2 SYNOPSIS

Name of the Sponsor/Company: Orexo AB	**Individual Trial Table Referring to Module 5 of the Dossier** **Volume:** **Page:** **Trial No.:**	**(For National Authority Use only)**
Name of Finished Product: OX51-3 sublingual tablet		
Name of Active Ingredient: Alfentanil hydrochloride		

TRIAL CODE:

OX51-002

TITLE OF TRIAL:

A randomized, double-blind, placebo-controlled, dose finding trial using sublingual alfentanil to alleviate pain associated with a prostate biopsy procedure

COORDINATING INVESTIGATOR:

Dr. Teuvo Tammela, Tampere University Hospital, Finland.

TRIAL CENTRES:

The trial was conducted at 14 selected trial centres in Finland, Denmark, the Czech Republic and Spain.

PUBLICATION (REFERENCE):

None as of the completion date for this report.

TRIAL PERIOD:

Date of first patient first visit: 30 October 2012

Date of last patient last visit: 04 June 2013

PHASE OF DEVELOPMENT:

Phase II-III

OBJECTIVES:

Primary Objective

The primary objective was to evaluate the analgesic efficacy of sublingual alfentanil tablets in patients who undergo prostate biopsy.

Secondary Objectives

The secondary objectives were:

1) To evaluate the safety and tolerability of sublingual alfentanil tablets.
2) To evaluate the patients' sedation after administration of sublingual alfentanil tablets.
3) To evaluate the relationship between dose and analgesic efficacy of sublingual alfentanil tablets in patients who undergo prostate biopsy.
4) To evaluate the post-procedural pain.
5) To evaluate the patients' and clinicians' satisfaction with the pain treatment of the procedure.
6) To evaluate the need for rescue medication.

Name of the Sponsor/Company: Orexo AB	Individual Trial Table Referring to Module 5 of the Dossier	(For National Authority Use only)
Name of Finished Product: OX51-3 sublingual tablet	**Volume:** **Page:** **Trial No.:**	
Name of Active Ingredient: Alfentanil hydrochloride		

7) To evaluate the pharmacokinetic (PK) profile of the sublingual alfentanil tablets in the target patient population.

8) To evaluate the post-procedural recovery time.

METHODOLOGY:

This was a double-blind, randomized, placebo-controlled, parallel trial in patients undergoing a transrectal, ultrasound-guided, multiple-core (10-12 core minimum) prostate biopsy. The trial was conducted in 4 countries in Europe and included 180 men aged 18 to 85 years. Patients were randomized into four treatment groups and received a single dose of either 350 µg, 700 µg or 1050 µg alfentanil or placebo (0 µg alfentanil).

The trial consisted of two visits to the clinic:

- During Visit 1 (treatment visit) patients performed screening and baseline procedures before the planned prostate biopsy procedure, and were resident at the clinic until completion of all Visit 1 trial procedures at approximately 4 hours after completion of the prostate biopsy procedure.
- Visit 2 (follow-up visit) was to take place 3 to 7 days after Visit 1 to perform safety assessments.

The following assessments were performed during Visit 1:

- Pain intensity experienced by the patient as assessed by a Numerical Rating Scale (NRS): prior to investigational medicinal product (IMP) dosing, “worst pain” during (assessed within 5 minutes after the prostate biopsy procedure), and following the end of prostate biopsy procedure.
- Patients’ sedation after administration of IMP as assessed objectively by Pasero Opioid-induced Sedation Scale (POSS) and subjectively by Patient Global Impression of Drowsiness (PGID).
- Patient’s and clinician’s impression of satisfaction with the pain treatment administered as assessed by Patient Global Impression of Satisfaction (PGIS) and by Clinician Global Impression of Satisfaction (CGIS).
- Need of rescue medication (local anaesthetic infiltration) if requested by the patient during the prostate biopsy procedure.
- Time of post-procedural recovery as assessed by the Aldrete score.
- Blood sampling for PK analysis at 5 to10 minutes after IMP administration, within 5 minutes after end of prostate biopsy procedure (immediately after assessment of pain intensity), and at 30, 60, and 150 minutes after end of prostate biopsy procedure.

Safety assessments were performed and included:

- Recording of adverse events (AEs) collected from IMP dosing until the follow-up visit (Visit 2) 3-7 days after IMP dosing.
- Changes in administered concomitant medication since baseline and until the follow-up visit (Visit 2) 3-7 days after IMP dosing.
- Assessment of local tolerability of the IMP conducted by visual inspection of the oral mucosa

Name of the Sponsor/Company: Orexo AB	**Individual Trial Table Referring to Module 5 of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: OX51-3 sublingual tablet	**Volume:** **Page:** **Trial No.:**	
Name of Active Ingredient: Alfentanil hydrochloride		

prior dose and compared with a visual inspection 60 minutes after the prostate biopsy procedure had ended.

- Blood sampling for haematology, biochemistry and urinalysis

NUMBER OF PATIENTS:

	Alfentanil 350 µg	Alfentanil 700 µg	Alfentanil 1050 µg	Placebo	Total
No. planned:					180
No. screened:					188
No. randomized and treated:	45	46	46	43	180
No. completed the study:	45	46	46	43	180
No. included in FAS:	45	46	46	43	180
No. included in safety population:	45	46	46	43	180

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Men, aged 18-85 years, who presented an abnormal digital rectal examination and/or elevated total prostate-specific antigen (tPSA) value > 4.0 ng/mL or increased Prostate Specific Antigen (PSA) velocity based on Investigator judgment for biopsy, had a body mass index (BMI) between 19.0 and 34.0 kg/m^2 inclusive, and had not previously undergone prostate biopsy, were included in the trial.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

- OX51-3 sublingual tablets containing 350 µg alfentanil
- OX51-3 sublingual tablets containing 700 µg alfentanil

Active ingredient: alfentanil hydrochloride

Dose: one single dose of either 0, 350 µg,700 µg or 1050 µg alfentanil, administered as two tablets given 15 minutes before the anticipated start of the prostate biopsy procedure:

A Alfentanil 350 µg dose (alfentanil 350 µg and placebo)

B Alfentanil 700 µg dose (alfentanil 700 µg and placebo)

C Alfentanil 1050 µg dose (alfentanil 350 µg and alfentanil 700 µg)

D Placebo (placebo and placebo)

Batch numbers:

Alfentanil 350 µg	F12-C056B
Alfentanil 700 µg	F12-C057B

DURATION OF TREATMENT:

Each patient received a single dose of either 350 µg,700 µg or 1050 µg alfentanil or placebo.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

- Placebo tablets containing no active substance

Name of the Sponsor/Company: Orexo AB	**Individual Trial Table Referring to Module 5 of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: OX51-3 sublingual tablet	**Volume:** **Page:** **Trial No.:**	
Name of Active Ingredient: Alfentanil hydrochloride		

Dose: one single dose consisting of two sublingual placebo tablets containing no active ingredient

Batch number:

Placebo	F12-C055A

CRITERIA FOR EVALUATION:

EFFICACY:

Primary Endpoint

1) Worst pain intensity experienced during prostate biopsy measured immediately after end of prostate biopsy procedure by NRS, Direction #2.

Secondary Endpoints

1) AEs, electrocardiograms (ECGs), pulse rate, blood pressure, respiratory rate, oxygen saturation (measured by pulse oximetry [SpO2]) and visual inspection of the oral mucosa.
2) a. Independent observer assessment of patient sedation by using POSS prior to IMP administration, at 5-10 minutes after IMP administration and at 10, 30, 60, 90, 120 and 240 minutes after end of prostate biopsy procedure.

   b. Patient subjective assessment of sedation by using PGID prior to IMP administration, at 5 to 10 minutes after IMP administration and at 10, 30, 60, 90, 120 and 240 minutes after end of prostate biopsy procedure.
3) Worst pain intensity experienced during prostate biopsy measured immediately after end of prostate biopsy procedure by NRS.
4) Pain intensity measured at 10, 30, 60, 90 and 240 minutes after end of prostate biopsy procedure, measured by NRS, Direction #3.
5) a. PGIS measured 90 minutes after end of prostate biopsy procedure.

   b. CGIS measured 90 minutes after end of prostate biopsy procedure.
6) Percentage of patients receiving rescue medication.
7) PK parameters.
8) Recovery criteria by Aldrete score prior to IMP administration and at 10, 30, 60, 90, 120, 180 and 240 minutes after end of prostate biopsy procedure.

SAFETY:

1) AEs
2) Vital signs (pulse rate, systolic and diastolic blood pressure)
3) Oxygen saturation
4) Physical examination
5) ECG
6) Clinical laboratory evaluation (Haematology, biochemistry and urinalysis)
7) Local tolerability

Name of the Sponsor/Company: Orexo AB	Individual Trial Table Referring to Module 5 of the Dossier	(For National Authority Use only)
Name of Finished Product: OX51-3 sublingual tablet	**Volume:** **Page:** **Trial No.:**	
Name of Active Ingredient: Alfentanil hydrochloride		

STATISTICAL METHODS:

In general, data are presented using summary statistics for each treatment group by visit and time-point, as applicable. For continuous data the number of observations, mean value, standard deviation (SD), median, minimum, maximum value and coefficient of variation (CV) expressed as a percentage are presented. Categorical data are presented as counts and percentages.

The mean and median are given with one decimal and SD with two decimals more than the original values, and percentages are given with one decimal. All other statistics are given with the same number of decimals as the original values.

For primary efficacy analysis, the difference between treatment groups is analysed using the stratified Wilcoxon rank-sum test with countries as the strata, and the correlation with Alfentanil dose will be assessed using the stratified Cochran-Mantel-Haenszel statistic.

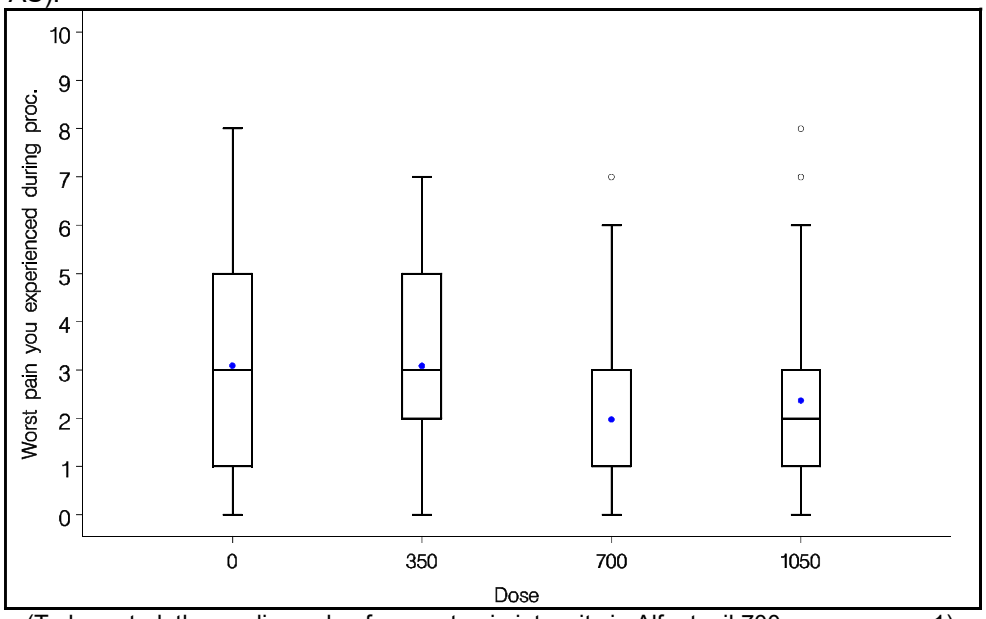
The results of the PK analysis are presented in a separate report.

SUMMARY OF RESULTS AND CONCLUSIONS:

SUMMARY OF EFFICACY RESULTS:

Primary Efficacy Outcome:

- The results from the assessment of worst pain intensity during prostate biopsy procedure showed that patients in the Alfentanil 700 µg dose group had the lowest mean value of pain intensity compared with the Placebo group, and that this difference was proven statistically significant according to the Hochberg procedure (actual p-value = 0.0046). The primary endpoint was thus fulfilled. There were no statistically significant difference between any of the other Alfentanil groups (Alfentanil 350 µg and Alfentanil 1050 µg) and the Placebo group (p>0.0500). The box plot below shows the graphical representation for worst pain intensity during prostate biopsy by NRS Direction #2 per treatment administered for the full analysis set (FAS).



(To be noted: the median value for worst pain intensity in Alfentanil 700 µg group was1).

Name of the Sponsor/Company: Orexo AB	**Individual Trial Table Referring to Module 5 of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: OX51-3 sublingual tablet	**Volume:** **Page:** **Trial No.:**	
Name of Active Ingredient: Alfentanil hydrochloride		

Secondary Efficacy Outcome:

- The results from the assessment of worst pain intensity during the prostate biopsy procedure indicated a significant correlation between the Alfentanil dose and the decreasing level of worst pain intensity during the prostate biopsy procedure (p=0.0111).
- The results from the assessment of post-procedural pain showed no statistically significant differences between the Alfentanil treatment groups and the Placebo group at any time point following the prostate biopsy procedure.
- The results from the assessments of patient sedation, as assessed by POSS and PGID, showed that there was no indication of clinically significant sedation at any Alfentanil dose level. Although patients in the Alfentanil 1050 µg group reported a higher mean value of impression of drowsiness with a statistically significant difference as compared to the Placebo group at 5-10 minutes after IMP administration (p=0.0086), only one patient in the Alfentanil 1050 µg group reported the sensation of been more than “A little drowsy”.
- The results from the assessments of impression of satisfaction with the pain treatment for the prostate biopsy procedure, as assessed by PGIS and CGIS, showed that the majority of patients and clinicians were “Very satisfied” with the pain relief treatment administered, and that there was no statistically significant difference between any of the Alfentanil treatment groups and the Placebo group.
- Rescue medication was not needed in any of the treatment groups at any time point.
- The results from the assessments of patient recovery, as assessed by the Aldrete recovery scale, showed that all patients were ready for discharge according to clinical praxis (score of 9 on the Aldrete recovery scale) 30 minutes after the prostate biopsy procedure. The lowest score on the Aldrete recovery scale was 8.

SUMMARY OF SAFETY RESULTS:

- In total, 62 AEs were reported by 49 of the 180 patients in the trial; 35 out of the 137 patients (25.5%) receiving Alfentanil and by 14 out of the 43 patients (32.6%) receiving placebo. The number of AEs reported were slightly higher in the Placebo group (19 AEs) than in the Alfentanil groups, in which 14, 18 and 11 AEs were reported in the 350 µg, 700 µg and 1050 µg groups, respectively.
  Thirteen of the 62 AEs reported in the trial were considered causally related to the IMP, as judged by the Investigator. These were reported by 8 patients in the Alfentanil 700 µg (3 AEs), 1050 µg (4 AEs) and Placebo (6 AEs) groups. Twenty-three patients reported at least one AE considered causally related to the prostate biopsy procedure, as judged by the Investigator. The system organ class (SOC) most commonly affected by AEs was Neoplasms benign, malignant and unspecified (incl cysts and polyps) (25 AEs), followed by *Renal and urinary disorders* (10 AEs) and *Gastrointestinal disorders* (7 AEs). The most commonly reported preferred terms were prostate cancer and haematuria.
  There were 3 serious adverse events (SAEs) reported in the trial and were all considered to have a causal relationship to the prostate biopsy procedure. None of the SAEs was considered to be causally related to the administration of the IMP. All 3 SAEs consisted of urinary tract infection and were reported by patients in the Alfentanil 350 µg, Alfentanil 1050 µg and Placebo groups. There were no deaths or AEs leading to treatment discontinuation reported in the trial.

Name of the Sponsor/Company: Orexo AB	Individual Trial Table Referring to Module 5 of the Dossier Volume: Page: Trial No.:	(For National Authority Use only)
Name of Finished Product: OX51-3 sublingual tablet		
Name of Active Ingredient: Alfentanil hydrochloride		

- The majority of patients had normal values for clinical laboratory parameters (haematology, biochemistry and urinalysis). There were no discernible patterns in changes from Visit 1 (before IMP administration) to Visit 2 (follow-up) for any of the treatment groups. One patient in the Placebo group had a clinically significant abnormal value for "blood" in the urinalysis at Visit 2, which was reported as an AE (Haematuria).
- There were no clinically relevant abnormal findings on vital signs (pulse rate and systolic and diastolic blood pressure) recorded in the trial.
- There were no clinically significant abnormal ECG results recorded in the trial.
- There were no clinically relevant abnormal findings on respiratory rate recorded in the trial.
- The results from assessment of oxygen saturation over time showed that the changes in mean values were small in all treatment groups and there were no significant differences in oxygen saturation between the treatment groups.

CONCLUSIONS:

In this study the results from the efficacy and safety analyses showed that

- Alfentanil 700 µg was found to be the dose with best analgesic efficacy and patients in this dose group experienced the lowest levels of pain during the procedure compared to patients who received placebo (actual p-value = 0.0046).
- There was a significant correlation between the dose administered and the analgesic efficacy of sublingual alfentanil tablets (p=0.0111).
- All Alfentanil doses showed satisfactory pain relief compared with placebo as assessed by both patients and clinicians
- There were no indications of clinically significant sedation at any dose level.
- There were no differences between the treatment groups in terms of patient recovery and patients were ready for discharge according to clinical praxis 30 minutes after prostate biopsy procedure.
- There was no need to use rescue medication in any of the treatment groups.
- All Alfentanil doses (300 µg, 700 µg and 1050 µg) were safe and well tolerated, and there were no signs of local tolerability issues.

DATE OF REPORT: 17 April 2014