Understanding Multiple Sclerosis and the REMODEL-1 (CLOU064C12301) Study

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Neuroscience DU

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Thank you for participating in the REMODEL-1 (CLOU064C12301) Study

Clinical trials are research studies designed to learn more about how the body responds to a certain treatment. They are important in finding safer and better treatments to help improve health care.

This book will provide you with an overview of:

- Multiple Sclerosis (MS)
- The REMODEL-1 (CLOU064C12301) Study
  - Purpose of study
  - Who can join
  - Study treatment (remibrutinib and teriflunomide)
  - Study visits and tests

The book also has space to write down notes and questions. Unfamiliar terms are explained in the glossary at the end.

Study contact information

Contact the study team if you have any questions or notice any changes in your health:

Study doctor's name: Mark Cascione, MD

Telephone number: (813) 353-9613

Study coordinator's name: Ellen Linden. RN, CCRC.

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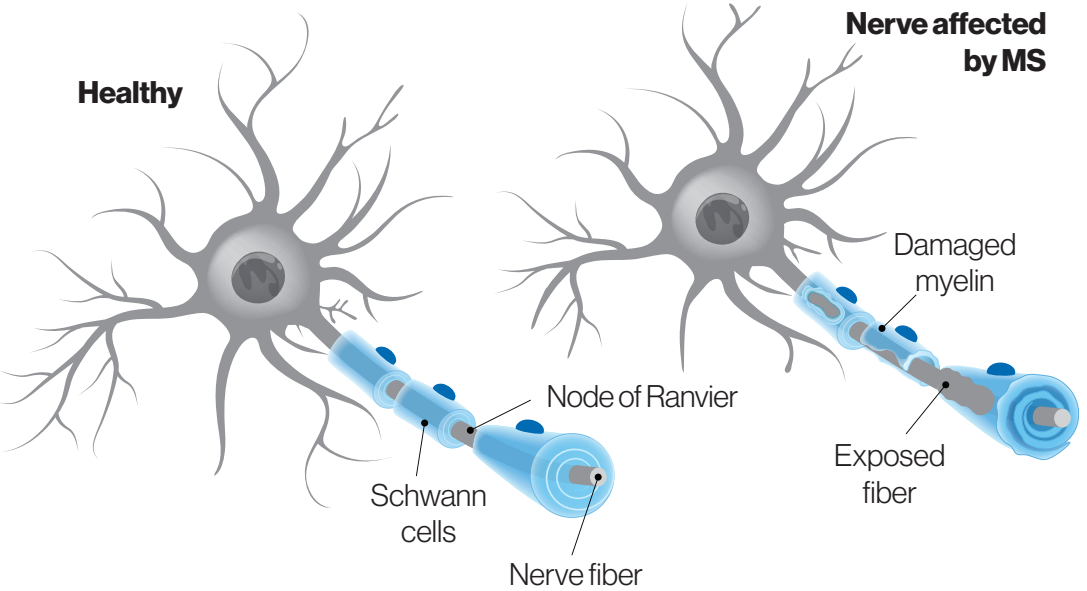
Being in a clinical study is voluntary and you can leave the study at any time.

What is multiple sclerosis (MS)?

MS is a chronic inflammatory autoimmune disease in which the body's immune system attacks its own tissue.

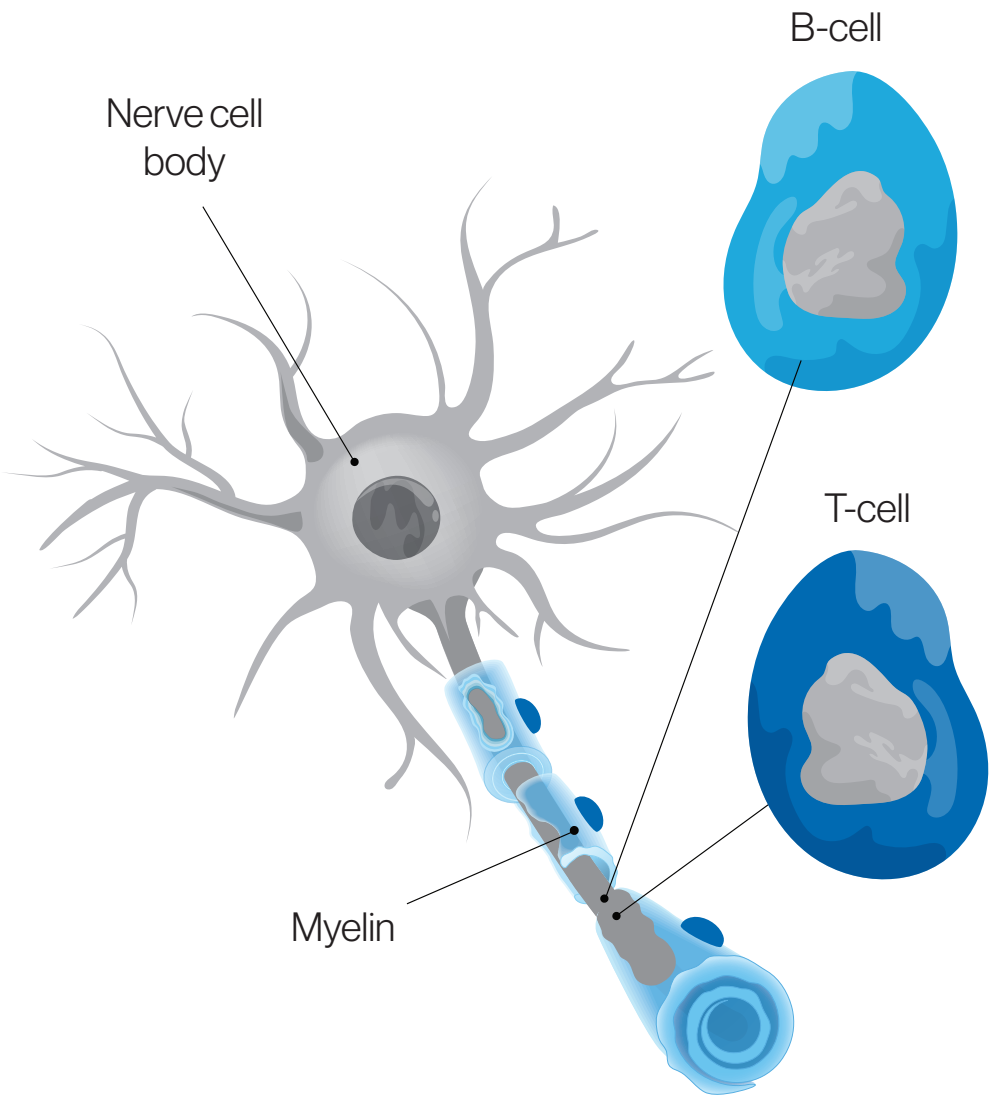
This means that the immune system destroys the fatty substance that coats and protects nerve fibers in the brain and spinal cord. This fatty substance is called myelin. This attack causes inflammation that destroys nerve cells and alters brain function.

Multiple Sclerosis



What is the role of B-cells in MS?

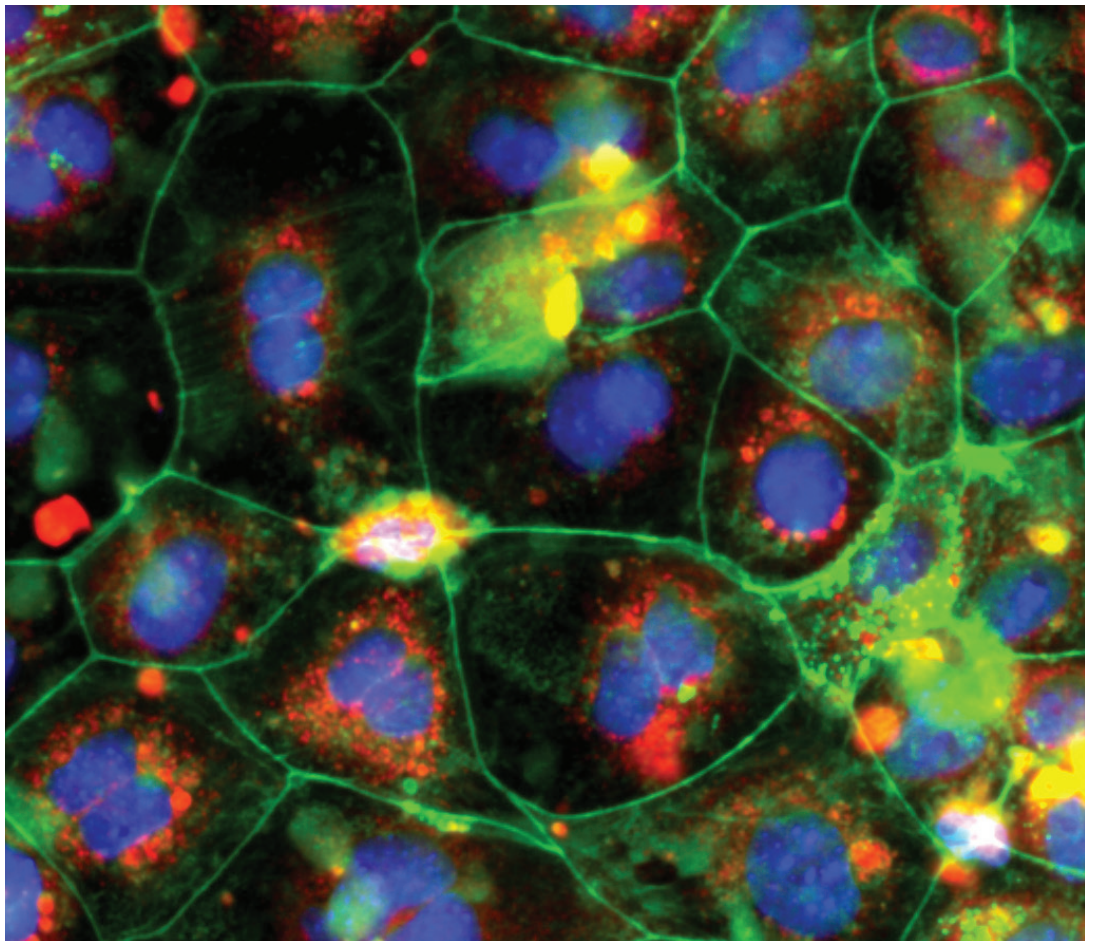
It is thought that B-cells and T-cells are drivers of MS attacks. Until recently, scientists have focused on T-cells as a primary target in treating MS. Scientists now believe that B-cells contribute to the development of MS in a number of different ways.



Using B-cell therapies to treat MS

Although there's been progress in the development of B-cell targeted therapies, a large unmet need remains. For example, current B-cell therapies wipe out all B-cells, which may make infections more likely.

Doctors are looking for better ways to target B-cells. One approach being studied is blocking Bruton's tyrosine kinase (BTK), an enzyme involved in B-cell development. BTK blockers may inhibit unwanted B-cells while leaving healthy ones alone.



Why is the REMODEL-1 (CLOU064C12301) Study being done?

This clinical study is being done to see if patients treated with a new investigational medicine called remibrutinib experience fewer multiple sclerosis MS relapses than patients treated with teriflunomide (also known as the approved medication Aubagio®).

Remibrutinib blocks the enzyme BTK, thought to play a role in MS. Because we do not yet know if remibrutinib is better than teriflunomide for the treatment of relapsing MS, this study will compare both drugs.

Who can join?

The studies are for adults aged 18 to 55 years who:

- Have a diagnosis of RMS:
  - Relapsing Remitting Multiple Sclerosis (RRMS).
  - Active Secondary Progressive Multiple Sclerosis (SPMS).
- Have had 1 documented relapse within the previous year OR 2 documented relapses within the previous 2 years OR 1 active Gadolinium-enhancing lesion* in the 12 months prior to screening.
- Have an expanded Disability Status Scale (EDSS) score of 0 to 5.5 (inclusive).
- Are neurologically stable, including no MS relapses, within 1 month prior to screening and baseline.

Gadolinium-enhancing lesions reflect active disease

What is the treatment?

Remibrutinib is being tested against approved drug teriflunomide, both are oral therapies. Remibrutinib is taken twice a day and teriflunomide is taken once a day.

During the Core Part of the study, you will have a 50% chance of receiving either remibrutinib or teriflunomide. Neither you nor the study doctor will know which treatment you are getting.

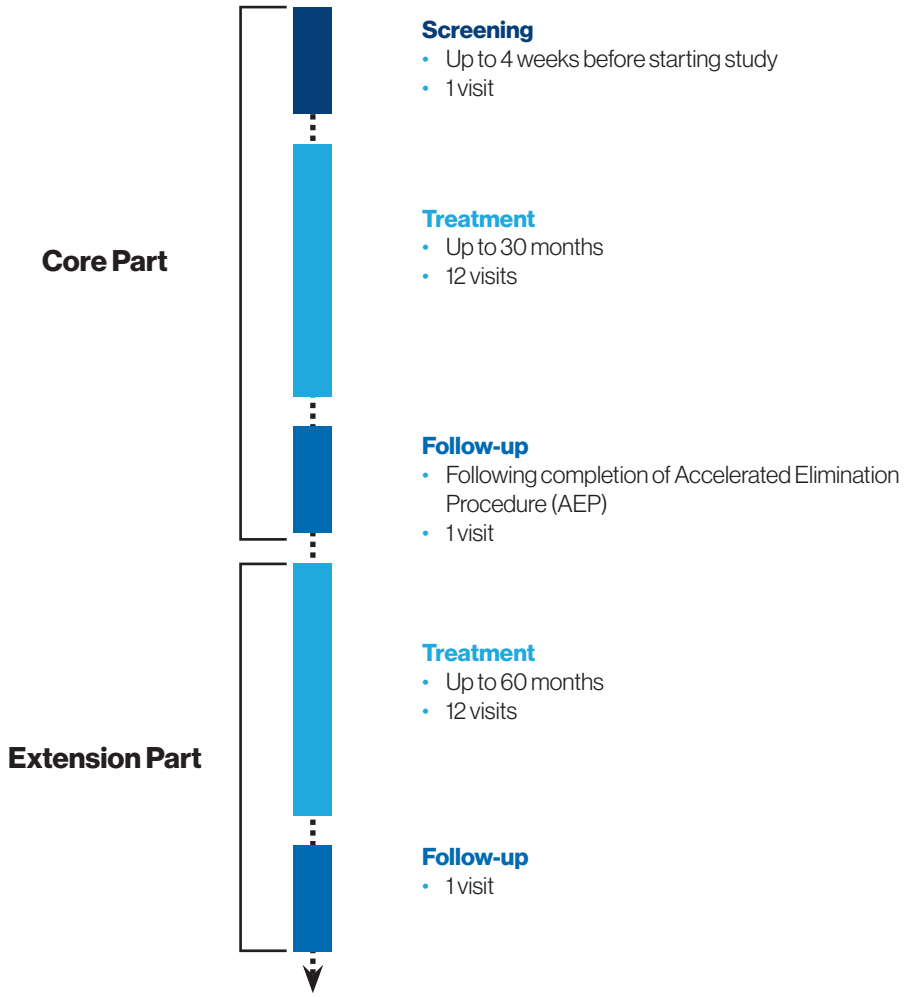
Remibrutinib Group	Teriflunomide Group
Active remibrutinib tablets twice a day	Placebo tablets twice a day
Placebo capsule once a day	Teriflunomide capsule once a day

During the Extension Part of the study, all eligible participants (who completed the Core Part on double-blind treatment) will receive remibrutinib.

What happens during the study?

The study has two parts. The first is the Core Part, which is made up of screening, treatment, and follow-up periods. You may be in the Core Part of the study for up to approximately 30 months and will have up to 14 site visits. If you decide to stop study treatment during the Core Part, you will have an end of treatment visit and may choose either to continue a schedule of shortened study visits (with fewer assessments) or to stop your participation completely.

If you complete the Core Part on study treatment you will be eligible to enter the Extension Part, which will be made up of treatment and follow-up periods. You may be in the Extension Part for up to 5 years and will have up to 13 site visits.



Which Patient Reported Outcomes (PROs) are included and why?

You will have to fill out six different questionnaires (patient reported outcomes (PROs)) about a wide range of symptoms throughout the study. Each questionnaire focuses on a different aspect of living with MS to provide a complete picture to the study team about life with MS.

Questionnaire	Focus
MSIS-29 Multiple Sclerosis Impact Scale	**Physical and psychological impact of MS**
FSIQ-RMS Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis	**Fatigue**
PHQ-9 9-Item Patient Health Questionnaire	**Depression**
GAD-7 7-Item Generalized Anxiety Disorder Scale	**Anxiety**
HUI-III Health Utilities Index	**Health status and ability**
BPI Brief Pain Inventory Scale	**Pain**

Participants are recommended to complete these questionnaires before any other assessments at any given visit (with the exception of pre-dose PK sampling/laboratory sampling).

Core Part: Screening

Up to 4 weeks before starting treatment | 1 visit

Before starting the study, you will give your permission by signing an informed consent form. This form includes information on the study, including the study design, what tests and procedures will take place during the study, and risks and side effects. The study doctor will then ask questions and run tests to make sure the study is right for you.

Health checks and key tests:

- Informed consent
- Medical history
- MS history
- Medicine review
- Vital signs
- Height and weight
- Physical exam
- Adverse events
- Heart activity (ECG)
- Suicide scale
- Contraception status
- Pregnancy test*
- Urine test
- Blood test
- Brain imaging (MRI)**
- MS relapse assessment
- Expanded Disability Status Scale (EDSS)

For participants of childbearing potential
****Not all participants***

Core Part: Treatment*

Up to 30 months | 12 visits

If the study doctor thinks you are right for the study, you will enter the treatment phase. During this phase, you will need to visit the study site 12 times for different health checks and tests. Not every health check and test will be done at each visit. The study staff will also contact you by telephone each month between scheduled visits (about 19 times during the Core Part).

Health checks and tests:

- Vital signs
- Body weight
- Physical exam
- Medicine review
- Adverse events
- Heart activity (ECG)
- Suicide scale
- Patient reported outcomes (PROs)
- Diary review
- Contraception status
- Pregnancy test**
- Exploratory DNA and RNA sampling (optional)
- Urine test
- Blood test
- Clotting test
- B-cell sample
- Biomarker sample
- Antibody levels
- Drug levels in body (PK)****
- Brain imaging (MRI)***
- MS relapse assessment
- Expanded Disability Status Scale (EDSS)
- Timed 25-Foot Walk (T25FW)
- Arm and hand function (9HPT)
- Information processing speed (SDMT)
- Accelerated elimination procedure

If participants discontinue treatment, they can still be part of the study and have shortened study visits.
****For participants of childbearing potential***
*****Not all participants***
******PK = pharmacokinetics = What drug does to body***

Core Part: Follow-up

Up to ~4 weeks after final study treatment in Core Part | 1 visit

Follow-up takes place up to 4 weeks after final study treatment in the Core Part to check on your safety.

Health checks and tests:

- Vital signs
- Body weight
- Physical exam
- Adverse events
- Medicine review
- Heart activity (ECG)
- Suicide scale
- Diary review
- Contraception status
- Pregnancy test*
- Urine test
- Blood test
- Clotting test
- MS relapse assessment
- Expanded Disability Status Scale (EDSS)

For participants of childbearing potential

Extension Part: Treatment

Up to 60 months | 12 visits

To enter the Extension Part of the study, you will need to complete the Core Part on study treatment and undergo the **Accelerated Elimination Procedure (AEP)** to remove traces of the study drug from your body. During the Extension Part, you will have 12 study visits for various health checks and tests. Not every check and test will be done at each visit.

The study staff will also contact you by telephone each month between scheduled visits during the first year of the Extension Part (about 9 times).

Health checks and tests:

- Vital signs
- Body weight
- Physical exam
- Adverse events
- Medicine review
- Heart activity (ECG)
- Suicide scale
- Patient reported outcomes (PROs)
- Diary review
- Contraception status
- Pregnancy test*
- Urine test
- Blood test
- Clotting test
- B-cell sample
- Biomarker sample
- Antibody levels
- MS relapse assessment
- Expanded Disability Status Scale (EDSS)
- Timed 25-Foot Walk (T25FW)
- Arm and hand function (9HPT)
- Information processing speed (SDMT)
- Brain imaging (MRI)**

For participants of childbearing potential
****Not all participants***

Extension Part: Follow-up

Up to ~4 weeks after final study treatment in Extension Part | 1 visit

You will have a follow-up safety visit up to 4 weeks after your final study treatment.

Health checks and tests:

- Vital signs
- Body weight
- Physical exam
- Adverse events
- Medicine review
- Heart activity (ECG)
- Suicide scale
- Diary review
- Contraception status
- Pregnancy test*
- Urine test
- Blood test
- Clotting ability
- MS relapse assessment
- Expanded Disability Status Scale (EDSS)

For participants of childbearing potential

Glossary

Accelerated elimination procedure: At the end of Core Part study treatment, the study drug (teriflunomide) will need to be removed from your body. Since the study drug stays in your body for a while, this process is sped up by taking a supplement given to you by the study doctor.

Adverse event: An unexpected medical problem that happens during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given.

Antibody levels: Through a blood test, IgG and IgM antibody levels will be measured to better understand how they change in response to the study drug.

Arm and hand function (9HPT): A 9-hole peg test to check how your upper limbs are working. During this test, you will be seated at a table with a small container holding nine pegs and a wood or plastic block containing nine empty holes. You will pick up the nine pegs one at a time and place them into the nine holes. Once they are in the holes, you will remove the pegs as quickly as you can, replacing them into the container. The time to complete the task is recorded.

B-Cell sample: B-cells are white blood cells (immune cells) thought to be involved in the progression of MS. Blood will be collected so your B-cells can be studied.

Biomarker sample: This blood test looks at certain molecules that may be associated with treatment response or may help predict response to treatment.

Blood tests: Small samples of blood will be taken using a needle inserted into a vein in your arm. Lab tests will be done on the samples to check your health.

Brain imaging (MRI): Some patients in the study will have an MRI, which is a type of imaging scan used to diagnose MS and to monitor the condition.

Clotting sample: This test checks for any problems with the proteins involved with blood clotting. Testing can help your doctor assess your risk of excessive bleeding or developing clots (thrombosis) somewhere in your blood vessels.

Contraception status: The study doctor will review contraception status with you at each clinic visit and monthly site contact to assure that you continue to comply with highly effective contraception as applicable.

Drug movement (PK): This blood test looks at the movement of remibrutinib into, through, and out of the body.

Expanded Disability Status Scale (EDSS): A method of measuring disability in multiple sclerosis and monitoring changes in the level of disability over time. It is widely used in clinical trials and in the assessment of people living with MS.

Exploratory DNA/RNA sampling (optional): Genetic research to better understand the effects of remibrutinib on DNA/RNA.

Heart activity (ECG): The electrical activity of your heart will be measured using a painless test called an electrocardiogram (ECG). For this test, you will lie down, and small, sticky pads will be attached to your skin. The pads are connected with wires to a computer that picks up signals every time your heart beats.

Information processing speed (SDMT): This is a simple and fast way for your study doctor to assess your information processing speed.

Informed consent: If you agree to join the trial, you will review and sign an informed consent form, which will give trial doctors the permission to collect your health information for trial purposes.

Medical history: During screening, the study doctor or nurse will ask questions about your general health now and in the past, including surgeries or procedures you have had.

Medicine review: The study doctor will ask about any medicines you are currently taking or have taken in the past.

MS relapse assessment: You will be asked about new symptoms and the reoccurrence or worsening of previous symptoms. The assessment, management, and reporting of an MS relapse is performed by the study doctor.

Physical exam: A complete physical examination includes assessment of skin, head and neck, lymph nodes, heart, lungs, abdomen, back, neurological function, and comments on general appearance.

Patient Reported Outcomes (PROs): You will complete several different questionnaires about your MS symptoms and how they affect your life.

Suicide scale: You will be asked to fill out a questionnaire that assesses suicidal ideation and suicidal behavior. This questionnaire is required in studies of drugs active in the central nervous system.

Timed 25-Foot Walk (T25FW): You will be directed to one end of a clearly marked 25-foot (7.62-meter) course and will be instructed to walk 25 feet as quickly as is safely possible. You will then be asked to walk back the same distance.. You may use assistive devices while doing this task.

Questions I have about the study:

Notes: