2 SYNOPSIS

Name of Sponsor/Company	**Name of Finished Product**	**Name of Active Ingredient**
Grünenthal GmbH	RTX-GRT7039	Resiniferatoxin

Protocol Number: KF7039-03

Title of Study: A single-arm, open-label, Phase III trial to evaluate the safety and tolerability of intra-articular injections of RTX-GRT7039 in subjects with moderate to severe pain associated with osteoarthritis of the knee

Investigators and Study Centers: The international coordinating Investigator was Prof Philip Conaghan. This study was conducted in six countries including Bulgaria, Japan, Poland, Romania, South Africa, and the United Kingdom

Study Period (years): 2.75 years **Date of First Enrollment:** 15 Aug 2022 **Date of Last Completion:** 15 May 2025	**Phase of Development**: Phase III

Background and rationale: This was a Phase III open-label safety study that evaluated the safety and tolerability of RTX-GRT7039 administered as an intra-articular injection or repeated intra-articular injections of 400 ng RTX-GRT7039 in participants with 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. Participants received up to four repeated injections between 3 and 12 months after the first injection based on the persistence or return of pain, with a minimum interval of 12 weeks between injections. This Phase III open-label safety study also aimed to evaluate the safety and tolerability of intra-articular injection in the index and non-index knee for participants with symptoms of bilateral knee osteoarthritis.

Objectives and Endpoints: The main objective of this study was to assess the safety and tolerability of intra-articular RTX-GRT7039 injection. The primary endpoint was the incidence of treatment-emergent adverse events (TEAEs) and incidence of TEAEs leading to discontinuation.

Methodology: This was a Phase III, open-label, single-arm study in participants with moderate to severe pain associated with osteoarthritis of the knee despite receiving continued treatment with optimal SoC or who are unable to receive SoC treatment due to contraindications or intolerability. Participants received either unilateral injections of RTX-GRT7039 into the index knee or bilateral intra-articular injections of RTX-GRT7039 in the index knee and non-index knee, as determined by their osteoarthritis pain status.

For unilateral painful knee osteoarthritis, participants received an intra-articular injection of 400 ng RTX GRT7039 at Day 1 in the index knee. Repeated intra-articular injections of 400 ng RTX GRT7039 were offered to eligible participants between 3 and 12 months after the first injection based on the persistence or return of pain. Eligibility for a repeated injection was assessed starting at Week 12. The minimum interval between repeated injections was 12 weeks, thereby allowing a maximum of four repeated injections (ie, a total of five injections) into the index knee until 12 months after the first injection. Efficacy and safety assessments were performed as indicated in the Schedule of Events (SoE).

For bilateral painful knee osteoarthritis, participants received an intra-articular injection of 400 ng RTX GRT7039 at Day 1 in the most painful knee (considered the index knee). In case of equal pain for both knees, the knee on the participant's dominant side was designated the index knee. An intra-articular injection of 400 ng RTX-GRT7039 in the non-index knee, if applicable, could be administered at Visit 3 (Day 8) after a gap of 1 week following the first Investigational Medicinal Product (IMP) injection in the index knee. A repeated intra-articular injection of RTX GRT7039 400 ng into either knee was offered to eligible participants between 3 and 12 months after the first injection based on the persistence or return of pain. Eligibility of the participant for a repeated injection was assessed starting at Week 12. The minimum interval between repeated injections was 12 weeks, thereby allowing a maximum of four repeated injections (ie, a total of five injections) into either knee until 12 months after the first injection.

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The study comprised of a Screening Period and an open-label Treatment and Follow-up Period, from Day 1 (Day 1, IMP injection index knee) up to Visit 8 or 9 at 52 weeks to 78 weeks.

Number of Participants (planned and analyzed): 715 planned
Safety Analysis Set: 714

Diagnosis and Main Criteria for Inclusion: Eligible participants were males and females aged ≥18 years with a diagnosis of osteoarthritis of the knee based on American College of Rheumatology criteria and a functional capacity class of I to III. Participants were required to have a baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score of ≥4 in one knee (eligible for mono-articular injection) or both knees (eligible for bilateral injections) at Screening and at baseline. Additionally, participants had to have a Kellgren-Lawrence (K-L) grade of 2 to 4 in the index knee and the non-index knee in the case of bilateral injections, and a documented history of insufficient pain relief with optimal SoC.

Test Product, Dose and Mode of Administration, Batch Number: 5 mL RTX-GRT7039 solution for intra-articular injection was constituted from two vials, 1.6 µg/mL RTX supplied in 0.4 mL ethanolic solution in one vial and the second vial containing 8 mL D-α-tocopherol polyethylene glycol succinate (TPGS) buffer. Participants received either unilateral (index knee) or bilateral (index and non-index knee) injections assisted by ultrasound if available. Premedication (ie, intra-articular local anesthetic, or non-intra-articular pretreatment approaches such as systemic pain medication) was administered as per local hospital policy before intra-articular injection of IMP.

The tables below present the batch numbers for RTX-GRT7039, buffer, and ropivacaine:

RTX Investigational Medicinal Product Packaging Batch	Active RTX Manufacturing Batch	Buffer RTX Manufacturing Batch
19620001	F21270	F21209
19620002	NA	NA
19620003	F22179	F21209
19620004	F22222	F21209
19620005	F22253	F22134
19620006	F23143	F22283
19620007	F23143	F23184
19620008	F23143	F23184
19620009	F23234	F21209
19620011	F23236	F23184

Ropivacaine Packaging Batch	Ropivacaine Marketed Batch	Country Use
19480002	TAFE	Poland, South Africa
19480019	TAGL	Poland, Romania. United Kingdom

Duration of Treatment: 52-78 weeks, including up to five injections in the index knee and non-index knee (if applicable) between 3 and 12 months (starting at Week 12)

Control Product, Dose and Mode of Administration, Batch Number:

Batch numbers for ropivacaine and buffer are listed above with the batch numbers for RTX-GRT7039.

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Endpoints: All safety and efficacy endpoints are presented in the Clinical Study Protocol, Section 1.2.

Statistical Methods:

Analysis Populations:

Safety Analysis Set – all participants with at least one IMP administration (including incomplete administrations).

Primary Endpoint:

Incidence of TEAEs.

Incidence of TEAEs leading to discontinuation.

Secondary Endpoints:

Analyses of secondary endpoints were performed using the following outcomes:

- Incidence of TEAEs representing structural changes of the knee joint as visualized by the imaging methods (X-ray and/or magnetic resonance imaging [MRI])
- Change from baseline to Week 12 in the WOMAC pain subscale score for the index and the non-index (where applicable) knee
- Change from baseline to Week 12 in WOMAC physical function subscale, WOMAC stiffness subscale, pain when walking on a flat surface (WOMAC A1) and total score
- Responder analysis (percentage of participants with ≥30%, 50%, and 70% reduction in WOMAC A1 and WOMAC pain subscale score [using 11 point [0-10] NRS] for the index knee and the non-index knee [where applicable] from baseline to Week 12)
- Patient Global Impression of Change (PGIC) at Week 12; Patient-specific Functional Scale (PSFS): change from baseline to Week 12
- Quality-of-life (QoL) questionnaire - 5-level EuroQol-5 Dimension Health Questionnaire (EQ-5D-5L): change from baseline to Week 12
- QoL questionnaire – Short Form-36® Health Survey (SF-36): change from baseline to Week 12
- Pharmacokinetic parameters included area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification (AUC_{0-t}); the maximum plasma concentration (C_{max}); time to reach maximum plasma concentration (t_{max}); and half-life ($t_{1/2}$), only in Japanese participants.

Safety Analysis:

All safety data were summarized descriptively by treatment group, using the Safety Analysis Set.

Summary of Results:

Participant disposition:

Of 1130 participants screened overall, 403 were screen failed and a total of 714 participants received at least one injection of RTX-GRT7039 (420 participants were treated unilaterally and 294 were treated bilaterally). Thirteen participants did not receive IMP despite being eligible; for 12 participants this was due to withdrawal of consent and for one participant this was due to an adverse event. The median number of IMP injections administered to the index and non-index knee was two injections. The percentage of participants that received only one injection in the index knee was 31.5% and in the non-index knee 34%., The percentage of participants that received two or more injections in the index knee was 68.5% and 66% of participants in the non-index knee. Out of a total of 2391 injections given overall, 2333 (97.6%) injections were administered with intra-articular local anesthetic premedication. The demographics, baseline disease characteristics, general medical history, and medication use (prior and concomitant) of participants enrolled in this study were similar across treatment groups (unilaterally or bilaterally treated participants) and were typical of the target population of participants with osteoarthritis of the knee, though with an overall high proportion of radiographic K-L grade of 3 or 4 (74.5% of all treated knees).

Participant demographic characteristics were overall well-balanced between the unilaterally treated and bilaterally treated groups. The median age was 66.0 years in both groups, and the majority of participants (84.7%) were below 75 years of age. Overall, most participants were female (548 [76.8%]), White (574 [80.4%]) with an average (± SD) body mass index (BMI) of 31.6 (± 4.5) kg/m^2.

Safety:

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- Overall, intra-articular administration of 400 ng RTX-GRT7039, including unilateral and bilateral multiple repeat doses (up to five injections, at least 12 weeks apart per knee) in this study was considered safe and well-tolerated
- The overall incidence of TEAEs was similar in the unilaterally and bilaterally treated groups (55.0% and 55.4%). The majority of TEAEs were mild (19.3%) or moderate (26.6%) in intensity.
- TEAEs leading to study discontinuation were rare (1.3%), occurred at similar rates in the unilaterally and bilaterally treated groups, and none were considered related to the IMP
- The overall incidence of TEAEs related to IMP was 9.9%
- The unilaterally versus bilaterally treated groups generally showed little difference in the incidence of common TEAE Preferred Terms. The most frequently reported (in ≥5% participants in any treatment group) Preferred Terms in the unilaterally and bilaterally treated groups were Procedural pain (7.1% and 8.2%), Osteoarthritis (5.2% and 3.1%), and Arthralgia (4.0% and 5.1%).
- Review of TEAEs starting on the day of and during the first week after IMP administration showed a decrease in the incidence of TEAEs reported over multiple injections
- Subgroup analyses for age and baseline osteoarthritis severity according to K-L grade suggested that participants ≥65 years of age and with a K-L grade of 3 and 4 may have had a slightly higher incidence of TEAEs
- The incidence of treatment-emergent serious adverse events (SAEs) was slightly higher in the unilaterally than in the bilaterally treated groups (9.5% and 6.1%). Only one SAE (loss of consciousness, which resolved after 1 minute) was assessed as related to IMP by the Investigator (ie, 1 SUSAR), none were assessed by the investigators as related to local anesthetic or injection procedures. Five SAEs were assessed by the Sponsor as related to the injection procedure.
- Four deaths, two in each treatment group were reported in this study. All of these were cardiac-related TEAEs, and none were considered related to the IMP.
- No trends or patterns were identified in the analyses of clinical laboratory tests, vital signs, ECG results, or imaging data
- Ten TEAEs representing structural changes of the knee joint as visualized by imaging methods were reported for seven participants, five in the bilaterally treated and two in the unilaterally treated group. One TEAE, RPOA type 1, was assessed by the Investigator as related to the IMP because a possible association could not be ruled out; however, it should be noted that the participant had a pre-existing meniscal tear, which is a risk factor for RPOA (Foreman et al., 2021). The remaining 9 TEAEs representing structural changes were not assessed as related to IMP.
- No pregnancies occurred in this study
- No new safety concerns were noted for RTX-GRT7039 from the analysis of SAEs, TEAEs leading to study discontinuation and the numbers of participants having total knee arthroplasty
- Efficacy:
- The secondary endpoints of change from baseline in the WOMAC pain and WOMAC physical function subscale score for the index and non-index knee at Week 12 showed a substantial reduction in both subscale scores
- These changes from baseline were overall consistent with the observations in the earlier studies of this investigational product

Conclusions:

Based on the data observed in KF7039-03, intra-articular administration of 400 ng RTX-GRT7039, including unilateral and bilateral repeat dosing (up to five injections per knee, administered at least 12 weeks apart) was considered safe and well tolerated. The overall incidence of TEAEs was 55.2%, and the majority were mild (19.3%) or moderate (26.6%) in intensity. TEAEs leading to discontinuation were rare (1.3%) and none were related to the IMP. The incidence of SAEs was 8.1%, with only 1 out of 70 events (Loss of consciousness) assessed by the Investigator as related to the IMP. No new safety concerns were identified from the analysis of TEAEs, SAEs, deaths, or structural changes of the knee joint. In terms of efficacy, compared to baseline, a substantial reduction of the WOMAC pain and WOMAC physical function subscale score, indicating reduction

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of pain, was observed in both the index and non-index knee at Week 12. The safety and efficacy findings in this study were overall consistent with those observed in earlier studies of RTX-GRT7039.

Date of the Report: 09 October 2025