2. SYNOPSIS

Name of Company: Mundipharma Medical Company Hamilton/Bermuda, Basel Branch St. Alban-Rheinweg 74 CH-4020 Basel, Switzerland	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Sevre-Long® capsules	Referring to Part … of the Dossier	
Name of Active Ingredient: Morphine sulphate	Volume: Page:	

Title of the Study:

Randomized, controlled clinical study regarding the feasibility of converting opiate dependents from methadone substitutes to slow release morphine sulphate (Sevre-Long®)

Study Code SUB9001

EudraCT No.: 2008-002185-60

Swissmedic No.: 2007DR3124

NIH Study code: NCT01079117

Investigators:

This was a multinational, multi-center study conducted in Switzerland and in Germany.

4 centres in Switzerland.

11 centres in Germany.

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
26-Jul-2007 to 29-Jun-2011 Cross-over Phase: First patient first visit: 26-Jul-2007 Last patient last visit: 23-Jan-2011 Extension Phase: First patient first visit: 17-Jan-2008 Last patient last visit: 29-Jun-2011	Completed	Phase 3

Objectives:

The objective of this study was to compare the efficacy of slow-release oral morphine (SROM) in patients that previously have been treated with methadone.

The primary efficacy endpoint in this study was the proportion of positive urine tests for co-consumption of target substances per subject. Target substances were defined as all opioids except the study drugs. The proportions were compared between substitution with methadone and SROM treatment in a cross-over design.

The secondary endpoints were:

(1) Effects of SROM on retention rate (Retention in treatment).
(2) Co-consumption of other drugs (cocaine, alcohol, cannabis, benzodiazepines).
(3) Occurrence of psychopathological and somatic symptoms.
(4) Effect of treatment on the ECG (QTc prolongation).
(5) Group characterisation of patients who were keen to change the medication.
(6) Change in dosage of treatment over time.
(7) Self-assessed craving for opioids.
(8) Self-assessed satisfaction with treatment.
(9) Nature, frequency and severity of adverse events in the two treatment groups.
(10) Assessment of safety parameters.

Methodology:

This was a multiple-dose, open label, randomized, cross-over study. The total duration of the study was 47 weeks; it was organized with two phases, a 22 week cross-over phase followed by a 25 week extension phase.

Cross-over phase:

The study hypothesis was to confirm that the efficacy of SROM is non-inferior to that of methadone when used for the maintenance treatment of opioid dependent subjects. Based on the cross-over design selected for this study, the primary efficacy parameter was the rate of co-consumption assessed as the proportion of positive urine tests for opioids except the study drugs. Patients had to be already included in a methadone maintenance therapy for at least 26 weeks in one of the study centers and were randomized into this study and allocated to either methadone or SROM treatment. Each cross-over period consisted of one week for dose adaptation followed by 10 weeks of treatment. Weekly urine samples were randomly collected and analyzed in a central laboratory. The proportion of urine samples positive for non-prescribed opioids was assessed for each treatment and sequence of cross-over. Control of craving for psychoactive substances under flexible dosing, subjective wellbeing and self-reported use of illicit substances were assessed as other treatment relevant effects.

Extension phase:

At the end of the cross-over phase (week 22) patients were offered to continue with or to switch back to SROM for another 6 months (week 23 to 47). During this extension phase primarily safety data were generated. In addition, treatment relevant effects were assessed, such as control of craving for psychoactive substances under flexible dosing of SROM, subjective wellbeing and self-reported use of illicit substances.

Number of Patients:		Cross-over phase	Extension phase
Planned: 270	Randomized (entered):	276	198
Planned per protocol (according to sample size calculation): 128	Completed:	157	150

Indication and Criteria for Inclusion:

Eligible for the study were all patients with opioid or multiple substance dependence (including opioids) (ICD classifications F11.22, F19.22), already included in a methadone maintenance therapy in one of the study centers. Male or female independent adult subjects aged 18 years or more, under maintenance treatment for at least 26 weeks and with a permanent domicile were randomized into the study.

Inclusion Criteria:

- Methadone dose of ≥ 50 mg/day (or levo-methadone dose of ≥ 25 mg/day) at inclusion (patients* on levo-methadone were informed and they agreed to be switched to methadone)
- Mature and capable of acting responsibly, in possession of all mental faculties
- Female subjects with a negative urine pregnancy test prior to the first dose of study medication
- Regular negative urine pregnancy tests every 4 weeks*
- Hormonal contraception (oral, transdermal, vaginal, intrauterine or subcutaneous) by women of child-bearing age
- No intention of reducing the substitute medication during the trial
- Acceptance of the trial rules and regulations
- Acceptance to participate in the study (informed consent).

*applicable to patients recruited in Germany

Exclusion Criteria:

- (Desired) pregnancy during the trial
- Breastfeeding women
- Grave or acute somatic illnesses (e.g. cardio-vascular, serious kidney or liver affection [ALAT or ASAT > 5 times exceeding the normal range]) or other clinically significant somatic disorders
- Severe unstable mental health problems
- Co-medication with MAO-inhibitors
- Intracranial injury
- Intracranial hypertension
- History of epilepsy
- Severe chronic obstructive lung disease
- Chronic respiratory failure
- Known hypersensitivity to morphine or methadone

- Pancreatitis
- Paralytic ileus
- Baseline QTc interval greater than 450 msec
- Long QT Syndrome
- Patients who have participated in another clinical trial involving a new chemical entity within 3 months of study entry
- Patients with pending imprisonment at the time of inclusion.

Test Treatment, Dose, and Mode of Administration:

Slow-release oral morphine (SROM): once-a-day administration, maximum daily dose 1200 mg.

Switzerland: SEVRE-LONG® capsules retard 60 mg, 120 mg and 200 mg (repacked from approved medicinal product).

Germany: Morphin-Retardkapseln 60 mg, 120 mg, 200 mg (repacked from approved medicinal product in Austria: Mundidol® UNO retard capsules).

Reference Treatment, Dose, and Mode of Administration:

Methadone (oral solution): once-a-day administration, maximum daily dose 200 mg.

Switzerland: Methadone oral solution containing 10 mg/ml (officinal preparation).

Germany: Methadone oral solution containing 5 mg/ml (Eptadone® 5 mg/ml oral solution; repacked from approved medicinal product in Germany).

Duration of Treatment:

Cross-over phase: 22 weeks (two times 11 weeks).

Extension phase: 25 weeks.

Treatment Schedule:

Once-daily oral administration of either methadone solution or SROM with flexible dosing according to the individual needs depending on an adequate control of craving for opioids.

Cross-over phase (22 weeks):

Period I (11 weeks): Adjustment phase I (Week 1) with randomly assigned treatment to methadone or SROM. Treatment phase I (Week 2-11) continued treatment with methadone or SROM.

Period II (11 weeks): Adjustment phase II (Week 12) change of treatment; subjects who have previously taken methadone were switched to SROM and vice versa. Treatment phase II (Week 13-22) continued treatment with methadone or SROM.

Extension phase (25 weeks):

Adjustment phase III (Week 23) for switching subjects who have previously taken methadone to SROM and continuation of treatment with SROM for 6 months (Week 24 to Week 47).

Methadone was switched to SROM in a ratio of 1:6 – 1:8 of the previous methadone dose. SROM was switched to methadone in a ratio of 6:1 – 8:1 of the previous SROM dose.

Criteria for Evaluation:

Efficacy:

Cross-over phase:

The primary efficacy parameter was the proportion of co-consumption of non-prescribed opioids per patient. This was assessed through urine analyses at each week during each cross-over period. Two urine samples per week were taken on two randomly assigned days; one of the two samples was randomly selected for analysis.

Patients received a weekly allowance for providing urine samples, and were ensured that the result of the analysis has neither any positive nor negative measures in consequence.

Secondary efficacy parameters such as self-reported drug consumption, psychic complaints, craving for illicit drugs etc. were assessed throughout the cross-over periods.

Extension phase:

Efficacy parameters related to co-consumption of non-prescribed opioids, self-reported drug consumption, psychic complaints, craving for illicit drugs were assessed throughout the extension phase.

Safety:

Safety was assessed by documentation of adverse events during the cross-over phase as well as the extension phase. Other safety endpoints included changes in vital signs, ECGs (QTc-interval) and extent of exposure to study treatments.

Bioanalytical Methods:

All urine samples were analyzed at the Department of Laboratory Medicine at the University Hospital, Basel, acting as central laboratory for all trial centres. Urine samples were analyzed under blind conditions.

The following methods for urine analyses were performed:

Immunoassay was performed by means of CEDIA® Test (cloned enzyme donor immunoassay). Every urine sample was semi-quantitatively analyzed for the following substances: benzodiazepines, cannabinoides, cocaine, methadone, methadone metabolite (EDDP), opiates, 6-MAM.

Liquid chromatography with mass spectrometry detection (LCMS) was performed to analyze every urine sample for 6-MAM, 6-acetylcodeine, morphine and its glucuronides, codeine and its glucuronides.

Statistical Methods:

Efficacy:

Intention to treat population (ITT population): All subjects who were randomized to receive a study medication.

Per protocol population (PP population, Efficacy Evaluable Population): All patients who completed the two cross-over treatment periods (11 weeks each = 77 days; i.e. ≥ 70 days and ≤ 84 days) and who had urine analyses for ≥ 9 out of 11 weeks per cross-over treatment period and no other major protocol violation.

Per Protocol Population plus patients who completed Period 1 only (PPC1, Efficacy Evaluable Population): All patients of the PP population plus all patients who completed only the first cross-over period per protocol (PPC1 population).

Cross-over phase:

The primary efficacy parameter was the proportion of positive urine analyses for the co-consumption of not prescribed opioids per patient. The primary analysis aiming for non-inferiority of morphine versus methadone was performed in the per protocol population. Non-inferiority would be concluded, if the two-sided 95% confidence interval is completely located above -10% (the pre-specified non-inferiority boundary). Statistical testing for the primary efficacy parameter was one-sided at the 2.5% level of significance. All other statistical testing was two-sided at the 5% level of significance.

All secondary efficacy variables were summarized by treatment group and sequence of cross-over period. Continuous variables were summarized using the following descriptive statistics: n, mean, standard deviation, median, and range. The frequency and percentage of observed levels was reported for categorical measures. In general, all data were listed, sorted by treatment, and sequence of cross-over.

Extension phase

Secondary efficacy variables were summarized for subjects who entered the extension phase. Continuous variables were summarized using the following descriptive statistics: n, mean, standard deviation, median, and range. The frequency and percentage of observed levels was reported for categorical measures. In general, all data were listed.

Safety:

Safety population: All subjects randomized to treatment who have taken at least one dose of study medication.

The nature and incidence of adverse events were summarized; incidence rates by severity and relationship, as well as incidence of serious adverse events were presented.

Descriptive statistics were used to summarize vital signs and ECG data and changes from baseline values as well as for changes per study medication and sequence of treatment during the cross-over phase.

Sample size calculation:

The sample size calculation was based on testing for non-inferiority within a cross-over design. Sixty-four per protocol patients per sequence (a total of 128 per protocol patients) were required to conclude with a power of 80% that a difference in co-consumption of illicit substances of less than 10% indicates non-inferiority, assuming a one sided significance level of 2.5%.

Assuming that up to 35% of the patients would not be part of the per protocol set, a total sample size of approximately 200 patients would be necessary for achieving the power of 80%. The sample size and power calculation was performed with SAS®, Version 9.1.3.

Results:

Efficacy: Two hundred and seventy six patients were randomized in this study. Demographic and background characteristics, together with the high rate of somatic and psychiatric co-morbidities observed in patients randomized to treatment, were similar to those of patients undergoing maintenance treatment in daily practice. Because of stringent criteria for evaluability, 157 (56.9%) patients qualified for the PP population.

Compliance with treatment and adherence to the criteria of random urine sampling was very high in each sequence and period of treatment, without any differences between treatments.

Retention in treatment during cross-over was high; 211 (76%) patients completed the 22 weeks of the cross-over period (37 [13%] patients withdrew under SROM and 27 [10%] patients under methadone).

In the PP population all patients adhered to scheduled visits. Less than 1% of urine samples were not collected, not shipped or refused by the patient; samples rated as manipulated were 1.1%. The percentage of samples analyzed as positive for opioids was 36.2. For efficacy evaluations the number of positive urine samples per number of weeks per cross-over periods was calculated as proportion of opioid-positive urine samples per patient.

Primary endpoint

Proportion of opioid-positive urine samples

The proportion of urine samples positive for opioids was significantly lower under SROM treatment (0.2658) compared to methadone (0.4537) (difference in mean -0.1879, CI 95% lower -0.2377; upper -0.1380) (p<.0001); superiority of SROM vs methadone was also confirmed in the ITT population and PPC1 population.

Secondary endpoints (PP population)

Proportion of heroin-positive urine samples: The proportion of urine samples positive for heroin under SROM (0.2020) treatment was non-inferior to the proportion of heroin-positive urine samples under methadone treatment (0.1508) (difference in mean 0.0513, CI 95% lower 0.0217; upper 0.0808) (p=0.0008); non-inferiority was also confirmed in the ITT population and PPC1 population.

Mental Health Problems (SCL-27): Significantly lower psychological distresses under treatment with SROM: Global Severity Index (GSI) (total per treatment) SROM 0.61 vs methadone 0.68 (p<0.0001), significantly (p<.05) lower scores for all sub-scales.

Craving for heroin: Significantly less intense craving for heroin under treatment with SROM (HCQBRIEF-score 2.62; VAS 2.57) compared to methadone (HCQBRIEF-score 2.88; VAS 3.33 (p<.0001)

Craving for cocaine: No differences in craving for cocaine (SROM: CCQBRIEF-score 2.10; VAS 1.43; methadone: CCQBRIEF-score 2.14; VAS 1.56 (n.s.).

Self-contentment with treatment: Significantly higher treatment satisfaction under SROM (VAS 7.65) compared to methadone (VAS 6.01) (p<.0001).

Self-reported use of psychoactive substances: No differences between treatments in the self-reported use (proportion of days with use per period) of psychoactive substances, e.g. heroin, cocaine, benzodiazepine, alcohol and other drugs.

Testing of urine samples positive for other drugs: No differences between treatments in the proportion (number of positive samples per period) of urine samples positive for other drugs, e.g. cannabis, cocaine and benzodiazepines.

Correlation of self-reported drug use and results of urine analyses: Self-reported use of heroin was significantly lower (approx. 45%) than the proportion of urine samples tested positive for opioids and heroin, respectively.

Dose Effect: A dose effect was shown for SROM by decreasing proportion of opioid- / heroin-positive urine samples with increasing doses.

Safety: Exposure to study medication was high. Days of treatment in the cross-over phase were close to 77 days per period (ITT population). The average mean daily dose of SROM was 777 mg, which corresponded to a total dose of 53.580 mg SROM per patient and sequence. Patients under methadone received mean daily doses of 105 mg equivalent to a total dose of 7.574 mg. Methadone doses were converted to SROM at a mean ratio of 1:7 and SROM doses to methadone at ratio of 8:1. Switching of treatment was simple without a single case with signs of overdose or opioid withdrawal. Only a few (approx. 10%) patients required dose adaptations during cross-over, primarily in periods with treatment switches from methadone to SROM.

One hundred and ninety eight patients entered the extension and were treated with SROM for 21 weeks on average. This corresponded to an overall exposure of 33.365 mg SROM. The mean daily dose of SROM at the start of the extension phase was 776 mg which was kept very stable throughout a period of 25 weeks (week 47: 768 mg SROM per day). There was no evidence for the development of tolerance during long-term treatment with SROM.

AEs in terms of frequency, SOCs, severity and relationship to study medication were comparable between methadone and SROM.

During the cross-over phase AEs were reported with similar frequencies in patients receiving SROM (81%) compared to methadone (79%). With regard to the System Organ Classes the most frequently reported AEs for both treatments were “Gastrointestinal disorders”, followed by “Psychiatric disorders”, “Skin and subcutaneous tissue disorders” and “Nervous system disorders”. There were no statistically significant differences between treatments.

Despite a somewhat lower frequency of 75%, AEs reported during the extension phase were similar by SOCs and MedDRA term to those reported for SROM in the preceding cross-over phase.

The incidence of SAEs was generally low in all treatment groups and study periods (3 to 6%). The majority of SAEs were rated as not related to study medication. There were 2 deaths reported during the study: one during the cross-over phase with methadone due to intentional multiple drug overdose (possibly related), the other one during the extension phase with SROM due to oesophagus varices haemorrhage (not related).

The numbers of significant AEs that led to premature discontinuation of the study, required a dose reduction or interruption of study medication or required additional therapy were also comparable between treatment groups and study phases, no notable differences were detected.

No significant changes of vital signs (systolic and diastolic blood pressure, heart rate, body weight) were seen in the course of the study.

Treatment with SROM was associated with significant reductions in the QTc-interval in patients who were previously treated with methadone. This was not only observed in the different periods of the cross-over phase but also in patients who were switched from methadone to SROM at the time of entering into the extension phase. The mean total QTc-interval under SROM was 418 msec and 434 msec under methadone ($p<.0001$), respectively. Changes in QTc-interval were associated with increasing methadone doses. However, the number of patients with QTc-changes under SROM was too small to confirm any dose-effect.

Conclusions: SUB9001 was an open, randomized cross-over, multicentre study to show non-inferiority of SROM and methadone by evaluating the extent of co-consumption of non-prescribed opioids under maintenance treatment in patients suffering from opioid dependence. The primary efficacy endpoint was the proportion of urine samples tested positive for opioids other than the study medications.

Under SROM treatment the proportion of urine samples tested positive for non-prescribed opioids was significantly lower than under methadone. The proportion of urine samples tested positive for heroin only under SROM treatment was non-inferior to methadone. A dose effect was shown for SROM in terms of decreasing proportions of opioid- / heroin-positive urine samples with increasing doses.

The retention rates in treatment during the cross-over phase as well as the extension phase were high. During 22 weeks of cross-over only 64 (23%) patients withdrew from the study: 37 (13%) patients under treatment with SROM and 27 (10%) patients under methadone.

Treatment switch from methadone to SROM and vice versa was easy to manage and was well accepted by patients. Conversion from methadone to SROM was done at a dose ratio of 1:7.7 independent from prior methadone dose levels. Similar dose ratios were applied when treatment was switched from SROM to methadone. Treatment switch was not associated with clinically relevant signs and symptoms of overdose and acute opioid withdrawal, respectively.

Craving for heroin was generally moderate but significantly less intense under SROM compared to methadone. No differences between treatments were noted in craving for cocaine.

Psychopathological symptoms (SCL-27-scale) were significantly less intense under SROM treatment compared to methadone. Self-contentment with SROM treatment was superior over methadone.

Self-reported use of other substances such as alcohol, cannabis, benzodiazepines or cocaine, were not different between SROM and methadone. Correlations of self-reported use and the results of urine analyses were high, except for heroin where rates of self-reports were low.

Approximately 70% of all patients recruited in this study accepted to continue for further 25 weeks with SROM treatment. No additional efficacy or safety related effects other than those experienced during cross-over were observed. However, it was not possible to identify specific patient-related characteristics which may have been indicative for a preference for SROM.

The two treatments were well tolerated without any changes in vital signs. The overall rate of AEs, severe AEs, SAEs and treatment-related AEs did not differ between treatments. In contrast to methadone treatment with SROM was not associated with any changes in the QTc-interval.

Study SUB9001 was the first confirmatory trial to compare SROM and methadone for the maintenance treatment of opioid-dependent patients. It was well controlled by considering established primary and secondary outcome measures and was sufficiently powered by adequate numbers of patients included in the trial. This study confirms that the efficacy and safety of SROM in the maintenance treatment was non-inferior to that of methadone.

Date of the Report: 15-Dec-2011