Phase 3 study to evaluate the efficacy and safety of naldemedine for the treatment of opioid-induced constipation (OIC) in cancer patients.

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Presented at APM Supportive and Palliative Care, 30-31 March 2017, Belfast, UK
Disclosures

• Takaaki Yokota and Yukio Tada are employees of Shionogi & Co., Ltd.
• Nobuyuki Katakami and Toshiyuki Harada were site investigators in the studies.
• Masaru Narabayashi and Narikazu Boku were the medical experts for the studies.

This is an encore presentation from ASCO 2016 and ESMO 2016
• Murata T et al. Annals Oncol. 2016; 27: suppl 1466P.
Mechanism of Opioid-Induced Constipation (OIC)

- The clinical benefit of opioid analgesics may be compromised by side effects, including OIC, nausea, and CNS events (e.g., confusion, headache, and hallucination)\(^1,2\)

- Opioids act through the \(\mu\)-opioid receptors located in the enteric nervous system and can cause a reduction in gastrointestinal motility and fluid secretion, resulting in OIC\(^3\)
  
  – Laxatives, the most commonly used as the first-line treatment for OIC, have limited efficacy and do not address the underlying mechanism of opioids that leads to OIC\(^2,4\)

Naldemedine: A PAMORA for Treating OIC

Central (analgesic effect of opioid)

Peripheral (constipation side effect of opioid)

Naldemedine antagonises opioid action thereby alleviating constipation

PAMORA: peripherally-acting mu-opioid receptor antagonist
Naldemedine was effective and well-tolerated for both population

**Chronic non-cancer pain and OIC**
- 2 replicated 12-week R, D-B, P-C studies
  - M. Hale et al DDW 2016
- 52-week long term R, D-B, P-C study
  - L. Webster et al PAIN WEEK 2016

**Cancer and OIC**
- 2-week R, P-C, D-B study and 2-week open-label extension study

R: randomised, D-B: double-blind, P-C: placebo-controlled
• Eligible subjects were randomised 1:1 to receive oral naldemedine 0.2 mg or placebo QD for 2 weeks followed by a 12-week open-label extension study.
### Inclusion & Exclusion Criteria (DBT)

#### Key Inclusion Criteria
- Age $\geq 20$ years
- Cancer patients and use opioids for $\geq 2$ weeks
- Receiving laxatives for OIC, or had been treated but not currently receiving laxatives due to insufficient efficacy or other reasons
- Met the following definition of OIC:
  - $\leq 5$ SBMs during the 14-day screening period, and
  - $\geq 1$ of the following symptoms in at least 25% bowel movements: straining, lumpy/hard stools, sensation of incomplete evacuation
- ECOG Performance Status (PS) $\leq 2$

#### Key Exclusion Criteria
- Patients who were receiving or planned to start following therapy
  - New cancer chemotherapy regimen
  - Cancer chemotherapy considered to have obvious effects on GI functions
  - Surgical intervention such as nerve block, or radiotherapy which was considered to have obvious effects on GI functions
  - Manual disimpaction
  - Opioid receptor antagonists or partial agonists
- Significant structural abnormalities of GI
- Ileus within 1 year
- No bowel movements for 7 consecutive days prior to the enrollment

*SBM (Spontaneous Bowel Movement) was defined as a bowel movement that occurred without rescue-laxative use within previous 24 hrs*
Endpoints

• **Primary endpoint (DBT)**
  - SBM responder rate for 2-week treatment period*

• **Key secondary endpoints (DBT)**
  - Change from baseline in the frequency of
    - SBM
    - CSBM (SBM accompanied by feeling of complete evacuation)
    - SBM without straining
  - Onset of action after the first dose
    - Time to the first SBM and CSBM
    - Proportion of patients with at least 1 SBM/CSBM within 24 hours after the first dose

• **Safety assessments**
  - Adverse events
  - 11-point numeric rating scale (NRS) pain (DBT)
  - Clinical opiate withdrawal scale (COWS)

*An SBM responder rate was defined as percentage of patients with ≥ 3 SBMs per week and an increase from baseline of ≥ 1 SBM per week
# Baseline Characteristics (DBT, FAS)*

<table>
<thead>
<tr>
<th></th>
<th>Naldemedine 0.2 mg N = 97</th>
<th>Placebo N = 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ±SD)</td>
<td>63.8 ± 9.4</td>
<td>64.6 ± 11.8</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Male 59 (60.8)</td>
<td>60 (62.5)</td>
</tr>
<tr>
<td>BMI (kg/m², Mean ±SD)</td>
<td>21.54 ± 3.59</td>
<td>20.82 ± 3.63</td>
</tr>
<tr>
<td>ECOG Performance Status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>28 (28.9)</td>
<td>33 (34.4)</td>
</tr>
<tr>
<td>1</td>
<td>55 (56.7)</td>
<td>49 (51.0)</td>
</tr>
<tr>
<td>2</td>
<td>14 (14.4)</td>
<td>14 (14.6)</td>
</tr>
<tr>
<td>Inpatient/outpatient, n (%)</td>
<td>Outpatient 77 (79.4)</td>
<td>77 (80.2)</td>
</tr>
<tr>
<td>Received anticancer drugs, n (%)</td>
<td>72 (74.2)</td>
<td>62 (64.6)</td>
</tr>
<tr>
<td>Primary tumor, n (%)</td>
<td>Lung 42 (43.3)</td>
<td>45 (46.9)</td>
</tr>
<tr>
<td></td>
<td>Breast 22 (22.7)</td>
<td>17 (17.7)</td>
</tr>
<tr>
<td></td>
<td>Colorectal 3 (3.1)</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td></td>
<td>Other 30 (30.9)</td>
<td>31 (32.3)</td>
</tr>
<tr>
<td>Baseline SBM frequency /week (Mean ±SD)</td>
<td>1.01 ± 0.76</td>
<td>1.10 ± 0.85</td>
</tr>
<tr>
<td>Baseline daily dose of regular opioid (mg, Mean ±SD)**</td>
<td>57.3 ± 46.4</td>
<td>69.5 ± 99.5</td>
</tr>
</tbody>
</table>

*FAS (Full analysis set) was defined as population of patients obtained by excluding those with no baseline or post-baseline efficacy measurements and those having taken no doses of study drug from all randomised patients. **Oral morphine equivalent dose
Primary Endpoint

SBM responder rate* for 2-week treatment period (DBT, FAS)

*An SBM responder rate was defined as percentage of patients with \( \geq 3 \) SBMs per week and an increase from baseline of \( \geq 1 \) SBM per week. P-value by Chi-square test, 95% CI was calculated with the Clopper-Pearson method.
**Frequency of Bowel Movements (DBT, FAS)**

**SBM/week**

- Change from Baseline per week (LS Mean ± SE)
  - Naldemedine 0.2 mg: 5.16 (N=97)
  - Placebo: 1.54 (N=96)

**CSBM/week**

- Change from Baseline per week (LS Mean ± SE)
  - Naldemedine 0.2 mg: 2.76 (N=97)
  - Placebo: 0.71 (N=96)

**SBM without straining/week**

- Change from Baseline per week (LS Mean ± SE)
  - Naldemedine 0.2 mg: 3.85 (N=97)
  - Placebo: 1.17 (N=96)

Analysis method: The ANCOVA model has the terms for treatment group, baseline value as fixed effects
Time to First SBM/CSBM (DBT, FAS)

Median and 95% CI for Median were based on Kaplan-Meier estimates of time to first event. P-value was from the generalised Wilcoxon test.
Incidence of Patients with At Least 1 SBM/CSBM for Each Observation Point (DBT, FAS)
Safety Assessments (Safety population)*

11-point NRS score for pain evaluation (DBT)

Total COWS score (DBT)

Total COWS score (EXT)

* Safety population was obtained by excluding the patients who have not received the study drug at all, from all randomised (for DBT)/enrolled (for EXT) patients.
### Summary of Adverse Events
(Safety population)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>DBT&lt;sup&gt;1&lt;/sup&gt;</th>
<th>EXT&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naldemedine 0.2 mg, N = 97</td>
<td>Naldemedine 0.2 mg, N = 131</td>
<td></td>
</tr>
<tr>
<td>Any adverse events (AEs)</td>
<td>43 (44.3)</td>
<td>105 (80.2)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (2.1)</td>
<td>15 (11.5)</td>
</tr>
<tr>
<td>Serious AEs except death</td>
<td>7 (7.2)</td>
<td>14 (10.7)</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>9 (9.3)*</td>
<td>12 (9.2)</td>
</tr>
<tr>
<td>GI AEs ≥2% of patients in naldemedine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>group in DBT or EXT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>19 (19.6)</td>
<td>24 (18.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (3.1)</td>
<td>16 (12.2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (2.1)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2 (2.1)</td>
<td>6 (4.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1.0)</td>
<td>17 (13.0)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>0</td>
<td>3 (2.3)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Events reported during treatment period, <sup>2</sup>Events reported after initiation of extension treatment period.

*One more patient withdrew the study by AE but not summarised in the table due to the data handling standard.
Conclusion

• Treatment with naldemedine 0.2 mg given orally once daily was effective and significantly improved the symptoms of OIC in cancer patients.

• Naldemedine was generally well tolerated with the most commonly observed adverse events being GI disorders over 12 weeks.

• Naldemedine is a potential new treatment option for OIC in cancer patients.