COVER PAGE

Official Title	A Phase 2 Study to Evaluate the Safety and Efficacy of RTA 901 in Patients With Diabetic Peripheral Neuropathic Pain
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Name of Sponsor/Company:	Biogen MA Inc./Biogen Idec Research Limited
Name of Finish Product:	RTA 901/BIIB143
Name of Active Ingredient:	RTA 901/BIIB143
Study Indication	Diabetic peripheral neuropathic pain

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2. STUDY SYNOPSIS

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Title of Study:

A Phase 2 Study to Evaluate the Safety and Efficacy of RTA 901 in Patients With Diabetic Peripheral Neuropathic Pain

Number of Study Sites and Countries:

A total of 73 sites were activated for participant screening in the United States; 67 sites screened participants, and 48 sites randomized participants.

Study Period: Date of first treatment: 03 August 2023 End of Study date: 15 November 2024	**Phase of Development:** 2

Study Objectives:

Primary Efficacy Objective:

- To assess the efficacy of RTA 901 based on change from baseline in the average daily pain intensity score using the Numeric Pain Rating Scale (NPRS) after 12 weeks of treatment

Primary Safety Objective:

- To assess the safety and tolerability of RTA 901 during and following the Treatment Period

Secondary Objectives:

- To assess the efficacy of RTA 901 in achieving at least 30% decrease in the NPRS pain intensity score after 12 weeks of treatment
- To assess the efficacy of RTA 901 in achieving at least 50% decrease in the NPRS pain intensity score after 12 weeks of treatment
- To assess the percentage of participants using rescue medication for diabetic peripheral neuropathic pain (DPNP) treatment during the Treatment Period, as well as the quantity and timing of such medication use during the Treatment Period
- To assess the Daily Sleep Interference Scale (DSIS) score after 12 weeks of treatment

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[redacted]

Study Design:

Study 297DP201 was planned to be conducted in 2 parts: Part 1 investigated the efficacy and safety of 10 mg and 80 mg doses of RTA 901 administered once daily (QD), and Part 2 was planned to investigate doses of RTA 901 between 1 mg and 80 mg QD based on the planned interim E-R analysis for efficacy in Part 1. Randomization was planned to be stratified by standard of care pain medication (duloxetine, pregabalin, or gabapentin) using randomization and trial supply management.

The study did not meet the Part 1 primary efficacy endpoint required to proceed to Part 2 and was terminated on 12 February 2025. Study termination was not due to safety or tolerability. This abbreviated report presents results from Part 1 of the study.

During Screening, participants received an e-diary and were instructed to use it to record their NPRS score and rescue medication usage at bedtime and DSIS score upon waking.

After Screening, all eligible, consenting participants proceeded to the Run-in Period, which included 1 clinic visit during a 14 (± 2)-day period prior to Day 1. Participants who successfully met the Run-in eligibility criteria were enrolled and received single-blind placebo QD in the morning.

During the double-blind Treatment Period, participants were randomized 1:1:1 to either RTA 901 (10 mg or 80 mg) or placebo at Day 1 and stratified by standard of care medication for DPNP (duloxetine, pregabalin, or gabapentin). Following randomization, study treatment was dispensed, and participants were instructed to self-administer 3 capsules orally (1 capsule from each bottle in their study treatment kits) in an early fasted state.

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Participants were instructed to use the rescue medication as needed for DPNP and to continue recording, via the e-diary, their NPRS score and rescue medication use at bedtime and DSIS score upon waking.

[redacted]

Number of Participants (Planned and Analyzed):

Planned: Approximately 192 participants in Part 1

Analyzed: 206 participants were dosed in Part 1

Study Population:

Key inclusion criteria:

- Diagnosis of type 1 diabetes mellitus or type 2 diabetes mellitus at least 1 year prior to Screening
- Clinical diagnosis of DPNP defined as symptomatic distal symmetric polyneuropathy (secondary to diabetes) in the lower extremities, which may have included symptoms of pain that was burning, lancinating, tingling, or shooting (electric shock-like). Pain in the lower extremities may have occurred with paresthesia or dysesthesia (unpleasant sensations of burning). Neuropathic pain may have been accompanied by an exaggerated response to painful stimuli (hyperalgesia) and pain evoked by light touch or contact, e.g., with socks, shoes, and bedclothes (allodynia)
- A history of chronic pain related to DPNP present for at least 6 months prior to Screening
- Currently taking only 1 allowed prescribed standard of care pain medication for managing DPNP at a stable dose (not exceeding the maximum dose in the prescribing information) for approximately 4 weeks prior to Screening
- NPRS pain intensity score ≥ 4 on an 11-point scale at Screening
- Participant had a ≤ 3-point decline in NPRS pain intensity score during Run-in, which was calculated using the average score during the last 7 days of screening compared to the average score during the last 7 days of Run-in

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Key exclusion criteria:

- Had a condition other than DPNP that could confound the assessment of pain (e.g., fibromyalgia or regional pain caused by lumbar or cervical compression)
- Any acute or chronic medical condition or concurrent therapy (pharmaceutical or otherwise) which, in the opinion of the Investigator, could potentially have adversely impacted participant safety, response to study drug, or interfered with study assessments
- Use of any prohibited medication or device or prohibited procedure as defined in the protocol (refer to Run-in Period exclusion criteria 19 and 20 and Randomization exclusion criteria 2 and 3 for specific prohibited medications, devices, and procedures)

Study Treatment, Dose, and Mode of Administration:

RTA 901 capsules (10 mg or 80 mg) administered orally QD

Reference Therapy, Dose, and Mode of Administration:

Matching placebo capsules administered orally QD

Duration of Treatment and Follow-Up:

The duration for the study was approximately 20 weeks:

- Screening Period up to 2 weeks
- Run-in Period of 2 weeks
- Treatment Period of 12 weeks
- Follow-up Period of 4 weeks

Criteria for Evaluation:

The following is a description of all primary and secondary efficacy, [redacted] and safety assessments that were to be assessed for this study.

Efficacy:

Primary

- Change from baseline in the average daily NPRS pain intensity score during Week 12

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Secondary

- Proportion of participants who achieved at least a 30% decrease from baseline in the Week 12 average NPRS pain intensity score
- Proportion of participants who achieved at least a 50% decrease from baseline in the Week 12 average NPRS pain intensity score
- Proportion of participants who used rescue medication for DPNP, as well as the quantity and timing of such medication use during the Treatment Period
- Change from baseline in the average DSIS score during Week 12

[redacted]

Safety:

- Frequency, intensity, and relationship to study treatment of adverse events (AEs) and serious adverse events (SAEs) and change from baseline in the following assessments: physical examinations, vital sign measurements, electrocardiograms (ECGs), clinical laboratory measurements, and body weight

Statistical Methods:

Planned Analyses:

After all randomized participants completed the Part 1 End of Study (EOS) visit (Week 16), the formal planned analyses were conducted to evaluate the efficacy, [redacted] and safety of RTA 901 (10 mg or 80 mg) versus placebo.

Efficacy:

All efficacy analyses were performed on the scheduled visits/study weeks for the intent-to-treat (ITT) population. For NPRS and DSIS, the visit referred to study week. The primary hypothesis tested was whether there was a greater mean reduction from baseline in NPRS pain intensity for the RTA 901 arms compared with the placebo arm after 12 weeks of double-blind treatment.

For efficacy analyses, a sequential stepwise testing was performed on the primary endpoint for RTA 901 arms (80 mg, 10 mg) compared to the placebo arm to control the overall type I error at 2-sided alpha level of 0.05. First, the RTA 901 80 mg arm was compared with the placebo arm. If the p-value was < 0.05, the RTA 901 10 mg arm was to be compared to the placebo arm.

Primary Endpoint:

Change from baseline in weekly average NPRS score was evaluated by mixed model repeat measures (MMRM). The MMRM model included baseline NPRS score, visit, treatment, the interaction of treatment and visit, the interaction of baseline NPRS score and visit. The least squares (LS) means with standard errors of each dose level at each visit as well as of treatment differences between the RTA 901 arm (10 mg, 80 mg) compared with the placebo arm at each visit are provided, along with 95% confidence interval and p-value at each visit. Descriptive statistics for observed data, including NPRS score and change from baseline in the NPRS weekly average scores, were evaluated by treatment arm and visit (including the EOS visit) with descriptive statistics (mean, standard deviation [SD], median, first and third quartiles, range) in the ITT population.

The change from baseline of weekly average NPRS score was also analyzed for the per-protocol population using the same MMRM model as for the ITT population as a sensitivity analysis. A sensitivity analysis was performed excluding any data after a participant discontinued randomized study treatment.

Secondary Endpoints:

- The proportion of participants who achieved $\geq 30\%$ and $\geq 50\%$ decrease from baseline in the Week 12 average NPRS pain intensity score was analyzed with logistic regression using terms for treatment and baseline NPRS score. The odds ratio, its 95% confidence interval (CI), and the p-value for RTA 901 doses compared to placebo are provided. The proportion of participants who had $\geq 30\%$ and $\geq 50\%$ decrease from baseline at each week was summarized by visit and treatment arm. A responder curve of the proportion of participants achieving various level of percentage reduction thresholds from baseline in the weekly average NPRS score at Week 12 was generated.

- A logistic regression model was performed on the proportion of rescue medication use at Week 12, including baseline NPRS score and treatment. The odds ratio, its 95% CI, and the p-value for RTA 901 doses compared to placebo are provided.

- The amount of rescue medication used per day during the 12-week treatment period was calculated as the total dosage recorded divided by total days of study drug exposure during the double-blind

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Treatment Period. The rescue medication used per day was summarized using the mean, standard deviation, minimum, median, and maximum by treatment group. Rank analysis of covariance (ANCOVA) was performed by category of rescues medication use (paracetamol, nonsteroidal anti-inflammatory drugs [NSAIDs]). The model included rank of baseline NPRS and treatment group. P-values for the comparisons of RTA 901 arms (10 mg, 80 mg) compared with the placebo arm are provided.

- The proportion of first occurrence of rescue medication use was estimated using the Kaplan-Meier product limit method. Estimates of median time to first occurrence of rescue medication use, percentiles (fifth, tenth, twenty-fifth, fiftieth, and seventy-fifth) and associated 95% confidence limits are provided. P-values from a log-rank test are also provided.

- Descriptive statistics for observed data, including actual value and change from baseline in weekly average DSIS score, were evaluated by treatment arm and visit (including EOS visit) with descriptive statistics (mean, SD, median, first and third quartiles, range) in the ITT population. Change from baseline in weekly DSIS average score was analyzed by MMRM. The MMRM model included baseline DSIS score, visit, treatment, the interaction of treatment and visit, the interaction of baseline DSIS score and visit. Unstructured covariance was used. All analysis visits up to Week 12 were utilized. LS means and treatment differences will be presented with 95% confidence intervals, standard errors, p-values at each visit. A line plot of LS mean changes from baseline over time was generated. A sensitivity analysis was performed excluding any data after a participant discontinued randomized study treatment.

[redacted]

Safety:

The number and percent of participants with AEs were summarized for each treatment arm. Changes from baseline to each scheduled time point for physical examinations, vital sign measurements, ECGs, clinical laboratory measurements, and body weight were summarized by treatment arm.

Sample Size Calculations:

The sample size for Part 1 was based on a dose-ranging scheme to evaluate initial safety, efficacy, [redacted] of RTA 901 in participants with DPNP. With an assumed treatment difference of 1.2 points and standard deviation

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of 2.4 points in NPRS score, 64 participants per arm provided approximately 80% power with 2-sided alpha of 0.05.

Results:

Participant Accountability:

There were 770 participants screened, and 300 participants entered the Run-in Period of the study. A total of 209 participants were randomized, including 69 participants in the placebo arm and 70 participants each in the RTA 901 10 mg arm and 80 mg arm. The first participant was randomized and dosed with study treatment on 03 August 2023. The EOS date was 15 November 2024.

One participant in each treatment arm withdrew from the study prior to double-blind dosing, and the remaining 206 participants were dosed in the double-blind Treatment Period. Sixty-eight participants received placebo, 69 participants received RTA 901 10 mg, and 69 participants received RTA 901 80 mg. A total of 190 participants (90.9%) completed the study (65 participants [94.2%] in the placebo arm, 63 participants [90.0%] in the RTA 901 10 mg arm, and 62 participants [88.6%] in the RTA 901 80 mg arm), and 19 participants (9.1%) withdrew from the study.

In the placebo arm, 2 participants (2.9%) withdrew from the study due to AEs and 2 participants (2.9%) due to withdrawal by participant. In the RTA 901 10 mg arm, 2 participants (2.9%) withdrew from the study due to AEs, 2 participants (2.9%) due to withdrawal by participant, and 1 participant (1.4%) each due to lost to follow-up, noncompliance with study treatment, and failure to meet randomization criteria. In the RTA 901 80 mg arm, 4 participants (5.7%) withdrew from the study due to withdrawal by participant, 2 participants (2.9%) due to protocol deviations, and 1 participant (1.4%) each due to AEs and failure to meet randomization criteria.

Demographics and Baseline Disease Characteristics:

Demographics (age, sex, ethnicity, race, height, weight, and body mass index) were balanced across treatment arms. Overall, 111 participants (53.9%) were ≥ 65 years old, and the mean (standard deviation [SD]) participant age was 64.3 (8.33) years. A total of 152 participants (73.8%) overall were White and 106 participants (51.5%) were female.

Most participants (203 participants [98.5%]) had type 2 diabetes. At baseline, the overall mean (SD) duration of diabetes diagnosis was 15.93 (10.163) years, and the mean durations were balanced across treatment arms. The overall mean (SD) glycated hemoglobin and fasting glucose at baseline were 7.50% (1.220) and 7.57 (2.994) mmol/L, respectively, and both parameters were balanced across treatment arms. Overall mean (SD) duration since DPNP diagnosis was 7.21 (6.270) years, and most participants (> 84.0% in each treatment arm) used gabapentin as DPNP standard of care.

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Efficacy:

Treatment with either RTA 901 dose (10 mg or 80 mg) did not statistically significantly improve the NPRS score at Week 12 compared with placebo.

Primary endpoint was not met:

- There was no statistically significant difference in the NPRS score at Week 12 between either RTA 901 arm and the placebo arm (RTA 901 80 mg arm versus the placebo arm, p = 0.8223; RTA 901 10 mg arm versus the placebo arm, p = 0.5224).
  - LS mean differences (95% CI) between the RTA 901 10 mg and RTA 901 80 mg arms compared with the placebo arm were 0.23 (-0.468, 0.918), and -0.08 (-0.772, 0.614), respectively.

Secondary endpoints:

- There was no statistically significant difference in the proportion of ≥ 30% and ≥ 50% responders (i.e., ≥ 30% or ≥ 50% improvement in pain from baseline to Week 12) in either RTA 901 arm compared with the placebo arm.
  - There were 26 participants (38.2%) who achieved ≥ 30% decrease from baseline in NPRS score in the placebo arm, 22 participants (31.9%) in the RTA 901 10 mg arm, and 28 participants (40.6%) in the RTA 901 80 mg arm (logistic regression adjusted odds ratio of 0.74 [p = 0.3995] for the RTA 901 10 mg arm versus the placebo arm; odds ratio of 1.08 [p = 0.8329] for the RTA 901 80 mg arm versus the placebo arm).
  - There were 17 participants (25.0%) who achieved ≥ 50% decrease from baseline in NPRS score in the placebo arm, 12 participants (17.4%) in the RTA 901 10 mg arm, and 18 participants (26.1%) in the RTA 901 80 mg arm (logistic regression adjusted odds ratio of 0.62 [p = 0.2556] for the RTA 901 10 mg arm versus the placebo arm; odds ratio of 1.04 [p = 0.9204] for the RTA 901 80 mg arm versus the placebo arm).
- There was no statistically significant difference in the proportion of participants who used rescue medication in either RTA 901 arm compared with the placebo arm.
  - At Week 12, rescue medication was used by 10 participants (14.7%) in the placebo arm, 13 participants (18.8%) in the RTA 901 10 mg arm, and 14 participants (20.3%) in the RTA 901 80 mg arm. There were no statistically significant differences in rescue medication

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use in either RTA 901 arm compared with the placebo arm (logistic regression adjusted odds ratio of 1.53 [p = 0.3685] for the RTA 901 10 mg arm versus the placebo arm; odds ratio of 1.63 [p = 0.2994] for the RTA 901 80 mg arm versus the placebo arm).

- There was no meaningful difference in the time to first rescue medication use between any treatment arms, and the time to first rescue medication use was not statistically significant for either RTA 901 arm compared with placebo (RTA 901 10 mg versus placebo, p = 0.7347; RTA 901 80 mg versus placebo, p = 0.4033, log-rank test).

- LS mean differences in the amount of rescue NSAID use between either RTA 901 arm and the placebo arm were not statistically significant.

  – LS mean (95% CI) differences in the amount of rescue NSAID use in the RTA 901 10 mg arm and RTA 901 80 mg arm compared with the placebo arm were 6.02 (-7.96, 20.00) mg/day and 2.46 (-11.52, 16.44) mg/day, respectively.

- LS mean differences in the amount of rescue paracetamol use between either RTA 901 arm and the placebo arm were not statistically significant.

  – LS mean (95% CI) differences in the amount of rescue paracetamol used in the RTA 901 10 mg arm and RTA 901 80 mg arm compared with the placebo arm were -5.52 (-22.10, 11.06) mg/day and 3.12 (-13.46, 19.70) mg/day, respectively

- The LS mean change from baseline to Week 12 in DSIS score did not show statistically significant differences between either RTA 901 arm and the placebo arm.

- The LS mean (95% CI) difference compared with placebo was 0.16 (-0.511, 0.830) for the RTA 901 10 mg arm and -0.36 (-1.034, 0.309) for the RTA 901 80 mg arm.

[redacted]

Safety:

RTA 901 (10 mg or 80 mg) was generally safe and well tolerated, with no unexpected safety findings identified during the study. Most TEAEs observed were consistent with the population under study.

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- Overall, 117 participants (56.8%) experienced at least 1 TEAE.
- Most TEAEs were mild or moderate in severity and not related to study treatment. The most common (incidence > 10.0% overall) TEAEs by SOC were Infections and infestations, Investigations, and Metabolism and nutrition disorders. The most common (incidence ≥ 2.0% in any treatment arm) TEAEs by PT were urinary tract infection, lipase increased, upper respiratory tract infection, blood creatine phosphokinase increased, hyperkalemia, and fall.
- Overall, 5 participants (2.4%) experienced severe TEAEs, including supraventricular tachycardia (1 participant in the placebo arm), abdominal pain lower (1 participant in the placebo arm), diabetic ketoacidosis (1 participant in the placebo arm), neuropathy peripheral (1 participant in the RTA 901 80 mg arm), and hematuria (1 participant in the RTA 901 10 mg arm).
- A total of 17 participants (8.3%) experienced TEAEs that were considered related to study treatment (13 participants [9.4%] in the pooled RTA 901 arms and 4 participants [5.9%] in the placebo arm). There were no trends in the incidence of related TEAEs by treatment arm, and at the PT level, no related TEAEs occurred in more than 1 participant.
- No deaths were reported in the study. A total of 10 participants (4.9%) had an SAE. No SAEs were considered related to study treatment, and no SAE occurred in more than 1 participant at the PT level.
- Overall, 6 participants (2.9%) experienced a TEAE that led to discontinuation of study treatment, and 3 participants (1.5%) experienced a TEAE that led to withdrawal from the study. At the PT level, no TEAE that led to study treatment discontinuation or study withdrawal occurred in more than 1 participant.
- Overall, there were no clinically meaningful trends associated with RTA 901 treatment in clinical laboratory parameters, vital signs, ECGs, or physical examination over time.

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Conclusions:

Overall, the 10 mg and 80 mg doses of RTA 901 tested in Part 1 were safe and tolerable, but the study did not meet its primary efficacy endpoint (treatment with RTA 901 did not significantly improve the NPRS score at Week 12 versus treatment with placebo). Therefore, the study, including Part 2, was terminated.

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