



Clinical trial results:

A single-arm, open-label, multicentre, non-randomised, study to assess the effect and tolerability of standardised laxative therapy (SLT) for the reversal of opioid-induced constipation (OIC) in subjects suffering from malignant or non-malignant pain that requires around-the-clock opioid therapy.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-000180-81 |
| Trial protocol | GB SE |
| Global end of trial date | 27 August 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 16 July 2016 |
| First version publication date | 16 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | SLT4501 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Mundipharma Research GmbH & Co. KG |
| Sponsor organisation address | Höhenstrasse 10, Limburg, Germany, 65549 |
| Public contact | European Medical Operations, Mundipharma Research GmbH & Co. KG, 0044 1223424900, info@contact-clinical-trial.com |
| Scientific contact | European Medical Operations, Mundipharma Research GmbH & Co. KG, 0044 1223424900, info@contact-clinical-trial.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 27 August 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 August 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 August 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To assess the effect of SLT on the frequency of soft (stool of type 3, 4 or 5 on the Bristol Stool Form Scale (BSFS)) complete bowel movements (SCBMs) and SCBMs non-straining (NS) per week in subjects taking World Health Organisation (WHO) step II/III opioid analgesics at visit 8 (change from baseline to the final visit)
- To assess the number of subjects taking additional laxatives (including enema) or requiring procedures (e.g. manual bowel evacuation or surgical procedure) in addition to SLT.
- To assess symptoms of constipation in subjects taking SLT concomitantly with WHO step II/III opioid analgesics as measured by the Bowel Function Index (BFI).
- To assess the compliance with opioids/SLT in terms of number of subjects who did not discontinue prematurely, experience dose reduction or stop opioids/SLT due to insufficient effect and/or intolerability.

Protection of trial subjects:

1) Inclusion criteria:

- Females less than one year post-menopausal must have a negative pregnancy test prior to the first dose of study medication, be non-lactating, and willing to use adequate and highly effective methods of contraception throughout the study. (A highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly e.g. sterilisation, implants, injectables, combined oral contraceptives, some intrauterine devices ((IUDs), hormonal), sexual abstinence or vasectomised partner).
- Subjects must be willing and able (e.g. mental and physical condition) to participate in all aspects of the study, including use of medication, completion of subjective evaluations, attending scheduled clinic visits, completing telephone contacts, and compliance with protocol requirements as evidenced by providing written, informed consent.

2) Exclusion criteria:

- In the Investigator's opinion any contraindication and precautionary condition for laxative medication(s) used in the study as per the SmPC

3) Dose discontinuation:

Investigators may have stopped SLT at any time for safety reasons or if judged no longer appropriate for the Subject to continue.

4) Safety assessments consisted of monitoring and recording all AEs and SAEs, observed or volunteered, regardless of laxatives received or suspected causal relationship to the IMP. This included reactions, interactions, accidents, illnesses, misuse and abuse. In addition, safety was assessed by monitoring haematology, biochemistry, and urine values, periodic measurement of vital signs and ECGs and the performance of physical examinations.

Background therapy:

1) Analgesic Medication (NIMP)

WHO step II/III opioid analgesics

2a) Analgesic rescue medication for subjects on Oxy PR

During the Treatment Period subjects on Oxy PR were ideally prescribed Oxy IR as analgesic rescue medication for breakthrough pain. The need for rescue medication more than twice a day indicated that the dosage of Oxy PR tablets should be increased.

2b) Analgesic rescue medication for subjects on other opioids

For subjects who were on WHO step II/III opioids (with the exception of Oxy PR) the Investigator determined the type and dose of analgesic rescue medication for breakthrough pain.

3) Laxative Medication

Laxatives including study IMP taken before Visit 2 and after Visit 8 was considered "concomitant medication".

Evidence for comparator:

Not applicable

| | |
|---|-----------------|
| Actual start date of recruitment | 01 October 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Sweden: 25 |
| Country: Number of subjects enrolled | United Kingdom: 79 |
| Country: Number of subjects enrolled | France: 12 |
| Worldwide total number of subjects | 116 |
| EEA total number of subjects | 116 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 65 |
| From 65 to 84 years | 49 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at a total of 19 sites in 3 countries (4 sites in France, 5 in Sweden, and 10 in the United Kingdom). In addition, 7 sites (5 in France, 2 in Sweden) were initiated but did not recruit any subjects. The Netherlands were planned a study country but no Ethics approval was granted.

Pre-assignment

Screening details:

Visit 1 to Visit 2

Duration 7 days

Subjects continued on their pre-study medication (opioid and laxative) and completed a daily diary .

Screening failures:16 (13.8%)

Reasons:

Failed screening procedure 6 (5.2%)

Inclusion criteria 8 (6.9%)

Subject's choice1 (0.9%)

SAE 1 (0.9%)

Period 1

| | |
|------------------------------|-----------------------------------|
| Period 1 title | Treatment period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Swedish SLT regimen |

Arm description: -

| | |
|--|--------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Macrogol |
| Investigational medicinal product code | Macrogol |
| Other name | |
| Pharmaceutical forms | Powder and solvent for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Medication was used as directed in SmPC. Any other medication with the same active ingredient could be used.

| | |
|--|--------------------|
| Investigational medicinal product name | Sodium picosulfate |
| Investigational medicinal product code | Sodium picosulfate |
| Other name | |
| Pharmaceutical forms | Oral drops, liquid |
| Routes of administration | Oral use |

Dosage and administration details:

Medication was used as directed in SmPC. Any other medication with the same active ingredient could be used.

| | |
|--|--|
| Investigational medicinal product name | Second Line SLT |
| Investigational medicinal product code | Second Line SLT |
| Other name | |
| Pharmaceutical forms | Granules in sachet, Oral liquid, Capsule, Oral solution, Oral suspension, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

If required and deemed necessary by the Investigator, a third laxative could be administered as a

Second Line SLT. The choice was made by the Investigator, dose and route of administration of this third laxative (or enema) were according to country specific clinical practice guidelines, site specific standards, and the clinical condition of the Subject, either as regular administration or for immediate rescue purposes.

| | |
|--|--|
| Investigational medicinal product name | Additional laxative |
| Investigational medicinal product code | Additional laxative |
| Other name | |
| Pharmaceutical forms | Capsule, Granules in sachet, Oral liquid, Oral suspension, Oral/rectal solution, Suppository, Tablet |
| Routes of administration | Oral use, Rectal use |

Dosage and administration details:

If additional laxative (in addition to First and Second Line SLT) was deemed necessary, the choice was made by the Investigator, dose and route of administration of this additional laxative (or enema) were according to country specific clinical practice guidelines, site specific standards, and the clinical condition of the Subject, either as regular administration or for immediate rescue purposes.

| | |
|------------------|--------------------|
| Arm title | French SLT regimen |
|------------------|--------------------|

Arm description: -

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bisadodyl |
| Investigational medicinal product code | Bisacodyl |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Medication was used as directed in SmPC. Any other medication with the same active ingredient could be used.

| | |
|--|----------|
| Investigational medicinal product name | Sorbitol |
| Investigational medicinal product code | Sorbitol |
| Other name | |
| Pharmaceutical forms | Pouch |
| Routes of administration | Oral use |

Dosage and administration details:

Medication was used as directed in SmPC. Any other medication with the same active ingredient could be used.

| | |
|--|--|
| Investigational medicinal product name | Second Line SLT |
| Investigational medicinal product code | Second Line SLT |
| Other name | |
| Pharmaceutical forms | Capsule, Granules in sachet, Oral liquid, Oral solution, Oral suspension, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

If required and deemed necessary by the Investigator, a third laxative could be administered as a Second Line SLT. The choice was made by the Investigator, dose and route of administration of this third laxative (or enema) were according to country specific clinical practice guidelines, site specific standards, and the clinical condition of the Subject, either as regular administration or for immediate rescue purposes.

| | |
|--|--|
| Investigational medicinal product name | Additional laxative |
| Investigational medicinal product code | Additional laxative |
| Other name | |
| Pharmaceutical forms | Capsule, Granules in sachet, Oral liquid, Oral suspension, Oral/rectal solution, Suppository, Tablet |
| Routes of administration | Oral use, Rectal use |

Dosage and administration details:

If additional laxative (in addition to First and Second Line SLT) was deemed necessary, the choice was made by the Investigator, dose and route of administration of this additional laxative (or enema) were according to country specific clinical practice guidelines, site specific standards, and the clinical condition of the Subject, either as regular administration or for immediate rescue purposes.

| | |
|--|----------------|
| Arm title | UK SLT regimen |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Senna |
| Investigational medicinal product code | Senna |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Medication was used as directed in SmPC. Any other medication with the same active ingredient could be used.

| | |
|--|-----------------|
| Investigational medicinal product name | Docusate sodium |
| Investigational medicinal product code | Docusate |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Medication was used as directed in SmPC. Any other medication with the same active ingredient could be used.

| | |
|--|--|
| Investigational medicinal product name | Second Line SLT |
| Investigational medicinal product code | Second Line SLT |
| Other name | |
| Pharmaceutical forms | Capsule, Granules in sachet, Oral liquid, Oral solution, Oral suspension, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

If required and deemed necessary by the Investigator, a third laxative could be administered as a Second Line SLT. The choice was made by the Investigator, dose and route of administration of this third laxative (or enema) were according to country specific clinical practice guidelines, site specific standards, and the clinical condition of the Subject, either as regular administration or for immediate rescue purposes.

| | |
|--|--|
| Investigational medicinal product name | Additional laxative |
| Investigational medicinal product code | Additional laxative |
| Other name | |
| Pharmaceutical forms | Capsule, Granules in sachet, Oral liquid, Oral suspension, Oral/rectal solution, Suppository, Tablet |
| Routes of administration | Oral use, Rectal use |

Dosage and administration details:

If additional laxative (in addition to First and Second Line SLT) was deemed necessary, the choice was made by the Investigator, dose and route of administration of this additional laxative (or enema) were according to country specific clinical practice guidelines, site specific standards, and the clinical condition of the Subject, either as regular administration or for immediate rescue purposes.

| Number of subjects in period 1^[1] | Swedish SLT regimen | French SLT regimen | UK SLT regimen |
|---|---------------------|--------------------|-------------------|
| Started | 22 | 11 | 67 |
| Safety population | 22 | 11 | 67 |
| Full Analysis population | 22 | 11 | 67 |
| Full Analysis Population without deviat | 19 ^[2] | 9 | 62 ^[3] |

| | | | |
|--|----|---|----|
| Completed | 22 | 9 | 64 |
| Not completed | 0 | 2 | 3 |
| Adverse event, serious fatal | - | - | 1 |
| Administrative: Screening criteria not fulfilled | - | - | 1 |
| Adverse event, non-fatal | - | 2 | - |
| Lack of efficacy | - | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 116 subjects were enrolled. 16 failed Screening. 100 subjects were treated and included in the safety and full analysis populations. 90 subjects were included in the Full Analysis without Deviations Population.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only subjects without protocol deviations were included in the "Full Analysis without Deviation" Population.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only subjects without protocol deviations were included in the "Full Analysis without Deviation" Population.

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Treatment period |
|-----------------------|------------------|

Reporting group description: -

| Reporting group values | Treatment period | Total | |
|--|------------------|-------|--|
| Number of subjects | 100 | 100 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 57 | 57 | |
| From 65-84 years | 41 | 41 | |
| 85 years and over | 2 | 2 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 61.3 | | |
| standard deviation | ± 13.3 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 59 | 59 | |
| Male | 41 | 41 | |
| Race | | | |
| Units: Subjects | | | |
| Caucasian | 99 | 99 | |
| Black | 0 | 0 | |
| Asian | 0 | 0 | |
| Other | 1 | 1 | |
| Age median | | | |
| Units: years | | | |
| median | 62 | | |
| full range (min-max) | 30 to 87 | - | |

Subject analysis sets

| | |
|----------------------------|-------------------|
| Subject analysis set title | Safety population |
|----------------------------|-------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The safety population was defined as all subjects who received at least one dose of IMP.

Note: Subjects who were taking one or two laxatives in SLT and discontinued the study before Visit 2 were not included into the safety population as SLT treatment intakes before Visit 2 were not meant to be intakes of the IMP by the definition. The safety population was used to assess all safety evaluations

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Full analysis population |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The full analysis population was defined as all subjects who

- received at least one dose of IMP,
- had at least one baseline measure (i.e. a pre-switch (prior to Visit 2) value during the screening period) and
- had at least one post-baseline measure for Soft Complete Bowel Movements (SCBMs).

Subjects who were found to violate any of the inclusion /exclusion criteria (after starting study treatment) were also included in this population.

| | |
|----------------------------|--|
| Subject analysis set title | Full Analysis Population without Deviations (FAPwoD) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

In addition to the FAP the FAPwoD was defined as a subset of all subjects from the FAP who:

- Did not violate any inclusion/exclusion criteria.
- Did not take prohibited concomitant therapies during the Treatment Period.
- Did not take more than the maximum dose of laxatives (both first and second line SLT as per SmPC).

The following concomitant therapies were considered prohibited:

- Medications which substance name or part of their substance name contains one of the following: naloxone, naltrexone, methylnaltrexone.
- Medications with ATC 4th level code N07BC.

| Reporting group values | Safety population | Full analysis population | Full Analysis Population without Deviations (FAPwoD) |
|--|-------------------|--------------------------|--|
| Number of subjects | 100 | 100 | 90 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 57 | 57 | 52 |
| From 65-84 years | 41 | 41 | 36 |
| 85 years and over | 2 | 2 | 2 |
| Age continuous Units: years | | | |
| arithmetic mean | 61.3 | 61.3 | |
| standard deviation | ± 13.3 | ± 13.3 | ± |
| Gender categorical Units: Subjects | | | |
| Female | 59 | 59 | |
| Male | 41 | 41 | |
| Race Units: Subjects | | | |
| Caucasian | 99 | 99 | |
| Black | | | |
| Asian | | | |
| Other | 1 | 1 | |

| | | | |
|----------------------|----------|----------|--|
| Age median | | | |
| Units: years | | | |
| median | 62 | 62 | |
| full range (min-max) | 30 to 87 | 30 to 87 | |

End points

End points reporting groups

| | |
|--------------------------------|---------------------|
| Reporting group title | Swedish SLT regimen |
| Reporting group description: - | |
| Reporting group title | French SLT regimen |
| Reporting group description: - | |
| Reporting group title | UK SLT regimen |
| Reporting group description: - | |
| Subject analysis set title | Safety population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety population was defined as all subjects who received at least one dose of IMP.

Note: Subjects who were taking one or two laxatives in SLT and discontinued the study before Visit 2 were not included into the safety population as SLT treatment intakes before Visit 2 were not meant to be intakes of the IMP by the definition. The safety population was used to assess all safety evaluations

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Full analysis population |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The full analysis population was defined as all subjects who

- received at least one dose of IMP,
- had at least one baseline measure (i.e. a pre-switch (prior to Visit 2) value during the screening period) and
- had at least one post-baseline measure for Soft Complete Bowel Movements (SCBMs).

Subjects who were found to violate any of the inclusion /exclusion criteria (after starting study treatment) were also included in this population.

| | |
|----------------------------|--|
| Subject analysis set title | Full Analysis Population without Deviations (FAPwoD) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

In addition to the FAP the FAPwoD was defined as a subset of all subjects from the FAP who:

- Did not violate any inclusion/exclusion criteria.
- Did not take prohibited concomitant therapies during the Treatment Period.
- Did not take more than the maximum dose of laxatives (both first and second line SLT as per SmPC).

The following concomitant therapies were considered prohibited:

- Medications which substance name or part of their substance name contains one of the following: naloxone, naltrexone, methylnaltrexone.
- Medications with ATC 4th level code N07BC.

Primary: Soft complete bowel movements (SCBMs) per week

| | |
|-----------------|---|
| End point title | Soft complete bowel movements (SCBMs) per week ^[1] |
|-----------------|---|

End point description:

The primary objective was to assess the effect of SLT on the frequency of soft (stool of type 3, 4 or 5 on the Bristol Stool Form Scale (BSFS)) complete bowel movements (SCBMs) per week in subjects taking WHO step II/III opioid analgesics at Visit 8 (change from baseline to the final visit).

Bowel movements were characterised by the following criteria:

- S: Soft bowel movement was defined as stool of type 3, 4 or 5 on the Bristol Stool Form Scale (BSFS).
- C: Completeness of the bowel movement was rated as Yes.
- BM: The occurrence of a bowel movement (any passage of stool).
- NS: Straining or Squeezing was rated as Absent (0) or Mild (1).

Criteria were considered as not met if information relevant to the criteria was missing

A bowel movement was classified as a Soft Complete Bowel Movement (SCBM) if the following criteria were met: S, C and BM.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

over 4 weeks (change from visit 2 to visit 8).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As this was an exploratory study, no statistical analyses were done for this endpoint.

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Full analysis population |
|--------------------------------------|---------------------|--------------------|-----------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 22 | 11 | 66 | 99 |
| Units: mean change in SCBMs per week | | | | |
| arithmetic mean (standard deviation) | | | | |
| From diaries | 0.88 (± 2.87) | -0.13 (± 0.98) | 2.12 (± 2.86) | 1.6 (± 2.82) |
| At visits | 0.9 (± 2.57) | -0.07 (± 0.93) | 2.25 (± 3.01) | 1.69 (± 2.86) |

| End point values | Full Analysis Population without Deviations (FAPwoD) | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 90 | | | |
| Units: mean change in SCBMs per week | | | | |
| arithmetic mean (standard deviation) | | | | |
| From diaries | 1.78 (± 2.79) | | | |
| At visits | 1.87 (± 2.86) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency SCBM per week

| | |
|-----------------|-------------------------|
| End point title | Frequency SCBM per week |
|-----------------|-------------------------|

End point description:

Bowel movements were characterised by the following criteria:

- S: Soft bowel movement was defined as stool of type 3, 4 or 5 on the Bristol Stool Form Scale (BSFS).
- C: Completeness of the bowel movement was rated as Yes.
- BM: The occurrence of a bowel movement (any passage of stool).
- NS: Straining or Squeezing was rated as Absent (0) or Mild (1).

Criteria were considered as not met if information relevant to the criteria was missing

A bowel movement was classified as a Soft Complete Bowel Movement (SCBM) if the following criteria were met: S, C and BM.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 LOCF

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Full analysis population |
|--------------------------------------|---------------------|--------------------|-----------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 22 | 11 | 66 | 99 |
| Units: Number of SCBMs per week | | | | |
| arithmetic mean (standard deviation) | | | | |
| from diary | 1.75 (± 2.69) | 0.38 (± 0.69) | 2.61 (± 2.88) | 2.17 (± 2.76) |
| at visit | 1.65 (± 2.43) | 0.38 (± 0.69) | 2.67 (± 3.01) | 2.19 (± 2.82) |

| End point values | Full Analysis Population without Deviations (FAPwoD) | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 90 | | | |
| Units: Number of SCBMs per week | | | | |
| arithmetic mean (standard deviation) | | | | |
| from diary | 2.2 (± 2.84) | | | |
| at visit | 2.23 (± 2.91) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency SCBMs-NS per week

| | |
|-----------------|-----------------------------|
| End point title | Frequency SCBMs-NS per week |
|-----------------|-----------------------------|

End point description:

Bowel movements were characterised by the following criteria:

- S: Soft bowel movement was defined as stool of type 3, 4 or 5 on the Bristol Stool Form Scale (BSFS).
- C: Completeness of the bowel movement was rated as Yes.
- BM: The occurrence of a bowel movement (any passage of stool).
- NS: Straining or Squeezing was rated as Absent (0) or Mild (1).

Criteria were considered as not met if information relevant to the criteria was missing

A bowel movement was classified as a Soft Complete Bowel Movement (SCBM) if the following criteria were met: S, C and BM.

A bowel movement was classified as a Soft Complete Bowel Movement – Non Straining (SCBM-NS) if the following criteria were met: S, C, BM and NS.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 LOCF

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Full analysis population |
|--------------------------------------|---------------------|--------------------|-----------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 22 | 11 | 66 | 99 |
| Units: Number of SCBM-NS per week | | | | |
| arithmetic mean (standard deviation) | | | | |
| from diary | 1.19 (± 2.37) | 0.09 (± 0.3) | 1.44 (± 2.27) | 1.24 (± 2.19) |
| at visit | 1.14 (± 2.17) | 0.09 (± 0.3) | 1.48 (± 2.31) | 1.25 (± 2.18) |

| End point values | Full Analysis Population without Deviations (FAPwoD) | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 90 | | | |
| Units: Number of SCBM-NS per week | | | | |
| arithmetic mean (standard deviation) | | | | |
| from diary | 1.24 (± 2.28) | | | |
| at visit | 1.26 (± 2.26) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects taking additional laxatives (including enema) or requiring procedures

| | |
|--|--|
| End point title | Number of subjects taking additional laxatives (including enema) or requiring procedures |
| End point description: | |
| It was analysed how many subjects required additional laxatives (number of analysed subjects) and mean (SD) number of days on which laxatives were used. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to week 4 | |

| End point values | Safety population | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 49 ^[2] | | | |
| Units: Incidence (days) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall incidence (days) | 2.69 (± 5.209) | | | |
| Incidence per week (days) | 0.73 (± 1.464) | | | |

Notes:

[2] - This is the number of subjects who required additional laxatives.

Statistical analyses

No statistical analyses for this end point

Secondary: Bowel function index

| | |
|-----------------|----------------------|
| End point title | Bowel function index |
|-----------------|----------------------|

End point description:

The BFI score is the mean of the following items (assessed at each visit): Ease of defecation (numerical analogue scale (NAS), 0=easy/no difficulty; 100=severe difficulty), Feeling of incomplete bowel evacuation (NAS, 0=not at all, 100=very strong), Personal judgment of constipation (NAS, 0=not at all, 100=very strong).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 LOCF

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Safety population |
|--------------------------------------|---------------------|--------------------|-----------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 22 | 11 | 66 | 99 |
| Units: BFI score | | | | |
| arithmetic mean (standard deviation) | 30 (± 16.91) | 50 (± 28.81) | 35.7 (± 30.94) | 36 (± 28.48) |

| End point values | Full analysis population | Full Analysis Population without Deviations (FAPwoD) | | |
|--------------------------------------|--------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 99 | 90 | | |
| Units: BFI score | | | | |
| arithmetic mean (standard deviation) | 36 (± 28.48) | 35.5 (± 27.92) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance

| | |
|-----------------|------------|
| End point title | Compliance |
|-----------------|------------|

End point description:

The numbers and percentages of subjects

- who had at least one SLT (first or second line) dose reduction based on Laxative therapy CRF data was calculated.
- who had at least one opioid dose reduction based on Regular Analgesic Medication CRF data was calculated.
- who had at least one opioid dose reduction /increase based on diary data (took more / took less regular opioid medication as prescribed by doctor). This was also recalculated using only those diaries which reasonably reflect medication used according investigator's check.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to week 4

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Full analysis population |
|--|---------------------|--------------------|-----------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 22 | 11 | 67 | 100 |
| Units: number of subjects who did not discontin | | | | |
| Completed as defined in the protocol | 22 | 9 | 64 | 95 |
| Discontinued due to lack of therapeutic effect | 0 | 0 | 1 | 1 |
| Subjects with SLT therapy dose reduction | 14 | 8 | 28 | 50 |
| Subjects with opioid dose reduction (CRF) | 1 | 3 | 6 | 10 |
| Subjects who took more opioid medications (diary) | 3 | 2 | 8 | 13 |
| Subjects who took less opioid medications (diary) | 1 | 2 | 10 | 13 |
| Subjects who took more opioid medications (checked | 3 | 2 | 7 | 12 |
| Subjects who took less opioid medications (checked | 1 | 2 | 10 | 13 |
| Number of subjects with any change or interruption | 20 | 11 | 67 | 98 |

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability

| | |
|-----------------|--------------|
| End point title | Tolerability |
|-----------------|--------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to week 4, and follow up of 7 days after week 4

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Safety population |
|--|---------------------|--------------------|-----------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 22 | 11 | 67 | 100 |
| Units: Number of subjects | | | | |
| Subjects with SLT-related AEs | 16 | 9 | 41 | 66 |
| Subjects with SLT-related gastrointestinal AEs | 15 | 9 | 37 | 61 |
| Subjects who discontinued | 0 | 2 | 3 | 5 |
| Subjects who discontinued due to AEs | 0 | 2 | 1 | 3 |

Statistical analyses

No statistical analyses for this end point

Secondary: Withdrawal symptoms using SOWS and COWS

| | |
|-----------------|---|
| End point title | Withdrawal symptoms using SOWS and COWS |
|-----------------|---|

End point description:

Opioid withdrawal symptoms were assessed by the modified Subjective Opiate Withdrawal Scale (SOWS). The scale consists of 15 items that reflect the common motor, autonomic, gastrointestinal, musculoskeletal, and psychic symptoms of opiate withdrawal. The modified SOWS excluded the SOWS item, 'I feel like shooting up today', since it does not apply to the target subject population. The COWS is a clinician administered instrument that rates 11 common opiate withdrawal signs or symptoms. The score for each item reflects the severity of the sign or symptom. The total score was used to assess a Subjects' level of opiate withdrawal and to make inferences about their level of physical dependence on opioids.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Screening, week 1, week 4

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Full analysis population |
|--|---------------------|--------------------|-------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 22 ^[3] | 11 ^[4] | 67 ^[5] | 100 ^[6] |
| Units: Total score per week | | | | |
| arithmetic mean (full range (min-max)) | | | | |
| SOWS screening | 7.1 (0 to 26) | 14.8 (2 to 33) | 8.9 (0 to 34) | 9.1 (0 to 34) |
| SOWS week 1 | 7.1 (0 to 31) | 7.5 (0 to 29) | 6.9 (0 to 38) | 7 (0 to 38) |
| SOWS week 4 | 4.9 (0 to 21) | 10.5 (0 to 26) | 6 (0 to 27) | 5.2 (0 to 24) |
| COWS screening | 1.2 (0 to 6) | 5.3 (0 to 12) | 1.3 (0 to 8) | 1.7 (0 to 12) |
| COWS week 1 | 1.2 (0 to 4) | 3.9 (0 to 12) | 0.9 (0 to 7) | 1.3 (0 to 12) |
| COWS week 4 | 1.6 (0 to 6) | 3.3 (0 to 17) | 0.7 (0 to 5) | 1.1 (0 to 17) |

Notes:

[3] - 22 at Screening
13 at Week 1
13 at Week 4

[4] - 11 at Screening
 10 at week 1
 8 at week 4
 [5] - SOWS
 67 at Screening
 59 at week 1
 62 at week 4
 COWS
 67 at Screening
 61 at week 1
 62 at week 4
 [6] - SOWS:
 100 at Screening
 82 at week 1
 83 at week 4
 COWS:
 100 at Scr.
 84 at week 1
 83 at week 4

Statistical analyses

No statistical analyses for this end point

Secondary: Average pain over last 24 hours

| | |
|---|---------------------------------|
| End point title | Average pain over last 24 hours |
| End point description: | |
| The average pain over the last 24 hours at screening, baseline and each week (including Week 4 (LOCF)). Pain scale from 0 (no pain) to 10 (worst imaginable pain) | |
| End point type | Secondary |
| End point timeframe: | |
| Average pain in the last 24 hours, assessed at each visit | |

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Safety population |
|---|---------------------|--------------------|-------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 22 ^[7] | 11 ^[8] | 67 ^[9] | 100 ^[10] |
| Units: Pain score on pain intensity scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Screening | 5.7 (± 2.34) | 5.3 (± 2.67) | 6 (± 2.01) | 5.9 (± 2.14) |
| Baseline (visit 2) | 5.7 (± 1.94) | 5.7 (± 1.74) | 6.5 (± 2.19) | 6.3 (± 2.11) |
| Week 1 | 6.1 (± 2.19) | 4.8 (± 2.3) | 5.9 (± 2.52) | 5.8 (± 2.44) |
| Week 2 | 5.2 (± 2.14) | 5.6 (± 2.12) | 6.1 (± 2.53) | 5.9 (± 2.42) |
| Week 3 | 5.4 (± 2.15) | 5.5 (± 1.93) | 5.8 (± 2.47) | 5.7 (± 2.34) |
| Week 4 | 5.3 (± 2.6) | 5 (± 2.73) | 5.9 (± 2.41) | 5.7 (± 2.47) |
| Week 4 LOCF | 5.4 (± 2.48) | 5 (± 3) | 5.8 (± 2.44) | 5.6 (± 2.5) |

Notes:

[7] - Numbers of analysed subjects vary between 15 and 22.

[8] - Numbers of analysed subjects vary between 8 and 11.

[9] - Numbers of analysed subjects vary between 61 and 67.

[10] - Number of analysed subjects varies between 100 and 86.

| End point values | Full analysis population | Full Analysis Population without | | |
|------------------|--------------------------|----------------------------------|--|--|
|------------------|--------------------------|----------------------------------|--|--|

| | | Deviations (FAPwoD) | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 100 ^[11] | 90 ^[12] | | |
| Units: Pain score on pain intensity scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Screening | 5.9 (± 2.14) | 5.9 (± 2.18) | | |
| Baseline (visit 2) | 6.3 (± 2.11) | 6.2 (± 2.09) | | |
| Week 1 | 5.8 (± 2.44) | 5.8 (± 2.51) | | |
| Week 2 | 5.9 (± 2.42) | 5.9 (± 2.45) | | |
| Week 3 | 5.7 (± 2.34) | 5.7 (± 2.35) | | |
| Week 4 | 5.7 (± 2.47) | 5.7 (± 2.5) | | |
| Week 4 LOCF | 5.6 (± 2.5) | 5.6 (± 2.56) | | |

Notes:

[11] - Number of analysed subjects varies from 100 to 86.

[12] - Numbers of analysed subjects vary between 90 and 78.

Statistical analyses

No statistical analyses for this end point

Secondary: Health Status & Quality of life - SF36V2 and EQ5D

| | |
|--|---|
| End point title | Health Status & Quality of life - SF36V2 and EQ5D |
| End point description: | |
| <p>The SF-36 v2TM Health Survey[®] (SF-36 v2) is a validated scale to measure quality of life aspects. The summary scores that were employed are the SF-36 v2 scores for the eight health domains: role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, the general health question, and two summary measures of physical health (aggregate of physical functioning, role-physical, bodily pain and general health scales) and mental health (aggregate of the vitality, social functioning, role-emotional and mental health scales). Each domain score was transformed to a scale from 0 to 100. The SF-36 v2 domain scores were mapped into the EQ-5D utility score. The EQ-5D is the most widely used generic preference-based measure of health-related quality of life which produces utility scores anchored at 0 for dead and 1 for perfect health. Mapping model was used to covert SF-36 domain scores to EQ-5D utility score.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Screening, week 1, week 4 | |

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Full analysis population |
|--------------------------------------|---------------------|--------------------|--------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 21 ^[13] | 11 ^[14] | 66 ^[15] | 98 ^[16] |
| Units: EQ-5D Utility Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Screening | 0.533 (± 0.1577) | 0.446 (± 0.2115) | 0.383 (± 0.2287) | 0.422 (± 0.2204) |
| Week 1 | 0.545 (± 0.1371) | 0.437 (± 0.2243) | 0.414 (± 0.2542) | 0.437 (± 0.239) |
| Week 4 | 0.582 (± 0.1689) | 0.444 (± 0.2166) | 0.443 (± 0.2344) | 0.456 (± 0.2271) |

Notes:

[13] - 21 at Screening

13 at week 1

13 at week 4

[14] - 11 at Screening
10 at week 1
8 at week 4
[15] - 66 at Screening
61 at week 1
61 at week 4
[16] - 98 at Screening
84 at week 1
82 at week 4

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Assessment of Constipation Quality of Life (PAC QOL)

| | |
|-----------------|--|
| End point title | Patient Assessment of Constipation Quality of Life (PAC QOL) |
|-----------------|--|

End point description:

The Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire is an instrument to evaluate the impact of constipation on daily life over time.

PAC-QOL assessments were performed at clinic visits V1, V5 and V8.

The final PAC-QOL contained 28 items grouped into four subscales covering: Worries and concerns (11 items), Physical discomfort (4 items), Psychosocial discomfort (8 items), and Satisfaction (5 items).

Scale scores were then computed as the average item response within the scale.

Global score was calculated as the mean of the 28 items.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 4

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Full analysis population |
|--------------------------------------|---------------------|--------------------|--------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 22 ^[17] | 11 ^[18] | 67 ^[19] | 100 ^[20] |
| Units: PAC QOL Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Total score screening | 1.9 (± 0.68) | 2.3 (± 0.65) | 2.1 (± 0.72) | 2.1 (± 0.7) |
| Total score week 1 | 1.7 (± 0.63) | 2.1 (± 0.74) | 1.6 (± 0.83) | 1.7 (± 0.8) |
| Total score week 4 | 1.2 (± 0.69) | 1.9 (± 0.99) | 1 (± 0.97) | 1.1 (± 0.95) |
| Satisfaction score screening | 3.3 (± 0.63) | 3.3 (± 0.9) | 3.2 (± 0.83) | 3.2 (± 0.79) |
| Satisfaction score week 1 | 2.5 (± 0.66) | 2.9 (± 1.1) | 2.6 (± 1.02) | 2.6 (± 0.98) |
| Satisfaction week 4 | 1.9 (± 0.76) | 2.4 (± 1.06) | 1.5 (± 1.27) | 1.7 (± 1.21) |

Notes:

[17] - 22 at Screening
13 at week 1
13 at week 4

[18] - 11 at Screening
10 at week 1
8 at week 4

[19] - 67 at Screening
60 at week 1 total
61 at week 1 satisfaction
61 at week 4

[20] - 100 at Screening
83 at week 1 total
84 at week 1 satisfaction
82 at week 4

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) severity scale

| | |
|-----------------|---|
| End point title | Clinical Global Impression (CGI) severity scale |
|-----------------|---|

End point description:

The Clinical Global Impression (CGI) scale is a 7-point scale to assess the severity of illness for a given disease. This scale uses the clinical impression to grade the severity of subjects' illness into "normal, not at all ill", "borderline ill", "mildly ill", "moderately ill", "markedly ill", "severely ill", and "among the most extremely ill subjects". The CGI consists of further three subscales, and in addition to the overall severity there is a subscale for change, for therapeutic effect, and for side effects. The CGI for change makes a global rating of the change of condition, and grades it into very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse. The CGI item 1 (severity of illness) was assessed at Visit 1 and Visit 8. Items 2 – 4 (2 - global rating of change of condition, 3 - therapeutic effect, 4 - side effects) were assessed at Visit 5 and Visit 8.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Screening and Week 4 or Week 1 and Week 4 (see description)

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Full analysis population |
|---|---------------------|--------------------|--------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 22 ^[21] | 11 ^[22] | 67 ^[23] | 100 ^[24] |
| Units: Number and percentage of subjects | | | | |
| Severity of illness (Screening)-not at all ill | 0 | 0 | 7 | 7 |
| Severity of illness (Screening) borderline ill | 2 | 0 | 9 | 11 |
| Severity of illness (Screening) mildly ill | 7 | 2 | 25 | 34 |
| Severity of illness (Screening) moderately ill | 8 | 4 | 22 | 34 |
| Severity of illness (Screening) markedly ill | 4 | 4 | 4 | 12 |
| Severity of illness (Screening) severely ill | 0 | 1 | 0 | 1 |
| Severity of illness (Screening) extremely ill | 1 | 0 | 0 | 1 |
| Severity of illness (Week 4) not at all ill | 1 | 0 | 11 | 12 |
| Severity of illness (Week 4) borderline ill | 2 | 1 | 18 | 21 |
| Severity of illness (Week 4) mildly ill | 4 | 4 | 16 | 24 |
| Severity of illness (Week 4) moderately ill | 5 | 3 | 16 | 24 |
| Severity of illness (Week 4) markedly ill | 1 | 0 | 1 | 2 |
| Severity of illness (Week 4) severely ill | 0 | 0 | 0 | 0 |
| Severity of illness (Week 4) extremely ill | 0 | 0 | 0 | 0 |
| Change of condition (Week 1) very much improved | 1 | 1 | 0 | 2 |
| Change of condition (Week 1) much improved | 0 | 3 | 11 | 14 |
| Change of condition (Week 1) minimally improved | 6 | 3 | 17 | 26 |
| Change of condition (Week 1) no change | 4 | 3 | 25 | 32 |

| | | | | |
|---|---|---|----|----|
| Change of condition (Week 1) minimally worse | 2 | 0 | 4 | 6 |
| Change of condition (Week 1) much worse | 0 | 0 | 3 | 3 |
| Change of condition (Week 1) very much worse | 0 | 0 | 1 | 1 |
| Change of condition (Week 4) very much improved | 2 | 0 | 13 | 15 |
| Change of condition (Week 4) much improved | 7 | 4 | 12 | 23 |
| Change of condition (Week 4) minimally improved | 1 | 2 | 16 | 19 |
| Change of condition (Week 4) no change | 3 | 2 | 14 | 19 |
| Change of condition (Week 4) minimally worse | 0 | 0 | 7 | 7 |
| Change of condition (Week 4) much worse | 0 | 0 | 0 | 0 |
| Change of condition (Week 4) very much worse | 0 | 0 | 0 | 0 |
| Therapeutic effect (Week 1) not assessed | 0 | 0 | 2 | 2 |
| Therapeutic effect (Week 1) marked | 2 | 1 | 3 | 6 |
| Therapeutic effect (Week 1) moderate | 3 | 5 | 13 | 21 |
| Therapeutic effect (Week 1) minimal | 6 | 2 | 21 | 29 |
| Therapeutic effect (Week 1) unchanged or worse | 2 | 2 | 22 | 26 |
| Therapeutic effect (Week 4) not assessed | 0 | 0 | 0 | 0 |
| Therapeutic effect (Week 4) marked | 5 | 3 | 20 | 28 |
| Therapeutic effect (Week 4) moderate | 7 | 3 | 19 | 29 |
| Therapeutic effect (Week 4) minimal | 0 | 2 | 16 | 18 |
| Therapeutic effect (Week 4) unchanged or worse | 1 | 0 | 7 | 8 |
| Side effects (Week 1) not assessed | 0 | 0 | 0 | 0 |
| Side effects (Week 1) none | 8 | 2 | 29 | 39 |
| Side effects (Week 1) no significant interference | 4 | 5 | 28 | 37 |
| Side effects (Week 1) significant interference | 1 | 3 | 4 | 8 |
| Side effects (Week 1) outweigh therapeutic effect | 0 | 0 | 0 | 0 |
| Side effects (Week 4) not assessed | 0 | 1 | 0 | 1 |
| Side effects (Week 4) none | 6 | 2 | 40 | 48 |
| Side effects (Week 4) no significant interference | 3 | 5 | 20 | 28 |
| Side effects (Week 4) significant interference | 3 | 0 | 2 | 5 |
| Side effects (Week 4) outweigh therapeutic effect | 1 | 0 | 0 | 1 |

Notes:

[21] - 22 at Screening

13 at week 1

13 at week 4

[22] - 11 at Screening

10 at week 1

8 at week 4

[23] - 67 at Screening

61 at week 1

62 at week 4
 [24] - 100 at Screening
 84 at week 1
 83 at week 4

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency SCBM per week in Opioid subgroups

| | |
|-----------------|---|
| End point title | Frequency SCBM per week in Opioid subgroups |
|-----------------|---|

End point description:

Bowel movements were characterised by the following criteria:

- S: Soft bowel movement was defined as stool of type 3, 4 or 5 on the Bristol Stool Form Scale (BSFS).
- C: Completeness of the bowel movement was rated as Yes.
- BM: The occurrence of a bowel movement (any passage of stool).
- NS: Straining or Squeezing was rated as Absent (0) or Mild (1).

Criteria were considered as not met if information relevant to the criteria was missing

A bowel movement was classified as a Soft Complete Bowel Movement (SCBM) if the following criteria were met: S, C and BM.

Subgroups of

- Subjects taking SLT and any opioid, excluding Oxy PR (SLT + Non Oxy PR).
- Subjects taking SLT and Oxy PR (SLT + Oxy PR).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 LOCF

| End point values | Full analysis population | Full Analysis Population without Deviations (FAPwoD) | | |
|--------------------------------------|--------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 99 ^[25] | 90 ^[26] | | |
| Units: Number of SCBMs per week | | | | |
| arithmetic mean (standard deviation) | | | | |
| data from diaries (Oxy group) | 1.35 (± 2.43) | 1.32 (± 2.5) | | |
| data from diaries (Non-Oxy group) | 2.38 (± 2.81) | 2.43 (± 2.9) | | |
| data from visits (Oxy group) | 1.38 (± 2.44) | 1.34 (± 2.5) | | |
| data from visits (Non-Oxy group) | 2.4 (± 2.88) | 2.46 (± 2.98) | | |

Notes:

[25] - Oxy Group: 20 subjects

Non-Oxy Group: 79 subjects

[26] - Oxy Group: 19 subjects

Non-Oxy Group: 71 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency SCBMs-NS per week in opioid subgroups

| | |
|-----------------|---|
| End point title | Frequency SCBMs-NS per week in opioid subgroups |
|-----------------|---|

End point description:

Bowel movements were characterised by the following criteria:

- S: Soft bowel movement was defined as stool of type 3, 4 or 5 on the Bristol Stool Form Scale (BSFS).
- C: Completeness of the bowel movement was rated as Yes.
- BM: The occurrence of a bowel movement (any passage of stool).
- NS: Straining or Squeezing was rated as Absent (0) or Mild (1).

Criteria were considered as not met if information relevant to the criteria was missing

A bowel movement was classified as a Soft Complete Bowel Movement (SCBM) if the following criteria were met: S, C and BM.

A bowel movement was classified as a Soft Complete Bowel Movement – Non Straining (SCBM-NS) if the following criteria were met: S, C, BM and NS.

Subgroups of

- Subjects taking SLT and any opioid, excluding Oxy PR (SLT + Non Oxy PR).
- Subjects taking SLT and Oxy PR (SLT +

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 LOCF

| End point values | Full analysis population | Full Analysis Population without Deviations (FAPwoD) | | |
|--------------------------------------|--------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 99 ^[27] | 90 ^[28] | | |
| Units: Number of SCBMs-NS per week | | | | |
| arithmetic mean (standard deviation) | | | | |
| data from diaries (Oxy group) | 0.88 (± 2.38) | 0.87 (± 2.45) | | |
| data from diaries (Non-Oxy group) | 1.33 (± 2.15) | 1.34 (± 2.24) | | |
| data from visits (Oxy group) | 0.89 (± 2.39) | 0.89 (± 2.46) | | |
| data from visits (Non-Oxy group) | 1.34 (± 2.13) | 1.36 (± 2.22) | | |

Notes:

[27] - Oxy Group: 20 subjects

Non-Oxy Group: 79 subjects

[28] - Oxy Group: 19 subjects

Non-Oxy Group: 71 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Bowel function index in Opioid subgroups

| | |
|-----------------|--|
| End point title | Bowel function index in Opioid subgroups |
|-----------------|--|

End point description:

The BFI score is the mean of the following items (assessed at each visit): Ease of defecation (numerical analogue scale (NAS), 0=easy/no difficulty; 100=severe difficulty), Feeling of incomplete bowel evacuation (NAS, 0=not at all, 100=very strong), Personal judgment of constipation (NAS, 0=not at all, 100=very strong).

Subgroups:

- Subjects taking SLT and any opioid, excluding Oxy PR (SLT + Non Oxy PR).
- Subjects taking SLT and Oxy PR (SLT + Oxy PR).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 LOCF

| End point values | Full analysis population | Full Analysis Population without Deviations (FAPwoD) | | |
|--------------------------------------|--------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 99 ^[29] | | | |
| Units: BFI score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Oxy group | 42.5 (± 30.19) | 42.7 (± 30.99) | | |
| Non-Oxy group | 34.4 (± 28) | 33.6 (± 2.695) | | |

Notes:

[29] - Oxy Group: 20 subjects

Non-Oxy Group: 79 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression Improvement (PGI-I) scale

| | |
|-----------------|---|
| End point title | Patient Global Impression Improvement (PGI-I) scale |
|-----------------|---|

End point description:

The patient global impression of improvement (PGI-I) is a global index that may be used to rate the response of a condition to a therapy. It is a simple, direct, easy to use scale that is intuitively understandable to patients.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Visit 8 (week 4)

| End point values | Swedish SLT regimen | French SLT regimen | UK SLT regimen | Full analysis population |
|--|---------------------|--------------------|-----------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 20 | 9 | 62 | 91 |
| Units: Number of subjects with this response | | | | |
| Very much improved | 2 | 1 | 8 | 11 |
| Much improved | 5 | 3 | 19 | 27 |
| Minimally improved | 7 | 4 | 22 | 33 |
| No change | 6 | 1 | 9 | 16 |
| Minimally worse | 0 | 0 | 4 | 4 |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events were recorded from the point at which the Informed Consent was signed until 7-10 days after the subject left the study. SAEs were followed until the event resolved or the event or sequelae stabilised.

Adverse event reporting additional description:

Related AEs include those that were assessed as definitely, probably, possibly or unlikely related to IMP.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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| Dictionary name | MedDRA |
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| Dictionary version | 16.0 |
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Reporting groups

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|-----------------------|-----------|
| Reporting group title | Oxycodone |
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Reporting group description:

The subgroup of subjects taking Oxycodone prolonged-release (Oxy PR).

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|-----------------------|---------|
| Reporting group title | Non-Oxy |
|-----------------------|---------|

Reporting group description:

The subgroup of subjects taking other opioids than Oxycodone prolonged-release as pain medication.

| Serious adverse events | Oxycodone | Non-Oxy | |
|---|---|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 3 / 80 (3.75%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm progression | Additional description: Treatment at onset: FIRST LINE: MACROGOL; SODIUM PICOSULFATE Unrelated to IMP and Opioid Ongoing at study end Important medical event | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | Additional description: SLT at onset: FIRST LINE: MACROGOL; SODIUM PICOSULFATE Unrelated to IMP and Opioid Caused hospitalisation | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|--|----------------|--|
| Chest pain | Additional description: Treatment at onset: FIRST LINE: DOCUSATE SODIUM; SENNA ALEXANDRINA Unrelated to IMP and Opioid Important medical Event Recovered on the same day | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | Additional description: At the time of database lock, the death was assessed as unlikely to be related to SLT (docusate sodium and senna alexandrina) and opioid (fentanyl). A post-mortem report received post database lock revealed that the SAE was unrelated to SLT or opioid | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 80 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Oxycodone | Non-Oxy | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 20 (85.00%) | 68 / 80 (85.00%) | |
| Injury, poisoning and procedural complications | | | |
| Back injury | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 80 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 80 (1.25%) | |
| occurrences (all) | 1 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 5 / 80 (6.25%) | |
| occurrences (all) | 1 | 6 | |
| Tremor | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 80 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear and labyrinth disorders | | | |
| Meniere's disease | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 80 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|------------------|------------------|--|
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 20 (50.00%) | 25 / 80 (31.25%) | |
| occurrences (all) | 13 | 36 | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 16 / 80 (20.00%) | |
| occurrences (all) | 3 | 30 | |
| Nausea | | | |
| subjects affected / exposed | 4 / 20 (20.00%) | 11 / 80 (13.75%) | |
| occurrences (all) | 4 | 16 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 12 / 80 (15.00%) | |
| occurrences (all) | 2 | 15 | |
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 4 / 80 (5.00%) | |
| occurrences (all) | 2 | 4 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 5 / 80 (6.25%) | |
| occurrences (all) | 0 | 6 | |
| Flatulence | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 3 / 80 (3.75%) | |
| occurrences (all) | 1 | 3 | |
| Eructation | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 80 (1.25%) | |
| occurrences (all) | 1 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 80 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal and urinary disorders | | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 80 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 6 / 80 (7.50%) | |
| occurrences (all) | 3 | 6 | |

| | | | |
|--|----------------------|---------------------|--|
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 1 / 80 (1.25%) 1 | |
| Infections and infestations | | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 80 (2.50%) 2 | |
| Gastroenteritis viral subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 0 / 80 (0.00%) 0 | |
| Vulvovaginal candidiasis subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 1 / 80 (1.25%) 1 | |
| Breast infection subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 80 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 03 September 2013 | Protocol Amendment No. 1 was dated 03-Sep-2013, which was before the recruitment of the first Subject into the study. It amended protocol version 1 dated 04-Mar-2013. French EC had requested that the 12 objectives be graded into primary and secondary according to French regulations on Clinical Trials. In addition changes made to the operational management of the study have been amended in the protocol and typographical / administrative errors were corrected. |
| 08 November 2013 | Protocol Amendment No. 2 was dated 08-Nov-2013 and amended protocol version 2, dated 03-Sep-2013. As Ethics approval was not granted in the Netherlands, all references to that study country were removed from the protocol. This occurred after the first subject had been recruited, but had no influence on the study conduct in the countries that were already recruiting subjects. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported