Clinical trial results:
Exploratory, randomized, double-blind, placebo-controlled evaluation of efficacy, tolerability, and safety of intravesical instillation of GRT6010 compared to placebo in subjects with bladder pain syndrome

Summary

EudraCT number	2016-003940-35
Trial protocol	DE PL
Global end of trial date	02 May 2018

Results information

Result version number	v1 (current)
This version publication date	14 February 2019
First version publication date	14 February 2019

Trial information

Trial identification

Sponsor protocol code	KF6010-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1188-0214

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52078
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	11 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 May 2018
Global end of trial reached?	Yes
Global end of trial date	02 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluate the efficacy of intravesical instillation of GRT6010 on pain.

Protection of trial subjects:

The trial was conducted according to ICH-GCP guidelines, the applicable local law and regulations, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Regulatory authorities were notified of the trial as required by national regulations, necessary relevant authorization was obtained. Furthermore, the competent authorities were notified of this trial in accordance with national requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 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	Poland: 71
Country: Number of subjects enrolled	Germany: 6
Worldwide total number of subjects	77
EEA total number of subjects	77

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)	67
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject signed informed consent on the 26 July 2017 and the last subject completed the trial on the 02 May 2018.

Pre-assignment

Screening details:

A total of 77 subjects signed an informed consent. 57 of these subjects were allocated to treatment (25 Placebo, 32 GRT6010). 2 placebo subjects and 1 GRT6010 subject never received IMP.

Pre-assignment period milestones

Number of subjects started	77
Number of subjects completed	54

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 5
Reason: Number of subjects	Inclusion criteria not met/exclusion criteria met: 14
Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	No IMP administration: 3

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

This trial used double blind methods to guarantee the blinding of all personnel involved in the trial. Subjects and investigators were blinded to the subjects' treatments.

Arms

Are arms mutually exclusive?	Yes
Arm title	GRT6010

Arm description:

Subjects received 4 instillations (1 instillation at each Treatment Visit) of GRT6010 solution.

Arm type	Experimental
Investigational medicinal product name	GRT6010 solution for instillation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for intravesical solution
Routes of administration	Intravesical use

Dosage and administration details:

10 ml of a GRT6010 solution (30 µg/mL) were instilled in the bladder at each of the 4 Treatment Visits via single use bladder catheters.

Arm title	Placebo

Arm description:

Subjects received 4 instillations (1 instillation at each Treatment Visit) of matching placebo solution.

Arm type	Placebo

Investigational medicinal product name	Matching placebo solution for instillation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for intravesical solution
Routes of administration	Intravesical use

Dosage and administration details:

10 ml of a placebo solution were instilled in the bladder at each of the 4 Treatment Visits via single use bladder catheters.

Number of subjects in period 1[1]	GRT6010	Placebo
Started	31	23
Completed	31	23

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 77 subjects signed an informed consent. 54 subjects received at least one dose of investigational medicinal product.

Baseline characteristics

Reporting groups	
Reporting group title	GRT6010
Reporting group description:	
Subjects received 4 instillations (1 instillation at each Treatment Visit) of GRT6010 solution.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 4 instillations (1 instillation at each Treatment Visit) of matching placebo solution.	

Reporting group values	GRT6010	Placebo	Total
Number of subjects	31	23	54
Age categorical			
Units: Subjects			
Adults (18-64 years)	26	21	47
From 65-84 years	5	2	7
Age continuous			
Units: years			
arithmetic mean	50.2	42.9	
standard deviation	± 15	± 16.3	-
Gender categorical			
Units: Subjects			
Female	31	23	54
Male	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	31	23	54
Other	0	0	0
Not reported	0	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	31	23	54
Unknown	0	0	0
Not reported	0	0	0
Height			
Units: meter			
arithmetic mean	1.632	1.643	
standard deviation	± 0.064	± 0.064	-
Weight			
Units: kilogram(s)			
arithmetic mean	68.16	64.10	
standard deviation	± 13.64	± 9.60	-
Body Mass Index			

Units: kilogram(s)/square meter			
arithmetic mean	25.64	23.82	
standard deviation	± 5.25	± 3.92	-
Baseline pain intensity			
The baseline daily pain score was calculated as the pain intensity averaged over the last 3 days prior to first IMP. Subjects were documenting pain intensity scores using an e-diary. Pain scores were obtained twice daily (morning and evening). Subjects were asked: “Please indicate how much bladder pain you had on average since the last assessment”. The visual analog scale (VAS) 0-100 were labeled with 0 = "no pain” and 100 = "pain as bad as you can imagine”. At least 4 out of 6 ratings and at least 1 rating per day were required for an evaluable baseline assessment.			
Units: units on a scale			
arithmetic mean	76.8	79.6	
standard deviation	± 10.6	± 10.9	-
Baseline micturition frequency			
Average number of daily micturition at baseline was calculated as the number of micturitions averaged over the last 3 days prior to Treatment Visit 1.			
Units: frequency			
arithmetic mean	12.3	12.5	
standard deviation	± 4.1	± 4.6	-
Baseline urine volume per voiding			
Average daily urine volume per voiding at baseline was calculated as the volume per voiding over the last 3 days prior to Treatment Visit 1.			
Units: milliliter(s)			
arithmetic mean	140.0	147.4	
standard deviation	± 72.7	± 84.4	-
Baseline intensity of urgency			
Intensity of urgency was assessed on a 0–100 VAS twice daily (morning and evening). Average daily intensity of urgency at baseline was calculated as the intensity of urgency averaged over the last 3 days prior to Treatment Visit 1. Subjects were asked: “Please indicate the intensity of your micturition urgency on average since the last assessment”. The VAS was labeled with 0 = "no urgency” and 100 = "urgency as bad as you can imagine”.			
Units: units on a scale			
arithmetic mean	74.3	79.0	
standard deviation	± 14.5	± 11.5	-
Baseline O’Leary/Sant questionnaire scores - Symptom Index			
The O’Leary/Sant questionnaire consists of 2 brief, self-administered indices for measuring lower urinary tract symptoms and their impact in patients with bladder pain syndrome (BPS). It assesses severity of symptoms and how much of a problem the symptoms cause for the patient. Symptom and problem index scores are scored from 0 to 20 (0 = no symptoms/problems, 20 = worst symptoms/problems). The symptom index is able to discriminate characteristics between patients and controls (O’Leary et al. 1997). A 1 month recall period was used.			
Units: units on a scale			
arithmetic mean	15.4	14.5	
standard deviation	± 2.8	± 2.4	-
Baseline O’Leary/Sant questionnaire scores - Problem Index			
The O’Leary/Sant questionnaire consists of 2 brief, self-administered indices for measuring lower urinary tract symptoms and their impact in patients with BPS. It assesses severity of symptoms and how much of a problem the symptoms cause for the patient. Symptom and problem index scores are scored from 0 to 20 (0 = no symptoms/problems, 20 = worst symptoms/problems). The symptom index is able to discriminate characteristics between patients and controls (O’Leary et al. 1997). A 1 month recall period was used.			
Units: units on a scale			
arithmetic mean	14.2	13.8	
standard deviation	± 2.0	± 2.2	-
Baseline Bladder Pain/Interstitial Cystitis Symptom Score			
The Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) is an 8-item measure (score from 0 to			

38; 0 = no burden and 38 = max. burden), developed to identify an appropriate bladder pain syndrome (BPS) population for clinical trials to evaluate new treatments for BPS. Subjects were asked to consider the past seven days. Baseline is defined as the last observation (scheduled or unscheduled) prior to IMP.			
Units: units on a scale			
arithmetic mean	30.2	29.3	
standard deviation	± 3.1	± 3.7	-
Baseline SF-12 Physical component summary			
The SF-12 acute version is a subset of the SF-36®, whose scoring algorithms involve weighted item responses. The SF-12 acute version has 12 questions covering 8 health domains commonly represented in health surveys: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role functioning emotional, and mental health. Results are expressed in terms of 2 meta-scores: the Physical Component Summary and the Mental Component Summary. The summaries are scored from 0 to 100 . Baseline is defined as the last observation prior to IMP.			
Units: units on a scale			
arithmetic mean	35.326	39.023	
standard deviation	± 8.391	± 7.108	-
Baseline SF-12 Mental component summary			
The SF-12 acute version is a subset of the SF-36®, whose scoring algorithms involve weighted item responses. The SF-12 acute version has 12 questions covering 8 health domains commonly represented in health surveys: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role functioning emotional, and mental health. Results are expressed in terms of 2 meta-scores: the Physical Component Summary and the Mental Component Summary. The summaries are scored from 0 to 100 . Baseline is defined as the last observation prior to IMP.			
Units: units on a scale			
arithmetic mean	37.621	41.188	
standard deviation	± 9.737	± 10.836	-

End points

End points reporting groups

Reporting group title	GRT6010
Reporting group description:	
Subjects received 4 instillations (1 instillation at each Treatment Visit) of GRT6010 solution.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 4 instillations (1 instillation at each Treatment Visit) of matching placebo solution.	

Primary: Change in average daily pain scores

End point title	Change in average daily pain scores

End point description:

The pain scores were assessed on a 0-100 Visual analog scale (VAS) twice daily (morning and evening) using an e-diary. Subjects were asked: "Please indicate how much bladder pain you had on average since the last assessment". The VAS was labeled with 0 = "no pain" and 100 = "pain as bad as you can imagine".
For this end point, the value reported as arithmetic mean is the posterior mean from the Bayesian analysis with corresponding standard deviations. A probabilistic approach based on Bayesian methodology was used to estimate the probability of a treatment effect.
Thus 95% credibility interval (Credibility intervals are used in Bayesian analyses and are analogous to confidence intervals but there are important differences) are reported.
The statistical analysis was performed using a Bayesian variant of the MMRM using pain scores as dependent variable. The model accounted for the effects of treatment, time, their interaction, and baseline (as covariate).

End point type	Primary
End point timeframe:	
Baseline to end-of-treatment.	

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[1]	23[2]		
Units: units on a scale				
arithmetic mean (standard deviation)	-21.7 (± 7.35)	-14.3 (± 6.26)		

Notes:

[1] - Full Analysis Set

[2] - Full Analysis Set

Statistical analyses

Statistical analysis title	Change in average daily pain intensity

Statistical analysis description:

The primary analysis was performed under Bayesian paradigm. Point (mean) and interval estimates (2-sided 95% credibility interval) for the treatment difference to placebo based on the posterior distribution are reported. Baseline was defined as the last 3 days prior to Treatment Visit 1. End of treatment was defined as assessments during the 2 days after the fourth instillation at Treatment Visit 4 (starting with the morning assessment of the next day).

Comparison groups	GRT6010 v Placebo

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.944 [4]
Method	Bayesian analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.1
upper limit	1.17
Variability estimate	Standard deviation
Dispersion value	4.46

Notes:

[3] - The informative prior for the placebo effect followed a normal distribution with a mean of −13 and a variance of 49. All other parameters followed a vague normal distribution, respectively vague truncated normal distributions for the variance. The chosen covariance structure was compound symmetry.
[4] - This is not a frequentist analysis and the p-value entry is the Bayesian posterior probability. In this case it shows the probability of an effect larger than 0. The effect is the difference of the treatment effect compared to placebo.

Statistical analysis title	Sensitivity analysis 1

Statistical analysis description:

Sensitivity analysis 1 - Adjusting primary analysis using a non-informative prior for the placebo effect.

Comparison groups	GRT6010 v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.932 [6]
Method	Bayesian analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.95
upper limit	1.34
Variability estimate	Standard deviation
Dispersion value	4.54

Notes:

[5] - All parameters followed a vague normal distribution, respectively vague truncated normal distributions for the variance, including the placebo effect.
[6] - This is not a frequentist analysis and the p-value entry is the Bayesian posterior probability. In this case it shows the probability of an effect larger than 0. The effect is the difference of the treatment effect compared to placebo.

Statistical analysis title	Sensitivity analysis 2

Statistical analysis description:

Sensitivity analysis 2 - Adjusting primary analysis using an unstructured covariance matrix.

Comparison groups	GRT6010 v Placebo

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.892 [8]
Method	Bayesian analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.05
upper limit	3.94
Variability estimate	Standard deviation
Dispersion value	5.71

Notes:

[7] - The informative prior for the placebo effect followed a normal distribution with a mean of -13 and a variance of 49. An inverse Wishart distribution was used as prior for the covariance matrix with variance of 1. All other parameters followed a vague normal distribution.

[8] - This is not a frequentist analysis and the p-value entry is the Bayesian posterior probability. In this case it shows the probability of an effect larger than 0. The effect is the difference of the treatment effect compared to placebo.

Statistical analysis title	Sensitivity analysis 3

Statistical analysis description:

Sensitivity analysis 3 - Adjusting primary analysis using a non-informative prior for the placebo effect as well as an unstructured covariance matrix.

Comparison groups	GRT6010 v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.882 [10]
Method	Bayesian analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.97
upper limit	4.07
Variability estimate	Standard deviation
Dispersion value	5.64

Notes:

[9] - An inverse Wishart distribution was used as prior for the covariance matrix with variance of 1. All other parameters followed a vague normal distribution.

[10] - This is not a frequentist analysis and the p-value entry is the Bayesian posterior probability. In this case it shows the probability of an effect larger than 0. The effect is the difference of the treatment effect compared to placebo.

Secondary: Plasma concentrations of GRT6010

End point title	Plasma concentrations of GRT6010[11]

End point description:

Plasma samples were analyzed to determine concentrations of GRT6010, using validated bioanalytical assays. Pre-dose concentrations of GRT6010 above the lower limit of quantification were reported for all visits in almost all subjects are reported for all visits following the first instillation.

End point type	Secondary

End point timeframe:

Blood samples for pharmacokinetic assessment were taken less than 30 min before IMP administration and 2 hours (± 15 min) after IMP administration (4 treatment visits).

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Plasma concentrations of GRT6010 were analyzed and reported.

End point values	GRT6010			
Subject group type	Reporting group			
Number of subjects analysed	31[12]			
Units: pg/mL				
arithmetic mean (standard deviation)				
Treatment Visit 1, 2h post-dose (N = 21)	308 (± 488)			
Treatment Visit 2, pre-dose (N = 29)	232 (± 266)			
Treatment Visit 2, 2h post-dose (N = 20)	600 (± 647)			
Treatment Visit 3, pre-dose (N = 30)	398 (± 386)			
Treatment Visit 3, 2h post-dose (N = 24)	677 (± 693)			
Treatment Visit 4, pre-dose (N = 30)	526 (± 540)			
Treatment Visit 4, 2h post-dose (N = 24)	881 (± 867)			
Follow-up Visit (N = 30)	708 (± 794)			
End-of-trial Visit (N = 25)	222 (± 273)			

Notes:

[12] - Pharmacokinetic Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change in average pain intensity over the last 12 hours

End point title	Change in average pain intensity over the last 12 hours

End point description:

The pain scores were assessed on a 0-100 Visual analog scale (VAS) twice daily (morning and evening) using an e-diary. Subjects were asked: "Please indicate how much bladder pain you had on average since the last assessment". The VAS was labeled with 0 = "no pain" and 100 = "pain as bad as you can imagine".
Analysis including only the last assessment on the 2 days after Treatment Visit 4 using an ANCOVA-like model with a Bayesian approach. For this end point, the value reported as arithmetic mean is the posterior mean from the Bayesian analysis with corresponding standard deviations. The informative prior for the placebo effect followed a normal distribution with a mean of -13 and a variance of 49. All other parameters followed a vague normal distribution, respectively vague truncated normal distribution for the variance.

End point type	Secondary

End point timeframe:

Baseline to end-of-treatment.

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[13]	23[14]		
Units: units on a scale				
arithmetic mean (standard deviation)	-19.0 (± 8.69)	-14.8 (± 6.85)		

Notes:

[13] - Full Analysis Set

[14] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change in average number of daily micturition

End point title	Change in average number of daily micturition

End point description:

Average number of daily micturition at Baseline is calculated as the number of micturitions averaged over the last 3 days prior to Treatment Visit 1. Average number of daily micturition after Treatment Visit 4 (end-of-treatment) is the average number during the 2 days following instillation/Treatment Visit (starting with the morning assessment of the next day).

End point type	Secondary

End point timeframe:

Baseline to end-of-treatment.

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[15]	23[16]		
Units: number of micturition				
arithmetic mean (standard deviation)	-2.2 (± 4.2)	-1.9 (± 3.2)		

Notes:

[15] - Full Analyses Set (N = 27)

[16] - Full Analyses Set (N = 20)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in average daily urine volume per voiding

End point title	Change in average daily urine volume per voiding

End point description:

Average daily urine volume per voiding at baseline was calculated as the volume per voiding over the last 3 days prior to Treatment Visit 1. Average daily urine volume per voiding after the End-of-Treatment Visit was the average during the 2 days following instillation/Treatment Visit (starting with the morning assessment of the next day).

End point type	Secondary

End point timeframe:

Baseline to end-of-treatment.

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[17]	23[18]		
Units: milliliter(s)				
arithmetic mean (standard deviation)	26.0 (± 33.0)	-7.9 (± 41.1)		

Notes:

[17] - Full Analyses Set (N = 24)

[18] - Full Analyses Set (N = 15)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in average daily intensity of urgency

End point title	Change in average daily intensity of urgency

End point description:

Intensity of urgency was assessed on a 0–100 VAS twice daily (morning and evening). Average daily intensity of urgency at baseline was calculated as the intensity of urgency averaged over the last 3 days prior to Treatment Visit 1. Average daily intensity of urgency after the End-of-Treatment Visit was the average during the 2 days following the instillation/Treatment Visit (starting with the morning assessment of the next day). The VAS was labeled with 0 = "no urgency" and 100 = "urgency as bad as you can imagine".

End point type	Secondary

End point timeframe:

Baseline to end-of-treatment.

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[19]	23[20]		
Units: units on a scale				
arithmetic mean (standard deviation)	-19.3 (± 19.6)	-16.5 (± 17.2)		

Notes:

[19] - Full Analysis Set (N = 29)

[20] - Full Analysis Set (N = 21)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in O'Leary/Sant questionnaire (Symptom Index)

End point title	Change in O'Leary/Sant questionnaire (Symptom Index)

End point description:

The O'Leary/Sant questionnaire consists of 2 brief, self-administered indices for measuring lower urinary tract symptoms and their impact in patients with bladder pains syndrome (BPS). It assesses the severity of symptoms and how much they bother the patient. Symptom and problem index scores are scored from 0 to 20 (0 = no symptoms/problems, 20 = worst symptoms/problems). The symptom index is able to discriminate characteristics between patients and controls (O'Leary et al. 1997).

A recall period of 3 days was used.

End point type	Secondary

End point timeframe:

Baseline to follow-up visit.

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[21]	23[22]		
Units: units on a scale				
arithmetic mean (standard deviation)	-5.5 (± 4.0)	-3.7 (± 3.8)		

Notes:

[21] - Full Analyses Set (N = 24)

[22] - Full Analyses Set (N = 20)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in O'Leary/Sant questionnaire (Problem Index)

End point title	Change in O'Leary/Sant questionnaire (Problem Index)

End point description:

The O'Leary/Sant questionnaire consists of 2 brief, self-administered indices for measuring lower urinary tract symptoms and their impact in patients with bladder pains syndrome (BPS). It assesses the severity of symptoms and how much they bother the patient. Symptom and problem index scores are scored from 0 to 20 (0 = no symptoms/problems, 20 = worst symptoms/problems). The symptom index is able to discriminate characteristics between patients and controls (O'Leary et al. 1997).
A recall period of 3 days was used.

End point type	Secondary

End point timeframe:

Baseline to follow-up visit.

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[23]	23[24]		
Units: units on a scale				
arithmetic mean (standard deviation)	-4.8 (± 3.6)	-3.3 (± 3.4)		

Notes:

[23] - Full Analyses Set (N = 24)

[24] - Full Analyses Set (N = 20)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS)

End point title	Change in Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS)

End point description:

The Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) is an 8-item measure (score from 0 to 38; 0 = no burden and 38 = max. burden), developed to identify an appropriate bladder pain syndrome (BPS) population for clinical trials to evaluate new treatments for BPS. Subjects were asked to consider the past seven days.

End point type	Secondary

End point timeframe:

Baseline to follow-up visit.

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[25]	23[26]		
Units: units on a scale				
arithmetic mean (standard deviation)	-8.7 (± 5.9)	-7.4 (± 5.9)		

Notes:

[25] - Full Analyses Set (N = 30)

[26] - Full Analyses Set (N = 22)

Statistical analyses

No statistical analyses for this end point

Secondary: 12-Item Short Form Health Survey (Physical component summary)

End point title	12-Item Short Form Health Survey (Physical component summary)

End point description:

The SF-12 acute version is a subset of the SF-36®, whose scoring algorithms involve weighted item responses. The SF-12 acute version has 12 questions covering 8 health domains commonly represented in health surveys: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role functioning emotional, and mental health. Results are expressed in terms of 2 meta-scores: the Physical Component Summary and the Mental Component Summary. Physical and mental component summaries are scored from 0 to 100.

End point type	Secondary

End point timeframe:

Baseline to follow-up visit.

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[27]	23[28]		
Units: units on a scale				
arithmetic mean (standard deviation)	5.512 (± 8.020)	4.723 (± 4.624)		

Notes:

[27] - Full Analysis Set (N = 30)

[28] - Full Analysis Set (N = 22)

Statistical analyses

No statistical analyses for this end point

Secondary: 12-Item Short Form Health Survey (Mental component summary)

End point title	12-Item Short Form Health Survey (Mental component summary)

End point description:

The SF-12 acute version is a subset of the SF-36®, whose scoring algorithms involve weighted item responses. The SF-12 acute version has 12 questions covering 8 health domains commonly represented in health surveys: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role functioning emotional, and mental health. Results are expressed in terms of 2 meta-scores: the Physical Component Summary and the Mental Component Summary. Physical and mental component summaries are scored from 0 to 100.

End point type	Secondary

End point timeframe:

Baseline to follow-up visit.

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[29]	23[30]		
Units: units on a scale				
arithmetic mean (standard deviation)	4.930 (± 9.179)	2.947 (± 8.931)		

Notes:

[29] - Full Analysis Set (N = 30)

[30] - Full Analysis Set (N = 22)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient's Global Impression of Change (PGIC)

End point title	Patient's Global Impression of Change (PGIC)

End point description:

The 7-point Patient's Global Impression of Change (PGIC) is a complementary assessment of analgesic efficacy. Subjects respond to the question “Since the start of the trial, my overall status is:” with 1 of 7 possible responses (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse). A response of very much improved or much improved is generally regarded as a clinically important outcome. PGIC was assessed at the End-of-trial visit or, in case of premature discontinuation, the End-of-trial for discontinued subjects.

End point type	Secondary

End point timeframe:

End of the trial.

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[31]	23[32]		
Units: Subjects				
Very much improved	1	1		
Much improved	8	6		
Minimally improved	8	4		
No change	11	12		
Minimally worse	3	0		
Much worse	0	0		
Very much worse	0	0		
Missing	0	0		

Notes:

[31] - Full Analysis Set

[32] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Clinician's Global Impression of Change (CGIC)

End point title	Clinician's Global Impression of Change (CGIC)

End point description:

The investigators were rating the subject’s global improvement and satisfaction with the treatment on a 7-point scale that ranges from “very much improved” to “very much worse” with “no change” as the mid-point. The CGIC (Schneider et al. 1997) was chosen as a complementary assessment of analgesic efficacy.
CGIC was assessed at the End-of-trial visit or, in case of premature discontinuation, the End-of-trial for discontinued subjects.

End point type	Secondary

End point timeframe:

End of the trial.

End point values	GRT6010	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[33]	23[34]		
Units: Subjects				
Very much improved	0	1		
Much improved	15	6		
Minimally improved	10	6		
No change	5	9		
Minimally worse	1	1		
Much worse	0	0		
Very much worse	0	0		
Missing	0	0		

Notes:

[33] - Full Analysis Set

[34] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were documented from the time of enrollment (i.e., the time the informed consent form is signed) up to the time of the last protocol scheduled contact, i.e., date of last visit/contact.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	GRT6010
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	GRT6010	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	GRT6010	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 31 (41.94%)	9 / 23 (39.13%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

Medical device pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	0 / 31 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Vulvovaginal pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Laryngeal pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Throat irritation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	4	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Heart rate increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Burn oral cavity			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	4	
Post-traumatic pain			

subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	3 / 31 (9.68%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Migraine			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	2 / 31 (6.45%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	2 / 31 (6.45%)	0 / 23 (0.00%)	
occurrences (all)	6	0	
Dry mouth			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Mouth ulceration			

subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	3 / 31 (9.68%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Dysuria			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	5 / 31 (16.13%)	5 / 23 (21.74%)	
occurrences (all)	5	5	
Vaginal infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Vulvitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2017	Amendment 01 of 29 Mar 2017 The protocol was amended based on feedback from the German Federal Institute for Drugs and Medical Devices and the ethics committee in Munich, Germany. Major changes are listed here. • Exclusion criteria and discontinuation criteria based on corrected QT interval (QTc) prolongation and liver parameters were defined. • Twelve-lead ECG recordings were added at Treatment Visit 1, Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4. • The time window for the diagnostic cystoscopy with hydrodistension was extended. • Reference to the anesthesia required for the diagnostic cystoscopy with hydrodistension was made. • Details pertaining to preparation of IMP prior to instillation were added. • Rationale for the dose selection was added. • The sponsor's medically qualified person and signatory were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Ninety subjects were planned to be treated in the trial. Owing to slow recruitment, fewer subjects than planned were treated. At the time at which the trial was terminated, 54 subjects had been treated.

Notes: