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 Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 57.38 ± 14.35	 -	
Gender categorical Units: Subjects			
Female	146	146	
Male	156	156	

End points

End points 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.

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[1]

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

End point values	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)

End point values	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)

End point values	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 (± 2.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Severe Pain (Pain intensity >=7) Measured by NRS

End point title	Severe Pain (Pain intensity >=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 (± 13.77)			
First postoperative day (n=289)	3.43 (± 8.92)			
Second postoperative day (n=274)	1.58 (± 5.04)			
Third postoperative day (n=203)	1.37 (± 7.31)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Time-weighed 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)]*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

End point values	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

End point values	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:

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:

72 hours after handing over the device to subjects

End point values	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:

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:

Baseline, end of treatment (i.e. up to 72 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)				
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)

End point values	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)

End point values	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 %

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

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

Pleural effusion			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	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 subjects affected / exposed occurrences (all)	2 / 302 (0.66%) 2		
Skin injury subjects affected / exposed occurrences (all)	1 / 302 (0.33%) 1		
Cardiac disorders			
Bradycardia subjects affected / exposed occurrences (all)	2 / 302 (0.66%) 2		
Tachycardia subjects affected / exposed occurrences (all)	1 / 302 (0.33%) 1		
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	20 / 302 (6.62%) 21		
Dizziness postural subjects affected / exposed occurrences (all)	1 / 302 (0.33%) 1		
Headache subjects affected / exposed occurrences (all)	11 / 302 (3.64%) 11		
Paraesthesia subjects affected / exposed occurrences (all)	3 / 302 (0.99%) 3		
Somnolence subjects affected / exposed occurrences (all)	12 / 302 (3.97%) 12		
Syncope subjects affected / exposed occurrences (all)	1 / 302 (0.33%) 2		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	12 / 302 (3.97%) 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		

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported