Trial code:	KF7039-02
Title of trial:	A randomized, double-blind, placebo-controlled, Phase III trial to evaluate the efficacy and safety of a single intra-articular injection of RTX-GRT7039 in adult subjects with pain associated with osteoarthritis of the knee
Brief title:	Comparison of a single RTX-GRT7039 and placebo intra-articular injection for pain associated with osteoarthritis of the knee
Indication:	Moderate to severe pain associated with osteoarthritis of the knee
International Coordinating Investigator: [a]	PPD
Trial site(s):	Approximately 50 sites globally Documentation of the involved trial site(s) will be maintained
Trial sponsor:	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's medically qualified person [a]**:**	PPD
Sponsor's signatory:	PPD
Public contact point:	Email: clinical-trials@grunenthal.com PPD

a) Contact detail changes during the trial will be documented and do not require a protocol amendment.

Version	**Date**	**DMS version number**	**Valid for**
Original:	03 Dec 2021	3.0	All countries
Universal Trial Number:	U1111-1268-7267	**EudraCT number:**	2021-005020-38

1 PROTOCOL SYNOPSIS

1.1 Trial design

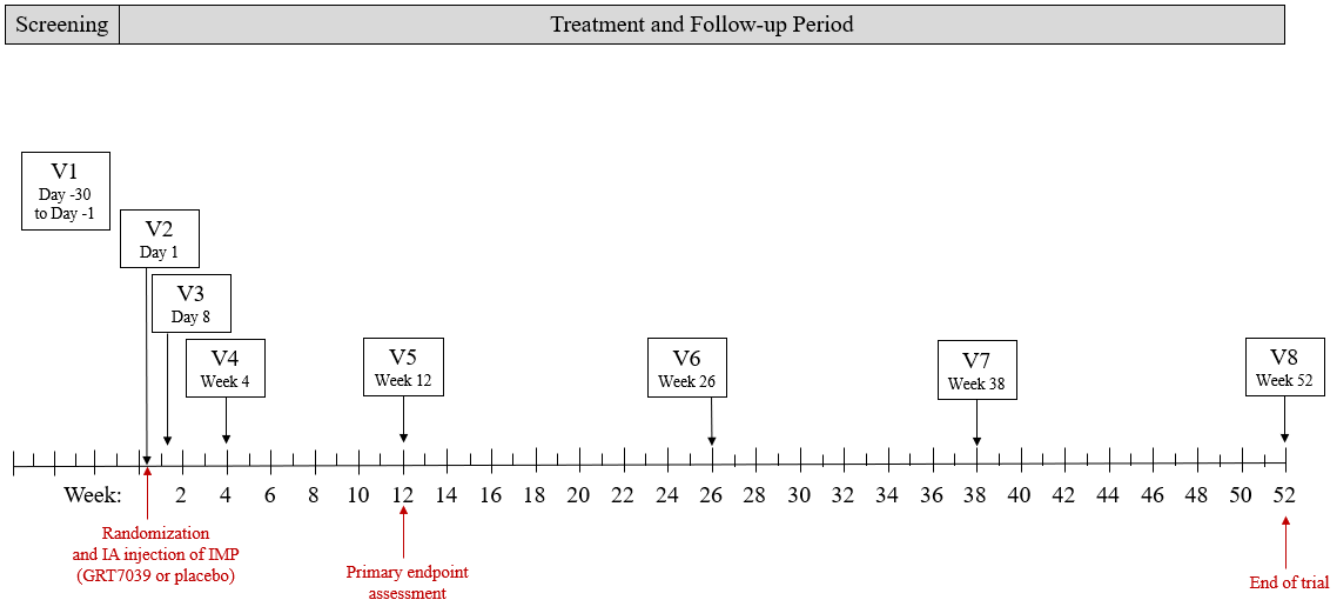
This is an interventional, Phase III, double-blind, randomized, placebo-controlled, parallel-group, multi-site, clinical trial to confirm the efficacy and safety of a single intra-articular injection of RTX-GRT7039 versus placebo in subjects who have moderate to severe pain associated with osteoarthritis of the knee despite receiving continued treatment with optimal standard of care (SoC) or who are unable to receive SoC treatment due to contraindications or intolerability.

Approximately 450 subjects will be randomized to receive a single dose of either RTX-GRT7039 or placebo in a 1:1 ratio, with a safety follow-up duration of 52 weeks. In addition to continued SoC treatment, subjects will receive 1 of the following treatments:

- RTX-GRT7039 400 ng single intra-articular injection.
- Placebo to match RTX-GRT7039 single intra-articular injection.

1.1.1 Trial Design Chart

See Figure 1 for an illustration of the trial design.



IA = intra-articular; IMP = investigational medicinal product; V = Visit

Figure 1: Trial design chart

1.1.2 Brief description of the sequence and duration of all trial periods

This trial comprises a Screening Period, a double-blind Treatment and Follow-up Period with a single intra-articular investigational medicinal product (IMP) injection, at Day 1 culminating in a Final Visit at Week 52.

Each subject is expected to be in the trial for up to 56 weeks (i.e., the Screening Period of up to 30 days followed by the 52-week Treatment and Follow-up Period).

See Section 1.1.1 for a trial design chart and Section 1.6 for a tabular schedule of events (SoE).

1.2 Trial objectives and endpoints/outcomes

Objective	Endpoint/Outcome
Primary	**Primary**
Demonstrate the analgesic efficacy of intra-articular RTX-GRT7039 compared with placebo in change from baseline at Week 12.	Change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score in the index knee to the score at Week 12. The WOMAC pain subscale, which consists of 5 questions, will be assessed and reported in the electronic diary (e-diary) once weekly with a 48-hour recall, using an 11-point numeric rating scale (NRS, from 0 = no pain to 10 = pain as bad as you can imagine). Timeframe for the assessment: from baseline (assessment at V2) to V5 (Week 12/Day 84). **Estimand** The primary comparison of interest is the difference in mean change from baseline in 48-hour WOMAC pain subscale at Week 12 in the index knee using an 11-pt NRS (0-10) between RTX-GRT7039 and placebo, in subjects who initiate treatment, as if substantial changes in background medication or addition of new analgesics were not available.
Key Secondary	**Key Secondary**
Demonstrate the analgesic efficacy of intra-articular RTX-GRT7039 compared with placebo in change from baseline at Week 26.	Change from baseline in WOMAC pain subscale score in the index knee based on the 11-point (0-10) NRS to the score at Week 26. **Estimand** The secondary comparison of interest is the difference in mean change from baseline in 48-hour WOMAC pain subscale at Week 26 in the index knee using an 11-pt (0-10) NRS between RTX-GRT7039 and placebo, in subjects who initiate treatment, as if substantial changes in background medication or addition of new analgesics were not available.
Demonstrate the efficacy of intra-articular RTX-GRT7039 on function compared with placebo in change from baseline at Week 12 and at Week 26.	Change from baseline in WOMAC physical function subscale score at Week 12 and at Week 26.

Objective	Endpoint/Outcome
	Estimand The secondary comparison of interest is the difference in mean change from baseline in 48-hour WOMAC physical function subscale at Week 12 and at Week 26 in the index knee using an 11-point numeric pain rating scale (NRS) from (0-10) between RTX-GRT7039 and placebo, in subjects who initiate treatment, as if substantial changes in background medication or addition of new analgesics were not available.
To assess the safety and tolerability of RTX-GRT7039 intra-articular injection.	Incidence of treatment-emergent adverse events (TEAEs). Incidence of TEAEs representing structural changes of the knee joint as visualized by the imaging methods assessed by the Investigator as clinically relevant (thus constitute an adverse event [AE]) and as at least possibly related to the IMP (and not attributable to the natural progression of the disease in an individual subject)
Secondary	**Secondary**
Demonstrate the efficacy of intra-articular RTX-GRT7039 compared with placebo in change from baseline to Week 38 and from baseline to Week 52 in the WOMAC pain subscale score and WOMAC physical function subscale score	Change from baseline in WOMAC pain subscale score and WOMAC physical function subscale score at Week 38 and at Week 52
Demonstrate the efficacy of intra-articular RTX-GRT7039 compared with placebo in change from baseline to Week 12, to Week 26, to Week 38, and to Week 52 in the WOMAC stiffness subscale score, WOMAC total score, and on pain when walking on a flat surface (WOMAC A1)	Change from baseline in WOMAC stiffness subscale, WOMAC total score, and pain when walking on a flat surface (WOMAC A1) at Week 12, Week 26, Week 38, and Week 52
Demonstrate the efficacy of intra-articular RTX-GRT7039 compared with placebo in percentage of subjects with ≥ 30%, 50%, and 70% reduction in pain from baseline at Week 12, at Week 26, at Week 38, and at Week 52.	Percentage of subjects with ≥ 30%, 50%, and 70% reduction in WOMAC pain subscale in the index knee from baseline at Week 12, from baseline at Week 26, from baseline at Week 38, and from baseline at Week 52. Percentage of subjects with ≥ 30%, 50%, and 70% reduction in pain when walking on a flat surface (WOMAC A1) in the index knee from baseline at Week 12, from baseline at Week 26, from baseline at Week 38, and from baseline at Week 52.

Objective	Endpoint/Outcome
Demonstrate the efficacy of intra-articular RTX-GRT7039 compared with placebo in percentages of subjects responding according to OMERACT-OARSI criteria at Week 12 at Week 26, at Week 38, and at Week 52.	Percent of responders according to OMERACT–OARSI criteria after a single injection into the index knee at Week 12, Week 26, Week 38, and Week 52.
Demonstrate the efficacy of intra-articular RTX-GRT7039 compared with placebo in patient global impression of change (PGIC).	PGIC at Week 12, Week 26, Week 38, and Week 52.
Demonstrate the quality of life after treatment with RTX-GRT7039 compared with placebo.	Quality of life – EuroQol-5 Dimension Health Questionnaire 5 Levels (EQ-5D-5L): changes from baseline to Week 12, Week 26, Week 38, and Week 52.
	Quality of life – Short form-36 (SF-36): changes from baseline to Week 12, Week 26, Week 38, and Week 52.
Investigate durability of effect (until recurrence of pain).	Durability of effect is defined as time from an improvement in WOMAC pain subscale to pain recurrence.

Other data to be collected that are not directly attributed to an endpoint

To evaluate subject eligibility and to describe the trial population

- Demographic and other baseline characteristics: Date of signature on the informed consent form, sex, age, body weight, height, body mass index (BMI), race, ethnic group.
- Relevant prior/concomitant treatments (i.e., non-pharmacologic and pharmacologic) used to treat osteoarthritis and osteoarthritis pain and reasons for discontinuing will be collected. Prior and concomitant medications other than for osteoarthritis will be collected.
- Thorough musculoskeletal history (incl. current and history of osteoarthritis, joint surgeries, fractures, joint injuries) and physical examination (incl. evaluation of joints for swelling, redness, tenderness).
- Imaging data (X-ray and magnetic resonance imaging [MRI]), pregnancy test, and drugs of abuse test.

To assess the efficacy

- Patient global assessment (PGA) of osteoarthritis.
- Patient-specific functional scale (PSFS).
- Durability of effect – return of pain.
- WOMAC, PGIC, SF-36, and EQ-5D-5L data at time points not related to the primary and secondary endpoints.

To assess the safety and tolerability of RTX-GRT7039

- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate).
- Electrocardiogram (ECG).
- Safety laboratory parameters (hematology, clinical chemistry, clotting, and urinalysis dipstick panel).
- Physical examination findings.
- Assessment of procedural pain related to the IMP injection.

• Imaging data (X-ray and MRI).
To assess the treatment satisfaction
• Treatment Satisfaction Questionnaire for Medication (TSQM) scores.

1.3 Trial subjects – the population to be studied

Inclusion criteria are reviewed at the Screening Visit (V1) and at Baseline (i.e., V2 before IMP administration). Subjects will only receive IMP if documentation is available showing that they meet all of these inclusion criteria and none of the exclusion criteria.

1.3.1 Inclusion criteria

1. The subject has given written informed consent to participate.
2. The subjects are ≥18 years of age at the Screening Visit.
3. The subjects have a BMI ≤40.0 kg/m^2.
4. The subject is willing to adhere to the restricted use of concomitant treatments (see concomitant treatments in Section 1.4.3).
5. The subject has a diagnosis of osteoarthritis of the knee based on American College of Rheumatology criteria and functional capacity class of I-III. Pain at the index knee must be present for at least 6 months prior to Screening Visit.
6. The subject has a Kellgren-Lawrence (KL) grade of 2-4 in the index knee (based on X-ray performed during Screening Visit, assessed by central readers).
7. There is a documented history indicating that subject has insufficient pain relief with optimal standard of care (SoC), i.e.,
    a. non-pharmacological treatment, and
    b. 1 or more courses of oral non-steroidal anti-inflammatory drugs (NSAIDs) prescribed by their physician and
    c. where appropriate, opioids, intra-articular treatment with corticosteroids, and intra-articular treatment with hyaluronic acid

    in combination or as monotherapies,

    or subject is unable to take SoC due to contraindication or intolerability to 1 or more of the SoC treatments above.

    Further details on the definition of documented history will be provided in the electronic case report form (eCRF) guidance document.
8. The investigator does not consider that any additional benefit can reasonably be expected from further adjustments to the subject's pain treatment.
9. The subject must have a baseline WOMAC pain subscale score ≥5 on the 11-point (0-10) NRS for the index knee at Screening (assessment in e-diary at V1) and at baseline (assessment in e-diary at V2).
10. Women of child-bearing potential must have a negative pregnancy test at the Screening Visit and prior to the administration of IMP. They must also agree to practice, at a minimum, acceptable measures of birth control for 90 days following administration of IMP.

11. Male subjects must agree to use barrier contraception (condom) during sexual intercourse with women of child-bearing potential after administration of IMP for 90 days. The male subject is willing to ensure that during this period the female sexual partner is additionally practicing contraception, if of childbearing potential.

1.3.2 Exclusion criteria

A single re-screening is accepted for items 4, 5, 6, and 7.

1. The subject reports a WOMAC pain subscale score of 10 on the 11-point (0-10) NRS at Screening (assessment in e-diary at V1) or at baseline (assessment in e-diary at V2) for the index knee.
2. The subject has a WOMAC pain subscale score of ≥ 4 on the 11-point (0-10) NRS in the non-index knee at Screening.
3. The subject has past joint replacement surgery of the index knee.
4. The subject had an intra-articular injection of either corticosteroid or intra-articular visco-supplementation (i.e., hyaluronic acid) into the index knee within 90 days of screening.
5. The subject had an injection of platelet-rich plasma or stem cells into the index knee within 6 months of screening.
6. The subject applied topical capsaicin on the index knee within 3 months of Screening.
7. The subject has a history of significant trauma or surgery (e.g., open or arthroscopic) to the index knee within 12 months of Screening.
8. The subject has any known active infection of the index joint, including suspicion of intra-articular infection, ulcer, or open wound anywhere on the index knee.
9. The subject has periarticular pain from any cause other than osteoarthritis, including referred pain, bursitis, or tendonitis.
10. The subject has ipsilateral clinical hip osteoarthritis on the side of the index knee.
11. The subject has pre-existing osteonecrosis, subchondral insufficiency fracture, atrophic osteoarthritis, severe bone on bone osteoarthritis, knee pain attributable to disease other than osteoarthritis, or the subject has rapidly progressing osteoarthritis (RPOA) Type I or Type II.
12. The subject has significant malalignment of anatomical axis (medial angle formed by the femur and tibia) of the target knee (varus >10°, valgus >10°) by X-ray as assessed by independent central readers at Screening Visit.
13. The subject has other conditions that could affect trial endpoint assessments of the index knee, including, but not limited to, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, gout or pseudogout, inflammatory bowel disease related arthropathy, peripheral neuropathy (e.g., diabetic neuropathy), lupus erythematosus, significant skin conditions overlying the index knee, acromegaly, metabolic joint diseases, and fibromyalgia.
14. The subject has significant pain in other areas, which may confound discrimination of pain assessment in the index knee.
15. The subject has evidence of cognitive impairment including dementia that may interfere with the subject's ability to complete patient reported outcomes (PROs).

16. The subject had systemic (except inhaled corticosteroid) immunosuppressant agent within 6 months prior to trial medication administration.
17. The subject has any surgery scheduled during the trial period.
18. The subject has current clinically significant disease(s) or condition(s) (including clinically significant cardiovascular disease) that may affect efficacy or safety assessments, or any other reason which, in the investigator's opinion, may preclude the subject's participation in the full duration of the trial.
19. The subject has a major bleeding disorder encompassing, but not limited to coagulopathy and any current antithrombotic and anticoagulant events.
20. The subject has a history of severe allergic or anaphylactic reactions.
    - The subject has history of hypersensitivity to local anesthetic (e.g., lidocaine, ropivacaine).
    - The subject has history of hypersensitivity to resiniferatoxin (RTX) or any similar component (capsaicin, chili peppers).
21. The subject has a known infection with human immunodeficiency virus or known current acute or chronic hepatitis B or C infection.
22. The subject has unstable or poorly controlled blood pressure which, in the opinion of the investigator, would put the subject at risk of severe adverse blood pressure increases upon IMP application.
23. The subject has evidence or history of severe psychiatric illness/disorder during the 3 years prior to the Screening Visit that, in the investigator's opinion, may affect efficacy or safety assessments or may compromise the subject's safety during trial participation (e.g., major depression, major anxiety disorder, psychosis, severe personality disorders).
24. The subject has a history of alcohol or drug abuse or was actively abusing drugs (including alcohol, medication) during the 1 year prior to the Screening Visit as judged by the investigator.
25. The subject has past or pending litigation due to chronic pain or disability.
26. The subject is known or suspected of not being able to comply with the requirements of the trial protocol or the instructions of the trial site staff.
27. The subject is not able to communicate meaningfully with the trial site staff.
28. The subject is currently participating or was participating in another investigational drug trial within 3 months prior to Screening visit.
29. The subject is an employee of the investigator or trial site, with direct involvement in the proposed trial or other trials under the direction of that investigator or trial site or is a family member of the employees or the investigator.
30. The subject has contraindications to an MRI of the index knee.
31. The subject has a history of malignancy within 2 years prior to the Screening Visit, with the exception of basal cell carcinoma.
32. The female subject is pregnant, planning on becoming pregnant, or is currently breastfeeding.

1.4 Trial treatments

1.4.1 Investigational medicinal products

The IMPs used in this trial are given below:

- 5 mL RTX-GRT7039 solution for intra-articular injection is constituted from 2 vials: 1 vial containing 1.6 µg/mL RTX supplied in 0.4 mL ethanolic solution and 1 vial containing 8 mL D-α-tocopherol polyethylene glycol succinate (TPGS) buffer.
- 5 mL placebo solution for intra-articular injection is constituted from 2 vials: 1 vial containing 0.4 mL ethanolic solution (placebo to match RTX-GRT7039) and 1 vial containing 8 mL TPGS buffer.

Details will be outlined in the pharmacy manual.

Five mL of IMP will be injected following ropivacaine administration (see Section 1.4.2), into the knee joint.

It is strongly recommended that the injection be assisted by ultrasound. Once completed, the needle and syringe will be removed, and an adhesive bandage applied.

The IMP injection will occur at the Randomization Visit (V2/Day 1).

1.4.2 Local anesthetic before IMP injection

Fifteen minutes prior to the intra-articular injection of IMP, a 5 mL intra-articular injection of ropivacaine 0.5% will be administered as a local anesthetic. Separate needles should be used for each, and the skin should be cleaned again prior to the administration of IMP.

Further details regarding the administration of ropivacaine are specified in a separate manual.

1.4.3 Prohibited and allowed medications or therapies

Subjects should not receive any of the following medications or therapies for the indicated times specified below:

- Intra-articular injection of corticosteroid or intra-articular visco-supplementation (i.e., hyaluronic acid) into the index knee within 90 days of screening and throughout the trial
- Injection of platelet-rich plasma or stem cells into the index knee within 6 months of screening and throughout the trial
- Topical capsaicin on the index knee within 3 months of screening and throughout the trial
- Any surgical intervention on the index knee (including but not limited to, arthroscopic interventions and knee replacement surgery) throughout the trial
- Any other investigational treatment or therapy

Subjects should continue their baseline non-pharmacological treatments and baseline analgesic and osteoarthritis medication(s) if the medications are not prohibited as outlined above, if they are on a stable, well-defined treatment regimen for at least 1 month before allocation to IMP and are anticipated to be able to maintain the treatment regimen in the opinion of the investigator.

There should be no changes (increases, decreases, or switches) from or additions to baseline analgesic medications (NSAIDs, opioids, other) and nonpharmacologic treatments after the Screening Visit through at least Week 26 (V6). This is designed to minimize possible confounding treatment effects due to alterations in pain medications.

Furthermore, subjects should not schedule any medical procedures, which would likely require an adjustment in pain medications during the trial and in particular for Weeks 10 to 12 and Weeks 24 to 26 if possible. Subjects not taking opioids at baseline should similarly refrain from starting opioid treatment.

If for any reason deemed necessary by the investigator, a subject requires additional medication(s) or change of dose, the medication(s), dosage change, route of administration, start and stop dates, and the indication for which it was given must be recorded in the source documents and a specific page in the eCRF.

All vaccinations, including coronavirus disease 2019 (COVID-19), are permitted during the trial.

1.5 Statistical analyses

All statistical methods will be detailed in a statistical analysis plan (SAP). The SAP will be finalized prior to database lock and unblinding.

1.5.1 Sample size rationale

Effect size estimates were based on relevant literature and the results of available MTX-071-P03 trial results utilizing the absolute change from baseline to Week 12 endpoint. A total number of 382 subjects are required to achieve an overall power of at least 90% to reject the null hypothesis of no treatment difference in treatment group means between RTX-GRT7039 and placebo (2-sided t-test, type I error of $\alpha = 0.05$). This is based upon an expected treatment difference of at least 1 point on 11-point (0-10) NRS (absolute change from baseline in the WOMAC pain subscale score) on the primary efficacy endpoint and a standard deviation of 3 in both treatment groups.

To be able to conduct confirmatory testing for the secondary endpoints, an alpha-adjustment will need to be taken into consideration. The sample size is, therefore, expected to be approximately 450 subjects (225 receiving placebo and 225 receiving RTX-GRT7039).

Assuming a screening failure rate of about 40%, approximately 750 subjects are planned to be screened to randomize 450 subjects for the primary analysis (225 evaluable subjects for the RTX-GRT7039 treatment arm, and 225 for the placebo arm, 1:1 randomization).

1.5.2 Subject populations

Safety Analysis Set

All subjects with at least 1 IMP administration (including incomplete administrations)

Analyses on the Safety Analysis Set (SAF) will be conducted based on actual treatment received.

Full Analysis Set

All randomly assigned subjects with at least 1 IMP administration (including incomplete administrations)

Analyses on the Full Analysis Set (FAS) will be conducted based on the treatment as randomized (i.e., based on planned treatment).

1.5.3 Statistical methods and analysis

To evaluate the primary endpoint, the WOMAC pain subscale with a 48 hour recall period will be assessed weekly using e-diaries. The WOMAC pain subscale is comprised of 5 questions regarding the amount of pain experienced due to osteoarthritis in the index knee in the past 48 hours using an 11-point (0-10) NRS. The WOMAC pain subscale score is calculated as the mean of the scores from the 5 individual questions, which may not be a whole (integer) number. The baseline WOMAC pain subscale score is defined as the assessment made at the Randomization Visit (V2).

The estimand of interest for the primary efficacy analysis is the difference in mean change from baseline in 48-hour WOMAC pain subscale at Week 12 in the index knee using an 11-pt NRS (0-10) between RTX-GRT7039 and placebo, in subjects who initiate treatment, as if substantial changes in background medication or addition of new analgesics were not available.

The primary efficacy analysis will be performed using a mixed-effects model for repeated measures (MMRM). The model will include fixed effects of treatment, country/region, gender, time (corresponding to trial week), and treatment-by-time interaction. The baseline value will be a covariate. Time will be included in the MMRM analysis to account for the correlation in repeated measures within-subject. An unstructured [UN] covariance matrix will initially be fitted to the MMRM. If the analysis model does not converge, then the Toeplitz [TOEP] will be used as the covariance matrix. The auto-regressive (1) [AR(1)] covariance matrix will be used if TOEP also fails to converge. In the event that AR(1) also results in non-convergence, the compound symmetry covariance matrix [CS] will be used.

Individual sites will be pooled by geographic region. Geographic regions will be defined in the SAP and correspond to the country/region used in the stratified randomization.

For the primary analysis the following intercurrent events will be considered:

- A substantial change in the analgesic osteoarthritis background therapy (optimal SOC) will be considered as an intercurrent event. For this, a hypothetical policy estimand strategy is applied. Values after the occurrence of the intercurrent event will be excluded from the analyses and will be imputed by the baseline value.
- Any other substantial change in analgesic medication given for any other indication will be considered an intercurrent event. For this, a hypothetical policy estimand strategy is applied. Values after the occurrence of the event will be excluded from the analyses and will be imputed by the last observation.

Sensitivity analyses will be performed.

Subgroup analyses may be considered if appropriate and will be specified in the SAP.

1.5.4 Interim analysis

Not applicable as no interim analysis is planned.

1.6 Schedule of events

Trial Period	**Screening Period**	**Treatment and Follow-up Period**						
Visit	**V1 (Screening Visit)**	**V2[a] (Randomization Visit)**	**V3 ± 3 days**	**V4 ± 3 days**	**V5 ± 3 days**	**V6 ± 3 days**	**V7 ± 7 days**	**V8 Final Visit or Early Termination Visit [b] ± 7 days**
Day	**-30 to -1**	**1**	**8**	**29**	**85**	**183**	**267**	**365**
Week			**1**	**4**	**12**	**26**	**38**	**52**
Obtain informed consent	X							
Collect demographic data	X							
Record general and musculoskeletal specific medical history [c]	X							
Record prior medications/therapies [c]	X							
Record concomitant medications/therapies	X	X	X	X	X	X	X	X
Perform physical exam [d]	X	X	X [d]	X [d]	X [d]	X	X [d]	X
Perform scheduled X-rays of index knee	X [e]					X		X
Perform MRI of the index knee [f]	X [g]							
Record vital signs	X	X	X [h]	X [h]	X	X [h]	X	X
ECG	X	X				X		X
Check inclusion/exclusion criteria	X	X						

Trial Period	**Screening Period**	**Treatment and Follow-up Period**						
Visit	**V1 (Screening Visit)**	**V2[a] (Randomization Visit)**	**V3 ± 3 days**	**V4 ± 3 days**	**V5 ± 3 days**	**V6 ± 3 days**	**V7 ± 7 days**	**V8 Final Visit or Early Termination Visit [b] ± 7 days**
Day	**-30 to -1**	**1**	**8**	**29**	**85**	**183**	**267**	**365**
Week			**1**	**4**	**12**	**26**	**38**	**52**
Train subjects on e-diaries	X							
Dispense e-diary	X							
Placebo response reduction training and accurate pain reporting training for subjects	X				X			
Ask subject to record WOMAC pain subscale score on the non-index knee in their e-diary	X							
Ask subject to record WOMAC assessments on the index knee in their e-diaries [i]	X	X	X	X	X	X	X	X
Check e-diary compliance [j]	X	X	X	X	X	X	X	X
Dispense subject trial card	X							
Ask subject to complete questionnaires on tablet computer at site								
PGIC					X	X	X	X
PGA		X	X	X	X	X	X	X
PSFS		X	X	X	X	X	X	X
EQ-5D-5L		X	X	X	X	X	X	X

Trial Period	**Screening Period**	**Treatment and Follow-up Period**						
Visit	**V1 (Screening Visit)**	**V2[a] (Randomization Visit)**	**V3 ± 3 days**	**V4 ± 3 days**	**V5 ± 3 days**	**V6 ± 3 days**	**V7 ± 7 days**	**V8 Final Visit or Early Termination Visit [b] ± 7 days**
Day	**-30 to -1**	**1**	**8**	**29**	**85**	**183**	**267**	**365**
Week			**1**	**4**	**12**	**26**	**38**	**52**
SF-36		X			X	X	X	X
TSQM					X	X	X	X
Randomization to treatment		X						
Pre-treatment with ropivacaine intra-articular injection		X						
Collect urine and perform pregnancy (if applicable) and drugs of abuse testing	X	X						
Safety laboratory	X	X				X		X
Intra-articular IMP injection		X						
Ask subjects to rate their procedural pain [k]		X						
Record adverse events [l]	X	X	X	X	X	X	X	X
Collect e-diary								X
Collect subject trial card								X

a) All other assessments are completed prior to IMP administration, assessment of procedural pain, and recording of adverse events.

b) Subjects who discontinue or who are discontinued earlier from the trial will have the Final Visit/Early Termination Visit as a last trial visit, if possible.

c) At Screening, a comprehensive musculoskeletal medical history is obtained. History of insufficient pain relief, inability to tolerate or contraindication to take the specified SoC treatments should be collected. Any prior use of medication used to treat osteoarthritis and osteoarthritis pain and prior use for all other medications should be collected.

d) Physical examination of only the index knee at specified visits.

e) To be performed at V1 or between V1 and V2, only if all inclusion criteria and no exclusion criteria that can be evaluated at Screening are met.

f) Follow up MRIs may be performed in case of index knee-related adverse events or unexpected increased pain scores of severe intensity, which are persistent for at least 2 weeks despite treatment with analgesic medication according to investigator judgement.

g) Historical MRI scans from 30 days before screening is permitted, provided no relevant change in pain occurred since then (according to investigator and subject judgement) and the protocols described in Section 12.4.6 are followed. For all other subjects, MRI scans should be conducted prior to V2 once all other screening criteria have been met (e.g., inclusion and exclusion criteria).

h) Body weight and BMI are not recorded at these visits

i) In the first week after an intra-articular IMP injection, subjects will assess the WOMAC pain and physical function subscales with 48-hour recall period every 2 days. After the first week post IMP injection, the WOMAC pain subscale score will continue to be assessed weekly in the e-diary and the complete WOMAC will be assessed and recorded in the subject's e-diary at the visits specified in this SoE.

j) Starting after Visit 1, until the Final Visit, the e-diary will be reviewed for completeness prior to initiating any treatment-associated procedures; the subject will be re-trained if needed.

k) Subjects will be asked to rate their procedural pain (current pain intensity on the 11-point [0-10] NRS) using the tablet computer at the site at the following time points: -0.5 h, 0 h, 0.5 h, 1 h, 1.5 h and 3 h relative to intra-articular IMP injection, with time point 0 occurring immediately before IMP injection.

l) Adverse events of sensory loss and decrease of motor function at the index knee/the leg of the index knee should be evaluated by additional physical examinations, X-rays, MRIs as deemed required by the investigator.

BMI = body mass index; ECG = electrocardiogram; e-diary = electronic diary; EQ-5D-5L = EuroQol-5 Dimension Health Questionnaire 5 Levels; exam = examination; IMP = investigational medicinal product; MRI = magnetic resonance imaging; NRS = numeric rating scale; PGIC = patient global impression of change; PGA = patient global assessment of osteoarthritis; PSFS = patient-specific functional scale; SF-36 = Short Form-36 Health Survey; SoC = standard of care; SoE = schedule of events; TSQM = Treatment Satisfaction Questionnaire for Medication; V = Visit; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index