DMS version	1.0
Type of report	Abbreviated
Trial code	KF7019-01
Title of trial	An exploratory, randomized, double-blind, double-dummy, placebo- and active-controlled Phase II trial to evaluate the efficacy and safety of a topical application of GRT7019 in subjects with chronic pain due to knee osteoarthritis
Brief title	Lidocaine/diclofenac epolamine patch (GRT7019) Phase II proof-of-concept trial in subjects with chronic pain due to knee osteoarthritis
Trial design	Exploratory, interventional, randomized, multi-site, double-blind, double-dummy, placebo- and active-controlled, parallel-group, multiple administration trial
Development phase	Phase II
EudraCT number	2016-002611-18 Universal Trial Number U1111-1184-3912
Investigational medicinal products	• GRT7019 (patches containing 5% lidocaine and 1.3% diclofenac epolamine) • Versatis® (lidocaine 5% medicated plaster) • Diclo 75 SL® (diclofenac sodium sustained-release [62.5 mg]/immediate-release [12.5 mg] tablets) • Placebo patches (matching GRT7019 and Versatis) and placebo capsules (matching over-encapsulated diclofenac sodium tablets).
Indication	Chronic pain due to knee osteoarthritis (OA)
Coordinating investigator	Prof Dr med [redacted] Charité - Universitätsmedizin Berlin, Campus Virchow-Klinikum, Klinik für Anästhesiologie mit Schwerpunkt operative Intensivmedizin, Augustenburger Platz 1, 13353 Berlin, Germany
Trial sites	Austria (4 sites), Germany (11 sites), Poland (8 sites), Spain (6 sites).
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's signatory	[redacted] MD (International Clinical Lead) Contact number: +49 (0) 241-569-3223
Trial period	First subject in: 12 Jun 2017 Last subject out: 17 Jan 2018

Trial objectives

Primary objective:

- Evaluation of the analgesic efficacy of a once daily application of GRT7019 for 4 weeks compared to placebo.

Secondary objectives:

- Further characterization of the efficacy of GRT7019, oral diclofenac, lidocaine patch, and placebo.
- Evaluation of the quality of life after treatment with GRT7019, oral diclofenac, lidocaine patch, and placebo.
- Evaluation of the safety and tolerability of GRT7019, oral diclofenac, lidocaine patch, and placebo.

Trial treatments

Investigational medicinal products (IMPs)

- GRT7019 containing 5% lidocaine (700 mg) and 1.3% diclofenac epolamine (182 mg): batch number X1619A, expiration date 30 Sep 2017; batch number 41720A, expiration date 31 Mar 2018.
- Lidocaine patch (Versatis [lidocaine 5% medicated plaster containing 700 mg of lidocaine]): batch number X6122, expiration date 30 Sep 2019.
- Over-encapsulated diclofenac sodium sustained-release (62.5 mg)/immediate-release (12.5 mg) tablets (Diclo 75 SL - 1A Pharma): batch number GD0877, expiration date 31 Jan 2019.
- Placebo patches matching GRT7019 and lidocaine patches: batch number X1619P, expiration date 30 Sep 2019; batch number 41720P, expiration date 31 Mar 2018, and Placebo capsules matching over-encapsulated diclofenac sodium tablets: batch number E1603490001E001, expiration date 31 Jan 2019.

Allocation was performed using a stratified block randomization with country as stratification factor. Subjects who complied with all inclusion criteria and did not meet any of the exclusion criteria were randomly allocated to 1 of the 4 treatment arms P1, T1, C1, and C2 in a 1:1:1:1 ratio:

- Treatment T1: GRT7019 patch + placebo capsules.
- Treatment P1: Placebo patch + placebo capsules.
- Treatment C1: Lidocaine patch + placebo capsules.
- Treatment C2: Oral diclofenac capsule + placebo patch.

All IMPs were administered in a double-dummy design to maintain the blinding. Patches were administered once daily for 4 weeks with a planned wearing time of up to 18 hours but not less than 11 hours. Patches had to be administered in the morning at a time suitable to accommodate the subjects' needs and were to be fixed at the bent knee with an elastic mesh bandage. Capsules were administered twice daily, i.e., in the morning and in the evening (before a meal), for 4 weeks. No dose adjustments were allowed.

Trial-specific co-medication (non-IMP)

- Over-encapsulated pantoprazole 20-mg tablets: batch number 02969, expiration date 31 Oct 2018 (Pantoprazol-ratiopharm 20 mg magensaftresistente Tabletten).
- Placebo capsules matching over-encapsulated pantoprazole 20-mg tablets: batch number E1603490001E001, expiration date 31 Jan 2019.

Over-encapsulated pantoprazole 20-mg tablets were taken once daily in the morning in the diclofenac treatment arm (C2) to prevent gastrointestinal (GI) system related injuries/bleeding that might have resulted from the treatment with oral diclofenac. Placebo capsules matching the over-encapsulated pantoprazole tablets were taken once daily in all other treatment arms to maintain blinding.

Rescue medication

Paracetamol 500-mg tablets (batch number PL2405, expiration date 31 May 2020) were provided as rescue medication for unacceptable pain due to chronic OA. No rescue medication was allowed during the last 3 days before the Baseline Visit (Visit 4). The maximum total daily dose of paracetamol was 2000 mg during the Washout Phase (Visit 1 to Visit 3) and after allocation to treatment with the IMPs until the Follow-up Visit (Visit 7). During the Treatment Period, paracetamol had not to be taken for more than 3 consecutive days at the maximum allowed total daily dose.

Trial population

Male or female subjects aged 40 years to 80 years, who had given written informed consent, and presented with a diagnosis of OA of the index knee (the one under investigation) based on American College of Rheumatology (ACR) criteria and functional capacity class of I-III could enroll in this trial. They had to be on stable treatment with analgesics for their condition with regular intake for at least 3 months prior to enrollment. Subjects' pain had to be present for at least 3 months before the Enrollment Visit. After washout of previous analgesics, and in the absence of any rescue medication intake, subjects had to report an average pain intensity of equal to or above 4 and below 8 on the 11-point numerical rating scale (NRS).

Pregnant women and subjects meeting at least 1 of the following criteria were excluded: evidence or history of alcohol or drug abuse; intake of opioids or cannabinoids in the last 3 months before the Enrollment Visit; past or pending litigation due to chronic pain or disability; skin injuries or open wounds at the site of planned patch application; surgery of any joint within 3 months of enrollment; conditions that required treatment with forbidden medication; painful conditions other than due to OA that could contribute relevantly to pain and confound the assessment of self-evaluation of pain; clinically relevant history of hypersensitivity, allergy, or presence of contraindications to any of the IMPs' drug substances and excipients, or to pantoprazole or paracetamol; any clinically significant disease that in the investigator's opinion could affect efficacy or safety assessments or could have compromised the subject's safety during trial participation.

Summary of the trial procedures and assessments

The trial consisted of 3 periods: an Enrollment Period (comprising a Washout Phase for subjects' previous analgesic treatment and a treatment-free Baseline Phase for the assessment of the baseline pain intensity), a 4-week double-blind Treatment Period, and a Follow-up Period (before re-starting prior or a new analgesic treatment). During the Enrollment Period, the investigator called up the

subjects twice to reassess their eligibility and to remind them to start the treatment-free Baseline Phase. Demographic data and baseline characteristics (medical history, OA history, prior and concomitant medication, physical examination outcomes including skin checks at the planned patch application sites, pregnancy test results [in women with childbearing potential], drugs of abuse test results) were collected. Up to 180 subjects suffering from pain due to knee OA were planned to be allocated to treatment in this trial and to be equally distributed between the 4 treatment arms. All subjects received a step activity tracker which they were asked to wear throughout the Treatment Period.

Throughout the trial, subjects recorded their pain intensity on the NRS twice daily (morning and evening) with a half-day recall period and any use of rescue medication on a daily basis in an electronic diary (eDiary). Safety and further efficacy/quality of life assessments were performed according to a pre-defined schedule on site at enrollment (Visit 1), at the Baseline Visit (Day 1, Visit 4), as well as after 2 weeks (Visit 5) and 4 weeks (Visit 6) of treatment. A safety follow-up visit was scheduled 2 days after end of treatment (Visit 7). Efficacy/quality of life data comprised subject's expectations of the treatment they were to receive (Stanford Expectations of Treatment Scale, SETS), pain intensity after physical exercise after subjects walked a stair for a minute, patch adhesiveness, Patient Global Impression of Change (PGIC), Clinician's Global Impression of Change (CGIC), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and treatment preference. Safety assessments included the recording of adverse events, skin checks at patch application sites, vital signs and body weight measurements, and safety laboratory parameters. Blood samples were collected pre-dose and at Visit 4 and Visit 5 (4 hours to 6 hours after IMP intake/application) to determine individual plasma concentrations of lidocaine and diclofenac.

Trial performance

There were no protocol amendments. There was no premature trial termination or suspension (clinical hold) of the trial.

Summary of the statistical methods

All analyses in this trial are of exploratory nature. No formal hypothesis testing was performed. A confidence interval (CI) based approach was used to estimate the effect of GRT7019 in comparison to placebo for the primary outcome parameter. The trial was analyzed once all the data were cleaned and the database was locked.

Sample size rationale

Assuming 45 subjects per treatment arm of the Full Analysis Set (FAS) and a standard deviation of 2.5 points (NRS), half-width of the 2-sided 70% CI would be about 0.55. Hereby a power of 80% could be achieved given a treatment difference of 1 point on the NRS on the weekly average pain intensity between placebo and GRT7019 with respect to the primary efficacy endpoint (superiority of GRT7019 versus placebo).

A 1-sided significance level of 15% was considered appropriate given the trial characteristic and exploratory pilot nature of the trial (Lee et al. 2014).

Subject populations

The Enrolled Set includes all subjects who signed the informed consent form. The Allocated Set includes all subjects who were allocated to IMP. The Safety Set (SAF) includes all subjects with at least 1 IMP administration. The FAS includes all subjects allocated with at least 1 IMP administration and with at least 1 non-missing post-baseline assessment of morning or evening average pain. The Per Protocol Set (PPS) defines a subset of the subjects in the FAS without any key protocol deviation.

Statistical methods and analysis

All data collected in this trial were summarized descriptively. The analysis of the primary efficacy endpoint was performed on the FAS and as a sensitivity analysis on the PPS. All other efficacy analyses were performed on the FAS. Descriptive statistics for the safety and tolerability parameters were based on the SAF.

The primary endpoint which was compared to placebo is the change from baseline to Week 4 of the double-blind Treatment Period in the weekly average pain intensity. Pain intensities were assessed twice daily in the morning and the evening using an 11-point NRS with a half-day recall period.

The primary endpoint was analyzed by means of a mixed-effects model for repeated measures (MMRM). The model includes fixed effects of pooled sites, treatment, time (in weeks), treatment-by-time interaction, positive expectancy score (of SETS questionnaire), and baseline pain intensity score. The subject was included as a random effect. The primary analysis consists of the contrast of GRT7019 versus placebo for Week 4 of the double-blind Treatment Period.

Confidence intervals of different width for the treatment difference of GRT7019 versus placebo were investigated (Lee et al. 2014) and reported. No formal hypothesis testing was provided. The presentation of CIs for the treatment difference starts with the 2-sided 95% CI, and continues in steps of 5% until the 2-sided 70% CI is reached.

To investigate the robustness of the primary analysis against choice of analysis set, the MMRM analysis as described above was repeated as sensitivity analysis on the PPS.

Robustness of the primary analysis against deviations from missingness assumptions was investigated by 3 additional sensitivity analyses based on the FAS and using the following imputation techniques to impute missing weekly averages in the 4 weeks of the double-blind Treatment Period: single imputation modified Baseline Observation Carried Forward (mBOCF), multiple imputation (MI) assuming missing at random (MAR), multiple imputation using Placebo Multiple Imputation (PMI) as Pattern Mixture Model (PMM) approach. The imputed data from Week 4 were analyzed by analysis of covariance (ANCOVA) models with pooled sites and treatment as factors and treatment expectance score (of SETS questionnaire) and baseline pain intensity score as covariates.

All secondary endpoints and additional evaluations were analyzed descriptively.

Summary of results

Subject disposition

A total of 229 subjects (79 men and 150 women) were enrolled and 185 of these subjects (64 men and 121 women) were allocated to IMP and treated. The number of subjects was balanced among

the treatment arms (45-48 subjects per arm). Twenty-one (11.4%) of all allocated subjects discontinued during the course of the trial: 1 subject due to lack of efficacy, 5 subjects due to adverse events, 2 subjects due to protocol deviations, and 1 subject for technical reasons. For 6 subjects, a specific reason was not provided. Six subjects withdrew their consent. A total of 164 subjects (88.6%) completed the trial.

Demographics

For the SAF, the mean age between treatment arms ranged from 60.7 years to 63.4 years, mean height ranged from 167.2 cm to 170.8 cm, mean weight ranged from 83.0 kg to 83.1 kg, and mean body mass index (BMI) ranged from 28.4 kg/m^2 to 29.8 kg/m^2. Overall, 117 subjects were 18 to less than 65 years old, and 68 subjects 65 to less than 85 years old.

Pharmacokinetics

Data indicate a low but similar systemic exposure to lidocaine after the topical application of GRT7019 and the lidocaine patch. Systemic exposure to diclofenac was as expected after oral administration of diclofenac 75 mg twice daily and was up to 100-fold higher than after topical application of GRT7019.

Efficacy

- Pain reduction was observed in all treatment arms over time. The magnitude of pain reduction from baseline (mean [SD] 5.55 (0.78) to 5.76 [0.93] on the NRS) at Week 4 was similar across all treatment arms, ranging from -1.49 to -2.43 on the 11-point NRS (observed values).
- For the change from baseline to Week 4, the least square (LS) mean (standard error [SE]) were -1.83 (0.27) for GRT7019 and -2.03 (0.27) for placebo, and the difference between GRT7019 and placebo was 0.21 (0.36).
- Also lidocaine (LS mean [SE] -1.44 [0.27]) and oral diclofenac (-2.16 [0.26]) did not separate from placebo at Week 4.
- Results of the secondary efficacy endpoints and quality of life outcomes were similar to those of the primary endpoint.

Safety and tolerability results

- There were no drug-related serious adverse events (SAEs) in this trial.
- The incidence rate of treatment emergent adverse events (TEAEs) was numerically lower for subjects in the GRT7019 arm (26.1%) and the placebo and lidocaine arms (34.8% and 35.6%) than in the diclofenac arm (43.8%).
- Most frequently reported TEAEs across all subjects were nasopharyngitis (reported in 7 of 185 subjects [3.8%] in the overall trial population), abdominal pain upper (reported in 6 of 185 subjects [3.2%]), and diarrhea, headache, or glomerular filtration rate (GFR) decreased (reported in 4 of 185 subjects each [2.2%]).
- The incidence rate of subjects with skin-related TEAEs was low in all treatment arms, i.e., below 7%.

Conclusions

- The topical treatment with GRT7019 showed no statistically significant difference to the efficacy reported for the treatment with placebo.
- Results of the secondary efficacy endpoints and quality of life outcomes were similar to those of the primary endpoint.
- Treatment with GRT7019 was well tolerated.

Reference

Lee EC, Whitehead AL, Jacques RM, Julious SA: The statistical interpretation of pilot trials: should significance thresholds be reconsidered? BMC Med Res Methodol 2014; 14: 41.