



## Clinical trial results:

**A multicenter, open-label, single-arm, Phase IIIb trial to evaluate the effectiveness, safety, tolerability, usability and health economics resource utilization of Zalviso® for management of acute moderate to severe postoperative pain.**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2016-002259-11  |
| Trial protocol           | ES              |
| Global end of trial date | 19 October 2017 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 08 July 2021 |
| First version publication date | 08 July 2021 |

### Trial information

#### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | GRT-ZVO-2016-01 |
|-----------------------|-----------------|

#### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN)   | - |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Grünenthal GmbH   |
| Sponsor organisation address | Zieglerstr. 6, Aachen, Germany, 52099   |
| Public contact               | Grünenthal Trial Information Desk, Grünenthal GmbH, 49 2415693223, Clinical-Trials@grunenthal.com |
| Scientific contact           | Grünenthal Trial Information Desk, Grünenthal GmbH, 49 2415693223, Clinical-Trials@grunenthal.com |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 27 October 2020 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 19 October 2017 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

Evaluate the effectiveness of Zalviso® for the management of acute postoperative pain by using a Patient Global Assessment (PGA) of the method of pain control.

Protection of trial subjects:

The trial was conducted according to Good Clinical Practice guidelines, the applicable local laws, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The competent authority approved the trial as required by national regulations. The regulatory authority was notified of the trial and amendments as required by national regulations.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 30 January 2017 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Spain: 302 |
| Worldwide total number of subjects   | 302        |
| EEA total number of subjects         | 302        |

Notes:

### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 191 |
| From 65 to 84 years                       | 109 |
| 85 years and over                         | 2   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 16 sites in Spain. A total of 350 subjects were enrolled between 30 January 2017 and 19 October 2017, of which 302 subjects were included to receive the Investigational Medicinal Product (IMP).

### Pre-assignment

Screening details:

The study was conducted in subject hospitalised for a surgical intervention and were instructed on how to operate the Zalviso® administration device to self-administer sufentanil tablets.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Non-randomised - controlled    |
| Blinding used                | Not blinded                    |

### Arms

|           |          |
|-----------|----------|
| Arm title | Zalviso® |
|-----------|----------|

Arm description:

Subjects received Sufentanil 15 micrograms sublingual tablets administered through an administration device Zalviso® designed to deliver single tablets on a subject-controlled basis with a minimum of 20 minutes between doses over a period of 72 hours.

|  |                |
|--|----------------|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Sufentanil     |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Tablet         |
| Routes of administration               | Sublingual use |

Dosage and administration details:

Sufentanil 15 micrograms sublingual tablets administered through an administration device designed to deliver single tablets on a subject-controlled basis.

| Number of subjects in period 1                    | Zalviso® |
|---|----------|
| Started   | 302      |
| Treated   | 302      |
| Completed   | 207      |
| Not completed                                     | 95       |
| Unsatisfactory analgesia                          | 4        |
| Screening failure who took one dose of the IMP    | 1        |
| Unspecified                                       | 24       |
| Analgesia with strong opioids no longer necessary | 52       |
| Adverse drug reaction                             | 14       |



## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description:

Subjects received Sufentanil 15 micrograms sublingual tablets administered through an administration device designed to deliver single tablets on a subject-controlled basis with a minimum of 20 minutes between doses over a period of 72 hours.

| Reporting group values  | Overall Study    | Total |  |
|---|------------------|-------|--|
| Number of subjects  | 302              | 302   |  |
| Age categorical<br>Units: Subjects                                      |                  |       |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 57.38<br>± 14.35 | -     |  |
| Gender categorical<br>Units: Subjects                                   |                  |       |  |
| Female  | 146              | 146   |  |
| Male  | 156              | 156   |  |

## End points

### End points reporting groups

|   |          |
|---|----------|
| Reporting group title   | Zalviso® |
| Reporting group description:<br>Subjects received Sufentanil 15 micrograms sublingual tablets administered through an administration device Zalviso® designed to deliver single tablets on a subject-controlled basis with a minimum of 20 minutes between doses over a period of 72 hours. |          |

### Primary: Percentage of Subjects Who Reported Success Rate on the Patient's Global Assessment (PGA) Method of Pain Control on the Second Postoperative Day

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Who Reported Success Rate on the Patient's Global Assessment (PGA) Method of Pain Control on the Second Postoperative Day <sup>[1]</sup> |
|-----------------|---|

#### End point description:

PGA of pain control was assessed by asking a question from subjects: "How would you rate the treatment with Zalviso®?". Subjects responded using a 4-point categorical scale, where 1= Excellent; 2= Good; 3=Fair and 4=Poor. Higher scores indicated worsening of condition. Success rate on the PGA was defined as the percentage of subjects with a response of "good" or "excellent" in the PGA method of pain control. Analysis was performed on the effectiveness analysis set which included all subjects who received at least one dose of the IMP and had at least one PGA of the method of pain control available.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

#### End point timeframe:

48 hours (second post-operative day) after handing over the device to subjects

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were presented for the primary efficacy variable, along with 95% confidence intervals. The success rate was compared to a threshold of 60% using the exact test of one proportion (using the binomial distribution) with a one-sided significance level of 2.5%.

| End point values              | Zalviso®        |  |  |  |
|-------------------------------|-----------------|--|--|--|
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 301             |  |  |  |
| Units: percentage of subjects |                 |  |  |  |
| number (not applicable)       |                 |  |  |  |
| Excellent response            | 52.9            |  |  |  |
| Good response                 | 38.8            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Who Reported Success Rate on the Patient's Global Assessment (PGA) Method of Pain Control on the Day of Surgery and the First and Third Postoperative Days

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Who Reported Success Rate on the Patient's Global Assessment (PGA) Method of Pain Control on the Day of Surgery and the First and Third Postoperative Days |
|-----------------|---|

End point description:

PGA of pain control was assessed by asking a question from subjects: "How would you rate the treatment with Zalviso®?". Subjects responded using a 4-point categorical scale, where 1= Excellent; 2= Good; 3=Fair and 4=Poor. Higher scores indicated worsening of condition. Success rate on the PGA was defined as the percentage of subjects with a response of "good" or "excellent" in the PGA method of pain control. Analysis was performed on the effectiveness analysis set.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

surgery day, 24 hours (first postoperative day) and 72 hours (third postoperative day) after handing over the device to subjects

| End point values                             | Zalviso®        |  |  |  |
|--|-----------------|--|--|--|
| Subject group type                           | Reporting group |  |  |  |
| Number of subjects analysed                  | 301             |  |  |  |
| Units: percentage of subjects                |                 |  |  |  |
| number (not applicable)                      |                 |  |  |  |
| Excellent response (surgery day)             | 41.9            |  |  |  |
| Good response (surgery day)                  | 49.2            |  |  |  |
| Excellent response (first postoperative day) | 46.2            |  |  |  |
| Good response (first postoperative day)      | 47.2            |  |  |  |
| Excellent response (third postoperative day) | 52.7            |  |  |  |
| Good response (third postoperative day)      | 42.5            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Healthcare Professionals Who Reported Success Rate on the Healthcare Professional Global Assessment (HPGA) Method of Pain Control on the Day of Surgery and the First, Second and Third postoperative days

|                 |  |
|-----------------|--|
| End point title | Percentage of Healthcare Professionals Who Reported Success Rate on the Healthcare Professional Global Assessment (HPGA) Method of Pain Control on the Day of Surgery and the First, Second and Third postoperative days |
|-----------------|--|

End point description:

HPGA of pain control was assessed by asking a question from healthcare professionals: "How would you rate the treatment with Zalviso®?". Healthcare professionals responded using a 4-point categorical scale, where 1= Excellent; 2= Good; 3=Fair and 4=Poor. Higher scores indicated worsening of condition. Success rate on the HPGA was defined as the percentage of healthcare professionals with a response of "good" or "excellent" in the HPGA method of pain control. Analysis was performed on the effectiveness analysis set.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

surgery day, 24 hours (first postoperative day), 48 hours (second postoperative day) and 72 hours (third postoperative day) after handing over the device to subjects

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| <b>End point values</b>                       | Zalviso®        |  |  |  |
| Subject group type                            | Reporting group |  |  |  |
| Number of subjects analysed                   | 301             |  |  |  |
| Units: percentage of healthcare professionals |                 |  |  |  |
| number (not applicable)                       |                 |  |  |  |
| Excellent response (surgery day)              | 52.2            |  |  |  |
| Good response (surgery day)                   | 44.5            |  |  |  |
| Excellent response (first postoperative day)  | 52.4            |  |  |  |
| Good response (first postoperative day)       | 44.5            |  |  |  |
| Excellent response (second postoperative day) | 52.9            |  |  |  |
| Good response (second postoperative day)      | 44.2            |  |  |  |
| Excellent response (third postoperative day)  | 56.0            |  |  |  |
| Good response (third postoperative day)       | 41.1            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total Score on the Nurse Ease of Care (EOC) Questionnaire at the End of Treatment

|                 |   |
|-----------------|---|
| End point title | Total Score on the Nurse Ease of Care (EOC) Questionnaire at the End of Treatment |
|-----------------|---|

End point description:

The Nurse EoC questionnaire consisted of 23 questions, 20 of which were scored on a scale of 0 to 5 (where 0=not at all and 5=a very great deal) and summarised into two subscale scores (time-consuming and bothersome) and a total EoC score. Two other questions (satisfaction with level of pain control and satisfaction with device) were scored on a 6-point scale (extremely dissatisfied to extremely satisfied) and combined into a total satisfaction score. The last question asked how many years has the nurse cared for subjects. For nursing subscale scores, lower was considered as better (i.e. less time-consuming), but these were converted back to the 0 to 5 scale (where 5=highest score) for the nurse EoC total score. The total score was calculated as the mean of the items for all the questions. Analysis was performed on effectiveness analysis set. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

End of treatment (i.e. up to 72 hours after handing over the device to subjects)



|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Zalviso®        |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 294             |  |  |  |
| Units: units on a scale              |                 |  |  |  |
| arithmetic mean (standard deviation) | 4.6 (± 0.4)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Total Score on the Patient Ease of Care (EOC) Questionnaire At the End of Treatment

|                 |   |
|-----------------|---|
| End point title | Total Score on the Patient Ease of Care (EOC) Questionnaire At the End of Treatment |
|-----------------|---|

End point description:

The Patient EoC questionnaire consisted of 23 questions, 20 of which were scored on a scale of 0 to 5 (where 0=not at all and 5=a very great deal) and summarised into 6 subscale scores (confidence with the device, comfort with the device, movement, dosing confidence, pain control and knowledge/understanding) and a total EoC score. The two other questions (satisfaction with level of pain control and satisfaction with method of administration of pain medication) were scored on a 6-point scale (0= extremely dissatisfied to 6=extremely satisfied) and combined into a total satisfaction score. The total score was calculated as the mean of the items for all the questions. Analysis was performed on effectiveness analysis set. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

End of treatment (i.e. up to 72 hours after handing over the device to subjects)

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Zalviso®        |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 295             |  |  |  |
| Units: units on a scale              |                 |  |  |  |
| arithmetic mean (standard deviation) | 4.5 (± 0.5)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pain Intensity Measured by Numerical Rating Scale (NRS)

|                 |   |
|-----------------|---|
| End point title | Pain Intensity Measured by Numerical Rating Scale (NRS) |
|-----------------|---|

End point description:

NRS measured pain intensity experienced by the subject on a scale of 0 to 10, where 0 means no pain and 10 mean the worst possible pain. Subject's pain intensity was assessed by asking following question: "Please, rate your pain intensity by assessing the one number that best describes your pain right now"; on a scale of 0 to 10 where 0 means no pain, and 10 means the worst possible pain. Higher scores indicated worst possible pain. Analysis was performed on effectiveness analysis set. Here, "n" = subjects with available data for each specified category.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1, 2, 3, 4, 8, 12, 16, 20, and 24 hours after handing over the device to subjects

| End point values                     | Zalviso®        |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 301             |  |  |  |
| Units: units on a scale              |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| After 1 hour (n=298)                 | 3.08 (± 2.07)   |  |  |  |
| After 2 hours (n=293)                | 2.55 (± 2)      |  |  |  |
| After 3 hours (n=288)                | 2.22 (± 1.79)   |  |  |  |
| After 4 hours (n=290)                | 2.1 (± 1.8)     |  |  |  |
| After 8 hours (n=273)                | 2.21 (± 2.12)   |  |  |  |
| After 12 hours (n=250)               | 2.08 (± 2.14)   |  |  |  |
| After 16 hours (n=266)               | 2.31 (± 2.06)   |  |  |  |
| After 20 hours (n=287)               | 2.15 (± 1.8)    |  |  |  |
| After 24 hours (n=278)               | 2.1 (± 1.87)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Worst Pain Intensity Measured by Numerical Rating Scale (NRS)

|                 |   |
|-----------------|---|
| End point title | Worst Pain Intensity Measured by Numerical Rating Scale (NRS) |
|-----------------|---|

End point description:

NRS measured worst pain intensity experienced by the subject on a scale of 0 to 10, where 0 means no pain and 10 mean the worst possible pain. subject's pain intensity was assessed by asking following question: "Please, rate your pain intensity by assessing the one number that best describes your pain right now"; on a scale of 0 to 10 where 0 means no pain, and 10 means the worst possible pain. Higher scores indicated worst possible pain. Analysis was performed on effectiveness analysis set. Here, 'n' = subjects with available data for each specified category.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

surgery day, 24 hours (first postoperative day), 48 hours (second postoperative day) and 72 hours (third postoperative day) after handing over the device to subjects

| End point values                     | Zalviso®        |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 301             |  |  |  |
| Units: units on a scale              |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Surgery day (n=299)                  | 5.12 (± 2.01)   |  |  |  |
| First postoperative day (n=289)      | 4.47 (± 2.36)   |  |  |  |
| Second postoperative day (n=271)     | 3.43 (± 2.39)   |  |  |  |

|                                 |                    |  |  |  |
|---------------------------------|--------------------|--|--|--|
| Third postoperative day (n=197) | 2.76 ( $\pm$ 2.14) |  |  |  |
|---------------------------------|--------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Severe Pain (Pain intensity $\geq 7$ ) Measured by NRS

|                 |  |
|-----------------|--|
| End point title | Severe Pain (Pain intensity $\geq 7$ ) Measured by NRS |
|-----------------|--|

End point description:

NRS measured pain intensity experienced by the subject on a scale of 0 to 10, where 0 means no pain and 10 mean the worst possible pain. Subject's pain intensity was assessed by asking following question: "Please, rate your pain intensity by assessing the one number that best describes your pain right now"; on a scale of 0 to 10 where 0 means no pain, and 10 means the worst possible pain. Higher scores indicated worst possible pain. Analysis was performed on effectiveness analysis set. Here, 'n' = subjects with available data for each specified category.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

surgery day, 24 hours (first postoperative day), 48 hours (second postoperative day) and 72 hours (third postoperative day) after handing over the device to subjects

| End point values                     | Zalviso®            |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 301                 |  |  |  |
| Units: units on a scale              |                     |  |  |  |
| arithmetic mean (standard deviation) |                     |  |  |  |
| Surgery day (n=300)                  | 4.96 ( $\pm$ 13.77) |  |  |  |
| First postoperative day (n=289)      | 3.43 ( $\pm$ 8.92)  |  |  |  |
| Second postoperative day (n=274)     | 1.58 ( $\pm$ 5.04)  |  |  |  |
| Third postoperative day (n=203)      | 1.37 ( $\pm$ 7.31)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time-weighted Summed Pain Intensity Difference Over the First 24 Hours (SPID24)

|                 |   |
|-----------------|---|
| End point title | Time-weighted Summed Pain Intensity Difference Over the First 24 Hours (SPID24) |
|-----------------|---|

End point description:

NRS measured pain intensity experienced by the subject on a scale of 0 to 10, where 0 means no pain and 10 mean the worst possible pain. Subject's pain intensity was assessed by asking following question: "Please, rate your pain intensity by assessing the one number that best describes your pain right now"; on a scale of 0 to 10 where 0 means no pain, and 10 means the worst possible pain. Higher scores indicated worst possible pain. A time-weighted SPID24 was calculated as: Time-weighted SPID24 =  $[t(i) - t(i-1)] \times \text{PID}(i)$ ; Where:  $t(0)$  = time 0 (at the handling the device),  $t(i)$  is the scheduled or

unscheduled assessment time (in hours from time 0), and pain intensity differences (PIDs) (i) is the PID score at time i for i=0 to 24 hours. Greater SPID24 values represent greater reductions of pain intensity. Analysis was performed on effectiveness analysis set.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 0 to 24 hours        |           |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Zalviso®        |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 301             |  |  |  |
| Units: units on a scale              |                 |  |  |  |
| arithmetic mean (standard deviation) | 55.23 (± 39.75) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Quality of Sleep Measured by Numerical Rating Scale (NRS)

|                 |   |
|-----------------|---|
| End point title | Quality of Sleep Measured by Numerical Rating Scale (NRS) |
|-----------------|---|

End point description:

The quality of sleep was assessed using 0-10 point NRS. The subjects were asked the following question: "Please, rate your quality of sleep by assessing the one number that best describes the average pain related impairment of sleep in the previous night:" on a scale of 0 to 10 where 0 means no pain, and 10 means the worst possible pain. Higher scores indicated worst possible pain. Analysis was performed on effectiveness analysis set. Here, "n" = subjects with available data for each specified category.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 hours (first postoperative day), 48 hours (second postoperative day) and 72 hours (third postoperative day) after handing over the device to subjects

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Zalviso®        |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 301             |  |  |  |
| Units: units on a scale              |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| First postoperative day (n=288)      | 2.83 (± 2.64)   |  |  |  |
| Second postoperative day (n=275)     | 2.2 (± 2.52)    |  |  |  |
| Third postoperative day (n=203)      | 1.6 (± 2.09)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Patient Mobility Status Assessed After the Surgery

|  |  |
|--|--|
| End point title  | Patient Mobility Status Assessed After the Surgery |
| End point description:<br>The patient mobility status was rated using a 6-point categorical scale: where; Level 5= no mobility; Level 4= subject is mobile in bed or can be mobilised in bed, e.g. positioning; Level 3= subject is mobile up to a reclining position and/or edge of bed; Level 2: subject can be mobilised into a chair, can/is learning to walk a few steps; Level 1= subject can be mobilised on a chair, walks a few steps; Level 0= subject walks on his/her own. Analysis was performed on effectiveness analysis set. |  |
| End point type   | Secondary  |
| End point timeframe:<br>72 hours after handing over the device to subjects   |  |

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Zalviso®        |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 302             |  |  |  |
| Units: Subjects             |                 |  |  |  |
| No Mobility                 | 20              |  |  |  |
| Level 0                     | 108             |  |  |  |
| Level 1                     | 3               |  |  |  |
| Level 3                     | 13              |  |  |  |
| Level 4                     | 158             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Quality of Recovery (QoR-15) Questionnaire Total Score At the End of Treatment

|   |  |
|---|--|
| End point title   | Change from Baseline in Quality of Recovery (QoR-15) Questionnaire Total Score At the End of Treatment |
| End point description:<br>The QoR-15 questionnaire provided a valid, reliable, responsive and easy-to-use method of measuring the quality of a subject's postoperative recovery. QoR-15 is a 15 question assessment of subject recovery where individual items were assessed on a 0-10 scale where the higher scores, indicated better status. The total score (sum of all individual items) ranged from 0 to 150, where 0= less recovery and 150= more recovery. Analysis was performed on effectiveness analysis set. Here, "n" = subjects with available data for each specified category. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline, end of treatment (i.e. up to 72 hours after handing over the device to subjects)  |  |

|                                      |                  |  |  |  |
|--------------------------------------|------------------|--|--|--|
| <b>End point values</b>              | Zalviso®         |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 301              |  |  |  |
| Units: units on a scale              |                  |  |  |  |
| arithmetic mean (standard deviation) |                  |  |  |  |
| Baseline (n=300)                     | 120.88 (± 18.64) |  |  |  |
| Change at End of Treatment (n=294)   | 5.3 (± 22.55)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Resource Utilization: Number of Nights Spent in the Hospital By Subjects

|                 |  |
|-----------------|--|
| End point title | Resource Utilization: Number of Nights Spent in the Hospital By Subjects |
|-----------------|--|

End point description:

Cumulative number of nights spent in hospital up to the end of treatment were computed and summarised using mean and standard deviation (SD). Analysis was performed on effectiveness analysis set. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to end of the treatment (i.e. up to 72 hours after handing over the device to subjects)

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Zalviso®        |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 300             |  |  |  |
| Units: nights                        |                 |  |  |  |
| arithmetic mean (standard deviation) | 6.2 (± 7.7)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

An Adverse Event (AE) was any untoward medical occurrence in a subject administered a pharmaceutical product and which did not necessarily had to have causal relationship with treatment. TEAEs were defined as AEs that occurred between first dose of the IMP until the end of the study (i.e. up to 72 hours after handing over the device to subjects). SAE was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. Analysis was performed on safety analysis set that included all subjects who took at least one dose of the IMP.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| First dose of the IMP until the end of the study (i.e. up to 72 hours after handing over the device to subjects) |           |

|                                     |                 |  |  |  |
|-------------------------------------|-----------------|--|--|--|
| <b>End point values</b>             | Zalviso®        |  |  |  |
| Subject group type                  | Reporting group |  |  |  |
| Number of subjects analysed         | 302             |  |  |  |
| Units: subjects                     |                 |  |  |  |
| number (not applicable)             |                 |  |  |  |
| Any TEAE                            | 188             |  |  |  |
| Any serious TEAE                    | 7               |  |  |  |
| Any TEAE leading to discontinuation | 11              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Event (AE) data were collected from first dose of the IMP until the end of the study (i.e. up to 72 hours after handing over the device to subjects).

Adverse event reporting additional description:

Reported AE were treatment emergent AEs i.e. any AE (7 TEAE – 2 non-TEAE after treatment with Zalviso) that occurred between first dose of the IMP until the end of the study (i.e. up to 72 hours after handing over the device to subjects). Analysis was performed on safety analysis set.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Zalviso® |
|-----------------------|----------|

Reporting group description:

Subjects received Sufentanil 15 micrograms sublingual tablets administered through an administration device Zalviso® designed to deliver single tablets on a subject-controlled basis with a minimum of 20 minutes between doses over a period of 72 hours.

| Serious adverse events                            | Zalviso®        |  |  |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events |                 |  |  |
| subjects affected / exposed                       | 9 / 302 (2.98%) |  |  |
| number of deaths (all causes)                     | 1               |  |  |
| number of deaths resulting from adverse events    | 0               |  |  |
| Injury, poisoning and procedural complications    |                 |  |  |
| Procedural Pain                                   |                 |  |  |
| subjects affected / exposed                       | 1 / 302 (0.33%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| Vascular disorders                                |                 |  |  |
| Hypotension                                       |                 |  |  |
| subjects affected / exposed                       | 1 / 302 (0.33%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| Nervous system disorders                          |                 |  |  |
| Dysaesthesia                                      |                 |  |  |
| subjects affected / exposed                       | 1 / 302 (0.33%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal wall haemorrhage                      |                 |  |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Hypoxia   |                 |  |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Anuria  |                 |  |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Septic shock                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 302 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

|   |                    |  |  |
|---|--------------------|--|--|
| <b>Non-serious adverse events</b>                     | Zalviso®           |  |  |
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 186 / 302 (61.59%) |  |  |

|   |  |  |  |
|---|--|--|--|
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypertensive crisis<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypotension<br>subjects affected / exposed<br>occurrences (all)<br><br>Orthostatic hypotension<br>subjects affected / exposed<br>occurrences (all)   | 2 / 302 (0.66%)<br>2<br><br>1 / 302 (0.33%)<br>1<br><br>21 / 302 (6.95%)<br>21<br><br>2 / 302 (0.66%)<br>2 |  |  |
| General disorders and administration site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)<br><br>Temperature regulation disorder<br>subjects affected / exposed<br>occurrences (all)  | 1 / 302 (0.33%)<br>1<br><br>15 / 302 (4.97%)<br>15<br><br>1 / 302 (0.33%)<br>1                             |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Atelectasis<br>subjects affected / exposed<br>occurrences (all)<br><br>Bronchospasm<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Hiccups<br>subjects affected / exposed<br>occurrences (all) | 1 / 302 (0.33%)<br>1<br><br>1 / 302 (0.33%)<br>1<br><br>2 / 302 (0.66%)<br>2<br><br>3 / 302 (0.99%)<br>3   |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Pleural effusion<br>subjects affected / exposed<br>occurrences (all) | 1 / 302 (0.33%)<br>1 |  |  |
| Psychiatric disorders  |                      |  |  |
| Agitation  |                      |  |  |
| subjects affected / exposed  | 1 / 302 (0.33%)      |  |  |
| occurrences (all)  | 1                    |  |  |
| Anxiety  |                      |  |  |
| subjects affected / exposed  | 15 / 302 (4.97%)     |  |  |
| occurrences (all)  | 15                   |  |  |
| Confusional state  |                      |  |  |
| subjects affected / exposed  | 2 / 302 (0.66%)      |  |  |
| occurrences (all)  | 2                    |  |  |
| Delirium   |                      |  |  |
| subjects affected / exposed  | 1 / 302 (0.33%)      |  |  |
| occurrences (all)  | 1                    |  |  |
| Depression   |                      |  |  |
| subjects affected / exposed  | 1 / 302 (0.33%)      |  |  |
| occurrences (all)  | 1                    |  |  |
| Disorientation   |                      |  |  |
| subjects affected / exposed  | 2 / 302 (0.66%)      |  |  |
| occurrences (all)  | 2                    |  |  |
| Insomnia   |                      |  |  |
| subjects affected / exposed  | 13 / 302 (4.30%)     |  |  |
| occurrences (all)  | 13                   |  |  |
| Nervousness  |                      |  |  |
| subjects affected / exposed  | 2 / 302 (0.66%)      |  |  |
| occurrences (all)  | 2                    |  |  |
| Nightmare  |                      |  |  |
| subjects affected / exposed  | 1 / 302 (0.33%)      |  |  |
| occurrences (all)  | 1                    |  |  |
| Obsessive thoughts   |                      |  |  |
| subjects affected / exposed  | 1 / 302 (0.33%)      |  |  |
| occurrences (all)  | 1                    |  |  |
| Injury, poisoning and procedural complications                       |                      |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| Post procedural haematoma<br>subjects affected / exposed<br>occurrences (all) | 2 / 302 (0.66%)<br>2   |  |  |
| Skin injury<br>subjects affected / exposed<br>occurrences (all)               | 1 / 302 (0.33%)<br>1   |  |  |
| Cardiac disorders   |                        |  |  |
| Bradycardia<br>subjects affected / exposed<br>occurrences (all)               | 2 / 302 (0.66%)<br>2   |  |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)               | 1 / 302 (0.33%)<br>1   |  |  |
| Nervous system disorders  |                        |  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                 | 20 / 302 (6.62%)<br>21 |  |  |
| Dizziness postural<br>subjects affected / exposed<br>occurrences (all)        | 1 / 302 (0.33%)<br>1   |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                  | 11 / 302 (3.64%)<br>11 |  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)              | 3 / 302 (0.99%)<br>3   |  |  |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)                | 12 / 302 (3.97%)<br>12 |  |  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 302 (0.33%)<br>2   |  |  |
| Blood and lymphatic system disorders  |                        |  |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                   | 12 / 302 (3.97%)<br>12 |  |  |
| Coagulopathy  |                        |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 1 / 302 (0.33%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Gastrointestinal disorders  |                   |  |  |
| Abdominal distension        |                   |  |  |
| subjects affected / exposed | 2 / 302 (0.66%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Abdominal pain upper        |                   |  |  |
| subjects affected / exposed | 2 / 302 (0.66%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Aerophagia                  |                   |  |  |
| subjects affected / exposed | 2 / 302 (0.66%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Constipation                |                   |  |  |
| subjects affected / exposed | 17 / 302 (5.63%)  |  |  |
| occurrences (all)           | 17                |  |  |
| Dry mouth                   |                   |  |  |
| subjects affected / exposed | 3 / 302 (0.99%)   |  |  |
| occurrences (all)           | 3                 |  |  |
| Flatulence                  |                   |  |  |
| subjects affected / exposed | 2 / 302 (0.66%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Ileus                       |                   |  |  |
| subjects affected / exposed | 1 / 302 (0.33%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Ileus paralytic             |                   |  |  |
| subjects affected / exposed | 1 / 302 (0.33%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Nausea                      |                   |  |  |
| subjects affected / exposed | 79 / 302 (26.16%) |  |  |
| occurrences (all)           | 85                |  |  |
| Rectal haemorrhage          |                   |  |  |
| subjects affected / exposed | 1 / 302 (0.33%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Vomiting                    |                   |  |  |
| subjects affected / exposed | 41 / 302 (13.58%) |  |  |
| occurrences (all)           | 45                |  |  |

|   |   |  |  |
|---|---|--|--|
| <p>Skin and subcutaneous tissue disorders</p> <p>Blister</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hyperhidros</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 302 (0.33%)</p> <p>1</p> <p>4 / 302 (1.32%)</p> <p>4</p> <p>8 / 302 (2.65%)</p> <p>8</p> <p>1 / 302 (0.33%)</p> <p>1</p>   |  |  |
| <p>Renal and urinary disorders</p> <p>Anuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bladder dilatation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oliguria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 302 (0.33%)</p> <p>1</p> <p>1 / 302 (0.33%)</p> <p>1</p> <p>5 / 302 (1.66%)</p> <p>5</p> <p>10 / 302 (3.31%)</p> <p>10</p> |  |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Muscle spasms</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Musculoskeletal stiffness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neck pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 302 (0.33%)</p> <p>1</p> <p>1 / 302 (0.33%)</p> <p>1</p> <p>1 / 302 (0.33%)</p> <p>1</p>                                   |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Infections and infestations<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)            | 1 / 302 (0.33%)<br>1 |  |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 1 / 302 (0.33%)<br>1 |  |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)   | 4 / 302 (1.32%)<br>4 |  |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 302 (0.66%)<br>2 |  |  |
| Hypovolaemia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 302 (0.33%)<br>1 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 03 August 2016  | Following changes were made: • Initial sample size estimations considered two alternative scenarios, one with 200 subjects and another with 300 subjects, with appropriate calculations of statistical power. Due to budget constraints and the number of investigators willing to participate, the smaller size of 200 was considered in the final version of the protocol. However, once the protocol was approved by the Ethics Committees and before starting recruitment, it was noted that the availability of subjects and potential investigators would be greater than expected. Therefore, it was decided to switch to the larger scenario of 300 subjects. To achieve the new sample size without increasing the enrolment period, new sites were included. • Replaced the Medical Device Report Form to make the healthcare professionals' work easier. |
| 24 October 2016 | Following changes were made: •Extended the enrolment period given that the enrolment rate is lower than expected. The protocol was also updated with the inclusion of the Quality of Recovery-15 (QoR-15) questionnaire at the baseline data collection before starting treatment with Zalviso®.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported