OX20-005 CSR SYNOPSIS, 23Oct2012

Name of Sponsor/Company: Orexo AB	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Name of Finished Product: Abstral®		
Name of Active Ingredient: Sublingual (SL) fentanyl		

Trial code OX20-005	**EudraCT No** 2010-020239-38

Trial Title

Conversion of fast acting oral opioids to Abstral® (SL fentanyl) in opioid tolerant cancer patients with breakthrough pain.

Scientific advisor

Harald Breivik, MD, DMsc, FRCA (elected) Professor of Anaesthesiology
Faculty Division Rikshospitalet
University of Oslo, Norway

Co-ordinating Investigators

Norway[1]

Professor Audun Stubhaug, MD, PhD, Avdelingsleder
Avdeling for smertebehandling, Akuttklinikken
Oslo Universitetssykehus – Rikshospitalet, Oslo, Norway

Sweden

Jan Persson, MD, PhD
Smärtavdelning B42
Karolinska Universitetssjukhuset, Huddinge, Sweden

Trial Centers Sweden

Site 1

Jan Persson, MD, PhD
Smärtavdelning B42, Karolinska Universitetssjukhuset, Huddinge, Sweden

Site 2

Mariann Stenberg, MD, PhD
Onkologiska smärtenheten, Skånes Universitetssjukhus Lund

Site 3
Ulla Martinsson, MD, PhD
Onkologikliniken, Akademiska Sjukhuset, Uppsala

[1] Coordinating Investigator in Norway added in Substantial Protocol Amendment No. 1

Name of Sponsor/Company: Orexo AB	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Name of Finished Product: Abstral®		
Name of Active Ingredient: Sublingual (SL) fentanyl		

Trial code OX20-005	**EudraCT No** 2010-020239-38

Site 4[2]

Claes Norén, MD
SDF Askim Frölundahögsbo, Hemsjukvård och rehabilitering Västra Göteborg

Site 5
Maria Sandström, MD, PhD
Cancercentrum, Norrlands Universitetssjukhus, Umeå

Site 6

Susann Plate, MD
Kirurgkliniken, Sjukhuset i Arvika

Trial CentresNorway

Site 7[3]

Professor Audun Stubhaug, MD, PhD
Avdeling for smertebehandling, Akuttklinikken, Oslo Universitetssykehus – Rikshospitalet, Oslo

Site 8[4]
Gunnar Indrebø, MD
Palliativ enhet, Onkologisk avdeling, Ålesund Sjukehus, Helse Sunnmøre HF, Ålesund

Site 9[4]

Gernot Ernst, MD
Palliativ enhet, Anestesiavdelingen, Kongsberg Sykehus Vestre Viken HF, Kongsberg

Site 10[4]
Bardo Driller, MD
Palliativ enhet, Anestesiavdelingen, Molde Sjukehus, Helse Nordmøre og Romsdal HF, Molde

Publication (reference)

Not applicable.

[2] Change of study site (Substantial Protocol Amendment No. 1)

[3] Site added (Substantial Protocol Amendment No. 1)

[4] These sites were not included in the FINAL Trial Protocol or in a Substantial Protocol Amendment. The sites were approved by the Norwegian IEC and Competent Authorities before initiated.

Name of Sponsor/Company: Orexo AB	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Name of Finished Product: Abstral®		
Name of Active Ingredient: Sublingual (SL) fentanyl		

Trial code OX20-005	**EudraCT No** 2010-020239-38
Studied period Date of first enrolment: 21 February 2011 Date of last subject completed: 07 December 2011	**Phase of development** IV

Objectives and endpoints

Primary objective

To evaluate the responder rate in patients converted to SL fentanyl as assessed by the PID_{30}.

Primary endpoint:

The primary endpoint was the response rate in patients converted to SL fentanyl. A subject was defined as responder if the change of Pain Intensity (PI) on the Numerical Rating Scale (NRS) rated from 0 to10, at 30 minutes remained stable after the conversion compared to baseline (PID_{30}).

Secondary objectives and endpoints:

1. To evaluate the responder rate in patients converted to SL fentanyl as assessed by the PID_{15}.

   Endpoint

   A subject was defined as a responder if the change of Pain Intensity (PI) on the Numerical Rating Scale (NRS) rated from 0 to10, at 15 minutes remained stable after the conversion compared to baseline (PID_{15}).

2. To evaluate the Edmonton Symptom Assessment System (ESAS)

   Endpoint a:

   ESAS-Symptom Distress Score (ESAS-SDS), according to the 10-dimensional symptom assessment system with 11 points NRS from 0 to 10, the number to be circled that best describes; pain (at rest and in movement), tiredness, nausea, depression, anxiety, drowsiness, appetite, shortness of breath and well-being. Summate all item scores with equal weighting.

   Endpoint b

   Separate evaluations of the ESAS symptoms tiredness, drowsiness, nausea, appetite and well-being were to be made.

3. To evaluate the patients global assessment of treatment (patient satisfaction).

   Endpoint:

   The category to be marked, on a seven point scale, that best described patient satisfaction; excellent (7), very good (6), good (5), no change or no improvement (4), somewhat dissatisfied (3), poor (2) or very poor (1).

4. To evaluate the patients preference of treatment.

   Endpoint:

Name of Sponsor/Company: Orexo AB	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Name of Finished Product: Abstral®		
Name of Active Ingredient: Sublingual (SL) fentanyl		

Trial code OX20-005	**EudraCT No** 2010-020239-38

The number of patients who at the end of the study preferred baseline treatment or treatment with SL fentanyl.

5. To evaluate safety of treatment

Endpoints:
Occurrence of AEs, withdrawals

Trial design

This was a multi-center, open-label, single subject experimental design (SSED) study of breakthrough cancer pain (BTcP) in patients with locally advanced or generalized cancer. The basal, round the clock opioid treatment was continued throughout the study.

At Visit 1, patients were screened for eligibility and eligible patients were included in the baseline part of the study (maximum 21 days) on a stabilized dose of BTcP medication, either Oxycodone (p.o.) or Morphine (p.o.). BTcP episodes were treated according to standard care at the clinic and baseline pain intensity (PI) data were collected for 7-15 consecutive BTcP episodes. Study personnel contacted the patient by phone for scheduling of Visit 2.

At Visit 2, PI data for the last 7 consecutive BTcP episodes recorded during the baseline phase were automatically processed in a computerized web-application and eligibility for the intervention phase was evaluated based on maximum standard deviation and curve slope (inclusion criteria 8 and 9). Patients eligible for conversion to SL fentanyl were thereafter switched to SL fentanyl for treatment of BTcP by the dose conversion ratio 50:1 in morphine equivalents with subsequent dose titration, if necessary. The duration of the intervention phase was a maximum of 14-21 days and data from 8-15 BTcP episodes treated with SL fentanyl were collected.

During the intervention phase, daily telephone calls were made by a study nurse to patients in home care. The patient was asked for occurrence of AEs, intake of concomitant medications and was reminded to fill in the diaries and questionnaires.

The end-of study visit (Visit 3) was performed 2-21 days after Visit 2, as soon as PI data had been collected from 8-15 consecutive BTcP episodes treated with stable dose of SL fentanyl.

All study visits could be performed in the hospital or at home with the patient.

Number of subjects

Planned: 71 patients included in the intervention phase, 7-9 patients at each site

Screened: 11 patients

Enrolled to the baseline phase: 9 patients

Included in the intervention phase: 8 patients

Completed: 7 patients

Name of Sponsor/Company: Orexo AB	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Name of Finished Product: Abstral®		
Name of Active Ingredient: Sublingual (SL) fentanyl		

Trial code OX20-005	**EudraCT No** 2010-020239-38

Diagnosis and main eligibility criteria

Consenting adults (≥ 18 years) of both genders with advanced and/or generalized cancer according to Investigator judgment, opioid tolerant with at least 0,5 episodes of BTcP/day. The patients were allowed to take other treatments for their cancer disease apart from other BTcP medication.

Investigational Medical product (IMP)

Abstral® sublingual tablets (fentanyl citrate) in six different doses; 100µg, 200µg, 300µg, 400 µg, 600µg and 800 µg.

The following batches were used:

Strength	Batch nr
100 µg	RB04A9
200 µg	RC001A3
300 µg	RD001C5
400 µg	RG003A7
600 µg	RH905B4, RH004B3
800 µg	RK001A1

The dosing strategy was according to current recommendations apart from the start dose of SL fentanyl which was selected individually according to a standardized conversion ratio (50:1 in morphine equivalents). The maximum start dose was restricted to 400 µg. For a single BTcP episode no more than two tablets or a maximum dose of 800 µg was allowed. The patient was to be supervised when converted to SL fentanyl and during dose titration.

Comparator product, dosage and mode of administration, batch number

Not applicable.

Duration of treatment

The SL fentanyl was to be administered during a maximum of 15 BTcP episodes during a maximum period of 21 days.

Duration of subjects involvement in the trial

Maximum 42 days including screening, baseline data collection phase, intervention phase and end of study visit.

Name of Sponsor/Company: Orexo AB	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Name of Finished Product: Abstral®		
Name of Active Ingredient: Sublingual (SL) fentanyl		

Trial code OX20-005	**EudraCT No** 2010-020239-38

Efficacy assessments

- PI was assessed using a numerical rating scale (NRS), 0-10, where 0= no pain and 10= pain as bad as you can imagine. Registrations were made in the patient diary immediately before, 15 and 30 minutes after administration of BTcP treatment.
- The ESAS questionnaire including pain (at rest and in movement), tiredness, nausea, depression, anxiety, drowsiness, appetite, shortness of breath and wellbeing, was completed on a 24 hour basis during the entire study period, each day the patient experienced any BTcP.
- The patient's global assessment of the BTcP medication (patient satisfaction) was made at the end of the baseline phase (Visit 2) and at the end of the intervention phase (Visit 3).
- The patient answered a question regarding treatment preference at the end-of -study visit (Visit 3).

Safety assessments

- AE reporting
- Physical examination
- Vital signs

Statistical methods[5]

Sample size calculation

With an estimated true responder rate of 0.9, 59 patients would be required to show with 80% power that the lower limit of the confidence interval was above 75% i e the proportion of responders was above 75%. With an estimated rate of withdrawn patients due to non-drug related AEs of 20%, a sample size of 71 patients included in the intervention phase were needed.

Statistical methods used

Response rate was to be presented as the observed proportion with 95 % confidence interval for the proportion. Other endpoints were to be presented descriptively at the time points at which they are measured in tables and figures.

Analyses populations

Safety	All patients that received at least one dose of IMP, i.e. SL fentanyl.
The Intention To Treat (ITT)	All patients who were treated with IMP (SL fentanyl).
The Per Protocol (PP)	All patients who were treated with IMP (SL fentanyl), had no major protocol deviations, performed the study and have diary data from 0 and 30 minutes measurements of PI, from six (6) or more post-baseline BTcP episodes.

[5] Due to the small sample size, the statistical plans were adopted accordingly.

Name of Sponsor/Company: Orexo AB	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Name of Finished Product: Abstral®		
Name of Active Ingredient: Sublingual (SL) fentanyl		

Trial code OX20-005	**EudraCT No** 2010-020239-38

SUMMARY – CONCLUSIONS

EFFICACY RESULTS

Due to the low number of subjects included (8 out of 71 planned) no statistical analysis as described in the Trial Protocol has been performed. Patients have not been classified into the different analysis data sets defined in the Trial Protocol and only individual patient data is presented.

SAFETY RESULTS

Five (62 %) of the patients treated with SL fentanyl experienced at least one AE. Thirteen (87%) of the total number of AEs reported were assessed as not related or unlikely related to the study treatment. Two occurrences of headache were assessed as possibly related to the study product.

None of the events reported were assessed as severe and no SAEs or other significant AEs occurred.

No clinically significant findings were reported from the physical examination for any of the patients enrolled, at baseline or at the end of the study. There were no remarkable changes over time as regards any of the vital signs parameters.

There were no remarkable changes over time as regards any of the vital signs parameters.

CONCLUSION

Due to slow recruitment rate, only eight (out of 71 planned) subjects were included in this study. It is therefore not possible to draw any conclusions based on the findings in the study regarding either efficacy or safety of SL fentanyl.