest version of the model is 80% (290 days), This brings into the model the acquisition cost of prucalopride for the non-responders and allows for the potential cost reduction due to the intermittent use.

Primary endpoint responders are approximately 30% of the total on treatment, these patients have a sum of episodic days on treatment of 210 days per year.

Non-responders were therefore 70% of the total who were on treatment for 28 days. If 70% of patients have a drug acquisition cost based on 28 days, and these costs are added to the responder patient drug acquisition cost the total responder drug acquisition cost approximate to the same as increasing the days on treatment in the responder group to 290 days (365 x 0.8 = 292). Hence the use of 80% compliance.

The structure of the model assumes no benefit for patients who meet the requirements of the stopping rule (treatment continuation rule).

The new Excel version of the health economic model also includes a scenario for continuation of treatment in patients who meet the secondary endpoint of an increase of 1 SCBM per week with an improvement in HRQoL. An analysis of patient data that meet this scenario shows an average qaly gain of 0.038 at an average cost per qaly gain of £13,277.

7. If the model only considers responders, please provide an estimation of costs and QALYs for non-responders.

At four weeks (28 days) it is realistic and possible to identify patients who gain no benefit from treatment with prucalopride and discontinue treatment. The model considers both responders and non responders. Non-responders cease

treatment at 4 weeks and the cost of the initial four weeks is incorporated into the acquisition costs of the responders. The costs of non-responders are therefore included in the responder analysis.

The costs and QALYs of ignoring the stopping rule (i.e. aggregating responders and non responders) is included as scenario four in the new version of the health economic model. The average qaly gain in this scenario is 0.014 at an average cost per qaly gained of £34,606

8. Table 52 (page 121), describes 3 cycles one at 4 weeks, 12 weeks and 52 weeks. For each cycle please describe: The details (including source, characteristics and values) of the exact data used for the prucalopride arm

- The details of the exact data used for the placebo arm
- How the data were incorporated into each of the cycles

This model is not a Markov model, these time points are data collection points not cycles,. The model is a patient level model defining a year of their life, with all patient data taken from clinical trials.

The time points 4 weeks 12 weeks and 52 weeks were data collection points in the clinical trials. Elderly patients on 1mg had data collection points at 4 weeks and 52 weeks, adult patients had data collection points at 4 weeks, 12 weeks, and 52 weeks.

9. Page 118 states that 12 week data were used in the economic model. However, it appears that some of the trials only lasted for 4 weeks (pages 27-31, table 1). Please describe how data were used where studies only lasted 4 weeks.

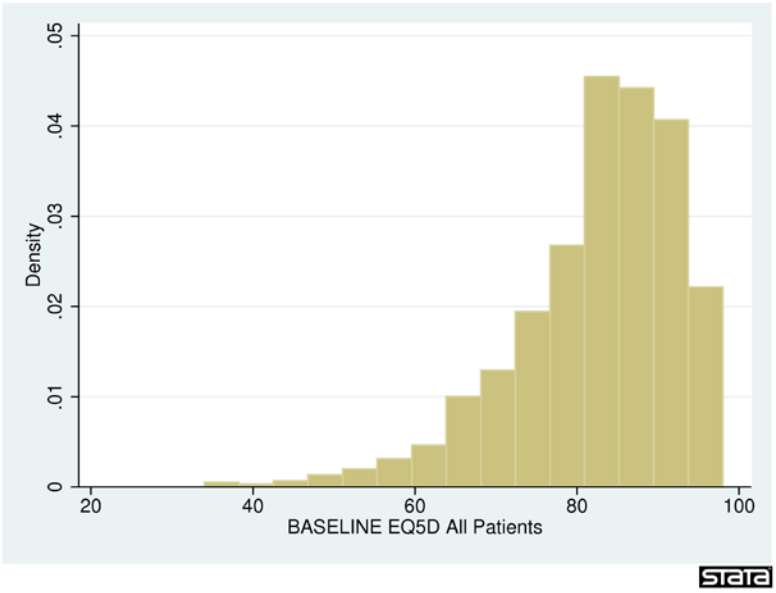
The trials of 4 weeks duration were compared to the trials of 12 week and 52 week duration at the 4 week time point. At this 4 week time point there is no statistically significant difference in outcome or variation in any of the above groups. It is therefore appropriate to model these patients to the 52 week endpoint.

10. On page 129, please explain how the baseline utility of 82.22 was derived. Please clarify which trials were used for this estimate.

The table below shows the trials used to derive the baseline utility

| | 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 baseline utility is the mean of all individual patient data prior to trial, mapped from PACQOL and PACSYM to eq5d ranged between 0.6 (60) and 0.98 (98). The mapping process effects the upper scale of the eq5d only (taken from evidence) as it assumes that chronic constipation does not cause severe pain or has severely disabling impact on the quality of life etc. The basline used in the model follows the same profile as all the clinical trials which is shown below.




11. On page 140, the submission describes how some people will take prucalopride on an intermittent basis while others will take it on a continuous basis. Please clarify how these two regimens are handled in the economic model:

- in terms of costs, and
- in terms of health related quality of life, is there a reduction in HRQOL for people who take the treatment intermittently and only take further treatment when symptoms reoccur?

Prucalopride acquisition cost is accounted for in the health economic model, days on treatment are amended through the compliance rate The use of prucalopride on an intermittent basis is therefore handled in the economic model by adjusting the Days on Treatment through amendments to the compliance and therefore acquisition cost. ( as described in question 19)

In terms of HRQoL, long-term data indicates that there is no reduction in the HRQoL associated with intermittent use of prucalopride.

12. Page 142 describes the cost assumptions in the economic model. The summary of product characteristics states that the 1mg dose may be increased to 2mg for the elderly population if required. Please clarify how this incorporated into the economic model

Dosage rather than age is the driver of acquisition cost, for the purposes of modelling, the highest dosage reported is the dosage used to calculate the drug acquisition cost, and assumes that this is the acquisition cost from day 1. This therefore produces a conservative drug acquisition cost.

13. The description of the economic model on page 142 of the submission suggests that it includes no costs for monitoring, administration or for medications that are not prucalopride. The summary of product characteristics states that in cases of prolonged treatment the benefit of prucalopride should be reassessed at regular intervals. Please provide cost estimates (including unit costs, and annual costs) for monitoring and follow up for people on prucalopride and standard care, including costs of interventions and medications (for example rescue medications or invasive procedures) that may be required for non-responders. Please incorporate these into an economic analysis or provide further rationale for their exclusion from the model.

General Practitioners will re-asses patients; there are no specific tests or interventions other than a face to face consultation for responders.

PAC-QOL and PAC-SYM may be used as a questionnaire to ensure patients are benefiting form treatment. The cost of the GP consultation is an opportunity cost.

As Resolor is a enterokinetic, response supports the correction of an underlying motility problem avoiding the need to do further tests such as motility tests.

The cost of typical rescue medication is 3 pence per suppository NHS tariff price 2010. Rescue medication is unlikely to be used in responders who achieve $\geq$3 per week.

No other costs are included in the Health Economic model because no health resource use data were collected in the clinical trials. A key objective in the development of the model was to keep assumption to a minimum in the model, therefore no assumptions on heath resource use were made. This will produce a conservative cost outcome as prucalopride responder patients will not require referral to secondary care and the consequent diagnostic and investigatory tests associated with current practice.

**Economic model assumptions**

14. Please clarify whether the key assumptions listed in section 6.3.8 (page 130) of the submission represent all the assumptions in the economic model. If not please list all the assumptions along with a justification for each.

As stated in reply to question 28, the number of assumptions are minimised to those listed in section 6.3.8 and the model maximised the use of evidence only. Potential other cost saving advantages for prucalopride (less doctors visits, less acute episodes of constipations requiring hospital care etc…) are ignored making the outputs conservative.

15. In figure 9 (page 119), please clarify whether in the assumptions of the economic model, patients in the comparator arm continue on the withdrawal from laxatives/rescue therapy regimen or whether they revert to their run in/pre-trial regimen. If the latter is the case, please clarify if the utility values for this arm would be expected to revert to baseline values go back to pre trial utility value,

As per previous answers, assumptions in the model are kept to a minimum, therefore patients in the comparator arm are continue on the trial regimen with baseline utility values, again this is a conservative estimate.

16. In section 6.3.8 (page 130), bullet-point 1 states that: "*Placebo data from the prucalopride clinical trial were taken as an approximation for the efficacy of response for patients on laxatives*." On page 156 (section entitled placebo response as comparator) the submission states: "*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*". Please clarify the justification for this assumption. It appears counterintuitive that withdrawing laxative and making it available only as "rescue therapy" would equate with continued use of laxative. Please supply/clarify any evidence that may justify this assumption.

Prucalopride is an enterokinetic agent, not a laxative and patients in the model are laxative refractory patients.

In the trials the patients were laxative refractory, failing to achieve adequate relief on laxatives, typically bulking agents, osmotic agents and stool softeners which have ceased to have an effect or provide an inadequate relief.

Laxative refractory patient still require some type of intervention to induce a bowel movement and will typically use a stimulant suppository or stimulant oral laxative to produce a, mostly non complete, bowel movement. Hence the use of rescue medication with placebo is a close approximation of current standard care and an ideal comparator.

The problem is that there are no compelling data in the literature on the sustained efficacy of laxatives over 12 weeks and beyond in the intended laxative refractory patient population, and this is the reason why the use of rescue medication is taken as a proxy

17. For figure 14 (page 159), please describe the basis for the assumption that, of people with chronic constipation, 10% will fail to respond to laxatives.

This figure of 10% was arrived at by consensus of Consultant Gastroenterologists at a national meeting convened to discuss this question. It is

important to differentiate between dissatisfaction with laxatives, (up to 80%) and the proportion of patients who fail to achieve adequate relief with laxatives.

Further, in a 4 week placebo controlled randomised clinical trial by Mueller-Lissner (The American Journal of Gastroenterology January 2010) investigating efficacy of laxatives, showed 87.7 percent of patients achieve adequate relief, therefore 12.3% are refractory to laxatives.

This figure can be further supported by referring to US population study 557 people (who met eligibility criteria), 12% of respondents who worked or went to school, reported missing time from work or class, a mean 2.4 days because of symptoms of chronic constipation.(Alimentary Pharmacology 25 page 599 to 608). Twelve percent has been rounded down to 10%.

**Population in the economic model:**

18. Table 53 (page 124) of the submission suggests that all patients in the pivotal studies were included in the cost effectiveness model but some of these patients were men and some appear not to have had previous laxative treatment. Please clarify whether male patients and those who had undergone no previous laxative treatments were excluded from economic modelling.

The Pivotal trails and other trials were the source of patient data, All patients were used to estimate the parameters of the model, but only patients that matched the licensed indication were modelled for cost effectiveness.

19. In table 53 (page 124), no overall data for the patients included in the economic model appears to have been provided. Please provide the following data for the treatment and placebo arms for patients included in the economic model:

    - Demographics
    - Duration of constipation
    - Ave frequency of stools per week at baseline
    - Previous laxative use
    - Overall assessment of therapeutic efficacy of previous treatment for constipation

- Current treatments
- SCBM ≥3/week
- Average increase of ≥1 SCBM/week
- Average increase of ≥SBM/week
- Average number of SCBM/week
- Total number of BM (spontaneous and non-spontaneous)
- Number of days with bisacodyl use
- Number of days with enemas
- Patient assessment of constipation severity
- Patients rating their treatment as quite a bit or extremely or extremely effective

Below is a table showing the trials used to provide patient data to populate the health economic 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 table below is a summary of the demographic profile of the above trials.

| Characteristic | Prucalopride, 2mg (N=924) | Prucalopride, 4mg (N=844) | Placebo (N=955) |
|---|---|---|---|
| **Race or ethnic group - no. (%)** | | | |
| White | 847 (91.7) | 766 (90.8) | 883 (92.5) |
| Black | 43 (4.7) | 41 (4.9) | 35 (3.7) |
| Hispanic | 10 (1.1) | 18 (2.1) | 13 (1.4) |
| Oriental | 10 (1.1) | 2 (0.2) | 6 (0.6) |
| Other | 13 (1.4) | 16 (1.9) | 18 (1.9) |
| Mixed | 1 (0.1) | 1 (0.1) | 0 |
| **Sex - no. (%)** | | | |
| Female | 804 (87.0) | 729 (86.4) | 838 (87.7) |
| Male | 120 (13.0) | 115 (13.6) | 117 (12.3) |
| **Age - yr** | | | |
| Mean (±SE) | 49.1±0.56 | 49.6±0.57 | 48.1±0.54 |
| Range | 17-95 | 18-95 | 18-98 |
| **Height - cm** | | | |
| Mean (±SE) | 165.3±0.29 | 165.4±0.3 | 165.7±0.27 |
| Range | 104-193 | 130-192 | 107-196 |
| **Weight - kg** | | | |
| Mean (±SE) | 68.8±0.49 | 68.8±0.52 | 67.6±0.45 |
| Range | 39-162 | 37-147 | 41-131 |
| **Duration of constipation - yr** | | | |
| Mean (±SE) | 19.58±0.529 | 20.35±0.578 | 20.06±0.508 |
| Range | 0.5-70 | 0.3-82 | 0.5-77 |
| **Average frequancy of spontaneous stools per week, 6 mo before study entry - no.(%)** | | | |
| 0 | 323 (36.0) | 320 (38.0) | 314 (33.5) |
| >0 to ?1 | 308 (34.3) | 281 (33.3) | 326 (34.8) |
| >1 to ?3 | 235 (26.2) | 215 (25.5) | 258 (27.5) |
| >3 | 31 (3.5) | 27 (3.2) | 39 (4.2) |
| **Overall assesment of therapeautic efficacy of previous treatment of constipation - no. (%)** | | | |
| Adequate | 164 (18.9) | 134 (16.5) | 145 (16.6) |
| Inadequate | 704 (81.1) | 678 (83.5) | 728 (83.4) |

Please see the appendix to this document for further demographic information on the trials used in the model.

Please see pages 3 and 4 of the submission document, full information required to answer the above question is provided with the submission.

20. On page 122, the submission states "*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*)". Please clarify if and how the costs of these reassessments were incorporated into the model.

The costs included in the model are restricted to drug acquisition costs only. The patients general practitioner will re-asses the patient at four weeks (the GP consultation is an opportunity cost), no tests or investigations are necessary. Treatment will cease for patients who have not responded to treatment. The drug acquisition cost for these patients is added to the drug acquisition costs for the patients who do achieve $\geq$3 SCBM. Patients who achieve an increase of 1 SCBM per week, with an improvement in HRQoL are included in the model and show an average qaly gained of 0.038 with cost-effectiveness shown by a cost per qaly of £13,277.

21. With reference to the 4 week stopping rule on page 123, the submission states: "…*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*". If the 4 week stopping rule identifies patients that potentially have other conditions that require investigation then these are likely to occur almost exclusively in the intervention arm (since the placebo arm has no stopping rule). Please clarify if, in the pivotal trials and in extension follow-up to 52 weeks, any of these patients actually received such investigations and if so what investigations.

The continuation / stopping rule was a consequence of the outcome from the pivotal trials. Exploratory analysis showed that patients who had failed to respond at four weeks where the same patients who had failed to respond at 12 weeks, hence we now know that if patients fail to respond by four weeks, no purpose is served by continuing treatment.

The extension of the pivotal trials from 12 to 52 weeks was an open label investigation of safety and tolerability, the placebo arm was not therefore continued to 52 weeks. Being an open label continuation studies the protocols for the extensions did not include placebo patients, therefore no data were collected on the investigations these patients may have gone on to endure.

**Sensitivity analyses**

22. On page 144, the submission states that an alternative process mapping SF-36 to SF-6D was undertaken and compared to the mapping used in the base-case analysis. Please clarify the nature of this analysis and present the results.

The nature of this alternative analysis was to explore the differences between EQ5D and SF6D as utility measures for acedemic purposes. Movetis has no access to this information: Movetis provided an educational grant to assist with the independent development of the mapping disease specific patient assessed instruments on to generic preference based measures of health.

According to the academic developers this exercise highlights the difference in measurement of utility between these tools, but reinforce the necessity of using conservative assumptions.

**Section C: Textual clarifications and additional points**

23. Please provide protocols for the pivotal, elderly and retreatment trials

Please see appendix 2

Appendix1

MOVETIS--PRUCALOPRIDE SUMMARY OF SAFETY

DISPLAY SUB.2.1.1.C: SUBJECT DEMOGRAPHICS FOR TRIALS FRA-1,GBR-4,INT-1,INT-12,INT-2,INT-6,USA-11,USA-13,USA-26,USA-3

POPULATION: ALL SUBJECTS
INDICATION: CHRONIC CONSTIPATION

| PARAMETER | PLACEBO | PRU 0.5mg | PRU 1mg | PRU 2mg | PRU 4mg | ALL PRU |
|---|---|---|---|---|---|---|
| TOTAL NO. OF SUBJECTS | 955 | 110 | 308 | 924 | 844 | 2186 |
| **GENDER** | | | | | | |
| DISTRIBUTION, N (%) | | | | | | |
| FEMALE | 838 ( 87.7%) | 95 ( 86.4%) | 273 ( 88.6%) | 804 ( 87.0%) | 729 ( 86.4%) | 1901 ( 87.0%) |
| MALE | 117 ( 12.3%) | 15 ( 13.6%) | 35 ( 11.4%) | 120 ( 13.0%) | 115 ( 13.6%) | 285 ( 13.0%) |
| **AGE, years** | | | | | | |
| NUMBER ASSESSED | 955 | 110 | 308 | 924 | 844 | 2186 |
| DISTRIBUTION, N (%) | | | | | | |
| <18 | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.1%) | 0 ( 0.0%) | 1 ( 0.0%) |
| 18-40 | 338 ( 35.4%) | 43 ( 39.1%) | 104 ( 33.8%) | 321 ( 34.7%) | 270 ( 32.0%) | 738 ( 33.8%) |
| 41-64 | 440 ( 46.1%) | 42 ( 38.2%) | 91 ( 29.5%) | 400 ( 43.3%) | 397 ( 47.0%) | 930 ( 42.5%) |
| 65-75 | 110 ( 11.5%) | 5 ( 4.5%) | 59 ( 19.2%) | 125 ( 13.5%) | 108 ( 12.8%) | 297 ( 13.6%) |
| >75 | 67 ( 7.0%) | 20 ( 18.2%) | 54 ( 17.5%) | 77 ( 8.3%) | 69 ( 8.2%) | 220 ( 10.1%) |
| MEAN (SE) | 48.1 (0.54) | 50.2 (1.95) | 53.6 (1.19) | 49.1 (0.56) | 49.5 (0.57) | 49.9 (0.38) |
| (95% CI) | (47.01;49.11) | (46.32;54.04) | (51.27;55.96) | (47.95;50.16) | (48.4;50.61) | (49.19;50.67) |
| MEDIAN (MIN;MAX) | 46 (18 ; 98) | 46 (18 ; 98) | 51 (18 ; 96) | 46 (17 ; 95) | 48 (18 ; 95) | 48 (17 ; 98) |
| (95% CI) | (44;48) | (42;50) | (48;55) | (45;48) | (46;49) | (46;48) |
| **RACE** | | | | | | |
| DISTRIBUTION, N (%) | | | | | | |
| BLACK | 35 ( 3.7%) | 4 ( 3.6%) | 6 ( 1.9%) | 43 ( 4.7%) | 41 ( 4.9%) | 94 ( 4.3%) |
| CAUCASIAN | 883 ( 92.5%) | 102 ( 92.7%) | 286 ( 92.9%) | 847 ( 91.7%) | 766 ( 90.8%) | 2001 ( 91.5%) |
| HISPANIC | 13 ( 1.4%) | 3 ( 2.7%) | 4 ( 1.3%) | 10 ( 1.1%) | 18 ( 2.1%) | 35 ( 1.6%) |
| MIXED | 0 ( 0.0%) | 1 ( 0.9%) | 0 ( 0.0%) | 1 ( 0.1%) | 1 ( 0.1%) | 3 ( 0.1%) |
| ORIENTAL | 6 ( 0.6%) | 0 ( 0.0%) | 2 ( 0.6%) | 10 ( 1.1%) | 2 ( 0.2%) | 14 ( 0.6%) |
| OTHER | 18 ( 1.9%) | 0 ( 0.0%) | 10 ( 3.2%) | 13 ( 1.4%) | 16 ( 1.9%) | 39 ( 1.8%) |

MOVETIS--PRUCALOPRIDE SUMMARY OF SAFETY

DISPLAY SUB.2.1.1.C: SUBJECT DEMOGRAPHICS FOR TRIALS FRA-1,GBR-4,INT-1,INT-12,INT-2,INT-6,USA-11,USA-13,USA-26,USA-3 (CONTINUED)

POPULATION: ALL SUBJECTS
INDICATION: CHRONIC CONSTIPATION

| PARAMETER | PLACEBO | PRU 0.5mg | PRU 1mg | PRU 2mg | PRU 4mg | ALL PRU |
|---|---|---|---|---|---|---|
| TOTAL NO. OF SUBJECTS | 955 | 110 | 308 | 924 | 844 | 2186 |
| WEIGHT, kg | | | | | | |
| NUMBER ASSESSED | 954 | 110 | 308 | 924 | 842 | 2184 |
| DISTRIBUTION, N (%) | | | | | | |
| 30-<40 | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.3%) | 1 ( 0.1%) | 2 ( 0.2%) | 4 ( 0.2%) |
| 40-<50 | 39 ( 4.1%) | 6 ( 5.5%) | 22 ( 7.1%) | 51 ( 5.5%) | 37 ( 4.4%) | 116 ( 5.3%) |
| 50-<60 | 253 ( 26.5%) | 23 ( 20.9%) | 81 ( 26.3%) | 226 ( 24.5%) | 192 ( 22.8%) | 522 ( 23.9%) |
| 60-<70 | 315 ( 33.0%) | 31 ( 28.2%) | 125 ( 40.6%) | 267 ( 28.9%) | 286 ( 34.0%) | 709 ( 32.5%) |
| 70-<80 | 191 ( 20.0%) | 28 ( 25.5%) | 41 ( 13.3%) | 195 ( 21.1%) | 168 ( 20.0%) | 432 ( 19.8%) |
| 80-<90 | 80 ( 8.4%) | 14 ( 12.7%) | 29 ( 9.4%) | 98 ( 10.6%) | 78 ( 9.3%) | 219 ( 10.0%) |
| 90-<100 | 43 ( 4.5%) | 3 ( 2.7%) | 6 ( 1.9%) | 58 ( 6.3%) | 44 ( 5.2%) | 111 ( 5.1%) |
| 100-<110 | 25 ( 2.6%) | 3 ( 2.7%) | 2 ( 0.6%) | 15 ( 1.6%) | 21 ( 2.5%) | 41 ( 1.9%) |
| 110-<120 | 4 ( 0.4%) | 0 ( 0.0%) | 1 ( 0.3%) | 9 ( 1.0%) | 5 ( 0.6%) | 15 ( 0.7%) |
| 120-<130 | 2 ( 0.2%) | 2 ( 1.8%) | 0 ( 0.0%) | 2 ( 0.2%) | 5 ( 0.6%) | 9 ( 0.4%) |
| 130-<140 | 2 ( 0.2%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.1%) | 1 ( 0.0%) |
| 140-<150 | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.1%) | 3 ( 0.4%) | 4 ( 0.2%) |
| 160-<170 | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.1%) | 0 ( 0.0%) | 1 ( 0.0%) |
| MEAN (SE) | 67.6 (0.45) | 69.6 (1.43) | 64.5 (0.67) | 68.8 (0.49) | 68.8 (0.52) | 68.2 (0.31) |
| (95% CI) | (66.75;68.5) | (66.72;72.38) | (63.16;65.81) | (67.84;69.75) | (67.75;69.78) | (67.6;68.83) |
| MEDIAN (MIN;MAX) | 65 (41 ; 131) | 67.8 (40 ; 127) | 63 (40 ; 114) | 66.8 (39 ; 162) | 66 (37 ; 147) | 65.7 (37 ; 162) |
| (95% CI) | (64;65.8) | (64.4;72) | (62;64) | (65;67.7) | (65;67) | (65;66) |

MOVETIS--PRUCALOPRIDE SUMMARY OF SAFETY

DISPLAY SUB.2.1.1.C: SUBJECT DEMOGRAPHICS FOR TRIALS FRA-1,GBR-4,INT-1,INT-12,INT-2,INT-6,USA-11,USA-13,USA-26,USA-3 (CONTINUED)

POPULATION: ALL SUBJECTS
INDICATION: CHRONIC CONSTIPATION

| PARAMETER | PLACEBO | PRU 0.5mg | PRU 1mg | PRU 2mg | PRU 4mg | ALL PRU |
|---|---|---|---|---|---|---|
| TOTAL NO. OF SUBJECTS | 955 | 110 | 308 | 924 | 844 | 2186 |
| HEIGHT, cm | | | | | | |
| NUMBER ASSESSED | 952 | 110 | 308 | 921 | 840 | 2179 |
| DISTRIBUTION, N (%) | | | | | | |
| 90-<100 | 0 ( 0.0%) | 1 ( 0.9%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.0%) |
| 100-<110 | 1 ( 0.1%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.1%) | 0 ( 0.0%) | 1 ( 0.0%) |
| 120-<130 | 1 ( 0.1%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| 130-<140 | 1 ( 0.1%) | 0 ( 0.0%) | 1 ( 0.3%) | 4 ( 0.4%) | 4 ( 0.5%) | 9 ( 0.4%) |
| 140-<150 | 17 ( 1.8%) | 0 ( 0.0%) | 7 ( 2.3%) | 16 ( 1.7%) | 20 ( 2.4%) | 43 ( 2.0%) |
| 150-<160 | 186 ( 19.5%) | 16 ( 14.5%) | 68 ( 22.1%) | 192 ( 20.8%) | 161 ( 19.2%) | 437 ( 20.1%) |
| 160-<170 | 477 ( 50.1%) | 53 ( 48.2%) | 149 ( 48.4%) | 428 ( 46.5%) | 380 ( 45.2%) | 1010 ( 46.4%) |
| 170-<180 | 221 ( 23.2%) | 35 ( 31.8%) | 72 ( 23.4%) | 229 ( 24.9%) | 224 ( 26.7%) | 560 ( 25.7%) |
| 180-<190 | 45 ( 4.7%) | 4 ( 3.6%) | 9 ( 2.9%) | 44 ( 4.8%) | 46 ( 5.5%) | 103 ( 4.7%) |
| 190-<200 | 3 ( 0.3%) | 1 ( 0.9%) | 2 ( 0.6%) | 7 ( 0.8%) | 5 ( 0.6%) | 15 ( 0.7%) |
| MEAN (SE) | 165 (0.27) | 166.1 (0.94) | 164.6 (0.46) | 165.3 (0.29) | 165.4 (0.3) | 165.3 (0.19) |
| (95% CI) | (164.45;165.52) | (164.29;168) | (163.73;165.54) | (164.75;165.87) | (164.83;166.01) | (164.93;165.66) |
| MEDIAN (MIN;MAX) | 165 (107 ; 196) | 165.1 (98 ; 193) | 164 (138 ; 191) | 165 (104 ; 193) | 165 (130 ; 192) | 165 (98 ; 193) |
| (95% CI) | (165;165) | (165;168) | (163;165.1) | (165;165.1) | (165;166) | (165;165.1) |

MOVETIS--PRUCALOPRIDE SUMMARY OF SAFETY

DISPLAY SUB.2.2.1.E: HISTORY OF CONSTIPATION FOR TRIALS FRA-1,GBR-4,INT-1,INT-12,INT-2,INT-6,USA-11,USA-13,USA-26,USA-3

POPULATION: ALL SUBJECTS
INDICATION: CHRONIC CONSTIPATION

| PARAMETER | PLACEBO | PRU 0.5mg | PRU 1mg | PRU 2mg | PRU 4mg | ALL PRU |
|---|---|---|---|---|---|---|
| TOTAL NO. OF SUBJECTS | 955 | 110 | 308 | 924 | 844 | 2186 |
| **DURATION OF CONSTIPATION, years** | | | | | | |
| NUMBER ASSESSED | 936 | 89 | 283 | 896 | 843 | 2111 |
| DISTRIBUTION, N (%) | | | | | | |
| <1 | 25 ( 2.7%) | 0 ( 0.0%) | 6 ( 2.1%) | 20 ( 2.2%) | 21 ( 2.5%) | 47 ( 2.2%) |
| 1-<10 | 253 ( 27.0%) | 21 ( 23.6%) | 82 ( 29.0%) | 268 ( 29.9%) | 253 ( 30.0%) | 624 ( 29.6%) |
| 10-<20 | 207 ( 22.1%) | 22 ( 24.7%) | 63 ( 22.3%) | 203 ( 22.7%) | 161 ( 19.1%) | 449 ( 21.3%) |
| 20-<30 | 194 ( 20.7%) | 20 ( 22.5%) | 60 ( 21.2%) | 156 ( 17.4%) | 156 ( 18.5%) | 392 ( 18.6%) |
| 30-<40 | 119 ( 12.7%) | 12 ( 13.5%) | 35 ( 12.4%) | 112 ( 12.5%) | 115 ( 13.6%) | 274 ( 13.0%) |
| 40-<50 | 81 ( 8.7%) | 9 ( 10.1%) | 19 ( 6.7%) | 78 ( 8.7%) | 75 ( 8.9%) | 181 ( 8.6%) |
| >=50 | 57 ( 6.1%) | 5 ( 5.6%) | 18 ( 6.4%) | 59 ( 6.6%) | 62 ( 7.4%) | 144 ( 6.8%) |
| MEAN (SE) | 20.06 (0.508) | 20.72 (1.607) | 18.75 (0.899) | 19.58 (0.529) | 20.35 (0.578) | 19.83 (0.35) |
| (95% CI) | (19.066;21.058) | (17.526;23.912) | (16.983;20.524) | (18.545;20.621) | (19.219;21.488) | (19.14;20.515) |
| MEDIAN (MIN;MAX) | 18 (0.5 ; 77) | 20 (1 ; 61) | 15 (0.5 ; 66) | 15.75 (0.5 ; 70) | 17 (0.3 ; 82) | 16 (0.3 ; 82) |
| (95% CI) | (15.08;20) | (14;21) | (14;20) | (15;18) | (15;20) | (15;18) |
| **AVERAGE FREQ./WEEK SPONT. BM** | | | | | | |
| DISTRIBUTION, N (%) | | | | | | |
| NO SPONTANEOUS BM | 314 ( 33.5%) | 15 ( 17.2%) | 54 ( 19.1%) | 323 ( 36.0%) | 320 ( 38.0%) | 712 ( 33.7%) |
| >0 AND <=1 | 326 ( 34.8%) | 37 ( 42.5%) | 97 ( 34.3%) | 308 ( 34.3%) | 281 ( 33.3%) | 723 ( 34.3%) |
| >1 AND <=3 | 258 ( 27.5%) | 33 ( 37.9%) | 105 ( 37.1%) | 235 ( 26.2%) | 215 ( 25.5%) | 588 ( 27.9%) |
| >3 | 39 ( 4.2%) | 2 ( 2.3%) | 27 ( 9.5%) | 31 ( 3.5%) | 27 ( 3.2%) | 87 ( 4.1%) |
| **% BM THAT ARE HARD/VERY HARD** | | | | | | |
| DISTRIBUTION, N (%) | | | | | | |
| 0-25% | 94 ( 14.2%) | 0 ( %) | 0 ( %) | 106 ( 16.1%) | 111 ( 16.9%) | 217 ( 16.5%) |
| 26-50% | 93 ( 14.1%) | 0 ( %) | 0 ( %) | 89 ( 13.5%) | 88 ( 13.4%) | 177 ( 13.4%) |
| 51-75% | 155 ( 23.4%) | 0 ( %) | 0 ( %) | 136 ( 20.6%) | 135 ( 20.5%) | 271 ( 20.6%) |
| 76-100% | 319 ( 48.3%) | 0 ( %) | 0 ( %) | 328 ( 49.8%) | 323 ( 49.2%) | 651 ( 49.5%) |

MOVETIS--PRUCALOPRIDE SUMMARY OF SAFETY

DISPLAY SUB.2.2.1.E: HISTORY OF CONSTIPATION FOR TRIALS FRA-1,GBR-4,INT-1,INT-12,INT-2,INT-6,USA-11,USA-13,USA-26,USA-3 (CONTINUED)

POPULATION: ALL SUBJECTS
INDICATION: CHRONIC CONSTIPATION

| PARAMETER | PLACEBO | PRU 0.5mg | PRU 1mg | PRU 2mg | PRU 4mg | ALL PRU |
|---|---|---|---|---|---|---|
| TOTAL NO. OF SUBJECTS | 955 | 110 | 308 | 924 | 844 | 2186 |
| **SUBJECT MAIN COMPLAINT** | | | | | | |
| DISTRIBUTION, N (%) | | | | | | |
| ABDOMINAL BLOATING | 181 ( 19.4%) | 0 ( 0.0%) | 9 ( 3.2%) | 167 ( 18.7%) | 176 ( 20.9%) | 352 ( 16.7%) |
| ABDOMINAL DISCOMFORT/PAIN | 10 ( 1.1%) | 0 ( 0.0%) | 9 ( 3.2%) | 0 ( 0.0%) | 0 ( 0.0%) | 9 ( 0.4%) |
| ABDOMINAL DISTENSION | 29 ( 3.1%) | 17 ( 19.3%) | 20 ( 7.1%) | 25 ( 2.8%) | 16 ( 1.9%) | 78 ( 3.7%) |
| ABDOMINAL DISTENSION/BLOATI | 9 ( 1.0%) | 0 ( 0.0%) | 8 ( 2.8%) | 0 ( 0.0%) | 0 ( 0.0%) | 8 ( 0.4%) |
| ABDOMINAL PAIN | 116 ( 12.4%) | 8 ( 9.1%) | 18 ( 6.4%) | 127 ( 14.2%) | 97 ( 11.5%) | 250 ( 11.9%) |
| DIFFICULTY IN DEFAECATION | 51 ( 5.5%) | 23 ( 26.1%) | 63 ( 22.3%) | 43 ( 4.8%) | 40 ( 4.7%) | 169 ( 8.0%) |
| FEELING NOT COMPLETELY EMPT | 114 ( 12.2%) | 0 ( 0.0%) | 17 ( 6.0%) | 101 ( 11.3%) | 115 ( 13.6%) | 233 ( 11.0%) |
| FEELING OF INCOMPLETE EVACU | 14 ( 1.5%) | 2 ( 2.3%) | 24 ( 8.5%) | 15 ( 1.7%) | 4 ( 0.5%) | 45 ( 2.1%) |
| HARD STOOLS | 65 ( 7.0%) | 5 ( 5.7%) | 30 ( 10.6%) | 65 ( 7.3%) | 57 ( 6.8%) | 157 ( 7.4%) |
| INFREQUENT DEFAECATION | 261 ( 27.9%) | 32 ( 36.4%) | 70 ( 24.7%) | 268 ( 29.9%) | 238 ( 28.2%) | 608 ( 28.8%) |
| OTHER | 0 ( 0.0%) | 1 ( 1.1%) | 3 ( 1.1%) | 2 ( 0.2%) | 1 ( 0.1%) | 7 ( 0.3%) |
| STRAINING | 84 ( 9.0%) | 0 ( 0.0%) | 12 ( 4.2%) | 82 ( 9.2%) | 99 ( 11.7%) | 193 ( 9.2%) |
| **DIET** | | | | | | |
| DISTRIBUTION, N (%) | | | | | | |
| NO | 355 ( 39.5%) | 43 ( 48.3%) | 109 ( 44.7%) | 343 ( 38.2%) | 315 ( 37.3%) | 810 ( 39.0%) |
| YES | 544 ( 60.5%) | 46 ( 51.7%) | 135 ( 55.3%) | 555 ( 61.8%) | 529 ( 62.7%) | 1265 ( 61.0%) |
| **BULK FORMING AGENTS** | | | | | | |
| DISTRIBUTION, N (%) | | | | | | |
| NO | 388 ( 43.2%) | 64 ( 71.9%) | 146 ( 59.8%) | 396 ( 44.1%) | 372 ( 44.1%) | 978 ( 47.2%) |
| YES | 510 ( 56.8%) | 25 ( 28.1%) | 98 ( 40.2%) | 501 ( 55.9%) | 472 ( 55.9%) | 1096 ( 52.8%) |
| **LAXATIVE TAKEN** | | | | | | |
| DISTRIBUTION, N (%) | | | | | | |
| NO | 144 ( 15.4%) | 16 ( 18.0%) | 67 ( 23.6%) | 142 ( 15.8%) | 135 ( 16.0%) | 360 ( 17.0%) |
| YES | 792 ( 84.6%) | 73 ( 82.0%) | 217 ( 76.4%) | 756 ( 84.2%) | 709 ( 84.0%) | 1755 ( 83.0%) |

MOVETIS--PRUCALOPRIDE SUMMARY OF SAFETY

DISPLAY SUB.2.2.1.E: HISTORY OF CONSTIPATION FOR TRIALS FRA-1,GBR-4,INT-1,INT-12,INT-2,INT-6,USA-11,USA-13,USA-26,USA-3 (CONTINUED)

POPULATION: ALL SUBJECTS
INDICATION: CHRONIC CONSTIPATION

| PARAMETER | PLACEBO | PRU 0.5mg | PRU 1mg | PRU 2mg | PRU 4mg | ALL PRU |
|---|---|---|---|---|---|---|
| TOTAL NO. OF SUBJECTS | 955 | 110 | 308 | 924 | 844 | 2186 |
| OVERALL THERAPEUTIC EFFECT | | | | | | |
| DISTRIBUTION, N (%) | | | | | | |
| ADEQUATE | 145 ( 16.6%) | 23 ( 26.4%) | 46 ( 19.2%) | 164 ( 18.9%) | 134 ( 16.5%) | 367 ( 18.3%) |
| INADEQUATE | 728 ( 83.4%) | 64 ( 73.6%) | 193 ( 80.8%) | 704 ( 81.1%) | 678 ( 83.5%) | 1639 ( 81.7%) |

Appendix 2 (please double-click to open the protocol)

JANSSEN RESEARCH FOUNDATION
a division of Janssen Pharmaceutica N.V.

**International Clinical Research & Development**

**CLINICAL TRIAL PROTOCOL**

| | | | |
|---|---|---|---|
| **Final date:** | January 9, 1998 | **Drug number:** | R108512 |
| **Trial number:** | R108512-USA-11 | **Clinical Phase:** | III |

**Title:** A double-blind, placebo-controlled trial to evaluate the efficacy and safety of R108512 tablets in subjects with chronic constipation

**Summary:** Subjects with chronic constipation are given, in a double-blind fashion, either 2 mg or 4 mg R108512 tablets or placebo, once daily for 12 weeks. The efficacy and safety of R108512, as well as its effect on subject quality of life, will be evaluated.

**Principal Investigator:** Multicentre

**Trial Location:** Multicentre

**Sponsor:**
Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200
U.S.A.

**Trial Coordinator:**
Michael S. Woods, M.D./Rena M. Lambert, M.S.
Department of Clinical Research, Gastroenterology
Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200
U.S.A.
Tel.: (609) 730-3409 / FAX: (609) 730-3288

**Approvals:**

**Investigator**: ..... .....
..... (date)

**Director Internal Medicine:** ..... .....
**Janssen Research Foundation** (L. Lauwers, M.D.)..... (date)

**Clinical Research Director, U.S.** ..... .....
**Janssen Research Foundation** (A. Joslyn, Ph.D.) ..... (date)

JANSSEN RESEARCH FOUNDATION
a division of Janssen Pharmaceutica N.V.

**International Clinical Research & Development**

**CLINICAL TRIAL PROTOCOL**

| | | | |
|---|---|---|---|
| **Final date:** | January 9, 1998 | **Drug number:** | R108512 |
| **Trial number:** | R108512-USA-13 | **Clinical Phase:** | III |

**Title:** A double-blind, placebo-controlled trial to evaluate the efficacy and safety of R108512 tablets in subjects with chronic constipation

**Summary:** Subjects with chronic constipation are given, in a double-blind fashion, either 2 mg or 4 mg R108512 tablets or placebo, once daily for 12 weeks. The efficacy and safety of R108512, as well as its effect on subject quality of life, will be evaluated.

**Principal Investigator:** Multicentre

**Trial Location:** Multicentre

**Sponsor:** Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200
U.S.A.

**Trial Coordinator:** Michael S. Woods, M.D./Rena M. Lambert, M.S.
Department of Clinical Research, Gastroenterology
Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200
U.S.A.
Tel.: (609) 730-3409 / FAX: (609) 730-3288

**Approvals:**

| | | |
|---|---|---|
| **Investigator**: | ..... | ..... |
| | ..... | (date) |
| **Director Internal Medicine:** | ..... | ..... |
| **Janssen Research Foundation** | (L. Lauwers, M.D.)..... | (date) |
| **Clinical Research Director, U.S.** | ..... | ..... |
| **Janssen Research Foundation** | (A. Joslyn, Ph.D.) ..... | (date) |

# JANSSEN RESEARCH FOUNDATION

**a division of Janssen Pharmaceutica N.V.**

**International Clinical Research & Development**

**CLINICAL TRIAL PROTOCOL**

| | | | |
|---|---|---|---|
| **Version date:** | February 24, 1999 | **Drug number:** | R108512 |
| **Trial number:** | PRU-USA-28 | **Clinical Phase:** | III |

**Title:** A two-period, double-blind, placebo-controlled trial to evaluate the effects of re-treatment of prucalopride on efficacy and safety in subjects with chronic constipation.

**Summary:** After a two-week treatment-free run-in, subjects with chronic constipation will be given, in a double-blind fashion, either 4 mg prucalopride or placebo, once daily for four weeks. After a minimum two-week washout, subjects will be re-treated with the same dose as received during the first period of the trial, for an additional 4 weeks. The efficacy and safety of prucalopride will be evaluated during both double-blind treatment periods.

**Principal Investigator:** Multicenter

**Trial Location:** Multicenter

**Sponsor:**
Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200 (USA)

**Local Trial Coordinator:**
Michael S. Woods, MD/Rena M. Lambert, MS
Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200
Tel: (609) 730-3409 / FAX: (609) 730-3288

**Approvals:**

| | | |
|---|---|---|
| **Investigator:** | ..... | ..... |
| | (name, title) | (Date) |
| **Development Project Leader:** | ..... | ..... |
| Janssen Research Foundation | G. van 't Klooster, PhD | (Date) |
| **VP, Global Gastroenterology Clinical Research & Development:** | ..... | ..... |
| Janssen Research Foundation | L. Lauwers, MD | (Date) |
| **Clinical Research Director, U.S.:** | ..... | ..... |
| Janssen Research Foundation | A. Joslyn, PhD | (Date) |