SYNOPSIS

Name of the sponsor:

Grünenthal GmbH

German Sales Division

52099 Aachen

Trade name: ZALVISO®

Active agent: Sufentanil

Study title: ZEUS - 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:

March 2017 to October 2017

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 surgery characteristics of a patient-controlled analgesia (PCA) with Zalviso® were analysed for patients with postoperative 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 10 hospitals:

- BG Klinikum Unfallkrankenhaus Berlin gGmbH.
- Evangelisches Krankenhaus Hattingen gGmbH.
- Florence-Nightingale-Krankenhaus Düsseldorf.
- Josephs-Hospital Warendorf.
- Justus-Liebig Universität Gießen.
- Klinikum Fichtelgebirge, Marktredwitz.
- Universitätsklinikum Gießen und Marburg GmbH.
- Universitätsklinikum Würzburg.
- Vinzenz-Pallotti Hospital GmbH, Bergisch Gladbach.
- Westfälische Wilhelms-Universität Münster.

Number of patients (planned and analysed):

- N = 300 planned.
- N = 341 analysed.

Diagnosis and inclusion criteria:

Adult patients with acute moderate to severe postoperative pain.

Effectiveness parameters

- Pain intensity at 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).
- Patient Global Assessment (PGA). The assessment was done on a 4-point categorical scale (“excellent”, “good”, “fair”, “poor”).
- Patient's satisfaction concerning the level of pain control and the way of administration of pain medication. Both assessments were done on a 6-point scale ("extremely satisfied", "very satisfied", "satisfied", "dissatisfied", "very dissatisfied", "extremely dissatisfied").
- 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.

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:

A total of 345 patients were enrolled in this study. Four patients who had received the Zalviso® device did not take any Zalviso® tablets. These four patients were excluded from all analysis. Therefore, the efficacy analysis set (EAS) and the safety analysis set (SAS) consist of 341 patients each.

Patient data:

Demographic data

Of the 341 patients, 127 (37.24%) were male and 214 (62.76%) were female. None of the patients was younger than 18 years. The mean age was 56.33 ± 15.21 years. The mean body weight was 80.05 ± 18.96 kg and the mean BMI was 27.37 ± 5.60 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 "hysterectomy with or without adnexectomy" (17.60%, n = 60), followed by "radical prostatectomy" (8.21%, n = 28), "hernia repair" (6.74%, n = 23) and "spondylodesis" (6.74%, n = 23). For the clear majority of the surgeries general anaesthesia was used (97.95%, n = 334). Additionally or alternatively 7.04% (n = 24) of the patients received a regional anaesthesia and 3.81% (n = 13) a local anaesthesia.

Peri- and postoperative treatment with opioids and related side effects

In total 80.94% (n = 276) of the patients received opioids post- or perioperative. Side effects occurred in 15.94% (n = 44) of the 276 patients treated with opioids. Nausea was the most frequently mentioned side effect (9.42%, 26 of 276 patients with peri-/ postoperative opiates), followed by vomiting (2.90%, n = 8) and postoperative renal failure (2.54%, n = 7).

Treatment data:

PCA with Zalviso®

Treatment data were available for 339 out of 341 patients.
The mean number of total tablets consumed was 22.05 ± 15.57 (mean ± SD) tablets for all 339 patients. Patients who used Zalviso® up to 72 hours after hand-over (n = 247) took 25.54 ± 15.91 tablets. The Zalviso® device was used by the patient (duration of Zalviso® application) for 2.60 ± 0.71 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 45.25 hours. For two patients the maximum allowed duration of intake was exceeded: For one patient the defective device was replaced and the cumulative duration of intake amounted to 72.88 hours. In the second case, the device was reset due to a failure. The duration of intake was 83.80 hours.

Out of 341 treated patients 97.65% (n = 333) used the Zalviso® device at least up to the first day after hand-over, 92.38% (n = 315) up to the second day and 66.86% (n = 228) up to the third day after hand-over.

The most frequent reasons for discontinuation of treatment were "maximum treatment duration reached" (43.40%, n = 148) and "analgesia with strong acting opioids no longer necessary" (40.76%, n = 139). Further reasons were "adverse drug reaction" (4.99%, n = 17), "problems with the device / handling error" (3.81%, n = 13), "unsatisfactory analgesia" (2.93%, n = 10), "demission" (2.35%, n = 8), "patient's whish" (1.17%, n = 4) and for 1.47% (n = 5) other reasons were given.

Concomitant pain medication

During the PCA with Zalviso®, 91.20% (n = 311) of the patients received additional analgesics. Mostly non-opioid analgesics, such as metamizole sodium (65.10%, n = 222), ibuprofen (43.99%, n = 150) or paracetamol (19.06%, n = 65) were used.

Effectiveness results:

Pain intensity

The **pain intensity at rest** was assessed using an 11-point numerical rating scale (0 = no pain to 10 = maximum pain imaginable). At baseline (hand-over of Zalviso®) the mean pain intensity was 5.22 ± 2.25 (based on n = 336 ratings). The following pain controls showed a continuous decline in the pain intensity. At the end of treatment the mean pain intensity was 1.86 ± 1.68 (morning rating, n = 324). In patients with data at baseline (Zalviso® hand-over) and at the end of treatment (n = 321) the mean pain intensity decreased from 5.17 to 1.87 points, corresponding to a mean change of -3.30 ± 2.71 points.

At the day of hand-over of Zalviso® the mean **worst pain intensity** was 5.59 ± 2.04 (based on n = 324 ratings). At the end of treatment the mean worst pain intensity was 3.36 ± 2.25 (n = 308).

The mean temporal percentage of severe pain (defined as a pain intensity ≥ 7) decreased during treatment with Zalviso®. At the day of hand-over of Zalviso® the mean temporal percentage of severe pain was 9.63% ± 17.29% (based on n = 192). At the end of treatment the mean temporal percentage of severe pain was 5.50% ± 13.17% (n = 185).

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 first to the 3rd day after hand-over was 3.08 ± 2.27 (n = 321), 2.15 ± 2.05 (n = 306) and 1.78 ± 1.87 (n = 218). At the end of treatment the quality of sleep was rated at 1.99 ± 2.14 (n = 316).

Mobility

The day of hand-over of Zalviso® corresponded to the day of surgery for almost all patients and about half of the patients were not mobilized on this day (48.22%, 163 of 338 patients). If patients were mobilized, this was mostly done by the nurses (41.42%, n = 140 patients). Self-mobilization by the patient took place in 9.76% (n = 33). In general, the patient's mobilization was initiated on the 1st day after hand-over of Zalviso®. Only 13.25% (n = 44) of the patients were not mobilized and this proportion further decreased to 5.43% (n = 17) at the 2nd day and to 3.96% (n = 9) at the 3rd day. During the treatment with Zalviso®, the active mobilization was increasingly done by the patients themselves (1st day: 35.54%, n = 118; 2nd day: 61.98%, n = 194; 3rd day: 76.65%, n = 174). During the PCA with Zalviso® the mobility improved "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 "worse" than expected.

Patient's global assessment (PGA) and patient's satisfaction

At the end of treatment with Zalviso®, the patient's reported outcome was measured by the patient's global assessment (PGA), level of pain control and the satisfaction with the specific way of pain medication administration. A total of 36.07% (n = 123) of the 341 patients assessed the treatment with Zalviso® as "excellent", 51.03% (n = 174) as "good", 7.92% (n = 27) as "fair" and only 3.81% (n = 13) as "poor" (no data: 1.17%, n = 4).

In 25.81% (n = 88) of the patients the level of pain control by the Zalviso® device was assessed as "extremely satisfied", in 36.07% (n = 123) as "very satisfied", in 29.91% (n = 102) as "satisfied", in 4.99% (n = 17) as "dissatisfied", in 0.59% (n = 2) as "very dissatisfied" and in 0.29% (n = 1) "as "extremely dissatisfied" (no data: 2.35%, n =8).

The majority of patients were satisfied with the way of administration of Zalviso®: 29.03% (n = 99) were "extremely satisfied", 40.18% (n = 137) "very satisfied" and 26.69% (n = 91) were "satisfied". Only 1.47% (n = 5) of the patients were "dissatisfied" and 0.29% (n = 1) were "very dissatisfied" (no data: 2.35%, n = 8).

Ease of Care questionnaire EOC

The mean score for the subscale "time consuming" was 0.65 ± 0.47 (n = 338), for the subscale "bothersome" 0.54 ± 0.50" (n = 335) and the total score 4.41 ± 0.46 (n = 335). The mean score concerning the nurses' satisfaction was 3.84 ± 0.77 (n = 4.00).

Drug safety and tolerability results:

As the EAS, the safety analysis set (SAS) is based on 341 patients. A total of 98 adverse drug reactions (ADR) occurred in 61 patients (17.89%). The most frequently reported ADRs were nausea or procedural nausea (37 events), followed by vomiting or procedural vomiting (22 events), lack of efficacy (9 events), dizziness (4 events) and respiratory depression (4 events).

As to the degree of seriousness, seven of the total 98 adverse drug reactions (7.14 %) were assessed to be "serious". The seven serious ADRs occurred in two patients. Two adverse drug reactions "bradycardia" and “cardiac arrest” related to one patient were rated serious due to being an “other medically important condition”; whereas the remaining five serious ADRs “drug intoxication”, “respiratory insufficiency”, “sopor”, “respiratory rate decreased” and “oxygen saturation decreased” belonging to the second patient were rated serious due to being “life threatening”. Thus no fatal ADR occurred.

Overall, six events were "unlabelled": cardiac arrest, migraine, pain, respiratory failure, toxicity to various agents and visual hallucination.

Medical device vigilance and drug product quality complaint reports

During the ZEUS – Zalviso® after Surgery Non–Interventional Trial in Germany no medical device incident (as defined in MEDDEV 2.12-1, Rev 8), 27 medical device complaint reports and 9 drug product quality complaint reports were received.

The analyses of the 27 medical device complaint reports revealed no critical results with respect to the functionality of the medical device Zalviso® and patient safety. The 9 drug product complaint reports were all related to lack of efficacy which is considered as ADR case and drug

product quality complaint according to Grünenthal convention. The analyses of the 9 drug product quality complaint reports revealed no critical results with respect to patient safety.

Conclusions:

- This non-interventional trial presented data of patients with acute postoperative pain undergoing 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.