Naldemedine for opioid-induced constipation in adults

LAY SUMMARY

Opioids are a class of drugs that are commonly prescribed for pain. Constipation is a side effect that affects nearly all patients taking opioid treatment. There has been an increase in the use of opioids to treat chronic pain in recent years. Current treatment for opioid-induced constipation often involves laxatives. But, it has been estimated that 50–80% of people taking laxatives for opioid-induced constipation get only a limited improvement in symptoms.

Naldemedine is a new drug for the treatment of opioid-induced constipation in adults that is taken as a tablet once a day. If it is licensed for use in the UK, naldemedine may offer an additional treatment option for adults with this debilitating condition.

NIHR HSRIC ID: 5267
TARGET GROUP

- Opioid-induced constipation: in adults.

TECHNOLOGY

DESCRIPTION

Naldemedine (S-297995) is an orally-active peripheral opioid receptor antagonist intended for the treatment of opioid-induced constipation. In preclinical models, naldemedine suppressed morphine-induced nausea and vomiting, and small intestinal hypomotility but did not affect the analgesic action of morphine.

In the phase III clinical trial, naldemedine was administered orally at 0.2mg once daily.

Naldemedine is not currently licensed in the EU for any indication. It is also in phase II clinical trials for opiate-induced nausea and vomiting.

INNOVATION and/or ADVANTAGES

If licensed, naldemedine may offer an additional treatment option for adults with opioid-induced constipation.

DEVELOPER

Shionogi.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Opioids are a class of drugs that are commonly prescribed for their analgesic properties. They include substances such as morphine, codeine, oxycodone, and methadone. Opioid-induced bowel dysfunction can occur very quickly and is a side effect that affects nearly all patients taking opioid treatment, not just chronic opioid users, of which opioid-induced constipation is the most common manifestation. Other symptoms of opioid-induced bowel dysfunction include nausea, vomiting, and dyspepsia.

Opioid-induced constipation has been estimated to occur in 15 to 90% of chronic opioid users. Opioid-induced constipation is characterised by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency after initiating opioid therapy. In recent years there has been a large increase in the use of opioids for the treatment of chronic non-cancer pain, and patients are commonly treated with opioids for

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* Expert personal opinion.
months or even years. The effects of opioids on the gut are primarily mediated by mu-opioid receptors in the gastrointestinal tract. Opioid binding to these receptors decreases enteric nerve activity and gastrointestinal propulsive motor activity, inhibits ion and fluid secretion, and increases resorption of water, leading to constipation. The debilitating symptoms of opioid-induced constipation can seriously impair patients’ quality of life, comparable even to pain and up to a point where some prefer inadequate pain control to avoid these side effects.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:
- Improving quality of life for people with long term conditions (2013).

**CLINICAL NEED and BURDEN OF DISEASE**

Opioid-induced constipation is a side effect that affects nearly all patients taking opioid treatment and will persist unless treated. Reported prevalence rates of constipation in the UK vary widely from 4 to 20%. Estimates on the prevalence of opioid-induced constipation among people taking opioids may be around 45–57% for non-cancer pain patients and at least 90% for cancer-related pain. The population prevalence of opioid-induced constipation is not known. It has been estimated that 50–80% of people taking laxatives for opioid-induced constipation report limited improvement in symptoms. In England in 2015, there were 23,310,700 prescription opioid analgesic items dispensed with a total net cost of £313,531,600.

The population likely to be eligible to receive naldemedine could not easily be estimated from available routine published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**
- NICE technology appraisal in development. Lubiprostone for treating opioid induced constipation (ID646). Date of issue to be confirmed.
- NICE clinical guideline. Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults (CG140). May 2012

**Other Guidance**

CURRENT TREATMENT OPTIONS

Current opioid-induced constipation management consists of nonpharmacological and/or pharmacological approaches. These may include:16,3,6

- Lifestyle modification, such as increasing dietary fibre, fluid intake and physical activity. This should commence at the start of opioid therapy and continue for the duration of treatment. However, increasing dietary fibre and physical activity is very often not possible in patients with cancer pain taking opioidsb.
- Laxatives: combine a stimulant and stool softener, also recommended at the start of opioid therapy.
  - Senna or bisacodyl — a gastrointestinal stimulant.
  - Docusate — a surfactant emulsifier that facilitates the mixture of fat and water in faeces. It is a stool softenerc.
  - Mineral oil — a lubricant that delays the absorption of water from stools in the colon.
  - Lactulose or polyethylene glycol (PEG) — an osmotic that pulls water into the colon, thereby hydrating the stool.
  - Prostaglandins or prokinetic drugs—change the way the intestines absorb water and electrolytes, and increasing the weight and frequency of stools while reducing transit time.
- Enemas.
- Opioid-antagonists bind to opioid receptors without activating them, effectively blocking the receptors. These include:
  - Peripherally selective opioid antagonist:
    - Methylnaltrexone bromide — a selective antagonist at the mu receptor, which crosses the blood-brain barrier only poorly.
    - Naloxegol
  - Targinact — an oral combination of oxycodone and naloxone.
  - Lubiprostone — a selective chloride channel-2 activator that acts in the small intestine causing an increased fluid secretion and gut mobility.

Currently, there is a consensus that laxative treatment should commence with the opioid therapy and continue throughout treatment. However, lifestyle modification and laxatives can be insufficient in some patients and most patients receiving long-term opioid therapy will ultimately require more aggressive pharmacological treatment16,17.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>COMPOSE IV, JapicCTI-132340; naldemedine vs placebo; phase III.</th>
<th>COMPOSE V, JapicCTI-132342; naldemedine vs placebo; phase III extension.</th>
<th>COMPOSE I, NCT01965158, EudraCT2013-002241-11, 1314V9231; naldemedine vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Complete but unpublished.</td>
<td>Complete but unpublished.</td>
<td>Completed and published</td>
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b Expert personal communication.
<table>
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<tbody>
<tr>
<td>Location</td>
<td>Japan.</td>
<td>Japan.</td>
<td>EU (incl UK), USA, and other countries.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=193; chronic opioid therapy for cancer pain; opioid-induced constipation; spontaneous bowel movement (SBM) frequency &lt;3 per week; at least one of the following symptoms: staining during bowel movement, feeling of incomplete evacuation, or passage of hard stools or pellets; no hepatic or renal disorders; no constipation attributable to causes other than opioid analgesics.</td>
<td>n=100; age &gt;20yrs old; cancer patients with constipation associated with administration of opioid analgesics; SBM frequency per week is &lt;3 per week; at least one of the following symptoms: straining during bowel movement, feeling of incomplete evacuation, or passage of hard stools or pellets; no constipation potentially attributable to causes other than opioid analgesics; no hepatic or renal disorders.</td>
<td>n=547; age 18 to 80 years old; non-malignant chronic pain treated with opioids; opioid-induced constipation; treated with a stable opioid regimen at a total daily average dose of ≥ 30mg equivalent of oral morphine sulfate; not currently using laxatives or willing to discontinue laxative use, and willing to use only the rescue laxatives provided throughout the study; meet opioid-induced constipation criteria based on the BMCA diary; no significant structural abnormalities of the gastrointestinal tract; no active medical diseases affecting bowel transit; presence of pelvic disorders that may be a cause of constipation; no surgery (except for minor procedures) within 60 days of screening; no chronic constipation prior to starting analgesic medication or any potential non-opioid cause of bowel dysfunction that may be a major contributor to the constipation; no current use of opioid antagonists, partial agonists or mixed agonists/antagonists.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to 0.2mg naldemedine once daily or placebo, both oral.</td>
<td>Randomised to 0.2mg naldemedine once daily or placebo once daily, both oral.</td>
<td>Randomised to naldemedine 0.2mg oral once daily or placebo oral once daily.</td>
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<tr>
<td>Follow-up</td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>Active treatment for 12 weeks; follow-up not reported.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Primary proportion of SBM responders; mean change in the frequency of SBM, AEs, pharmacokinetics.</td>
<td>Safety (AEs).</td>
<td>Proportion of responders (defined as having ≥ 9 positive response weeks out of the 12 weeks, and 3 positive response</td>
</tr>
</tbody>
</table>
### Secondary outcome/s

| Secondary outcome/s | Not reported. | Assessments of constipation symptoms and Quality of Life (QOL). | Not reported. |

### Key results

| Key results | A statistically significant increase in the SBM responder rate compared to placebo was reported over 2 weeks. Naldemedine was generally well-tolerated and no attenuation of opioid analgesic effects was observed. | Not reported. | A statistically significant improved frequency of SBM compared with placebo was reported over 12 weeks; naldemedine was generally well-tolerated with the most commonly reported side effects being gastrointestinal disorders. |

### Adverse effects (AEs)

| Adverse effects (AEs) | Mild diarrhoea was the only AE reported in more than 5 % of subjects. | Not reported. | Abdominal pain and diarrhoea were the only treatment related adverse events reported. |

### Expected reporting date

| Expected reporting date | Not reported. | Not reported. | December 2014 (final data collection date for primary outcome measure). |

### Trial

| Trial | COMPOSE II, NCT01993940, EudraCT2013-002948-91; naldemedine vs placebo; phase III. | COMPOSE III, NCT01965652, EudraCT2013-002949-11; naldemedine vs placebo; phase III. |

### Sponsor

| Sponsor | Shionogi. | Shionogi. |

### Status

| Status | Ongoing. | Ongoing. |

### Source of information

| Source of information | Trial registry<sup>22</sup>. | Trial registry<sup>23</sup>. |

### Location

| Location | EU (not UK), USA and other countries. | EU (incl UK), USA, Canada and other countries. |

### Design

| Design | Randomised, placebo-controlled. | Randomised, placebo-controlled. |

### Participants

| Participants | n=553 (planned); aged 18 to 80 years; non-malignant chronic pain treated with opioids; opioid-induced constipation; treated with a stable opioid regimen at a total average daily dose of ≥ 30 mg equivalent of oral morphine sulfate; not currently using laxatives or willing to discontinue laxative use, and willing to use only the rescue laxatives provided throughout the study; meet opioid-induced constipation criteria based on the Bowel Movement and Constipation Assessment (BMCA) diary; no significant structural abnormalities of the gastrointestinal tract; no active medical diseases affecting bowel transit; no pelvic disorders that may be a cause of constipation; no surgery (except for minor procedures) within 60 days of screening; no chronic constipation prior to starting analgesic medication or any | n=1,200(planned); aged 18 to 80 years old; non-malignant chronic pain; opioid-induced constipation; treated with a stable opioid regimen at a total daily dose on average of ≥ 30 mg equivalent of oral morphine sulfate; may or may not be on routine laxative regimen at the time of screening; no significant structural abnormalities of the gastrointestinal tract; no active medical diseases affecting bowel transit; no pelvic disorders that may be a cause of constipation; no surgery (except for minor procedures) within 60 days of screening; no chronic constipation prior to starting analgesic medication or any |
presence of pelvic disorders that may be a cause of constipation; no surgery (except for minor procedures) within 60 days of screening; no chronic constipation prior to starting analgesic medication or any potential non-opioid cause of bowel dysfunction that may be a major contributor to the constipation; no current use of opioid antagonists, partial agonists, or mixed agonists/antagonists.

potential non-opioid cause of bowel dysfunction that may be a major contributor to the constipation; no subjects who have never taken laxatives for the treatment of opioid induced constipation.

Schedule  | Randomised to nalomedine 0.2mg oral once daily or placebo oral once daily. | Randomised to 0.2mg nalomedine once daily or placebo once daily, both oral.
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Follow-up  | Active treatment for 12-weeks; follow-up not reported. | Active treatment for 52 weeks; follow-up not reported.
Primary outcome/s  | Proportion of responders (defined as having ≥9 positive response weeks out of the 12 weeks, and 3 positive response weeks out of last 4 weeks of the 12 weeks, a positive response week defined as ≥ 3 SBMs per week and an increase from baseline of ≥ 1 SBM per week for that week). | Safety (AEs and serious adverse events).
Secondary outcome/s  | Not reported. | Not reported.
Key results  | A statistically significant improved frequency of SBM compared with placebo was reported over 12 weeks; nalomedine was generally well-tolerated with the most commonly reported side effects being gastrointestinal disorders. | –
Adverse effects (AEs)  | As above. No further details reported. | –
Expected reporting date  | May 2015 (Final data collection date for primary outcome measure). | January 2016 (final data collection date for primary outcome measure).

**ESTIMATED COST and IMPACT**

**COST**

The cost of nalomedine is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: *wider societal benefits - earlier return to normal activities, including employment*
- No impact identified

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Impact on Health and Social Care Services

- Increased use of existing services
- Decreased use of existing services: reduced complications of opioid therapy.
- Re-organisation of existing services
- Need for new services
- Other:
  - None identified

Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
  - Other reduction in costs: reduced complications of opioid therapy
- Other:
  - None identified

Other Issues

- Clinical uncertainty or other research question identified:
  - None identified

REFERENCES

11. NICE Costing statement Naloxegol for treating opioid-induced constipation(TA345).
16 Kumar L, Barker C and Emmanuel A. Opioid-induced constipation: pathophysiology, clinical consequences, and management. Gastroenterology Research and Practice. 2014; article ID 141737.


