Title of Study: Scintigraphic assessment of gastrointestinal transit following administration of KLEAN-PREP® (4L) or MOVIPREP® (2L) to healthy volunteers.

Investigators: Principal Scientific Investigator: Dr Alyson Connor
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Study centre: Ruddington, Nottingham, UK

Publication (reference): None

Studied Period: 03 July 2007 to 08 October 2007 | **Phase of development:** 1

Objectives:

Primary Objective (Part A and Part B)

- To assess the impact of administration of MOVIPREP® and KLEAN-PREP® on total and segmental colonic transit of the contents of the colon at the time of dosing, in comparison to baseline.

Secondary Objectives (Part A and Part B)

- To assess the gastrointestinal transit of MOVIPREP® and KLEAN-PREP®, in comparison to baseline;
- To assess the gastric emptying of MOVIPREP® and KLEAN-PREP® (to gain information for procedures which require general anaesthesia);
- To collect information about stool weight, visual characteristics and distribution of the radiolabel.

Additional Part A Objectives

- To optimise the radiolabelling methodology and imaging schedule in order to maximise the data obtained;
- To confirm whether the timing of the administration of the ^{111}In radiolabelled capsule is suitable for measurement of the transit of the colonic material at the time of dose administration;
- To qualitatively determine the rate of loss of radioactive material from the GI tract and hence the possibility of administering a second radioactive dose approximately 13 hours after the initial dose, in order to obtain a more detailed understanding of transit.

Methodology: This was a phase 1, open-label, randomised study performed in 2 parallel groups with Part A in 2 groups of 4 subjects prior to Part B in 2 groups of 12 subjects. Subjects attended a pre-study medical within 28 days of dosing and a post-study medical 5-10 days after the final dose. Within both Part A and Part B, subjects were required to attend the clinical unit for 2 study periods. The first comprised a baseline period to determine individual reference times for gastrointestinal transit. The second comprised the test period in which gastrointestinal transit following the administration of the test preparations was assessed.

Number of subjects (planned and analysed): 32 subjects were to be dosed (up to a maximum of 36) with 16 subjects in each group. 74 volunteers were screened and 32 entered and completed the study.

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Diagnosis and main criteria for inclusion: Healthy males aged between 18–65 years with a Body Mass Index of between 18 and 35 Kg/m^2.

Reference therapy:

Groups 1 and 2 (Regimens A and C, respectively): Baseline Period (study period 1)

1 x gelatin capsule containing not more than 1 MBq ^{111}In radiolabelled ion-exchange resin with 240 mL water administered with lunch at approximately 13:00 on Day 1.

Plus

500 mL water containing ^{99m}Tc-DTPA administered as a divided dose. Aliquot 1, 250 mL water containing not more than 4 MBq ^{99m}Tc-DTPA administered approximately at 18:00 (Part A) or 19:00 (Part B) on Day 1 and aliquot 2, 250 mL water containing not more than 4 MBq ^{99m}Tc-DTPA administered approximately 07:00 on Day 3 for Part A and at approximately 09:45 (Regimen A) or 08:45 (Regimen C) on Day 3 for Part B.

Each aliquot of water was consumed at an approximate rate of 250 mL per 15 minutes.

Test product, dose and mode of administration, batch number:

Groups 1 and 2 (Regimen B and D, respectively): Test Period (study period 2)

1 x gelatin capsule containing not more than 1 MBq ^{111}In radiolabelled ion-exchange resin with 240 mL water administered with lunch at approximately 13:00, Day 1.

Plus

KLEAN-PREP® (Batch No. 27001953) (4 L) (Regimen B) containing ^{99m}Tc-DTPA administered as a divided dose. 2 L (aliquot 1; with the first 250 mL containing not more than 4 MBq ^{99m}Tc-DTPA) administered approximately 18:00 (Part A) or 19:00 (Part B) on Day 1 and 2 L (aliquot 2; with the last 250 mL containing not more than 4 MBq ^{99m}Tc-DTPA) administered approximately 07:00 (Part A) or 08:00 (Part B) on Day 2.

Each aliquot of KLEAN-PREP® was consumed at an approximate rate of 250 mL per 15 minutes.

Or

MOVIPREP® (Batch No. 50670) (2 L) (Regimen D) containing radiolabelled ^{99m}Tc-DTPA administered as a divided dose. 1 L (aliquot 1; with the first 250 mL containing not more than 4 MBq ^{99m}Tc-DTPA) administered approximately 18:00 (Part A) or 19:00 (Part B) on Day 1 and 1 L (aliquot 2; with the last 250 mL containing not more than 4 MBq ^{99m}Tc-DTPA) administered approximately 07:00 (Part A) or 08:00 (Part B) on Day 2.

Each aliquot of MOVIPREP® was consumed at an approximate rate of 250 mL per 15 minutes and was followed by an additional 0.5 L clear liquid.

Duration of treatment: The study comprised of 2 study periods of approximately 91 and 45 hours duration for the baseline and test periods, respectively, separated by a minimum period of 48 hours between discharge from the baseline period and admission for the test period.

Criteria for evaluation:

Scintigraphic:

Interim data analysis:

- Qualitative assessment of image quality,
- Transit of the ^{111}In radiolabelled resin (gastric emptying (initial and complete), colon arrival (initial and complete) and location at 5 hours post-administration);
- Total colonic transit time of the first aliquot of the ^{99m}Tc radiolabelled test preparation (test period only) (time taken to completely empty from the colon and location at time of administration of second aliquot of ^{99m}Tc radiolabelled test preparation).

Main data analysis:

^{111}In radiolabelled ion-exchange resin: Location and time of initial and complete capsule disintegration, initial and complete gastric emptying time; initial and complete colon arrival time; rate of gastric emptying ($T_{50\%}$ and $T_{90\%}$), rate of colon arrival ($T_{50\%}$ and $T_{90\%}$), segmental colonic transit (GC analysis) at 4, 6, 8, 12, 16 and 24 hours post-dose, and 36 and 48 hours post-dose (for the baseline period only) and amount of radioactivity in the faecal effluent from each bowel movement was assessed as a percentage of total radiolabel in all bowel movements (test period only).

^{99m}Tc radiolabelled marker: Initial and complete gastric emptying time, initial and complete colon arrival time, rate of gastric emptying ($T_{50\%}$ and $T_{90\%}$), rate of colon arrival ($T_{50\%}$ and $T_{90\%}$), segmental colonic transit (GC analysis) at 2, 4, 6, 8, 12, 16, 24 hours post-dose, and 36 and 48 hours

postdose (for the baseline period only) for each radiolabelled sub-aliquot of the divided dose and amount of radioactivity in the faecal effluent from each bowel movement was assessed as a percentage of total radiolabel in all bowel movements (test period only).
Safety and tolerability: Subjects were routinely questioned at each study visit about the occurrence of any adverse events. Haematology, clinical chemistry and urinalysis were monitored before and after the study treatment period. Vital signs were recorded at pre-study, pre-dose, at discharge and post-study. ECGs were recorded at the pre- and post-study medicals.

Statistical methods: Descriptive statistics for demographic, adverse events, clinical laboratory, vital signs and scintigraphic data are presented.

Conclusions:
Scintigraphic conclusions:

- Administration of ^{99m}Tc aliquot 1 of KLEAN-PREP® and MOVIPREP® did not impact on the gastric emptying of the material in the gastrointestinal tract (^{111}In ion-exchange resin) at the time of product administration.
- Administration of ^{99m}Tc aliquot 1 of KLEAN-PREP® and MOVIPREP® increased the rate of small intestinal transit of the material in the gastrointestinal tract (^{111}In ion-exchange resin) and hence colon arrival of ^{111}In ion-exchange resin occurred earlier.
- The arrival of ^{99m}Tc aliquot 1 of KLEAN-PREP® and MOVIPREP® in the lower gastrointestinal tract resulted in the very rapid transit of the contents of the colon (^{111}In ion-exchange resin). The effect started at 2-3 hours after test product administration and by 6 or 7 hours post-administration of ^{99m}Tc aliquot 1 the majority of the ^{111}In ion-exchange resin had been defaecated.
- In general, gastric emptying of ^{99m}Tc aliquot 1 of KLEAN-PREP® and MOVIPREP® was similar to baseline, although a slower terminal phase was observed for MOVIPREP®.
- Colon arrival of ^{99m}Tc aliquot 1 of KLEAN-PREP® and MOVIPREP® occurred earlier than for baseline.
- Colon transit of ^{99m}Tc aliquot 1 of KLEAN-PREP® and MOVIPREP® were similar ($p \geq 0.1641$) and more rapid than baseline ($p < 0.0001$) with the majority of the aliquot defaecated by 4 hours post-dose of ^{99m}Tc aliquot 1.
- Gastric emptying of ^{99m}Tc aliquot 2 of KLEAN-PREP® was similar to baseline. For MOVIPREP®, gastric emptying had a slower terminal phase than baseline.
- In terms of administering a general anaesthetic after completion of aliquot 2 of KLEAN-PREP® or MOVIPREP®, complete gastric emptying ranged from 0.5 to 3.3 hours post-dose for Klean-Prep® and 0.7 to 4.7 hours post-dose for MOVIPREP®.
- Colon arrival of ^{99m}Tc aliquot 2 of KLEAN-PREP® and MOVIPREP® were similar and occurred earlier than for baseline ($p \leq 0.0126$).
- Colonic transit of ^{99m}Tc aliquot 2 of MOVIPREP® was quicker than for ^{99m}Tc aliquot 2 of KLEAN-PREP® ($p \leq 0.0011$). By 4 hours post-dose of ^{99m}Tc aliquot 2 the majority of ^{99m}Tc aliquot 2 of MOVIPREP® had been defaecated. Thereafter, there was a marked decrease in the rate of defaecation. Whereas for KLEAN-PREP®, the majority of the aliquot 2 was not defaecated until 8 hours after its administration again followed by a decrease in rate of colonic transit.
- $T_{50\%}$, $T_{90\%}$, and complete gastric emptying for the baseline and test periods for the KLEAN-PREP® group and $T_{90\%}$ and complete gastric emptying for baseline and test periods for the MOVIPREP® group occurred earlier for ^{99m}Tc aliquot 2 than for ^{99m}Tc aliquot 1.
- Colon arrival occurred earlier for ^{99m}Tc aliquot 2 of KLEAN-PREP® and MOVIPREP® compared with ^{99m}Tc aliquot 1, indicating that the effect on small intestinal transit is additive i.e. the more an individual drinks, the faster transit becomes.
- Colonic transit of ^{99m}Tc aliquot 1 of KLEAN-PREP® was quicker than for ^{99m}Tc aliquot 2. The colonic transit of MOVIPREP® was similar for ^{99m}Tc aliquots 1 and 2.

Safety and tolerability conclusion:
The MOVIPREP® treatment was generally well tolerated. 2 subjects were unable to tolerate the KLEAN-PREP® treatment and dosing was stopped following the 4th sub-aliquot of aliquot 2. Gastrointestinal side effects are a common adverse event of PEG-based gut cleansing solutions. The study confirmed that 11 of the 21 treatment emergent adverse events were gastrointestinal disorders. The 4L KLEAN-PREP® treatment was associated with 9 of these events, while the 2L

MOVIPREP® solution with only 2 events. Moreover 2 subjects had dosing suspended and terminated due to gastrointestinal side effects while receiving KLEAN-PREP®. These results suggest a difference in the frequency and severity of GI adverse events between the 2 treatments. One possible explanation for this is that the overall volume of PEG-based solutions might have an effect on the frequency of gastrointestinal side effects. However, other differences in the PEG-based solutions may also be responsible for the observed differences in the gastrointestinal side effect profile. There were no serious or severe adverse events. No clinically significant changes in vital signs or ECGs were observed.
Date of the report: 22 December 2008