SDR-CTR-SYN-06

Report date	17 Dec 2018	DMS version	1.0
Type of report	Full		
Trial code	KF6010-02		
Title of trial	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		
Trial design	Exploratory, randomized, double-blind, placebo-controlled trial of intravesical instillation of 300 µg GRT6010 twice weekly for 2 weeks in female subjects with bladder pain syndrome		
Development phase	Phase IIa		
EudraCT number	2016-003940-35	Universal trial number	U1111-1188-0214
Investigational medicinal product	GRT6010		
Indication	Bladder pain syndrome		
International coordinating investigator	[redacted] Department of General, Oncological and Functional Urology, Medical University of Warsaw, Warsaw, Poland		
Trial sites	Germany (2 sites), Poland (8 sites)		
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany		
Sponsor's signatory	Dr [redacted], Head of Clinical Science Contact number: [redacted]		
Trial period	First subject in:	26 Jul 2017	
	Last subject out:	02 May 2018	

Objectives

Primary

- Evaluate the efficacy of intravesical instillation of GRT6010 on pain.

Secondary

- Safety and tolerability of intravesical instillation of GRT6010.
- Systemic exposure to GRT6010 after intravesical instillation.
- Evaluate the efficacy of intravesical instillation of GRT6010 on pain and/or functional symptoms.

Investigational medicinal products (IMPs)

Investigational medicinal product was prepared for administration from GRT6010 stock solution or matching placebo solution using a solution for dilution.

GRT6010 stock solution had a batch number of P73302A and an expiration date of Apr 2018. Matching placebo solution had a batch number of P73305P and an expiration date of Apr 2018. Solution for dilution had a batch number of P73304P and an expiration date of Apr 2018.

Trial treatments

Subjects were randomized to receive either 10 mL of GRT6010 solution 30 µg/mL (equating to a 300 µg dose of GRT6010) or 10 mL of matching placebo solution by intravesical instillation 4 times over a 2-week period.

Trial population

Female subjects, aged 18 years to 75 years, with bladder pain syndrome (BPS).

Summary of the trial procedures and assessments

All visits were ambulatory.

Enrollment Period

Subjects who had not undergone cystoscopy with hydrodistension in the past 2 years attended an Enrollment Visit and a separate Pre-baseline Visit.

At the Enrollment Visit, assessments were performed to determine eligibility for the trial. Subjects completed questionnaires about their BPS symptoms (O'Leary/Sant questionnaire and bladder pain/interstitial cystitis symptom score [BPIC-SS]) and general aspects of their health (12-item short form health survey [SF-12®] acute version). At the visit or up to 5 days thereafter, subjects underwent cystoscopy with hydrodistension.

At the Pre-Baseline Visit, 18 days to 33 days after the Enrollment Visit, subjects were asked to start recording their average pain intensity and intensity of urgency twice a day every day. Subjects were instructed to document all voidings and voided volumes during the 3 days leading up to the next visit, Treatment Visit 1.

Subjects who had undergone cystoscopy with hydrodistension less than 30 days ago were asked not to enroll in the trial until 30 days had elapsed since the procedure. Subjects who had undergone cystoscopy with hydrodistension between 30 days and 2 years ago attended a single visit in the Enrollment Period. The visit combined all assessments scheduled for the Enrollment Visit and the Pre-Baseline Visit, excluding cystoscopy with hydrodistension.

Treatment Period

The Treatment Period comprised 4 visits (Treatment Visit 1 to Treatment Visit 4), the first of which took place 7 days to 12 days after the last visit in the Enrollment Period. Successive treatment visits were separated by 3 days or 4 days.

At each of the 4 treatment visits, subjects received IMP by intravesical instillation. The time and volume of the first voiding after instillation were recorded. Blood was collected before and 2 h after instillation for pharmacokinetic assessment. Subjects who had agreed to extended pharmacokinetic sampling provided additional blood samples up to 24 h after the instillation at Treatment Visit 1.

At Treatment Visit 1 and Treatment Visit 3, subjects completed the O'Leary/Sant questionnaire, BPIC-SS, and SF-12 acute version. At Treatment Visit 2 and Treatment Visit 4, subjects were asked to record all voidings and voided volumes for 48 h after the visit.

Follow-up Period

Subjects attended a Follow-up Visit 3 days or 4 days after Treatment Visit 4. Subjects completed the O'Leary/Sant questionnaire, BPIC-SS, and SF-12 acute version. Blood was collected for pharmacokinetic assessment.

The trial concluded 12 days to 16 days later at the End-of-trial Visit. Subjects completed the O'Leary/Sant questionnaire, BPIC-SS, SF-12 acute version, and the patient global impression of change (PGIC). The investigator responded to the clinician's global impression of change (CGIC). Subjects were instructed to stop recording their average pain intensity and intensity of urgency. Subjects were asked to guess which treatment they had received.

The end of trial visit for discontinued subjects, scheduled where possible 3 days or 4 days after the last instillation procedure, incorporated assessments from the Follow-up Visit and the End-of-trial Visit.

Trial performance

There were 2 protocol amendments.

Ninety subjects were to be treated in the trial. Owing to slow recruitment, fewer subjects than planned were treated prior to the expiration date of the available batch of IMP. At the time at which the trial was terminated, 54 subjects had been treated.

Summary of the statistical methods

This Phase IIa trial was explorative in nature and no frequentist hypothesis testing was performed. The probability of pre-specified events was calculated to support the proof-of-concept decision within a Bayesian framework (Fisch et al. 2015).

Sample size rationale

The sample size determination was performed by investigating the operating characteristics of the different design options and the corresponding documentation is available upon request. After the investigation of the operating characteristics (chances of making right and wrong decisions given a true effect) in a wider parameter space, the parameters of the sample size calculations were set to be $\alpha = 0.15$ (with $1-\alpha$ being the confidence threshold for significance), $\gamma = 0.55$ (confidence threshold for relevance), and TD = 6 (treatment difference).

With a total sample size of 90 subjects and with a true mean of the differences above 10, the probability for the trial analysis to support a "go" decision (thresholds for significance and relevance exceeded) was at least 78%, and the probability for the trial analysis to support a "no go" decision (threshold for neither significance nor relevance exceeded) was at most 11%.

Similarly, with a true mean of the differences below 4, the probability to support a "no go" decision was at least 56%, and the probability to support a "go" decision was at most 28%.

Based on this rationale, it was planned to allocate 40 subjects to placebo and 50 subjects to GRT6010.

Subject populations

Enrolled Set	The Enrolled Set includes all subjects who signed the informed consent form.
Allocated Set	The Allocated Set includes all subjects who were allocated to treatment.
Safety Set	The Safety Set (SAF) includes all subjects with at least 1 IMP administration.
Full Analysis Set	The Full Analysis Set (FAS) includes all subjects allocated with at least 1 IMP administration and with at least 1 non-missing post-baseline value of average pain.
Per Protocol Set	The Per Protocol Set (PPS) is defined as a subset of the subjects in the FAS without any key protocol deviation.
Extended Pharmacokinetic Set	The Extended Pharmacokinetic Set (ePKS) includes all subjects who were treated at least once with GRT6010 and provided blood samples at Treatment Visit 1 for the extended pharmacokinetic analysis.
Pharmacokinetic Set	The Pharmacokinetic Set (PKS) includes all subjects who were treated at least once with GRT6010 and provided samples for bioanalytical purposes.
Pharmacogenetic Set	The Pharmacogenetic Set includes all subjects who provided at least 1 sample for pharmacogenetic purposes and who had at least 1 non-missing post-baseline efficacy assessment.

Statistical methods and analysis

All data collected in this trial were summarized descriptively. Descriptive statistics for the efficacy parameters were based on the FAS and PPS and for the safety and tolerability parameters based on the SAF. Pharmacokinetic data summaries were provided for the PKS.

Baseline was defined as the 3 days prior to the first instillation at Treatment Visit 1. End of treatment was defined as the 2 days after the day of the final instillation at Treatment Visit 4.

Primary endpoint

The primary endpoint assessed the change in average daily pain intensity score from baseline to end of treatment. The average was calculated over the entries in the electronic diary (e-diary).

Data from a subject was required to fulfil the following criteria to be evaluable for assessment of the primary endpoint:

- During the last 3 days prior to Treatment Visit 1, at least 4 pain intensity ratings, including at least 1 per day, were available.
- During the 2 days following the fourth instillation (starting with the morning assessment of the next day), at least 2 pain intensity ratings, including at least 1 per day, were available.

The statistical analysis was performed using a Bayesian variant of the mixed effect model for repeated measures (MMRM) using the daily averages as dependent variable. The model accounted for the effects of treatment, time, their interaction, and baseline (as covariate). Subject specific values were incorporated by means of a hierarchical model. The averages over the last assessment points were explicitly calculated within the Monte-Carlo run. The requirements with respect to the above-mentioned minimum number of assessments were used as qualifier for the subject for the given analysis.

No other explicit imputation strategy was applied.

The trial decision was based on the following criteria.

- Significance: $Prob\{Effect > 0|Data\} > 1 - \alpha$
- Relevance: $Prob\{Effect > min.Effect|Data\} > \gamma$

"Effect" means, in this sense, the difference to placebo. The minimal effect (or TD) is the value below which a further development would not be deemed promising. α and γ are thresholds expressing the confidence level desired for the given decision. α corresponds to the Type I error in a frequentist setting and was set to 0.15 for this proof-of-concept trial (i.e., a high level of confidence that the treatment is superior to placebo). γ expresses the desired confidence level to have a relevant effect; this was set to 0.55.

A meta-analysis was performed to assess the placebo effect and to generate a corresponding informative prior for the placebo group. In this way, historical data were incorporated into the comparison and allowed fewer placebo subjects to be included (Neuenschwander et al. 2010 and Gsteiger et al. 2013).

As a sensitivity analysis, the frequentist MMRM model was applied with the same effects as for the Bayesian version.

Secondary endpoints

The secondary efficacy endpoints were summarized by treatment, visit, and, where applicable, time point using descriptive measures. The summaries were provided both for the FAS and PPS including changes to baseline for the daily averages, where applicable.

In addition to the descriptive statistics, the frequentist analysis described for the sensitivity analysis of the primary endpoint was performed for changes to baseline for average number of daily micturition, average daily urine volume per voiding, average daily intensity of urgency, O'Leary/Sant questionnaire (symptom and problem index), and BPIC-SS.

Analyses performed not directly supporting an objective

Additional endpoints not directly supporting an objective were summarized descriptively as described for the secondary endpoints.

Summary of results

Subject disposition

A total of 77 subjects were enrolled in the trial.

Of the 57 subjects who were allocated, 23 subjects were administered placebo, 31 subjects were administered GRT6010, and 3 subjects were not administered IMP. Subjects who were administered placebo make up the placebo group and subjects who were administered GRT6010 make up the GRT6010 group.

One subject in the placebo group and 1 subject in the GRT6010 group received 1 administration of IMP before discontinuing the trial.

Twenty-two subjects in the placebo group and 30 subjects in the GRT6010 group completed the trial.

The analysis populations are presented in the following table.

Population	Placebo N (%)	GRT6010 N (%)	Overall N (%)
Subjects allocated	25 (100)	32 (100)	57 (100)
Safety Set	23 (92.0)	31 (96.9)	54 (94.7)
Full Analysis Set	23 (92.0)	31 (96.9)	54 (94.7)
Per Protocol Set	22 (88.0)	30 (93.8)	52 (91.2)
Pharmacokinetic Set	n/a	31 (96.9)	31 (54.4)
Extended Pharmacokinetic Set	n/a	3 (9.4)	3 (5.3)

N = number of subjects; n/a = not applicable.

Demographics

All 54 subjects in the SAF were female, white, and not of Hispanic or Latino ethnicity. Mean (standard deviation [SD]) age was 47.1 (15.9) years. Mean (SD) body mass index (BMI) was 24.86 (4.78) kg/m^2. Demographic data were similar for the placebo and GRT6010 groups.

Efficacy

Results summarized here are for analysis of the FAS.

Primary endpoint

Mean (SD) change from baseline to end of treatment in average daily pain scores, rated on a 0-100 visual analog scale (VAS), was −16.4 (16.8) in the placebo group and −24.1 (22.2) in the GRT6010 group.

The main Bayesian analysis for the primary endpoint estimated a mean difference between the GRT6010 group and the placebo group of −7.3. The 95% credibility interval was −16.10 to 1.17. Probability(Effect>0|Data) was 0.9440, exceeding the confidence threshold for significance. Probability(Effect>min. Effect|Data) was 0.6260, exceeding the confidence threshold for relevance.

The results of the sensitivity analyses were mostly consistent with those of the main Bayesian analysis.

Secondary endpoints

Mean (SD) change from baseline to the last assessment on the 2 days after Treatment Visit 4 in average pain intensity over the last 12 h, rated on a 0–100 VAS, was −15.8 (18.6) in the placebo group and −18.8 (23.0) in the GRT6010 group.

Mean (SD) change from baseline to end of treatment in average daily number of micturition was −1.9 (3.2) in the placebo group and −2.2 (4.2) in the GRT6010 group.

Mean (SD) change from baseline to end of treatment in average daily urine volume per voiding was −7.9 (41.1) mL in the placebo group and 26.0 (33.0) mL in the GRT6010 group.

Mean (SD) change from baseline to end of treatment in average daily intensity of urgency, rated on a 0–100 VAS, was −16.5 (17.2) in the placebo group and −19.3 (19.6) in the GRT6010 group.

Mean (SD) change from baseline to the Follow-up Visit in the O'Leary/Sant questionnaire symptom index score was −3.7 (3.8) in the placebo group and −5.5 (4.0) in the GRT6010 group. Mean (SD) change from baseline to the Follow-up Visit in the O'Leary/Sant problem index score was −3.3 (3.4) in the placebo group and −4.8 (3.6) in the GRT6010 group.

Mean (SD) change from baseline to the Follow-up Visit in the BPIC-SS sum score was −7.4 (5.9) in the placebo group and −8.7 (5.9) in the GRT6010 group.

Mean (SD) change from baseline to the Follow-up Visit in the SF-12 acute version physical component sum score was 4.723 (4.624) in the placebo group and 5.512 (8.020) in the GRT6010 group. Mean (SD) change from baseline to the Follow-up Visit in the SF-12 acute version mental component sum score was 2.947 (8.931) in the placebo group and 4.930 (9.179) in the GRT6010 group.

At the end of trial, an answer to the PGIC indicating an overall improvement in status was reported by 11 subjects (47.8%) in the placebo group and 17 subjects (54.8%) in the GRT6010 group. The investigator's answer to the CGIC indicated an overall improvement in status for 13 subjects (56.5%) in the placebo group and 25 subjects (80.6%) in the GRT6010 group.

Of the secondary efficacy endpoints, only the mean change from baseline to end of treatment in average daily urine volume per voiding showed a statistically significant difference for the GRT6010 group compared to the placebo group. The main frequentist analysis of this endpoint estimated a 95% confidence interval of 14.85 mL to 57.67 mL. The p-value was 0.0012.

Results of analysis for the PPS were consistent with those for the FAS.

Pharmacokinetics

The highest plasma concentration of GRT6010 measured in a single subject was 3080 pg/mL, at the Follow-up Visit.

For the PKS, plasma concentrations of GRT6010 measured pre-dose increased with treatment visit, as did those measured 2 h post-dose. Mean (SD) concentration 2 h post-dose at Treatment Visit 4 was 881 (867) pg/mL. Mean (SD) concentration at the end of trial was 222 (273) pg/mL.

Pharmacodynamics

No trend was observed over time for interleukin 8 (IL-8) values in the placebo group or the GRT6010 group.

Safety

No deaths, serious treatment emergent adverse events (TEAEs), or adverse events leading to discontinuation were observed in the trial.

A total of 68 TEAEs were reported in 22 subjects (40.7%) in the SAF:

- 9 subjects (39.1%) reported 36 TEAEs in the placebo group.
- 13 subjects (41.9%) reported 32 TEAEs in the GRT6010 group.

The most frequent TEAE was urinary tract infection, reported in 5 subjects (21.7%) in the placebo group and 5 subjects (16.1%) in the GRT6010 group.

No clinically relevant trends were observed over time for clinical chemistry parameters, hematology parameters, clotting parameters, urinalysis parameters, vital signs, physical examination findings, or 12-lead electrocardiogram (ECG) findings.

Conclusions

- Intravesical instillation of 300 µg GRT6010 twice weekly for 2 weeks reduced pain intensity from baseline to the end of treatment, separating from placebo.

- The outcome of the primary endpoint analysis exceeded the thresholds for significance and relevance, thereby meeting the 'go' criteria and demonstrating proof of concept.
- Intravesical instillation of GRT6010 improved functional symptoms, showing a clinically meaningful difference to placebo only for volume of urine voided.
- Systemic exposure to GRT6010 after intravesical instillation was very low compared to that observed after oral administration in previous trials.
- Consistent with the low systemic exposure to GRT6010, there was no evidence of adverse systemic effects of intravesically instilled GRT6010.

The TEAEs of urinary tract infection observed in the trial may reflect the mode of administration and/or the underlying condition of the trial population.