SYNOPSIS

Name of the sponsor:

Laboratoires Grünenthal S.A.S

92024 Nanterre Cedex

Trade name: ZALVISO®

Active agent: Sufentanil

Study title: ZAS - Zalviso® in the EU after Surgery

A multicentre, non-interventional, prospective observational study of the use of the sufentanil sublingual tablet system (Zalviso®) for the management of acute postoperative pain in a hospital setting.

Study design:

This was a non-interventional, multicentre and prospective observational study. Due to the observational character of this non-interventional trial, visits and examinations followed the usual clinical practice. All patient-care decisions, including diagnostic and therapeutic interventions, were at the discretion of the participating centres according to their clinical standards of medical care.

Study period:

April 2017 to March 2018

Observation period per patient:

The observational period covered three treatment days, according to the maximum recommended treatment duration of 72 h.

Study objectives:

The present non-interventional trial had two aims. First, the demographic and surgical characteristics of a patient-controlled analgesia (PCA) with Zalviso® were analysed for patients with postoperative moderate to severe acute pain. Second, the efficacy, safety, tolerability, and quality of life under routine clinical practice were examined.

Participating centres:

The NIT was carried out in the anaesthesiology departments of the following 11 hospitals:

- Centre Hospitalier Universitaire Amiens Sud,
- Hôpital Ambroise Paré, Boulogne-Billancourt,
- Hôpital Beaujon, Clichy,
- Infirmerie Protestante de Lyon,
- Institut Regional Cancer Montpellier,
- Hôpital privé - Le confluent, Nantes,
- Centre Hospitalier Universitaire de Nîmes,
- Hôpital Pitié-Salpêtrière, Paris,
- Hôpital Cochin, Paris,
- Hôpital Tenon, Paris and
- Clinique Medipole Garonne, Toulouse.

Number of patients (planned and analysed):

- Planned patients: 300.
- Analysed patients: 276 (EAS) / 284 (SAS).

Diagnosis and inclusion criteria:

Adult patients with acute moderate to severe postoperative pain.

Effectiveness parameters

Primary endpoint

Patient Global Assessment (PGA). The assessment was done on a 4-point categorical scale (“excellent”, “good”, “fair”, “poor”) on each treatment day. Success (responder) was defined as a response of “good” or “excellent”.

Secondary endpoints

- Pain intensity at rest measured on an 11-point numerical rating scale (NRS with 0 = no pain and 10 = worst pain imaginable).
- Worst pain intensity (NRS with 0 = no pain and 10 = worst pain imaginable).
- Percentage of severe pain (= pain intensity ≥ 7).
- Quality of sleep measured on a 0 - 10 NRS (0 = no impairment, 10 = maximum impairment).
- Patient's mobility was assessed on a 5-point-scale (no mobility, level 4: patient is mobile and can be mobilized in bed, level 3: patient is mobile up to "Pilotsitz" and/or edge of bed, level 2: patient can be mobilized into a chair, can/is learning to walk a few steps, level 1: patient can be mobilized on a chair, walks a few steps, Level 0: patient walks on his/her own).
- Nurse Ease of Care (EOC) questionnaire.

Safety parameters:

- Occurrence of serious and non-serious adverse drug reactions (ADR) during the observation.

Statistical methods:

The analysis of the collected data was performed descriptively. The biometrical analysis was performed according to a statistical analysis plan.

Continuous data were described using mean, median, standard deviation, quartiles, minimum and maximum. Parameters specified using categories were displayed using absolute and relative frequencies.

The PGA response after 48 hours (2^{nd} postoperative day) was compared to a threshold of 60% by using a binomial test for single proportion with a one-sided significance level of 2.5%

For the frequency of side effects, the 95% confidence interval was calculated according to the method of Agresti and Coull (The American Statistician 1998; 52: 119-126).

Results

Patient disposition:

Until closure of the biometrical database on August 7th, 2018 case report forms (CRF) were available for 289 patients. Five patients did not take any Zalviso® tablets. They were excluded from the EAS and the SAS. For eight patients relevant effectiveness data were incomplete and were not completed even upon request. These patients were excluded from the EAS. Therefore, 284 were included in the SAS and 276 patients in the EAS.

Patient data (EAS):

Demographic data

Of the 276 patients, 124 (44.93%) were male and 152 (55.07%) were female. None of the patients was younger than 18 years. The mean age was 59.74 ± 15.67 years. The mean body weight was 80.82 ± 19.54 kg and the mean BMI was 28.49 ± 6.42 kg/m²

Surgery and anaesthesia

There were no restrictions concerning the type of surgery in this non-interventional trial. Therefore, a broad spectrum of surgeries were documented. The most commonly performed surgeries were "endoprothesis of the knee joint" (22.10%, n = 61), followed by "spondylodesis" (10.14%, n = 28), "excision / resection of the female breast" (9.06%, n = 25), "other joint operations on the lower extremity" (8.33%, n = 23) and "laparoscopic sleeve gastrectomy" (7.25%, n = 20). For the clear majority of the surgeries general anaesthesia was used (89.86%, n = 248). Additionally or alternatively 34.78% (n = 96) of the patients received a regional anaesthesia and 9.78% (n = 27) a local anaesthesia.

Peri- and postoperative treatment with opioids and related side effects

About half of the patients (53.26%, n = 147) received opioids in the context of the perioperative pain management. Side effects occurred in 8.16% (n = 12) of the 147 patients treated with opioids. Nausea was the most frequently mentioned side effect (4.76% n = 7), followed by vomiting (2.04%, n = 3).

Treatment data (EAS):

PCA with Zalviso®

Treatment data were available for 243 patients. The mean number of total tablets consumed was 18.48 ± 14.84 tablets for all 243 patients. Those who used Zalviso® up to 72 hours after hand-over took 19.27 ± 14.67 tablets. The Zalviso® device was used by the patient (duration of Zalviso® application) for 2.37 ± 0.82 days. The duration of intake of Zalviso® is restricted to a maximum of 72 h after first intake. The observed mean duration of Zalviso® intake defined as time of first intake to time of last intake was 40.42 ± 20.54 hours. For one patient the maximum allowed duration of intake was exceeded (87.20 hours). In the case of this patient the device was accidentally reset when changing the cartridge. The reset also restored the countdown of the 72 h limit.

Out of a total of 276 treated patients 97.46% (n = 269) used the Zalviso® device at least up to the first postoperative day, 86.23% (n = 238) up to the second postoperative day and 50.72% (n = 140) up to the third postoperative day.

The most frequent reason for discontinuation of treatment was "maximum treatment duration reached" (35.51%, n = 98). Further reasons were "analgesia with strong acting opioids no longer necessary" (18.12%, n = 50), "demission" (14.49%, n = 40), "transfer to another ward / another hospital" (10.87%, n = 30), "adverse drug reaction" (9.06%, n = 25), "unsatisfactory analgesia" (5.43%, n = 15), problems with the device / handling error" (3.62%, n = 10), "patient's wish" (0.72%, n = 2) and for 1.81% (n = 5) other reasons were given (no data: 0.36%, n = 1).

Concomitant pain medication

During the PCA with Zalviso®, 95.65% (n = 264) of the patients received additional analgesics. The most frequently given concomitant pain medication was paracetamol (94.20%, n = 260), followed by ketoprofen (44.20%, n = 122), nefopam (29.71%, n = 82) and tramadol (21.74%, n = 60).

Effectiveness results (EAS):

Patient's global assessment (PGA)

The primary effectiveness variable "Patient Global Assessment" (PGA) of treatment with Zalviso® was completed by the patient on all treatment days (preferably in the evening). The assessment was done on a 4-point categorical scale (“excellent”, “good”, “fair”, “poor”). Success (responder) was defined as a response of “good” or “excellent”. The PGA on the second postoperative day was defined as PGA after 48 hours and built the focus as the primary endpoint.

On the 2nd postoperative day response was assessed in 79.40% (185 out of 233 patients; 95% CI: 73.63% - 84.40%). The response rate differed with statistical significance from a presumed value of 60% ($p \leq 0.001$).

The responder rate on the day of surgery was 81.67% (205 of 251 patients), on the 1st postoperative day 77.86% (204 of 262 patients and on the 3rd postoperative day 80.29% (110 of 137 patients). At the end of treatment, the response was 76.12% (204 of 268 patients).

Pain intensity

The **pain intensity at rest** was assessed using an 11-point numerical rating scale (0 = no pain to 10 = maximum pain imaginable). Overall, the pain control achieved by perioperative anaesthesia could be maintained postoperatively by the PCA with Zalviso®. The pain intensity at rest was 2.60 ± 2.81 at the time of hand-over of Zalviso® (based on n = 241 ratings). During the first 24 hours after hand-over of Zalviso® the mean pain intensity score was below 3. At the end of treatment the mean pain intensity was 2.38 ± 2.26 (morning rating, n = 250).

The mean **worst pain intensity** declined during treatment with Zalviso®. At the day of surgery the mean worst pain was 4.61 ± 2.48 (based on n = 269 ratings). At the end of treatment the mean worst pain intensity was 3.34 ± 2.72 (n = 233).

The mean **temporal percentage of severe pain** (defined as a pain intensity ≥ 7) decreased during treatment with Zalviso®. At the day of surgery (postoperative) the mean temporal

percentage of severe pain was 4.10% ± 13.89% (based on n = 217). At the end of treatment, the mean temporal percentage of severe pain was 2.48% ± 12.13% (n = 189).

Quality of sleep

The quality of sleep was assessed by using a numeric rating scale 0 to 10 (0 = no impairment, 10 = maximum impairment). The mean quality of sleep during treatment from the 1st to the 3rd postoperative day was 2.87 ± 2.61 (n = 243), 2.80 ± 2.75 (n = 204) and 1.96 ± 2.36 (n = 112). At the end of treatment, the quality of sleep was rated as 2.50 ± 2.60 (n = 216).

Mobility

Often an immediate mobilization after surgery is neither possible nor intended. Therefore, about one third of the patients were not mobilized on the operation day (33.06%, 82 of 248 patients). If patients were mobilized, this was mostly done by the nurses (38.31%, n = 95 patients). Self-mobilization by the patient took place in 25.40% (n = 63) and mobilization by a physiotherapist in 12.50% (n = 31) of the cases (other person: 0.81%, n = 2). In general, the patient's mobilization was initiated on the 1st postoperative day. Only for 2.09% (n = 5) of the patients an active mobilization was not performed on the 1st postoperative day and this proportion decreased to 1.90% (n = 4) on the 2nd postoperative day and to 0.00% on the 3rd postoperative day. During the treatment with Zalviso® the active mobilization was increasingly done by the patients themselves (1st postoperative day: 47.28%, n = 113; 2nd postoperative day: 69.67%, n = 147; 3rd postoperative day: 82.79%, n = 101). During the PCA with Zalviso® the mobility improved towards "better" than expected for about one fifth of the patients, for about three quarters the mobility was "as expected". Only in few cases, the mobility developed towards "worse" than expected.

Ease of Care questionnaire (EOC)

The mean score for the subscale "time consuming" was 0.79 ± 0.85 (n = 255), for the subscale "bothersome" 0.67 ± 0.95" (n = 238) and the total score 4.27 ± 0.85 (n = 236). The mean score concerning the nurses' satisfaction was 3.52 ± 0.77 (n = 228).

Drug safety and tolerability results (SAS):

Non-interventional trials are an instrument for documenting adverse drug reactions occurring during routine administration of the medication and detecting events, which did not occur or could not be observed during the clinical development program.
The analysis of the safety profile of Zalviso® is based on 284 patients (SAS). For 94 patients (33.10%) a total of 150 adverse drug reactions were documented. The most frequently reported ADRs were nausea (52 events), followed by vomiting (34 events), lack of efficacy (14 events), constipation (10 events), dizziness (6 events), urinary retention (4 events) and pruritus (3 events).
As to the degree of seriousness, three of the 150 adverse drug reactions (2.00%) were assessed as "serious". The three serious ADRs ("postoperative wound infection", “incision site haematoma” and “haematuria”) occurred in one patient. No fatal ADR occurred.

The analysis of side effects shows no evidence for the occurrence of unknown (unlabelled) ADRs or a change of the characteristics of the known (labelled) ADRs. The results of this non-interventional trial do not change the qualitative and quantitative risk profile of Zalviso®.

Medical device vigilance and drug product quality complaint reports
During the ZAS – Zalviso® after Surgery Non–Interventional Trial in France no medical device incident (as defined in MEDDEV 2.12-1, Rev 8) was reported. A total of 19 Zalviso® related complaint reports were received by Grünenthal France. No complaint report was classified as RAS Class I and II. All medical device complaint reports were classified as RAS Class III or IV.

Conclusions:

- This non-interventional trial presented data of patients with acute postoperative pain following a broad variety of surgery types.
- The results showed an effective patient-controlled analgesia with Zalviso®.
- The successful pain management supported an early mobilization and resulted in a high level of acceptance of the sufentanil sublingual tablet system by the patients.
- The safety data confirms the safety and tolerability profile of Zalviso®.

Overall, the present results with Zalviso® in routine clinical practice, document the analgesic effectiveness of sufentanil and the successful and safe use of the sufentanil sublingual tablet system in patients with acute postoperative pain. The results are in line with former clinical trials.