2. SYNOPSIS

<table>
<tr><td>Name of Company:
Mundipharma Research Limited (MRL)</td><td>INDIVIDUAL STUDY TABLE</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
OxyNorm® 50 mg/mL, solution for injection or infusion</td><td rowspan="2">Referring to Part … of the Dossier

Volume: Page:</td></tr>
<tr><td>Name of Active Ingredient:
Oxycodone hydrochloride</td></tr>
<tr><td colspan="3">Title of the Study: An open, multi-centre, non-comparative observational study to assess the safety and tolerability of oxycodone hydrochloride injection 50 mg/mL as a subcutaneous infusion in subjects with severe cancer pain.</td></tr>
<tr><td colspan="3">Investigators: Dr Julia Riley, Royal Marsden Hospital, London, United Kingdom (UK) et al. Six study centres in the UK recruited subjects.</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td>Study Dates:
4 July 2008 to 29 May 2009</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase 3</td></tr>
<tr><td colspan="3">Objectives: To assess the safety and tolerability of oxycodone hydrochloride injection 50 mg/mL.
The primary endpoint was the incidence of site reactions.
The secondary endpoint was the incidence of adverse events (AEs) reported.</td></tr>
<tr><td colspan="3">Methodology: An open, multi-centre, single therapy, non-comparative study, using oxycodone hydrochloride injection 50 mg/mL delivered as a subcutaneous infusion to subjects with severe cancer pain, for up to 20 days.</td></tr>
<tr><td colspan="3">Number of Subjects: The study planned to enrol a total of 54 subjects; however, the Sponsor stopped the study early due to the following reasons: difficulties in subject recruitment; the fact that it became apparent that it was not possible to obtain clear data on the safety of oxycodone hydrochloride injection 50 mg/mL due to the administration of multiple concomitant medications via the same infusion line as the study medication and because some sites were diluting oxycodone hydrochloride injection 50 mg/mL down to a concentration of 10 mg/mL .
A total of 33 subjects were recruited, one subject completed the study (remaining in the study for the planned 20 days) and 32 subjects discontinued before Day 20. Twelve subjects discontinued due to adverse events (AEs) that were unrelated to study medication and 20 subjects discontinued due to the subject's choice. One subject discontinued due to an AE that started on Day 0 (i.e. was not treatment-emergent) therefore this subject is not counted as discontinuing due to AEs in the safety results section.</td></tr>
<tr><td colspan="3">Indication and Criteria for Inclusion: Male or female subjects aged 18 years and above, who had severe cancer pain and required a strong opioid by subcutaneous infusion to stabilise and manage their cancer pain effectively. Subjects receiving or planned to receive chemotherapy, subjects with any contraindications or hypersensitivity to oxycodone, and subjects with neutropenia, thrombocytopenia or coagulation disorders were excluded from the study.</td></tr>
<tr><td colspan="3">Test Treatment, Dose, and Mode of Administration: Oxycodone hydrochloride injection 50 mg/mL, supplied in 1 mL ampoules, administered by subcutaneous infusion by syringe driver. Batch number: PN3281.
The dosage of study medication for each subject was calculated by the Investigator based on the individual subject's previous opioid use and current analgesia requirements.</td></tr>
<tr><td colspan="3">Reference Treatment, Dose, and Mode of Administration: Not applicable.</td></tr>
<tr><td colspan="3">Duration of Treatment: Screening was within 3 days (7 days after approval of Substantial Amendment 3) of initiation of study treatment, and study medication was administered for up to 20 days. If a subject required treatment for longer than 20 days, then the Investigator was to contact the Sponsor to discuss continuing treatment on a subject-by-subject basis.</td></tr>
</table>

Treatment Schedule (Procedure): The syringes were filled with dose volumes according to National Health Service (NHS) practice within the sites (eg, 8 mL in a 10 mL syringe, 17 mL in a 20 mL syringe). The oxycodone hydrochloride injection was diluted with as small a volume as possible of sterile 0.9% saline, sterile 5% dextrose or sterile water for injection to provide the required dosage. The dosage of study medication for each subject was calculated by the Investigator based on the individual subject's previous opioid use and current analgesia requirements.

Criteria for Evaluation:

Analysis Populations:

The enrolled population was the group of individuals who provided informed consent.

The safety population was the group of subjects who received at least one dose of study medication and had at least one post-dose safety measurement.

Safety Assessments:

Adverse Events

The subjects' volunteered symptoms and AEs were recorded by spontaneous reporting throughout the study and at each infusion site assessment (every 24 hours and each time the infusion was re-sited) using the standard AE case report form (CRF) page.

Vital Signs

Weight and height were recorded at study entry only; temperature, blood pressure, respiration rate and pulse rate were recorded at the screening and completion/discontinuation visits.

Infusion Site Assessments

An assessment of the infusion site was recorded every 24 hours and every time the infusion was re-sited. The site was assessed as normal or abnormal. Any abnormalities, e.g. signs/symptoms of inflammation, were recorded as AEs.

Serious Adverse Events

These were recorded on the standard Serious Adverse Event (SAE) data form. Tumour progression and related SAEs (e.g. hospitalisation for surgery/diagnostic procedures, life threatening status, or death caused by the underlying malignant disease) were not considered and reported as SAEs if they were undoubtedly unrelated to study medication. This assessment of relationship to study medication was documented by the Investigator in the respective CRF.

Statistical Methods:

Safety Analyses:

The subjects' spontaneously reported AEs were categorised into preferred terms and associated system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system.

Treatment-emergent AEs were defined as AEs that started after the first dose of study medication or symptoms present at baseline that increased in severity after the first dose of study medication. Treatment-emergent AEs were assigned to a phase (treatment and outcome) according to their start date.

The number and percentage of subjects reporting treatment-emergent AEs was summarised by SOC, preferred term, and phase; this was repeated for treatment-emergent AEs that were considered unlikely, possibly, probably or definitely related to study medication.

The number and percentage of subjects reporting the most common treatment-emergent AEs (overall incidence ≥10%), and the most common (≥10%) treatment-emergent AEs that were considered unlikely, possibly, probably or definitely related to study medication were summarised by SOC, preferred term, and maximum severity.

The number and percentage of subjects reporting treatment-emergent AEs resulting in death, other SAEs, AEs that resulted in discontinuation from the study, AEs that resulted in a reduction of the dose of study medication, and AEs that required additional therapy were summarised overall and by SOC, preferred term, and phase (treatment, outcome and overall).

Vital signs

The vital signs recorded at screening and completion/discontinuation were listed and summarised.

Infusion site assessments

The responses to the infusion site assessments (Normal, Abnormal) and to whether or not the infusion site was changed (Yes, No) were summarised as the number and percentage of subjects with at least one response in either category and the total number of records for each category.

The number and percentage of subjects reporting infusion site AEs were summarised and the incidence of local site reactions was tested against the null hypothesis value of 25% using a binomial test. The null hypothesis value of 25% was based on the most common AE in a previous study of the subcutaneous infusion of morphine and hydromorphone (infusion site redness), but, as planned in the Statistical Analysis Plan, this was compared against the incidence of all infusion site reactions in the present study. Although other infusion site reactions were noted in the morphine/hydromorphone study, these were not included in the null hypothesis value. To provide a more balanced comparison, an additional post-hoc analysis was performed, which compared the incidence of infusion site erythema (i.e. redness) in the present study with the incidence of infusion site redness in the morphine/hydromorphone study.

Study medication

Extent of exposure was defined as the length of time between the first and last dose of study medication. Extent of exposure was summarised as continuous data. The daily dose of study medication that subjects received for maintenance was also summarised. The number of times that bolus doses of medication were given for breakthrough pain, and total dose administered for breakthrough pain, were summarised.

Sample Size Rationale:

This study was an exploratory, observational study, however, it was intended that it would provide sufficient data to make an assessment of the safety of oxycodone hydrochloride injection 50 mg/mL delivered as a subcutaneous infusion in subjects with cancer. With 54 subjects, it was anticipated that the study would show significant side effects that limit treatment such as severe local tolerability reactions that aren't typically seen with other opioids given by infusion. In a published paper (Local Toxicology during the subcutaneous infusion of narcotics; Cancer Nursing 1987; 10(4): 172-176), subcutaneous infusions of narcotics (morphine and hydromorphone) were given to 46 subjects. There were no incidences where subjects had to cease treatment due to local reactions. The most common AE at the site of infusion was redness in 28 subjects (23.8%). With 54 subjects, this study was expected to be able to demonstrate significant reactions resulting in a cessation of treatment, and as a guide for more commonly seen reactions such as redness at the site of infusion the study had 80% power at the 5% significance level to detect a difference in the incidence of local site reactions of 15% from the null hypothesis value of 25%.

Safety Results:

Overall, 18 subjects (55%) experienced infusion site AEs whilst on study medication. The most common infusion site AEs were erythema (12 subjects (36%)), infusion site pain (nine subjects (27%)) and infusion site mass (eight subjects (24%)). The incidence of infusion site reactions was statistically significantly higher than the null hypothesis value of 25% ($p<0.001$). However, only 33 subjects were enrolled and evaluated, compared with the planned sample size of 54 subjects. In addition, the null hypothesis value of 25% was based on the most common AE in a previous study of the subcutaneous infusion of morphine and hydromorphone (infusion site redness),[33] but this was compared against the incidence of all infusion site reactions in the present study. The incidence of infusion site erythema (i.e. redness) in the present study was 36%, which was statistically significantly higher than the null hypothesis value of 25% ($p=0.048$, post-hoc analysis). The assessment of infusion site reactions may also have been confounded by the administration of concomitant medications via the same infusion line as oxycodone; however, this reflects standard clinical practice. Twenty-nine subjects (88%) received concomitant medications via the same infusion line, the most common were levomepromazine (14 subjects (42%)), metoclopramide (10 subjects (30%)), haloperidol (nine subjects (27%)) and midazolam (eight subjects (24%)).

Although a high number of infusion site reactions were reported, the majority (48/61, 79%) were mild in nature, with 13/61 (21%) being of moderate severity. No severe infusion site reactions were reported. All infusion site reactions had resolved by the subject's last visit. One subject withdrew due to mild infusion site pain and erythema and multiple other AEs, one subject received additional treatment for infusion site erythema and a third subject received additional therapy for infusion site inflammation. All other infusion site AEs resolved without intervention.

The infusion site was changed following 60 out of 215 (28%) on-treatment infusion site assessments. The infusion site was assessed every 24 hours, and had to be changed at least every 96 hours. Twenty-nine infusion site changes (48%) were due to AEs.

A total of 13 subjects (39%) experienced an SAE during the study; 11 of these subjects (33%) died due to the SAEs. None of the SAEs or deaths were considered by the Investigator to be related to study medication; all were related to tumour progression or caused by the underlying malignant disease. Eleven subjects (33%) had treatment-emergent AEs leading to study discontinuation, three subjects (9%) had AEs that resulted in a reduction of the dose of study medication, and 23 subjects (70%) had AEs that required additional therapy. Treatment-related AEs accounted for 2/11 discontinuations, 3/3 dose reductions and 8/23 requirements for additional therapy. The treatment-related AEs leading to discontinuation were infusion site pain and erythema, visual disturbance, muscle twitching and dyskinesia in one subject and agitation in a second subject.

Overall, 30 subjects (91%) reported at least one AE during the study. The most frequently reported AEs (reported by five or more subjects overall) were infusion site erythema, infusion site pain, agitation, infusion site mass, nausea, vomiting, somnolence and general physical health deterioration. Agitation, nausea, vomiting and somnolence are consistent with the expected AE profile of opioid analgesics. All instances of general physical health deterioration were considered by the Investigator to be not related to study medication. Infusion site reactions such as infusion site erythema, infusion site pain and infusion site mass are clinically expected with the subcutaneous route of administration.

There were no clinically notable changes in vital signs from screening to completion/discontinuation.

Conclusions:

- The incidence of infusion site reactions (55%) was statistically significantly higher than the null hypothesis value of 25% ($p<0.001$). This comparison should be interpreted with caution because the sample size (33 subjects) was smaller than planned (54 subjects), and the null hypothesis value was based on the incidence of infusion site redness only. A post-hoc analysis showed that the incidence of infusion site erythema (i.e. redness, 36%) was statistically significantly higher than the null hypothesis value of 25% ($p=0.048$). In addition, the results are confounded by the administration of concomitant medications via the same infusion line as the study medication.
- There were no treatment-related deaths or other SAEs. Treatment-related AEs accounted for 2/11 discontinuations, 3/3 dose reductions and 8/23 requirements for additional therapy.
- A total of 30 subjects (91%) experienced AEs. The most frequently reported AEs (reported by five or more subjects overall) were infusion site erythema, infusion site pain, agitation, infusion site mass, nausea, vomiting, somnolence and general physical health deterioration. Agitation, nausea, vomiting and somnolence are consistent with the expected AE profile of opioid analgesics, and infusion site reactions are clinically expected with the subcutaneous route of administration. All instances of general physical health deterioration were considered not related to study medication by the Investigator.

Overall, this study did not raise any new safety concerns regarding treatment with oxycodone hydrochloride injection 50 mg/mL. The incidence of infusion site reactions was high (55%), however, the majority were mild in nature and resolved without intervention. The pattern of other AEs was consistent with the known safety profile of oxycodone hydrochloride injection, and all deaths and SAEs were caused by the subject's underlying disease.

Date of the Report: 5 February 2010