# CLINICAL STUDY REPORT SYNOPSIS OF P.R.E.V.E.N.T STUDY

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**Name of Sponsor/Company:** L. Molteni & C dei F.lli Alitti Società di Esercizio S.p.A., Strada Statale 67, Località Granatieri, Scandicci (FI), Italy

**Name of Active Ingredient:** Morphine sulphate (Oramorph®)

**Title of the study:** Pilot double blind study to assess the efficacy and tolerability of morphine sulphate oral solution (Oramorph®) given as add-on therapy in the preventive analgesia (pre-medication) in patients undergoing laparascopy cholecistectomy (PREVENT = **PR**eventive analgesia **EV**aluation of oral morphine's **E**fficacy as a **N**ew **T**reatment)

**Investigators:** one Principal Investigator in Italy

**Study centres:** one single investigational study site in Italy

**Publication (reference):** None

**Study period:** First patient enrolled: 03 Apr 2011; Last patient completed: 06 Dec 2011 | **Phase of development:** IIIB

**Objectives:**

The primary objective of the study was to assess the efficacy of morphine sulphate oral solution (Oramorph®) 30 mg given as add-on therapy in the pre-emptive analgesia (pre-medication) in patients undergoing surgical laparascopy cholecistectomy.

The secondary objectives of this study were:

- To assess the economic impact of morphine sulphate oral solution in reducing the use of analgesics (mainly opioids in PCA) and in reducing the post anaesthesia care unit (PACU) discharge time;
- To assess the sedative effects of the investigational medicinal product (IMP);
- To assess the local tolerability and general safety of the IMP.

**Methodology:**

This was a double blind, randomised, 2-arm, parallel group, placebo-controlled clinical trial.

After signing of informed consent, eligible patients were randomised to receive one of the following two treatments, which were administered one hour before the induction of anaesthesia:

- Oramorph® 30 mg by oral route administered before anaesthesia (Group A);
- Matched placebo by oral route administered before anaesthesia (Group B).

The study plan included the assessment of the anxiety state (before premedication, soon before the induction of anesthesia, and at 12 and 24 hours after the induction of anesthesia) and of pain at rest and on movement (immediately after awakening, every 1 min during the first 5 minutes, every 15 min up to 3 hours, and then every 3 hours during the first 12 hours, and after 24 hours from awakening, irrespective of the stay in recovery room or surgical ward).

Postoperative nausea and vomiting (PONV) were also evaluated every 1 min during the first 5 min from awakening, every 15 min up to 3 hours from awakening, every 3 hours during the first 12 from awakening and at 24 hours from awakening. The Mini-mental state examination (MMSE) form was completed before the intervention.

Patients received a tramadol loading dose iv of 100 mg in the recovery room for a Numerical Rating Score (NRS) for pain at rest greater than 4. If necessary, a patient controlled analgesia (PCA) pump for rescue analgesia was administered for the first 24 hours in both groups. Instructions about the PCA pump were given during the preoperative visit. The PCA pump was set to deliver tramadol iv with a bolus dose of 5 ml (concentration 10 mg/ml), a lock-out of 30 min and a maximum dose of 100 mg every 4 h.

The total consumption of analgesics in the post-surgical period and the necessity of use of anti-emetic medications, together with the time of administration, was recorded.

**Number of patients (total and in each arm):**

| | Randomised | ITT | PP | Safety | Completed |
|---|---|---|---|---|---|
| Total | 41 | 36 | 36 | 40 | 36 |
| Oramorph® | 20 | 17 | 17 | 19 | 17 |
| Placebo | 21 | 19 | 19 | 21 | 19 |

**Diagnosis and main criteria for inclusion:**

Written informed consent obtained; patients of either sex aged ≥ 18 and ≤ 65 years; patients candidate to surgical intervention of laparascopy cholecistectomy; patients in class I, II or III physical status of the classification system of American Society of Anesthesiologists (ASA); absence or mild pre-operative pain (i.e. a NRS score between 0-3); female subjects of childbearing potential had to be using an appropriate method of contraception (a negative pregnancy test on blood had to be obtained at the screening visit, if applicable); patient's co-operative attitude and able to understand and adhere to study protocol procedures and timelines.

**Test product, dose and mode of administration, batch no:**

Oramorph® 30 mg by oral route administered before anaesthesia. Oramorph® was provided in batch No. 11001, expiry 06/12.

**Duration of treatment:** single dose.

**Reference therapy, dose and mode of administration, batch no:**

Matched placebo by oral route administered before anaesthesia. Placebo was provided in batch No. 11001, expiry 06/12.

**Criteria for evaluation:**

**Efficacy**

The primary efficacy variable of the study was the mean change from baseline in pain score at rest measured in the first 3 hours following the end of anaesthesia by means of the NRS (0-10 score). Pain intensity was measured on an 11-point pain intensity scale, where 0 = no pain and 10 = worst possible pain.

The secondary efficacy variables of the study were:

- Pain score (at rest and on movement, i.e. on deep inspiration followed by cough) measured at any post-treatment time points (immediately after awakening, every 1 min during the first 5 minutes, every 15 min up to 3 hours, and then every 3 hours during the first 12 hours, and after 24 hours from awakening, irrespective of the stay in recovery room or surgical ward), by means of the NRS;
- Use of analgesics (mainly opioids in PCA) and tramadol as rescue use in the post-operative setting;
- Change of anxiety state from pre-medication to soon before the induction of anesthesia and to post-treatment time points (12 and 24 hours after induction of anaesthesia), as measured by means of the State Trait Anxiety Inventory (STAI);
- Postoperative nausea and vomiting (PONV), assessed every 1 min during the first 5 min from awakening, every 15 min up to 3 hours from awakening, every 3 hours during the first 12 from awakening and at 24 hours from awakening;
- Use of antiemetic drugs in the post-operative setting;
- Time to readiness to discharge from the PACU (White' s score ≥ 12);
- Time to readiness to discharge from the surgical ward (PADSS score ≥ 10).

**Safety**

Safety variables were:

- Adverse events (AEs) and adverse drug reactions (ADRs);
- Parameters monitoring during anaesthesia: non-invasive blood pressure (NIBP), heart rate, saturation of peripheral oxygen (SpO2), ECG;
- Vital signs (heart rate, blood pressure, saturation of peripheral oxygen, respiratory rate), measured before induction, every 5 minutes during the first hour of surgery, every 15 minutes until the end of surgery, every 1 min during the first 5 min from awakening, every 15 min up to 3 hours from awakening, every 3 hours during the first 12 from awakening and after 24 hours from awakening (irrespective of the stay in recovery room or surgical ward);
- ECG measured at screening and at 24 hours after induction of anaesthesia;
- Routine laboratory parameters (haematology and blood chemistry) measured pre-medication and 24 hours after induction of anaesthesia.

**Statistical methods:**

The following populations were considered for analysis: intention-to-treat population (ITT), defined as all randomised patients who received the study medication and who completed all measurements of primary variable post-operative pain; per-protocol population (PP), defined as all patients included in the ITT population who also met all inclusion/exclusion criteria and did not have any major protocol violation; safety population (SP), defined as all randomised patients who received the study medication. The ITT and the PP population coincided in this study.

The assessment of the difference between the treatment arms in the primary endpoint pain score at rest measured in the first 3 hours following the end of anaesthesia was performed using the analysis of variance (ANOVA). Treatment difference means and corresponding 95% CI were derived from the ANOVA model.

The analysis of overall pain score at rest and on movement during the first 24 hours post-surgery was performed as for the primary variable.

The analysis of the change of anxiety status and trait from pre-medication to post-treatment time points at 12 and 24 hours after induction of anaesthesia was performed using an analysis of covariance (ANCOVA) model, in which the screening value of the STAI state anxiety score at pre-medication was used as covariate.

The comparison between groups in use of analgesics and tramadol as rescue use, and of antiemetic drugs, in the post-operative setting, and of presence or absence of PONV, was performed using the Fisher's Exact test.

Time to readiness to discharge from the PACU was analysed using the survival curves technique by means of the Kaplan-Meier method (unadjusted analysis). Cox's proportional hazard regression model was also used to assess the influence of the variables ASA score and use of tramadol in recovery room on the response (adjusted analysis). Time to readiness to discharge from the surgical ward (PADSS score $\geq$ 10) not analysed using the survival curves techniques because all patients reached a PADDS score $\geq$ 10 at the first planned assessment (6 hours after awakening).

All AEs were assigned to a PT and were classified by primary SOC according to the MedDRA thesaurus version 14.0.

For each laboratory parameter the change from screening to post-surgery visit was calculated. Data were analysed as descriptive statistics and shift tables from screening to post-surgery visit based on the clinical assessment (within range, out of range non-clinically significant, out of range clinically significant). For each vital sign parameter the change from "before anaesthesia" to each time point was calculated. Descriptive statistics of the values over time and the changes from "before anaesthesia" were provided. Summary statistics of the overall evaluation of the ECG tracing were provided.

The following other exploratory analyses, not initially foreseen in the SAP, were performed: presence of pain at rest and on movement as qualitative response; time to readiness to discharge from the PACU in patients who did not receive tramadol as loading dose; summary, data listing and comparison between groups of cumulative dose of tramadol and summary of the number of boluses of tramadol taken as rescue medication; comparison between groups in the mean change from screening in pain score at rest and on movement during the first 3 hours after awakening, using an ANCOVA model; comparisons between groups of surgery and post-surgery parameters; comparisons between groups in MMSE, ASA physical status, Apfel score and height at baseline; presence of episodes of hypotension and bradicardia; presence of at least one episode of nausea and/or vomiting.

**Study population:**

Forty-one patients were screened for enrolment in the study and were randomised to receive the assigned treatment: 20 patients were randomised to the Oramorph® group and 21 were randomised to receive placebo. Thirty-six patients overall, 17 (85% of randomised) in the Oramorph® group and 19 (90.5%) in the placebo group, completed the study.

**Extent of exposure and compliance:**

Treatment was administered as single dose under the Investigator's supervision, who ensured correctness of procedure.

**Efficacy results:**

**Primary efficacy variable: mean change from baseline in pain score at rest measured in the first 3 hours following the end of anaesthesia (NRS 0-10 score)**

The mean (± SD) pain score at rest measured in the first 3 hours after awakening was 2.709 ± 1.101 (median 2.526) in the Oramorph® group and 2.979 ± 0.967 (median 3) in the placebo group. The difference between the Oramorph® and placebo group was -0.270 (95% CI: -0.970 to 0.430) and was not significant (p = 0.438). No statistically significant differences between groups were also observed in the analysis performed with the ANCOVA model that included the baseline STAI trait and state anxiety score, duration of surgery and body weight as covariate (p = 0.162).

**Secondary efficacy variables:**

Pain at rest measured at any post-treatment time points:

The mean score of pain at rest was slightly higher in the placebo group than in the Oramorph® group up to 12 hours from awakening.

The mean pain score at rest measured at 3 hours after awakening was 1.47 ± 1.50 (median 1.0) in the Oramorph® group and 1.89 ± 1.24 (median 2.0) in the placebo group. The difference between the Oramorph® and placebo group was -0.424 (95% CI: -1.355 to 0.507) and was not significant (p = 0.361).

The mean pain score at rest measured during the first 24 hours after awakening was 2.463 ± 0.933 (median 2.217) in the Oramorph® group and 2.741 ± 0.872 (median 2.783) in the placebo group. The difference between the Oramorph® and placebo group was -0.278 (95% CI: -0.889 to 0.334) and was not significant (p = 0.362).

The results of pain at rest as qualitative response (presence/absence of pain) showed that the rate of patients with pain at rest was slightly higher in the placebo group than in the Oramorph® group at most of time points. However, the comparison between groups showed that the difference between groups was statistically significant only at 105 minutes after awakening: 1 patient (5.9%) in the Oramorph® group and 8 (42.1%) in the placebo group reported pain (p = 0.020).

Pain on movement:

The mean score of pain on movement was slightly higher in the placebo group than in the Oramorph® group up to 24 hours from awakening.

The mean pain score on movement measured in the first 3 hours after awakening was 3.402 ± 1.252 (median 3.053) in the Oramorph® group and 3.979 ± 0.981 (median 4.211) in the placebo group. The difference between the Oramorph® and placebo group was -0.576 (95% CI: -1.334 to 0.181) and was not significant (p = 0.131). In the analysis performed with the ANCOVA model that included the baseline STAI trait and state anxiety score, duration of surgery and body weight as covariate, the difference between means in the Oramorph® and placebo group was -0.896 (95% CI: -1.723 to -0.069) and was statistically significant (p = 0.035), in favour of the Oramorph® group.

The mean pain score on movement measured at 3 hours after awakening was 2.18 ± 1.74 (median 2.0) in the Oramorph® group and 3.16 ± 1.38 (median 3.0) in the placebo group. The difference between the Oramorph® and placebo group was -0.981 (95% CI: -2.041 to 0.079) and was not significant (p = 0.069).

The mean pain score on movement measured during the first 24 hours after awakening was 3.153 ± 1.036 (median 2.87) in the Oramorph® group and 3.703 ± 0.883 (median 3.913) in the placebo group. The difference between the Oramorph® and placebo group was -0.550 (95% CI: -1.200 to 0.100) and was not significant (p = 0.095).

The results of pain on movement as qualitative response showed that the rate of patients with pain on movement was higher in the placebo group than in the Oramorph® group at most of time points. The comparison between groups showed that the difference between groups was statistically significant at 75 minutes after awakening [p = 0.033, with 8 patients (47.1%) in the Oramorph® group and 16 patients (84.2%) in the placebo group], 105 minutes after awakening [p = 0.018, with 5 patients (29.4%) in the Oramorph® group and 14 patients (73.7%) in the placebo group], 120 minutes after awakening [p = 0.023, with 4 patients (23.5%) in the Oramorph® group and 12 patients (63.2%) in the placebo group] and 135 minutes after awakening [p = 0.041, with 3 patients (17.6%) in the Oramorph® group and 10 patients (52.6%) in the placebo group].

Use of analgesics (tramadol) in the post-operative setting:

The rate of patients that used rescue analgesics (tramadol) in the post-operative setting was higher in the placebo group (18 patients, 94.7%) than in the Oramorph® group (13 patients, 76.5%). However, the difference between groups was not statistically significant (p = 0.114).

Use of tramadol in the post-operative setting:

The rate of patients that used tramadol as loading dose was comparable in the two groups (47.1% in the Oramorph® group and 47.4% in the placebo group). The comparison between groups did not show statistically significant differences (p = 0.985).

The mean cumulative dose of tramadol was 185.3 ± 142.3 mg (range: 0-550 mg) in the Oramorph® group and 263.2 ± 198.5 mg (100-700 mg) in the placebo group. The comparison between groups did not show statistically significant differences (p = 0.190). No statistically significant differences between groups were also observed in the analysis performed with the ANCOVA model that used the baseline STAI trait and state anxiety score, and duration of surgery, as covariate (p = 0.056).

The mean number of boluses of tramadol was 2.76 ± 2.7 in the Oramorph® group and 4.32 ± 3.7 in the placebo group (p = 0.067 between groups).

STAI anxiety score:

*State anxiety score*

The mean state anxiety score did not substantially change in both groups from pre-medication to soon after anaesthesia, while it decreased from premedication to both 12 and 24 hours after the induction of anaesthesia in both groups, with a similar extent in the two groups. No statistically significant differences between groups were observed at both 12 ($p = 0.691$) and 24 hours after the induction of anaesthesia ($p = 0.754$).

*Trait anxiety score*

The mean trait anxiety score did not substantially change in both groups from pre-medication to soon after anaesthesia, while it decreased more markedly in the placebo group than in the Oramorph® group from premedication to both 12 and 24 hours after the induction of anaesthesia. No statistically significant differences between groups were observed at both 12 ($p = 0.784$) and 24 hours after the induction of anaesthesia ($p = 0.412$).

Postoperative nausea and vomiting (PONV):

The rate of patients with onset of at least one episode of nausea was higher in the placebo group (10 patients, 52.6%) than in the Oramorph® group (6 patients, 35.3%). However, the difference between groups was not statistically significant ($p = 0.296$).

Five patients (29.4%) in the Oramorph® group had at least one episode of vomiting, compared to none (0.0%) in the placebo group. The comparison between groups showed a statistically significant difference ($p = 0.013$).

Nine patients (52.9%) in the Oramorph® group and 10 (52.6%) in the placebo group had at least one episode of nausea and/or vomiting. The difference between groups was not statistically significant ($p = 0.985$).

Use of anti-emetic drugs:

Only 1 patient (5.9%) in the Oramorph® group and 1 (5.3%) in the placebo group used anti-emetic drugs in the post-operative setting ($p = 0.936$ between groups).

Time to readiness to discharge from the PACU (White's score $\geq$ 12):

The mean White's fast track score in the first 5 minutes after awakening and up to discharge to surgical ward was comparable in the two groups.

The median time to readiness to discharge from the PACU (White's score $\geq$ 12) was 1 minute in both groups ($p = 0.107$ in the log rank test), as well as there were no differences between groups in patients that did not receive tramadol as loading dose ($p = 0.125$ in the log rank test).

Time to readiness to discharge from the surgical ward (PADSS score $\geq$ 10):

Almost all patients in both group had a score of 12 at 6, 12 and 24 hours from awakening. All patients in both groups reached a PADDS score $\geq$ 10 at 6 hours after awakening and, therefore, the time to readiness to discharge from the surgical ward (PADSS score $\geq$ 10) could not be calculated.

**Safety results:**

Adverse events:

A total of 28 AEs were reported: 14 AEs were reported in the Oramorph® group and 14 AEs in the placebo group. The patients with at least 1 AE were 10 patients (52.6%) in the Oramorph® group and 13 (61.9%) in the placebo group. Treatment-related AEs were reported in 10 patients (52.6%) in the Oramorph® group and in 12 (57.1%) in the placebo group. The proportion of patients with AEs and treatment-related AEs was comparable in the two groups.

Nausea, with 6 patients (31.6%) in the Oramorph® group and 10 (47.6%) in the placebo group, and vomiting, with 5 patients (26.3%) in the Oramorph® group, were the most common AEs reported by preferred term.

None of patients in both groups required that study drug was not administered or delayed, due to AE. No SAEs were reported in the Oramorph® group, while non-fatal SAEs were reported in 2 patients (9.5%) in the placebo group: only 1 of them was considered "unlikely to be related" to the treatment (i.e. it was an ADR)

Laboratory parameters and vital signs:

There were no differences between groups in mean changes from baseline in laboratory (haematology and blood chemistry), vital signs (blood pressure, heart rate, SpO2 and respiratory rate) and ECG.

**Conclusions:**

- Treatment with morphine sulphate oral solution (Oramorph®) given as add-on therapy in the pre-emptive analgesia in patients undergoing surgical laparascopy cholecistectomy was not significantly different from placebo in pain score at rest measured in the first 3 hours following the end of anaesthesia.
- Although the mean score of pain at rest and on movement and the rate of patients with pain were higher in the placebo group than in the Oramorph® group up to 12 hours from awakening, the difference between groups was not significant at most of the examined time points. However, a statistically significant difference between groups, in favour of the Oramorph® group, was observed for pain on movement measured in the first 3 hours after awakening in the analysis that included the baseline STAI trait and state anxiety score, duration of surgery and body weight as covariates. Moreover, the results of qualitative response (presence/absence of pain) showed statistically significant differences, in favour of the Oramorph® group, at 105 minutes after awakening for the presence of pain at rest, and at several time points after awakening for the presence of pain on movements.
- The rate of patients that used rescue tramadol in the post-operative setting, the mean cumulative dose of tramadol and the mean number of boluses of tramadol were higher in the placebo group than in the Oramorph® group, being the difference between groups clinically (although not statistically) relevant.
- The occurrence of post-operative nausea was more common in the placebo group than in the Oramorph® group, while more patients in the Oramorph® than in the placebo group had post-operative vomiting (with only one patient in both groups requiring the use of anti-emetic drugs). The overall assessment of nausea and/or vomiting showed comparable rates in the two groups.
- The mean state and trait anxiety score decreased in a similar extent in the two groups from premedication up to 24 hours after the induction of anaesthesia.
- The mean time to discharge from the PACU and to the surgical ward was short and comparable in the two groups.
- Oramorph® was well tolerated and exhibited a placebo-like safety profile in terms of adverse events and changes from baseline of laboratory parameters, vital signs and ECG.

In conclusion, a single pre-operative oral administration of Oramorph® did not improve pain at rest but improve pain on movement during the first 3 hours after awakening in patients undergoing laparoscopic cholecystectomy in the analysis that included the baseline STAI trait and state anxiety score, duration of surgery and body weight as covariates.

Moreover, although there were no statistically significant differences between Oramorph® and placebo groups, the rate of patients that used rescue tramadol in the post-operative setting, the mean cumulative dose of tramadol and the mean number of boluses of tramadol were higher in the placebo group than in the Oramorph® group. These results are relevant from a clinical point of view.

At the end, the post-surgery measurement of all parameters showed that Oramorph® was devoid of any depressive effect at the central nervous system or at the respiratory level, and that exhibited a placebo-like profile with this respect.

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