CLINICAL TRIAL RESULTS

A Study to Learn About the Safety of RTA 901 and Whether it Reduces Pain in Adults Who Have Diabetic Peripheral Neuropathic Pain

Protocol Number: 297DP201/901-C-2102 (CYPRESS)
Drug Studied: RTA 901 (BIIB143/cemdomespib)
Study Dates:
Start Date: July 28 2023
Completion Date: November 15 2024

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Thank you!

A clinical study participant belongs to the larger research community around the world. By participating in a study, they help researchers answer important health questions and learn about new medications.

In this study, researchers learned more about the **safety of investigational drug RTA 901 and if it reduces pain in people with diabetic peripheral neuropathic pain**. An investigational drug is one that has not yet been approved for use outside of clinical studies. This is also known as the **study drug**.

Biogen, the sponsor of this study, thanks those who participated and believes it is important to share the overall results of the study. If you have questions, please speak with the doctor or staff at the study research center.

Why was this study done?

Researchers are looking for a drug that may help people with **diabetic peripheral neuropathic pain**, also known as **DPNP**.

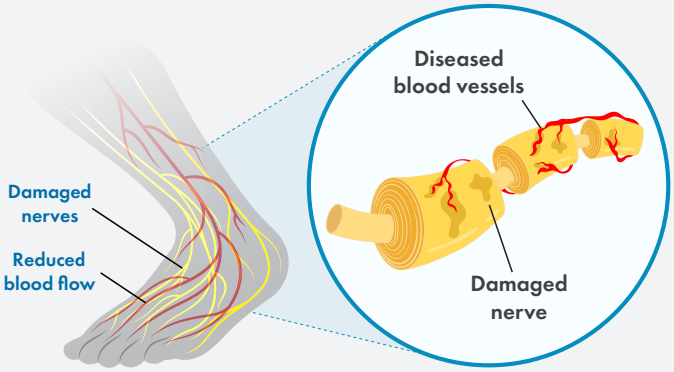
Diabetes is a disorder that affects how the body uses blood sugar. Over time, high blood sugar levels can lead to damage in many parts of the body, including the nerves.

When diabetes causes nerve damage, it is called **diabetic neuropathy**. This can affect any part of the nervous system. The most common form is called **diabetic peripheral neuropathy (DPN)**, which typically affects the feet and legs.

Some people with diabetic peripheral neuropathy also experience pain. It can feel like burning, tingling, or sharp, shooting sensations. This kind of pain is known as **diabetic peripheral neuropathic pain**. DPNP is a long-term condition that can affect a person's daily life and lower their quality of life.

DPNP is common in people with type 1 or type 2 diabetes. There are medications approved to help manage DPNP, but they do not work well for everyone. Some people stop taking them because the side effects are too hard to deal with or the medicine doesn't help enough with their pain. As a result, there is a need for new treatment options.

In this study, researchers tested a drug called **RTA 901**. In earlier studies done in animals, RTA 901 appeared to reduce pain. Researchers wanted to learn more about the safety of RTA 901 and whether it can help manage DPNP.



Nerve cells damaged by diabetes

The main questions that the researchers wanted to answer were:

- Did participants feel less neuropathic pain after taking RTA 901 for 12 weeks?
- How many participants had adverse events or serious adverse events?
- Did the participants' overall health change after taking RTA 901?
- What possible adverse reactions did the participants have?

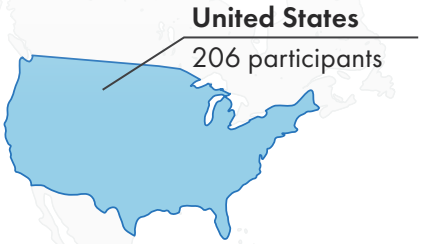
An **adverse event** is an unwanted health problem that may or may not be caused by the study drug. An **adverse reaction** is an adverse event that study doctors reported as possibly being caused by the study drug. This can happen during a clinical study or within a certain amount of time after the study has ended.

Who took part in the study?

The study included a total of **206 participants** who received treatment, which included 100 men and 106 women.

100 (49%) men

106 (51%) women



All participants were between **33 and 79 years old.**

Participants were enrolled at **48 research centers** in the United States.

Participants **were able to take part** in this study if they:

- Were 18 years of age or older
- Had been diagnosed with type 1 or type 2 diabetes at least 1 year before joining the study
- Had been diagnosed with DPNP and had related pain for at least 6 months
- Were taking no more than 1 prescribed medication for their DPNP and were on a stable dose for about a month

Participants **were not able to take part** in this study if they:

- Had another condition that caused pain that could make it harder to tell if the study drug was working

For more information on who could take part in this study, please refer to the website listed on the **last page of this summary.**

What **study drugs** did the participants receive?

Researchers studied the following drugs in this study:

- **RTA 901**, 10 or 80 milligrams (mg), given as capsules, taken by mouth once a day
- **Placebo**, given as capsules, and taken by mouth once a day to match RTA 901

> A **placebo** looks like a study drug but contains no real medicine. Using a placebo helps researchers learn about the effect of RTA 901.

Participants were required to continue taking their prescribed standard of care medication for DPNP during the study. **Standard of care** is the usual treatment or care given to patients for a disease. The standard of care medications for DPNP allowed in this study were duloxetine, pregabalin, and gabapentin. Participants could take only one of these medications during the study.

What happened during the study?

How was the study done?

This study was:

Phase 2

A step in clinical research where the goal is to focus on the safety of the study drug and to learn how it works in the body. These studies include up to several hundred participants who have the disease or condition being studied.

Double blind

The study was double blinded. This means that neither the researchers nor the participants knew if the participants took RTA 901 or the placebo.

Randomized

This means the researchers used a computer program to randomly choose the drug and dose each participant took. This helped make sure the groups were chosen fairly.

The study was originally planned to be done in 2 parts: **Part 1** and **Part 2**.
Part 2 was planned to be done the same way as Part 1, but with different doses of RTA 901 based on the results of Part 1.
However, after the first set of results from Part 1 became available, the study was stopped early, and Part 2 did not begin.

Part 1 was split into 4 periods: **Screening**, **Run-In**, **Treatment**, and **Follow-Up**.

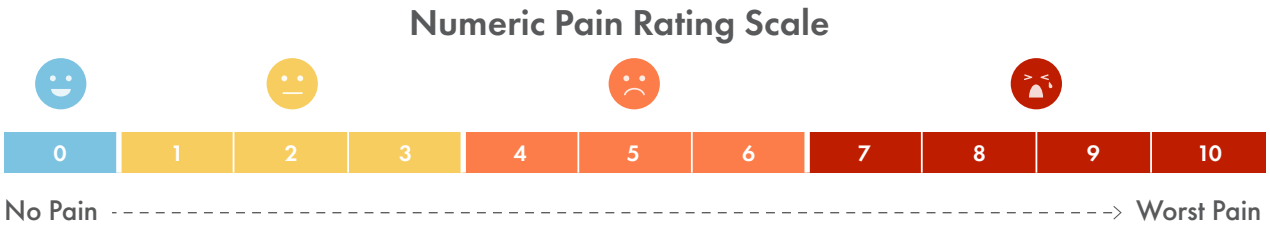
Screening Period – 2 weeks

- Participants were screened before they could join the study.
- At the screening visit, study doctors checked each participant's medical history.
- The screening also included:

Blood and urine tests | Physical exam | Heart rhythm test | Questionnaires and tests to measure pain and quality of life

- Throughout the study, researchers continued to perform the tests above regularly to follow the participants' health, safety, and the state of their disease.
- Participants were also given an **electronic diary** to use throughout the study. They were asked to record:
  - Each evening: how much pain they felt in the past 24 hours, on a scale of 0 to 10.
  - Each evening: whether they took any other medications for pain besides RTA 901.
  - Each morning: how much their pain made it harder to sleep the night before.

Participants used the **Numeric Pain Rating Scale (NPRS)** to measure pain, where 0 means no pain and 10 means the worst pain imaginable. Researchers looked at the NPRS scores participants recorded during the study to see if RTA 901 was having an effect on their pain.



Run-In Period – 2 weeks

- Researchers wanted to make sure participants' pain levels had not changed too much before starting treatment with RTA 901.
- To do this, all participants took the placebo for 2 weeks and continued to record their pain scores every day. They visited the study clinic once during the Run-In Period.
- Participants whose average scores went down more than 3 points could not move on to the main treatment period.

Treatment Period – 12 weeks

- Participants were randomly assigned to 1 of 3 groups:

Placebo	10 mg RTA 901	80 mg RTA 901
68 participants dosed	69 participants dosed	69 participants dosed

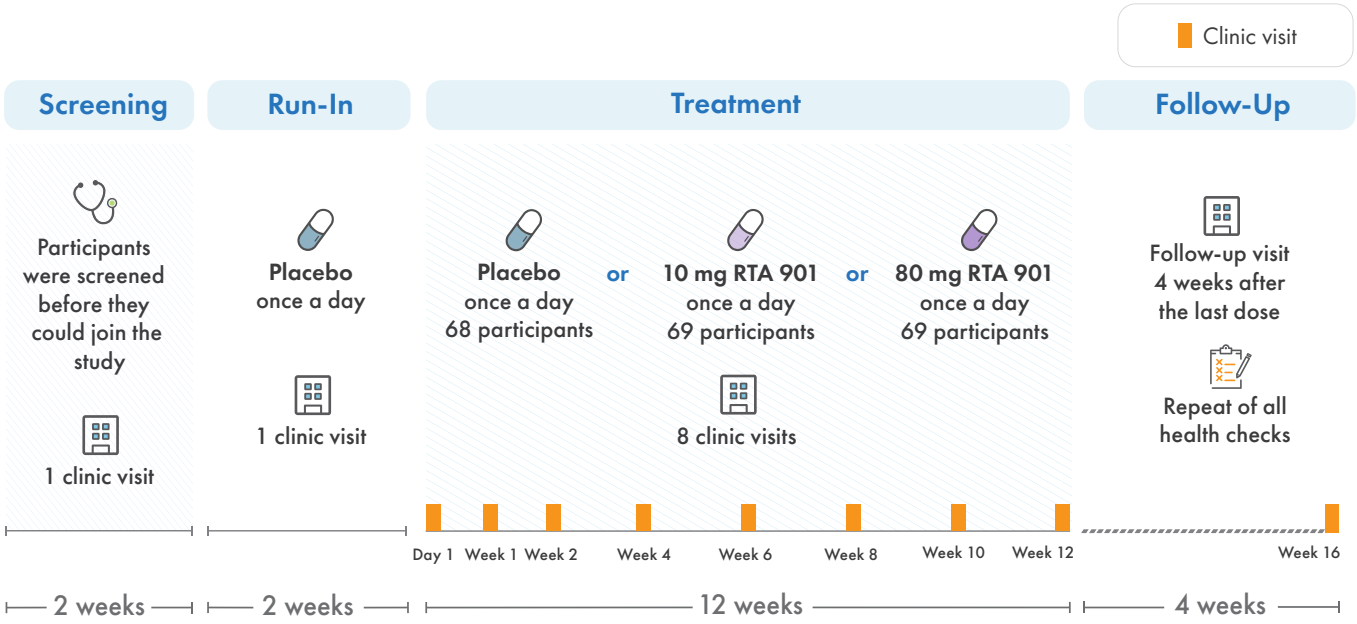
- Participants took their assigned treatment once a day for 12 weeks.
- They visited the study clinic 8 times during this period. Their end-of-treatment visit took place at Week 12.

Follow-Up Period – 4 weeks

- Participants visited the study clinic again 4 weeks after their last dose.

Participants who finished the Treatment and Follow-Up Periods stayed in the study for about 20 weeks.

The graphic below shows the study's design.



What were the **study results?**

When the study ended, Biogen created a report of the results. This is a summary of that report. The summary results are presented for 206 participants who took RTA 901 or the placebo. The individual results of each participant might be different and are not in this summary.

The study ended earlier than planned because RTA 901 did not work as expected to reduce pain more than placebo. This decision was not due to any concerns with the safety of RTA 901.

The results below are from this study only. Other studies may have different results. If you have questions, please ask your study doctor or study research center staff.

The following questions were the **primary endpoints** of the study. Primary endpoints are the main questions that researchers wanted to answer.

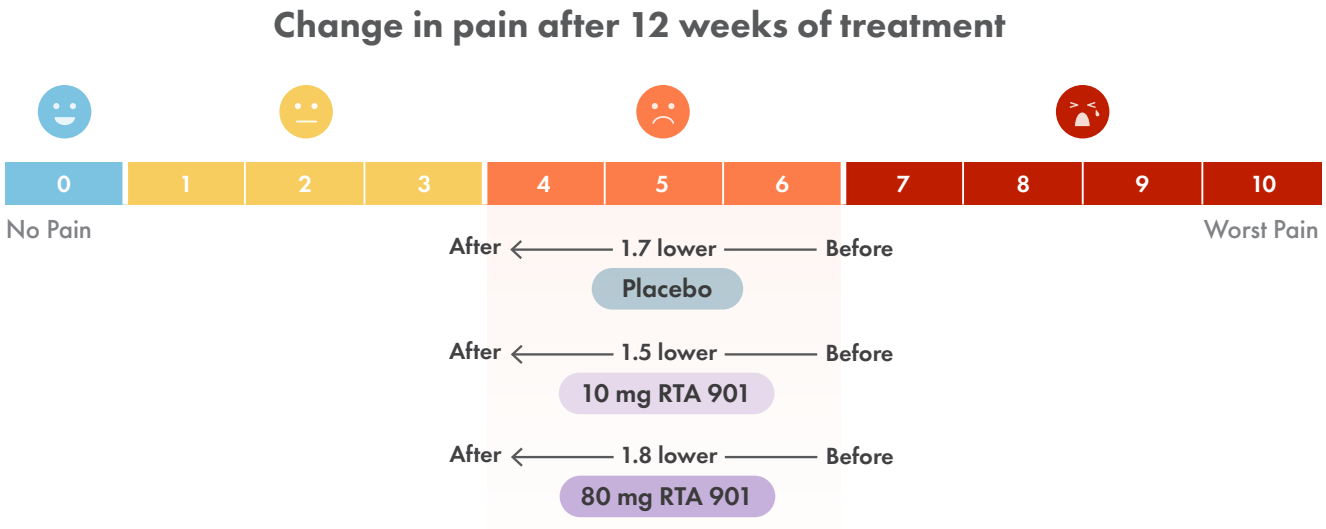
Did participants feel less neuropathic pain after taking RTA 901 for 12 weeks?

Participants recorded the amount of pain they felt every day in their electronic diaries. Researchers compared the average pain scores from before participants started the treatment period to the scores after 12 weeks of treatment.

Researchers found that:

- To start, the average pain scores in all groups were between 6 and 7.
- After 12 weeks of treatment, the pain scores went down by similar amounts:
  - About **1.7 points lower** in the placebo group.
  - About **1.5 points lower** in the 10 mg RTA 901 group.
  - About **1.8 points lower** in the 80 mg RTA 901 group.
- Overall, the differences between the groups were small and not considered meaningful.

The graphic below shows how pain scores changed in each group after 12 weeks.



Researchers concluded that RTA 901 did not help lower DPNP more than the placebo. As a result, Part 2 of the study was not done.

How many participants had adverse events or serious adverse events during the study?

An **adverse event** is an unwanted health problem that may or may not be caused by the study drugs. An adverse event is considered serious when it results in death, is life-threatening, causes lasting problems, or requires hospital care.

When new drugs are being studied, researchers keep track of all adverse events that participants have during the study. Not everyone experiences the same adverse events.

The table below shows how many participants had adverse events.

Summary of adverse events

	Placebo (68 participants)	10 mg RTA 901 (69 participants)	80 mg RTA 901 (69 participants)
How many participants had adverse events?	57% (39)	62% (43)	51% (35)
How many participants had serious adverse events?	6% (4)	7% (5)	1% (1)
How many participants stopped taking RTA 901 or placebo due to adverse events?	3% (2)	4% (3)	1% (1)

What were the most common serious adverse events?

No single serious adverse event happened in more than 1 participant.

- In total, there were 10 different serious adverse events, and each one happened in only 1 participant.

What were the most common adverse events?

The table below shows the most common adverse events that happened in at least 2% of all participants. There were other adverse events, but they did not happen as often and are not included in the table.

Most common adverse events

	Placebo (68 participants)	10 mg RTA 901 (69 participants)	80 mg RTA 901 (69 participants)
Bladder infection (urinary tract infection)	7% (5)	12% (8)	6% (4)
Higher levels of a digestive protein (lipase increased)	6% (4)	6% (4)	1% (1)
Infection of the upper airways (upper respiratory tract infection)	7% (5)	1% (1)	4% (3)
Increased muscle protein in the blood (blood creatine phosphokinase increased)	3% (2)	3% (2)	6% (4)
Too much potassium in the blood (hyperkalemia)	1% (1)	7% (5)	3% (2)
Fall	4% (3)	1% (1)	4% (3)
Reduced kidney function (glomerular filtration rate decreased)	1% (1)	3% (2)	3% (2)
Arm or leg pain (pain in extremity)	3% (2)	3% (2)	1% (1)

Did the participants' overall health change after taking RTA 901?

Researchers checked participants' vital signs and performed physical exams and medical tests to measure the overall health of the body.

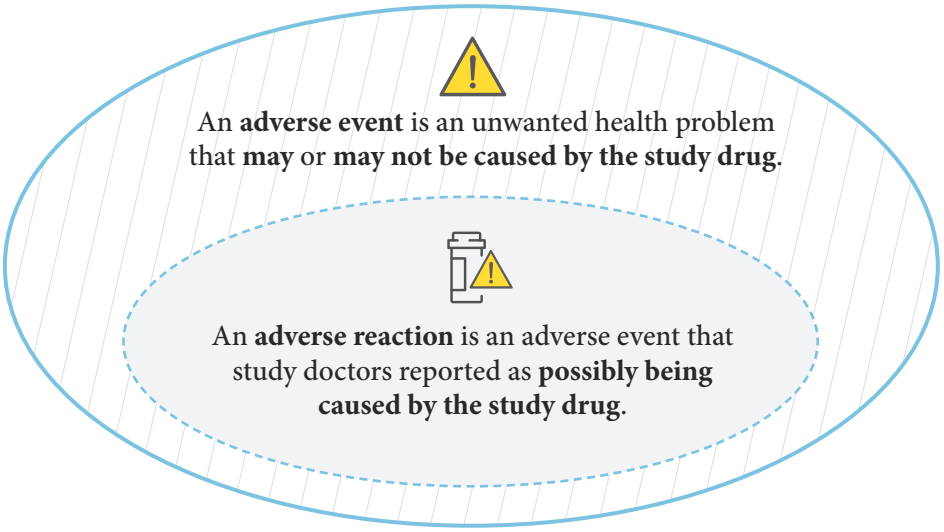
- **Vital signs** included temperature, blood pressure, heart rate, and breathing rate.
- **Medical tests** included blood tests, urine tests, and heart tests.

Researchers compared the results of these tests before and after treatment. Then, they judged if there was a possible health issue or a need for closer attention from doctors.

Researchers did not find any consistent or concerning changes in vital signs or medical tests after participants took RTA 901.

What **possible adverse reactions** happened during the study?

This section is a summary of the adverse reactions the participants had during the study.



An adverse reaction is considered **serious** when it results in death, is life-threatening, causes lasting problems, or requires hospital care.

Study doctors decide if an adverse event is possibly related to the study drug. When they make this decision, the study doctors do not know if a participant is receiving RTA 901 or placebo. This is important so that study doctors are not influenced when making decisions about the study drugs.

How many participants had adverse reactions during this study?

The table below shows how many participants had adverse reactions.

Summary of adverse reactions

	Placebo (68 participants)	10 mg RTA 901 (69 participants)	80 mg RTA 901 (69 participants)
How many participants had adverse reactions?	6% (4)	7% (5)	12% (8)
How many participants had serious adverse reactions?	0	0	0
How many participants stopped taking RTA 901 or placebo due to adverse reactions?	0	1% (1)	1% (1)

What serious adverse reactions happened during this study?

- None of the participants had serious adverse reactions during the study.
- None of the participants died during this study.

What were the most common adverse reactions that happened during this study?

No single adverse reaction happened in more than 1 participant.

- In total, there were 24 different adverse reactions, and each one happened in only 1 participant.
- Some participants had more than one of these adverse reactions.

There were 2 participants who stopped treatment due to adverse reactions:

- 1 participant who was taking 10 mg of RTA 901 had an accidental overdose. This meant they accidentally took too much of their assigned drug.
- 1 participant who was taking 80 mg of RTA 901 group had high levels of liver proteins in the blood, a condition called hypertransaminasemia.

How has this study **helped** patients and researchers?

This study helped researchers learn more about RTA 901 and the potential to help people with diabetic peripheral neuropathic pain (DPNP).

Overall, the researchers in this study found that:

- RTA 901 did not help lower DPNP more than the placebo.
- There were no major safety issues related to RTA 901 when compared to the placebo.

It is important to know that the results in this summary are from this study only. Other studies may have different results. There are no other studies currently planned to investigate RTA 901 in DPNP.

Where can I **learn more** about the study?

You can find more information about the study online at the following website:

ClinicalTrials.gov	https://clinicaltrials.gov/study/NCT05895552

Official Study Title: A Phase 2 Study to Evaluate the Safety and Efficacy of RTA 901 in Patients with Diabetic Peripheral Neuropathic Pain

If you have questions about RTA 901 or the results of this study, please speak with the doctor or staff at the study research center.

The results presented here are for a single study. You should not make changes to your therapy based on these results without first consulting your doctor.

Biogen, the sponsor of this study, has its headquarters in Cambridge, Massachusetts (USA).

Thank you!

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