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Efficacy and safety of remibrutinib compared to teriflunomide in participants with relapsing Multiple Sclerosis (MS)

Why is this research study being done?

We would like to invite you to be part of a research study. A research study is a way to test new medicines to see if they work just as well or better than available medicines. This form tells you about this research study and the choice that you have to take part in it. You can ask any questions that you have at any time.

This information document is made up of the following sections:

1. A summary of the study.
2. Questions and answers about the study with summary table of assessments
3. The main study consent form.
4. Information and optional consent forms

Please take some time to read this information carefully. We ask that you keep it confidential but you may discuss it with your family, friends and GP if you wish, before making up your mind. If anything in this information sheet is not clear, or if you have more questions, please ask the doctor who gave it to you.

If you have private medical or life insurance please check with your insurer that it is acceptable under the terms of your policy for you to take part in this research study.

Summary of the study

Approximately 800 participants in around 30 countries will take part in the study. A brief summary of this study is provided below:

What study treatment(s) will I get? The study has an initial core part (CP) of up to two and a half years followed by an extension part (EP), of up to a further five years. During the core part you will have a 50% chance (like flipping a coin) of receiving remibrutinib treatment or of receiving teriflunomide which is an approved medication for the treatment of relapsing remitting Multiple Sclerosis (RRMS). During the extension part all participants will receive remibrutinib treatment.
Who is paying for this study? A company called Novartis (also known as the "Sponsor") is paying for this study.
What happens at my study visits? During the core part of the study you will need to visit the study doctor, about 15 times over a two and a half year period. This is the maximum length of the core part of the study and it may be shorter than this and have less visits. During the five year extension part you will need to visit the study doctor about 13 times. At the study visits, all or some of the following procedures should happen: blood pressure and pulse measurement, physical examination, recording any change in medications, recording any side effects, electrocardiogram (ECG), blood and urine collection, pregnancy testing, completion of questionnaires, Expanded Disability Status Scale (EDSS) assessment, timed 25 foot walk test, nine-hole peg test (9-HPT, to test figure and hand movements), Symbol Digit Modalities Test (SDMT, a short neuropsychological assessment of brain function), checking for MS relapses, Magnetic Resonance Imaging (MRI) assessment (if your site is participating in MRI assessment and you have signed consent for this), diary review, study treatment dispensing and return.
Have others received this study treatment before? Remibrutinib has not been studied in relapsing multiple sclerosis. Thus, we do not know whether it will work for you. Your condition may improve, may get worse, or there may be no change. Remibrutinib has been studied in five completed and five ongoing clinical studies in other diseases (non-RMS) like Asthma, Atopic Dermatitis, Chronic Spontaneous Urticaria and Sjogren's Syndrome that included more than 900 participants who received single or multiple doses of remibrutinib for a duration of up to one year. Remibrutinib belongs to a class of drugs that have demonstrated potential benefit in RMS patients (in reducing MRI lesions in phase 2 studies) and are undergoing similar phase 3 studies to this one.
Do I have to join this study? You do not need to join this study to be treated for your relapsing multiple sclerosis (RMS). The Study Doctor and/or your Personal Doctor will discuss your treatment options and their risks and benefits with you before you make your decision and during your participation if you choose to join the study. If you choose not to join or choose to leave the study at any time, it will not affect your medical care. See section 1 for more details.
Are there any side effects? There may be side effects (or risks) from the study treatment and from tests done during the study. You should tell the study doctor if you have any new complaints, side effects, or had other doctor visits or hospitalisations outside the study. This is important because remibrutinib is in development, and human/patient experience is still limited. Based on the way remibrutinib works and on experience with other drugs acting in a similar way, the potential risks of remibrutinib include an increased susceptibility to infections, increased risk of bleeding and a decrease in blood cell count. Some of the most common side effects noted during the completed and ongoing studies of remibrutinib were headache and nasopharyngitis (cold virus). As remibrutinib is metabolised in the liver, it may interact with other drugs that are processed in a similar way and affect how well they work. Findings from one animal study suggests that remibrutinib could harm the foetus (developing baby) during pregnancy, although it is not fully understood what this means for humans. A more detailed list of the possible side effects that you may have are described later in this document. During the core part (CP) of the study half of participants will be receiving the teriflunomide treatment, the side effects of teriflunomide are also explained later in this document. The most common side effects of teriflunomide include headache, increase in liver enzyme (Alanine aminotransferase), diarrhoea, alopecia (hair loss) and nausea.
Are there any benefits to me? You may benefit by being a patient in this clinical research study by contributing to medical research, gaining access to a new research treatment, having access to expert medical care for the condition being studied, getting actively involved in your health care and having your health closely assessed and monitored. There is a chance that taking part in this research study may not benefit you directly.
What happens if I am hurt during the study? The Sponsor's insurance will pay for study-related injuries under the conditions mentioned later in this document.
Who has the rights to my data? The Sponsor owns all rights to the study results.

Will my information remain confidential? The Sponsor will follow all applicable laws to ensure your identity remains confidential.

QUESTIONS AND ANSWERS ABOUT THE STUDY

1 WHY HAVE I BEEN GIVEN THIS DOCUMENT TO READ?

This form tells you about the study, including possible risks and benefits. Before you decide whether to take part, you need to understand why the research is being done and what it will involve. This informed consent form tells you about the study that you are being asked to participate in.

Your decision to participate in this study is voluntary. This means:

- You are free to decide to participate in this study or not
- You are free to stop study treatment and study-related activities at any time and without the need for giving any reason
- If you do not want to participate in this study, then this decision will not affect your medical care

If there is new information that may be important to your decision to continue in the study, the study doctor will inform you in a timely manner.

2 WHAT IS A CLINICAL RESEARCH STUDY?

A clinical research study is a study involving humans to answer specific health questions.

Carefully conducted clinical research studies are the safest and most efficient way to find treatments that work in people and to establish new ways to improve health care. There are two goals of clinical research:

1. To find a treatment that may be better or safer than currently available treatment
2. To gain knowledge that may benefit others, even though at this time no one can be sure that this research treatment will be helpful for you.

3. WHAT IS THE PURPOSE OF THIS CLINICAL RESEARCH STUDY?

The main purpose of this study is to find out if patients treated with remibrutinib experience fewer MS relapses (also called clinical attacks, exacerbations or flare ups) than patients treated with teriflunomide (known as Aubagio®). Teriflunomide is an approved medication for the treatment of relapsing remitting MS.

The reason for including teriflunomide in this study is to find out if remibrutinib is better than teriflunomide as a treatment for relapsing MS. We do not know which medicine is best, so we are comparing.

4. WHAT IS ALREADY KNOWN ABOUT THE MEDICINE BEING TESTED?

Remibrutinib (also known as LOU064) is a medicine, which has not been approved by Medicines and Healthcare Regulatory Products Agency (MHRA) or any Health Authority for the treatment of people with relapsing MS. Remibrutinib is currently not “on the market”

(available for you to receive a prescription for) for RMS in any country. Data have shown remibrutinib is a selective and potent inhibitor of Bruton's tyrosine kinase (BTK) which is an enzyme responsible for the functioning of B-lymphocytes. B-lymphocytes are a type of white blood cell involved in the development of MS disease. Based on it's pharmacological action and data to date, remibrutinib may have beneficial clinical effects in a variety of autoimmune and chronic inflammatory diseases including RMS.

Approximately 900 people have been treated with this medicine in clinical studies to date.

Teriflunomide is an approved medication for the treatment of relapsing remitting MS.

The study is being organised and funded by Novartis Pharma AG, Lichstrasse 35, 4056 Basel Switzerland and is being run by the medical staff in Re:Cognition Health – London. Novartis will make payments into your study doctor's hospital research fund to cover the costs of this study.

5. WHO WILL TAKE PART IN THIS STUDY?

Approximately 800 participants with relapsing multiple sclerosis, between the ages of 18 and 55 years are being invited to join this study. Participants will be invited from 27 countries worldwide. If you wish to have further details on who can join, please ask your study doctor.

6. WHO CANNOT TAKE PART IN THIS STUDY?

As with any study medication, we do not know whether study medication can harm an unborn or breast-fed baby. Therefore, pregnant or breast-feeding women cannot take part in this study. If there is any possibility that you might become pregnant, you will be tested for pregnancy at the start of the study and again at the end of the study.

People taking certain medications or with other medical conditions may not be able to take part in this study. The study doctor will check your medical history to see whether you will be eligible to join the study.

7. HOW LONG WILL I BE IN THE STUDY?

Your study participation will last for up to two and a half years in the initial core part though this could be less, depending on when you join. After the initial core part the extension part will last for up to a further five years.

8. WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

You will be asked to visit the hospital more often than usual. You will first undergo screening tests to show that you meet the entry criteria for the study. Once you are confirmed to be eligible you will then start the study.

- You will also be asked about any medical conditions you may have.
- You will be asked about any medications you have been taking.

Your study doctor will perform other examinations, which will include:-

- A complete physical examination measuring your height, weight, temperature, blood pressure, pulse and breathing rate
- A check of your medical history and the MS treatments you have taken or are taking.
- Collection of blood samples to check your general health (Haematology, Biochemistry and Coagulation).

- Collection of blood samples for virology (presence of hepatitis B virus, hepatitis C virus, hepatitis E virus, HIV and syphilis), Tuberculosis (TB), serology (to detect serum antibodies or antibody-like substances that appear specifically in association with your disease), and cytokines (proteins produced by the immune system) analyses for safety purposes.
- Collection of blood to check for any teriflunomide drug in the body.
- Collection of blood to rule out pregnancy if you are a women able to become pregnant. The study doctor will also explain the methods of contraception that the study requires participants to follow.
- A urine analysis to check your kidney function, test for blood cells, other types of cells, sugar, acidity, proteins, and water content
- An electrocardiogram (ECG) will be done to check the functioning of your heart by measuring your heart's electrical activity. ECGs involve connecting wires to plastic pads placed on your chest and lying still for 5-10 minutes
- A questionnaire to assess your thoughts and feelings you may have had about suicide.
- A Magnetic Resonance Imaging (MRI) scan of your brain which takes around 45 minutes. An MRI uses magnetic energy to provide a picture of your brain. This will only be done if you hospital has MRI available for this study.
- An assessment of the disability you experience due to your MS. This measures your ability to walk, your balance, reflexes, muscle tone, eye movement, and hand-eye coordination among other things. This is called the Expanded Disability Status Scale (or EDSS) and will take 15-30 minutes.

Your study doctor will discuss with you if there is any need to stop taking any of your current medications before starting the study treatment. This is to avoid a mix-up of effects between your medication and the study treatment.

Your study doctor will review the results of the screening procedures and will tell you if you meet the requirements to continue to take part in the study; if that is not the case, your participation will end after the screening period and your study doctor will discuss other treatment options available to you.

If any other health problem shows up

It is possible that the health checks carried out before and during the study could show up a problem that you didn't know about. If this happens, you will be referred for suitable treatment and you may be told that you are not able to take part in the study.

We will let your General Practitioner (GP) know

By signing this consent you agree for us to let your GP know that you are taking part in the study. Your study doctor may need to contact your GP to obtain more information about you. Please ask your study doctor if you would like a copy of any correspondence.

Access to medical records

It may be necessary to access your original medical records. These may be stored by your GP or hospital. As a result of COVID-19, it may be necessary to access your records over the internet. Security measures will be in place to protect your information. By signing this form, you agree that your original medical records will be accessed as part of the study.

Travel Insurance

When you apply for travel insurance, insurers will typically ask questions about your health in order to make an accurate risk assessment. The insurer will often ask questions about any pre-existing health conditions and medical treatments for those conditions. Where an insurer asks about your participation in clinical research studies, the insurer must ensure the question is clear and you should answer it accurately and honestly.

Whilst having a condition itself may attract additional costs to travel insurance taking part in a clinical study is not something that would be expected to lead to increased premiums, penalties or insurance refusal. If you find that you are denied insurance or your premiums increase purely on the grounds of participation in this study please raise this with your study doctor.

9. WHAT HAPPENS DURING THE STUDY TREATMENT?

You will be in the core part of the study for up to 30 months (two and a half years) followed by an extension part of the study for up to five years (for participants completing the core part on study drug and completing the Accelerated Elimination Procedure (AEP which is explained later in this document).

In this study, you will need to visit the study doctor at the study site about 15 times during the core part and about 13 times during the extension part. Study staff will also contact you by telephone each month between scheduled visits; about 19 times during core part of the study and 9 times during the extension part. Telephone/remote contact will only be during the first year of the extension part of the study. At any time, your study doctor may need to contact your GP to get more information about your health if you allow this. If you are scheduled for any vaccination during the study treatment duration, please let your study doctor know.

In the core part of the study, you will get one of the following study treatments by chance, these will be given orally (by mouth) two times every day.

Study treatment during the core part

Investigational / Control Drug (Name and Strength)	Daily Dose	Frequency
Remibrutinib 100 mg/ Placebo	Total: 200 mg	100 mg twice daily (AM and PM dose)
Teriflunomide 14 mg/ Placebo	Total: 14 mg	14mg once daily (AM dose)

- Remibrutinib*:* You have a 1 in 2 chance of getting this treatment.
- Teriflunomide: You have a 1 in 2 chance of getting this treatment.
- Placebo: You will also receive placebo (which has no active ingredients), so that you or your study doctor (and his/her staff members) do not know which active treatment you are receiving.

Teriflunomide is an approved treatment for RRMS.

In the core part of the study, neither you nor your study doctor will know what treatment you are getting. However, if a serious problem with your health happens, your study doctor can find this out to decide on any necessary actions.

An Accelerated Elimination Procedure (AEP) treatment with charcoal or cholestyramine will be required for all participants to eliminate teriflunomide quickly from your body after

completion of treatment in the core part of the study, because neither you nor your study doctor will know the treatment you are getting. This AEP treatment will also be required if you discontinue core part study treatment early (e.g. for any serious adverse event or pregnancy). You must have completed this AEP procedure in order to be eligible for entry to the extension part of the study.

During the extension part of the study, both you and your study doctor will know that you are receiving remibrutinib 100 mg twice daily for up to five years.

Study treatment during the extension part

Investigational / Control Drug (Name and Strength)	Daily Dose	Frequency
Remibrutinib 100 mg	Total: 200 mg	100 mg twice daily (AM and PM dose)

It is very important to take the study treatment as you have been told/shown and store it as directed.

Other treatments you may be taking:

For your safety, you must tell the study doctor about any treatments or medications you are currently taking or may take during the course of the study (for example, prescriptions, vitamins, over-the-counter, herbal supplements etc.). Some of these may need to be stopped or have the dose(s) reduced.

Returning study treatment:

Return all extra / unused treatment pills and empty pill bottles/blister cards as instructed by study doctor or study nurse.

Summary of what will happen at your study visits

Here is a summary of what may happen during your study visits. However, not all assessments will happen at all visits. The tables in Appendix 1 explain the time points during the study when for each assessment.

Study Treatment:

- For the core part: You will get the study treatment supplies (oral capsules/tablets) on Day 1, Month 1, Month 3 and every 3 months thereafter up to Month 27 in the core part. After completing the core part, an AEP procedure within 4 weeks is required to be enrolled in the extension part.
- For the extension part: You will get the study treatment (remibrutinib tablets) on Day 1, Month 1, Month 6 and every 6 months thereafter up to Month 54. Study medication return will also be conducted at the site visits as applicable.
- Note: If you decide to stop study treatment during the core part of the study you may have an end of treatment visit and you may either choose to continue to have shortened schedule of safety study visits and fewer assessments (recommended) or discontinue your participation completely. If you choose to continue safety visits, you may take other available RMS treatment as advised by your study doctor.

In the Core Part (Note: Month 1 is represented as M1 etc):

Test or Procedure	How often will this be done?
Physical examination: A complete physical examination includes assessment of skin, head and neck, lymph nodes,	At Screening, Day 1, M1, M3, M6, M9, M12, M18, M24, M30/end of study, end of treatment and safety follow-up.

heart, lungs, abdomen, back, neurological function and comments on general appearance.	
Vital signs: Your pulse (heart) rate, blood pressure and oral temperature will be measured at each visit, body weight less frequently.	At Screening, Day 1, M1, M3, M6, M9, M12, M15, M18, M21, M24, M27, M30/end of study, end of treatment and safety follow-up.
Electrocardiogram (ECG): An ECG measures the heart's electrical activity (drawn as a graph) to help evaluate its function.	At Screening, Day 1, M1, M3, M6, M9, M12, M15, M18, M21, M24, M27, M30/end of study, end of treatment and safety follow-up. Additional ECG's may be performed or advised to you to be performed locally if the study doctor thinks they are necessary.
Pregnancy Test: Only if you are a woman able to become pregnant	Urine pregnancy test at, Day 1, M1, M3, M6, M9, M12, M15, M18, M21, M24, M27 and safety follow-up. Urine pregnancy test to also be performed monthly at home/locally (as applicable) between the scheduled hospital/clinic visits. Serum pregnancy test will be conducted at screening, end of study (M30) and end of treatment visits.
Contraception Status: Contraception (birth control) status must be reviewed and documented to ensure method of contraception continues to be appropriate per protocol requirement for highly effective contraception	At Screening, Day 1, M1, M3, M6, M9, M12, M15, M18, M21, M24, M27, M30/end of study, end of treatment and safety follow-up. You will be asked to record your contraception status each month in your electronic diary, this diary will be reviewed by investigator/study staff during each hospital/clinic visit and during monthly remote contact from investigator hospital/clinic.
Routine Laboratory evaluations: Blood and urine samples will be collected during the study to monitor your health and to allow researchers to analyse the way in which remibrutinib is absorbed and broken down. The amount of blood taken at each visit during the treatment period will vary (not including optional visits), but will not be more than 25mL (approximately 2 tablespoons*). * 1 tablespoon = 15 ml.	Haematology, blood chemistry (liver and renal function), urinalysis and additional blood panels (e.g. at screening a test for HIV, Tuberculosis, Syphilis; at treatment visits blood coagulation related tests aPTT, PT ,INR.) will be conducted at Screening, Day 1, M1, M3, M6, M9, M12, M15, M18, M21, M24, M27, M30/end of study, end of treatment and safety follow-up. Other assessments (B-cell levels, immunoglobulin levels, Transcriptomic assessment (RNA) (optional), and biomarkers) will be assessed less frequently. Exploratory DNA sampling (optional) will only be conducted on Day 1. Your study doctor may suggest unscheduled blood examinations based on your clinical or safety needs.
PK (Pharmacokinetic) Blood collection: This is to measure how long study medication remains in the body. The amount of blood taken at each time point during the study is 2mL (approximately half a teaspoon*). * 1 teaspoon = 5 ml.	PK Blood collection at Month 1 and Month 6, pre-dose (0 h) and 1.0 hour post-dose at both study visits. You must come to the clinic after an overnight fast for these visits and take your study medication at the clinic after the pre-dose blood sample has been taken. You must remain fasted until after the one-hour post-dose blood sample has been taken. The time of your last meal and last doses of study medication (both on the morning of the visit and the evening dose on the previous day) will be recorded.
"Rich PK sampling" Blood collection: This is only for "rich PK sampling" cohort participants from selected study sites who have consented to this sampling. The amount of additional blood taken in total is 8mL (approximately two teaspoons*). * 1 teaspoon = 5 ml.	Additional PK Blood samples at Month 1 (Day 28): Additional samples (i.e. as well as those described in the row above) will also be taken at 0.5, 2, 3 and 4 hours post-dose during the Month 1 visit. You must come to the clinic after an overnight fast for this visit and shall remain fasted until after the 4-hour post-dose PK sample has been taken. The time of your last meal and last doses of study medication (both on the morning of the visit and the evening dose on the previous day) will be recorded.
Columbia-Suicide Severity Rating Scale (CSSRS): The C-SSRS is a questionnaire used to assess any thoughts you may have about suicide during the study. You will use an electronic version of this questionnaire, which will be completed by phone via an automated Interactive response system. Your study doctor will instruct you how to use the system.	During Screening and every time you visit the study site and have an evaluation by study staff (planned or unplanned) during the study.
Magnetic resonance imaging (MRI) – only for MRI cohort participants from the selected study sites who have consented to this procedure: An MRI is a scan that uses magnetic energy to provide a picture of the area of interest.	If in the MRI Cohort, during Screening, M3, M6, M24, M30/end of study and end of treatment.

In this study, MRI will be used to detect inflammatory lesions in your brain due to multiple sclerosis. It will take approximately 40-45 minutes to get the images needed.	
Expanded Disability Status Scale (EDSS): EDSS is a scale used to assess the level of disability you experience due to multiple sclerosis. Your EDSS score is based on an examination performed by an independent health care professional (not by your study doctor). The examination measures your ability to walk, your balance, reflexes, muscle tone, eye movement, and hand-eye coordination among other things. It will take approximately 30 minutes to half an hour for this exam to be done.	At Screening, Day 1, M3, M6, M9, M12, M15, M18, M21, M24, M27, M30 / end of study, end of treatment and safety follow-up. The EDSS will also be done if you have a relapse
Timed 25-Foot Walk (T25FW): The T25FW is a test that measures walking speed. The time it takes you to walk 25 feet (7.62 meters) will be measured.	At Day 1, M6, M12, M18, M24, M30/end of study and end of treatment (each time the test will be done twice).
Nine Hole Peg Test (9HPT): 9HPT score is measured by assessing the time it takes you to insert and remove 9 pegs from a block designed to fit the 9 pegs. 9HPT is used to assess both left and right arm function.	At Day 1, M6, M12, M18, M24, M30/end of study and end of treatment (each time the test will be done twice for each arm).
Symbol Digit Modalities Test (SDMT): SDMT is an assessment of brain function that measures the speed at which you match paired numbers and symbols (number of symbols matched in 90 seconds).	At Day 1, M12, M24, M30/end of study and end of treatment
Multiple Sclerosis Impact Scale (MSIS-29): MSIS-29 is a questionnaire that asks about the physical and psychological impact of MS disease from your perspective.	At Day 1, M6, M12, M18, M24, M30/end of study and end of treatment.
Fatigue Symptoms and Impacts Questionnaire - Relapsing Multiple Sclerosis (FSIQ-RMS): FSIQ-RMS is a questionnaire that measures fatigue symptoms and impacts in relapsing multiple sclerosis.	At Day 1, M6, M12, M18, M24, M30/end of study and end of treatment.
Generalised Anxiety Disorder-7 (GAD-7): GAD-7 is used as a screening tool and severity indicator for generalised anxiety disorder.	At Day 1, M3, M9, M15, M21, M30/end of study and end of treatment.
Patient Health Questionnaire (PHQ-9): PHQ-9 is used for screening, diagnosing, monitoring and measuring the severity of depression.	At Day 1, M3, M9, M15, M21, M30/end of study and end of treatment.
Brief Pain Inventory (BPI): BPI is used to assess the severity of pain and the impact of pain on daily functions.	At Day 1, M3, M9, M15, M21, M30/end of study and end of treatment.
Health Utilities Index (HUI-III): The HUI-III is used for the purpose of measuring health status and reporting health-related quality of life.	At Day 1, M12, M24, M30/end of study and end of treatment.
Site contact with Participant: Remote contact with participants by site staff to discuss any new or worsening symptoms that may require an unscheduled visit to the site, changes in medications, compliance with study treatment, results of home pregnancy tests and compliance with contraception requirements (where applicable).	Once per month between scheduled study site visits.
Unscheduled Visit for evaluation of worsening of MS: you will need to notify the study doctor as soon as possible if you feel any new MS symptoms or a clear worsening of your MS symptoms. In that case, you may need to go to the clinic to have a neurological examination to evaluate whether or not you are having an MS attack or relapse. You may then also need to see the doctor/clinic or member of hospital staff who performs the EDSS assessment (not your study doctor).	As needed outside the visit schedule.
Unscheduled Safety Visits: Unscheduled study site visits may be required if your Study Doctor detects any test abnormality or new illness that needs to be investigated further, or for any other reasons as per discretion of your study doctor.	As needed outside the visit schedule.
Electronic Patient Diary: You will receive a patient diary in which you will record information including about side effects, changes in medication, study medication	To be completed from Day 1 onwards.

compliance (i.e. missed doses) and information about the urine pregnancy tests done between the study site visits.	
Accelerated Elimination Procedure: This is a procedure to remove teriflunomide quickly from the blood	This must be completed by all study participants after the Core Part EOT or EOS visits and can be done in two ways: either by taking a powder called cholestyramine dissolved in water every 8 hours for 11 days or taking a powder of 'activated' charcoal dissolved in water every 12 hours for 11 days.
Note : If you decide to stop study treatment during the core part of the study you may have an end of treatment visit and you may either choose to continue to have shortened schedule of safety study visits and fewer assessments (recommended) or discontinue your participation completely. If you choose to continue safety visits, you may take other available RMS treatment as advised by your study doctor.	

In the Extension Part

Test or Procedure	**How often will this be done?**
Physical examination	At EP Day 1, EP M1, M6, M12, M18, M24, M30, M36, M42, M48, M54, M60/end of study and EP safety follow-up.
Vital signs	At EP Day 1, EP M1, M6, M12, M18, M24, M30, M36, M42, M48, M54, M60/end of study and EP safety follow-up.
Electrocardiogram (ECG)	At EP Day 1, EP M1, M6, M12, M18, M24, M30, M36, M42, M48, M54, M60/end of study and EP safety follow-up. Additional ECGs may be performed if the study doctor thinks they are necessary.
Pregnancy Test	Urine pregnancy test At EP M1, M6, M12, M18, M24, M30, M36, M42, M48, M54 and EP safety follow-up. Urine pregnancy test to also be performed monthly at home/locally (as applicable) between the scheduled hospital/clinic visits. Serum pregnancy test will be conducted at EP Day 1 and EP end of study.
Contraception Status	At EP Day 1, EP M1, M6, M12, M18, M24, M30, M36, M42, M48, M54, M60/end of study and EP safety follow-up.
Laboratory evaluations: The amount of blood taken at each visit during the extension period will vary, but will not be more than 25 mL (approximately 2 table spoons).	Haematology, blood chemistry, urinalysis and coagulation panel will be conducted at EP Day 1, EP M1, M6, M12, M18, M24, M30, M36, M42, M48, M54 and M60/end of study. They may also be conducted at EP safety follow-up if required. Other assessments (B-cell levels, immunoglobulin levels and biomarkers) will be assessed less frequently. Your study doctor may suggest unscheduled blood examinations based on your clinical or safety needs.
Columbia-Suicide Severity Rating Scale (CSSRS)	Every time you visit the study site and have an evaluation by study staff (planned or unplanned) during the study.
Magnetic resonance imaging (MRI), (OPTIONAL) for MRI cohort participants only.	At EP Day 1, EP M36 and M60/EP end of study.
Expanded Disability Status Scale (EDSS)	At EP Day 1, EP M1, M6, M12, M18, M24, M30, M36, M42, M48, M54, M60/end of study and EP safety follow-up. The EDSS will also be assessed if you have a MS relapse.
Timed 25-Foot Walk (T25FW)	At EP Day 1, EP M6, M12, M18, M24, M30, M36, M42, M48, M54 and M60/end of study. (Each time the test will be done twice).
Nine Hole Peg Test (9HPT)	At EP Day 1, EP M6, M12, M18, M24, M30, M36, M42, M48, M54 and M60/end of study. (Each time the test will be done twice for each arm).
Symbol Digit Modalities Test (SDMT)	At EP M12, M24, M48 and M60/EP end of study.
Multiple Sclerosis Impact Scale (MSIS-29)	At EP Day 1, EP M6, M12, M24, M36, M48, M60/end of study.
Fatigue Symptoms and Impacts Questionnaire Relapsing Multiple Sclerosis (FSIQ-RMS)	At EP Day 1, EP M6, M12, M24, M36, M48, M60/end of study.
General Anxiety Disorder-7 (GAD-7)	At EP Day 1, EP M6, M12, M24, M36, M48, M60/end of study.
Patient Health Questionnaire (PHQ-9)	At EP Day 1, EP M6, M12, M24, M36, M48, M60/end of study.

Brief Pain Inventory (BPI)	At EP Day 1, EP M6, M12, M24, M36, M48, M60/end of study.
Health Utilities Index (HUI-III)	At EP Day 1, EP M12, M24, M36, M48, M60/end of study.
Site contact with Participant	Once per month until EP M12 visit between scheduled study site visits.
Unscheduled Visit for evaluation of worsening of MS	As needed outside of the visit schedule.
Unscheduled Safety Visits	As needed outside of the visit schedule.
Electronic Patient Diary	To be completed from EP Day 1 onwards.
Note: For the study participants eligible for extension part of study, Day 1 visit of the EP can be conducted on the same day as the safety follow-up visit for the core part.	

Some parts of this study may need to be conducted somewhere other than your study doctor's clinic. Please read the details of these "offsite activities" in the optional consent section.

More information about some of your assessments

ECG: An electrocardiogram (ECG) is performed to check the functioning of your heart. You may be asked during your study participation to have additional ECG assessments (e.g. if you take certain medications). Leads will be placed on your skin and you will be asked to lie down during the examination. While the decisions about your treatment remain with your study doctor, your ECGs will be sent to a central imaging vendor for analysis. Additional ECGs may be requested to be conducted locally to rule out any heart rhythm changes if you are taking treatment (for diseases other than RMS) which have the potential for drug interactions with either teriflunomide or remibrutinib.

Imaging: MRIs will only be done for patients from pre-selected study sites / clinics / hospitals. Details of the imaging are already outlined in the table above. These MRIs will be sent to a central MRI reading center for analysis.

Ask your study staff to explain the MRI procedures and their risks in detail. The risks are also explained in section 16. You may also ask the local imaging facility any questions that you have.

While the decisions about your treatment remain with your study doctor, your coded medical MRI images will be sent to a central imaging vendor for analysis. Your coded medical MRI images may also be used for the development and evaluation of new methods of analysis.

Patient-/participant-reported outcome measures (PROs): In this study PROs are used to assess changes in burden of disease from a MS patient's perspective. The disease-specific Multiple Sclerosis Impact Scale (MSIS-29) questionnaire is designed to characterise the overall health-related quality of life (HRQoL) for patients with MS. Symptom-specific questionnaires like Fatigue Symptoms and Impacts Questionnaire–Relapsing Multiple Sclerosis (FSIQ–RMS), 7-Item Generalised Anxiety Disorder Scale (GAD-7), Patient Health Questionnaire-9 (PHQ-9), and Brief Pain Inventory–short form (BPI-SF) are focused on change (improvement or worsening) in common MS symptoms (fatigue, anxiety, depression, and pain respectively) during the study. HUI-3 is a generic (non-MS specific) preference-based instrument designed to measure health status and health-related quality of life for the patients like you enrolled in the study. Not all PRO's will have to be completed at every visit during the core part of the study, on average, 20 minutes of your time will be needed to complete the designated PRO's for any assigned visit. During the extension part of the study PROs are to be completed at Month 6, Month 12 and then on an annual basis, the time needed to complete the PROs during these visits would be around 40 mins.

Study feedback questionnaire: You will be requested to complete this questionnaire at 3 time points for the core part (CP) of study and 1 time point during extension part (EP) of

study. This questionnaire does not ask questions about your disease, symptoms, treatment effect or adverse events but is to help understand how to improve the overall study process. Completion of this questionnaire is optional.

If you have any questions about any of these activities, please speak with your study doctor.

10. WHAT BIOLOGICAL SAMPLES WILL BE COLLECTED DURING THE STUDY?

Biological samples which include blood and urine from your body will be collected from you while you are in this study. These include:

Standard safety: Laboratory testing for your safety will include blood and urine tests that show how your kidneys and liver are working, and blood cell counts to assess your general health. For further details of standard safety tests ask your study doctor. Based on the local clinical practice and your safety needs, blood tests may be done at a local laboratory outside the study schedule based on the study doctor's judgement.

B Cells: Tests to see the effect of the study treatment on your B cells (known as B lymphocytes), which are types of white blood cells. These cells secrete antibodies and are a part of your immune system. B-cell levels are performed at Screening, Day 1, M3, M6, M12, M24, M30/EOS and EOT during Core Part (CP) and during the Extension Part (EP) are assessed at EP Day 1, EP M6, M12, M24, M36, M48, and M60/EP EOS.

Immunoglobulins (Total IgG and Total IgM): These are proteins (antibodies) that help to fight infection in your body, Immunoglobulin level assessments are performed during the Core Part at Screening, Day1, M3, M6, M12, M24, M30/EOS and EOT (end of treatment) and during the Extension Part at EP Day 1, EP M6, M12, M24, M36, M48 and M60/EP EOS.

Biomarkers: Blood samples will also be collected at various times during the study for tests and research called "biomarker analysis" including biomarkers of exploratory nature. A "biomarker" is an indicator that gives information about your health, illness or your response to treatment. These biomarker samples will be used to help answer scientific questions related to the effect of remibrutinib on cells or organs in the body, as well as the impact it has on MS. These biomarkers will include neurofilaments (NFL, a marker of damage to nerves) and glial fibrillary acidic protein (GFAP, a marker of nerve cellular injury within brain). In the Core Part, NFL and GFAP are tested at Day 1, M3, M6, M12 and M24 and at the EOS and EOT visits. In the Extension Part NFL and GFAP are tested at Day 1, M6 and M12 and annually thereafter until EOS.

Residual serum samples may be evaluated to look for protein markers that may be associated with treatment response or predict response to treatment. Additional markers related to MS may be assessed based on the research outcome of this study and/or similar studies in MS to identify and/or verify potential markers that may indicate disease activity, help predict the disease course and/or predict clinical response to treatment. Transcriptomic RNA sampling is optional and is explained in Appendix 4.

Exploratory DNA sampling (optional) is conducted once at Day 1 and is explained in an additional participant information leaflet with consent form.

Pharmacokinetics (PK): To see how the study treatment is processed (absorbed and eliminated) by your body. There are two PK groups, for "rich" and "sparse" sampling. "Rich PK sampling" will be performed in a minimum of 160 participants at the selected study sites. "Sparse PK sampling" will be performed in all other participants. PK assessments to be performed only during core part of the study. In addition, these samples may also help researchers understand how the drug works in the body.

11. CAN I STOP MY STUDY TREATMENT OR DECIDE NOT TO CONTINUE IN THE STUDY?

You are free to stop your participation in this study at any time. If you want to stop participation in the study, you should notify the study doctor. This could mean:

1. Stopping further study treatments but continuing study visits. You decide to stop study treatment, but will return to the study site for future visits per the visit schedule (or earlier if necessary).

OR

2. Stopping further study treatment and you no longer wish to come in for study visits. However, your study doctor or staff may ask you, if you agree, to participate in additional phone calls to check how you are doing. This is considered as withdrawal of your consent for participation in this study. If this is what you want, then it is important that you inform your Study Doctor of your decision to withdraw your consent. Novartis will continue to retain and use any research results that have already been collected for the study evaluation.

For both options, your already-collected data and samples will still be used for the purposes of this study, unless you decide that you want to stop study treatment and also do not want to come to any further visits and do not want to have any further assessments or contact by the study doctor, and do not want Novartis to analyse any blood samples or other biological samples already collected. This is considered as withdrawal of your consent for participation in this study. If this is what you want, then it is important that you inform your study doctor of your decision to withdraw your consent. Novartis will continue to retain and use any research results that have already been collected for the study evaluation. No further study-related activities will take place.

You will be asked to return to the hospital clinic as soon as possible to check how you are and you must return all unused study treatment to the clinic.

The choice to withdraw from the research study will not affect your future medical care in any way.

12. ARE THERE ANY REASONS THAT MY STUDY TREATMENT OR MY STUDY PARTICIPATION MAY BE STOPPED EARLY?

Sometimes, during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study.
If you decide to stop taking part in the study, your doctor will advise on the most suitable treatment for you. If you decide to continue in the study, you will be asked to sign a new Consent Form.
Also, on receiving new information, your study doctor might consider it best to take you out of the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

Your study doctor may remove you from this study for any of the following reasons:-

Examples why you may have to stop some or all study-related activities, including study treatment are:

1. You need treatment not allowed in this study
2. You fail to follow instructions
3. You become pregnant

4. You experience side effects from the study treatments that you find unacceptable
5. Your study doctor considers keeping you in the study might be harmful to you
6. Novartis decides to stop the study or the development of the study treatment
7. You no longer wish to continue in the study

Even if you are not continuing with study visits, **you will need to complete the AEP** and you may be asked to have some of the study procedures done at your final study visit. These may include a physical examination, weight measurements, vital signs assessments, an ECG, a pregnancy test, urine sample and blood samples for safety, patient reported outcomes (PROs), EDSS assessment and biomarkers.

13. WHAT WILL HAPPEN AFTER I COMPLETE THE STUDY?

After the study is completed, a summary of the overall study results written for study participants will be shared with your study doctor. Your study doctor and/or representatives will share these results with you. Any report that is published about the study will not identify you or any other patient taking part. The study results will also be made available at www.novctrd.com, at www.ClinicalTrials.gov, and/or https://eudract.ema.europa.eu. These websites will not include information that can identify you. You can search this website at any time by using the study number CLOU064C12302.

A summary of the study results may be published at conferences or in journals. If the results of the study are presented to the public, you will not be named. Some authorities may ask that the Sponsor disclose study data for transparency reasons. However, the data shared will not identify you.

You will not own any data or discoveries made during the study; this will be owned by the Sponsor.

14. WILL I HAVE ACCESS TO STUDY TREATMENT AFTER THE STUDY ENDS?

This study has a Core Part with a maximum of up to 2.5 years of study treatment with either remibrutinib or teriflunomide and if you complete the Core Part on study treatment and the AEP, you can receive treatment with remibrutinib for up to another 5 years duration during the Extension Part of the study.

If the Sponsor decides to stop research with the study treatment for any reason (for example, results show that the study treatment does not work), your study doctor will make sure you get an alternative treatment.

15. WHAT ARE THE POSSIBLE BENEFITS TO ME IF I CHOOSE TO TAKE PART IN THIS STUDY?

In this study, you have a 50% chance of receiving remibrutinib and placebo AND a 50% chance of receiving teriflunomide and placebo. You will not know which treatment you have been assigned to during the study. No patients will be assigned to just placebo or 'inactive' treatment. There is a chance that you may receive no direct benefit from being in this study. However, your taking part may help patients get better care in the future. This study, in which you are asked to participate, will include patients with relapsing MS, so not only RRMS (relapsing remitting MS) patients but also patients with secondary progressive form of MS (SPMS) who have relapsed. The study you are participating in has been designed to confirm whether remibrutinib is an effective treatment for relapsing MS. Teriflunomide is a treatment

which is already approved in many countries worldwide for use in patients with relapsing remitting MS and is the treatment remibrutinib is being compared to in this study. The effectiveness of teriflunomide in reducing relapses, disability worsening and lesions or 'spots' on MRI has already been demonstrated in clinical studies.

Some other benefits of being a patient in this clinical research study include:

- Helping others with the same medical condition by contributing to medical research
- Gaining access to a new research treatment
- Having access to expert medical care for the condition being studied
- Getting actively involved in your health care
- Having your health closely assessed and monitored

16. WHAT ARE THE POSSIBLE RISKS TO ME IF I CHOOSE TO TAKE PART IN THIS STUDY?

There is a possibility that you will experience side effects from the study treatments and/or procedures done. Because remibrutinib is in development, human/patient experience is still limited, and not all of the possible side effects of the study treatment are known at this time.

You should tell the study doctor if you have any unusual complaints, behaviours, or side effects, or had other doctor visits or hospitalisations outside the study.

For remibrutinib, the available clinical safety experience has shown favorable safety and tolerability in indications other than RMS. So, all the safety information of remibrutinib is based on Non-MS indications. Based on the way remibrutinib works and on experience with other drugs acting in a similar way, the potential risks of remibrutinib include an increased susceptibility to infections, increased risk of bleeding and a decrease in blood cell count.

Given that remibrutinib is metabolised in the liver it may interact with other drugs that are processed in a similar way and may affect how these drugs work.

Findings from animal and human studies to date show that a potential risk of significant QT prolongation (a condition in which the interval between the heart contracting and relaxing is longer than normal and which may cause an increased risk of serious abnormal heart rhythms) with the dose of remibrutinib used in this study may be increased under very specific circumstances, however overall is considered to be very low. To minimise the risk, the taking of certain medications (called strong *CYP3A4* inhibitors) at the same time as remibrutinib is not allowed in this study. Please, inform your study doctor of all medications that you are taking. In addition, abnormal heart rhythms (including atrial fibrillation and flutter) have been observed with approved medications for certain blood cancer treatments, that work in the same way as remibrutinib. Also, your heart rhythm will be monitored regularly during the study to detect emergence and for clinical management (including potential discontinuation from the study) of either condition.

Findings from animal studies suggest that remibrutinib could harm the unborn baby during pregnancy. Based on the available data, it is not fully understood what this means for humans or whether remibrutinib could harm unborn babies in humans, therefore, it is very important to adhere to the study requirements for use of highly effective contraception. See Section 17 for more details.

To date, more than 903 patients (healthy volunteers and patients suffering from chronic spontaneous urticaria (CSU), asthma, Sjogren's syndrome and atopic dermatitis) have been exposed to remibrutinib. The most common side effects experienced by CSU patients in a

previously completed study in 309 participants treated with remibrutinib (up to 100 mg twice per day, as investigated in the study you would participate in) were:

- Headache: in 9.7 % of patients treated with remibrutinib
- Nasopharyngitis [common cold]: in 8.6 % of patients treated with remibrutinib

However, these side effects were reported at a comparable rate by patients who received inactive placebo treatment.

Potential side effects of teriflunomide:

The other medication you may receive in the study, teriflunomide, is approved for the treatment of relapsing remitting MS and is being used during the Core Part of the study.

The most common adverse reactions noted during use of teriflunomide (also known as Aubagio®) treatment included:

Very common side effects (occur in 1 in every 10 patients or more in clinical studies): Headache, diarrhoea, nausea, increase in liver enzyme alanine aminotransferase (ALT) and hair loss (alopecia).

Common side effects (occur in 1 in 100 patients or more but less than 1 in 10 patients): Vomiting; influenza, upper respiratory tract infection; urinary tract infection; inflammation or infection of bronchi or sinuses or throat or voice box (bronchitis, sinusitis, pharyngitis, laryngitis); bladder infection (cystitis); viral inflammation or infection of the digestive system (viral gastroenteritis); cold sores (oral herpes); athlete's foot (tinea pedis); decrease in number of neutrophils, a type of white cells (neutropenia); decrease in number of red blood cells (anemia); mild allergic reactions, nerve compression in the hand (Carpal tunnel syndrome); tingling or burning sensations (paresthesia); toothache or tooth infection; lower back pain (sciatica); irregular heart beat (palpitations); increase in blood pressure (hypertension); anxiety; upper abdominal pain; decrease in weight; general pain or aching in the joints (arthralgia) or pain/aching in muscles (myalgia or musculoskeletal pain), increase in blood levels of enzyme creatinine phosphokinase, frequent urination (pollakiuria), increased menstrual bleeding (menorrhagia); lack of energy (asthenia); pancreatitis (in children), rash (skin hives), acne (pimples), increase in liver enzyme gamma-glutamyl transferase (GGT) and aspartate aminotransferase (AST)..

Uncommon side effect (less than 1 in 100 patient to more than 1 in 1000 patients): Severe infections including sepsis; mild decrease in platelet cell numbers (thrombocytopenia); hypersensitivity reactions including anaphylaxis and angioedema; severe skin reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TENS) and Drug reaction eosinophilia and systemic symptoms (DRESS); excessive skin hypersensitivity (hyperesthesia), nerve damage leading outside of brain or spine leading to pain, sensation changes or weakness (peripheral neuropathy); scarring or inflammation of the lungs (interstitial lung disease); sore or inflammation inside the mouth (stomatitis), abnormal levels (too high or too low) of blood lipids (dyslipidemia), nail disorders, psoriasis (including pustular), post traumatic pain; pancreatitis (in adults), colitis. Serious skin reactions and inflammation of the lungs can be potentially fatal.

Rare side effect (more than 1 in 1000 patients to 1 in 10,000 patients or more) or not known:

Acute liver inflammation (acute hepatitis) or drug induced liver injury (DILI), pulmonary hypertension.

Teriflunomide was associated with fetal abnormalities/deformities and embryofetal toxicity in animal studies and may cause serious birth defects when administered during pregnancy (Based on Summary of Product Characteristics January, 2022). Please refer to the current

local product information for more details. It is very important to adhere to the study requirements for use of high effective contraception. See Section 17 for more details.

Potential side effects of medications similar to remibrutinib:

Currently, there are medications similar to remibrutinib (BTK inhibitors, named ibrutinib, acalabrutinib, and zanubrutinib) approved for various non-MS treatments such as blood cancer treatment. Some additional potential side effects associated with these medications include irregular rapid heart beat and the risk of developing other cancers. The medication ibrutinib also has the potential side effects of heart failure, high blood pressure and tumour lysis syndrome (rapid destruction of cancer cells that can lead to abnormalities in blood chemistry and kidney function).

These other potential side effects may be more likely due to off-target effects (i.e. effects that are not due to BTK inhibition but are due to some other action of the drug) and/or due to the medical condition of blood cancer for which these approved BTK inhibitors are indicated.

As remibrutinib has high selectivity for inhibiting BTK and not for off-targets, the risk of such off-target side effects is potentially reduced. Also, other cancers and tumour lysis syndrome are side effects known to happen in patients with blood cancers, and are not expected for non-cancer conditions like multiple sclerosis for which remibrutinib is being studied.

In over 903 subjects exposed to remibrutinib across all ongoing and completed non-MS clinical studies, no signal for any of these safety concerns/off-target effects has been observed based on adverse events, ECG, vital signs and laboratory data monitoring.

You and your study doctor will be informed of important safety information that may affect your decision to continue participation in the study if and once it becomes available.

Tell your study doctor if you have any troublesome symptom or side effect including the ones listed above; you may have to stop taking study drug immediately and get immediate medical help.

Other risks or side effects

Vaccination: The impact of remibrutinib on the effectiveness of a vaccine is currently not known because specific studies investigating this have not yet been carried out. However, during treatment with remibrutinib, vaccination may be less effective. Therefore, it is recommended that you discuss this with your doctor and perform necessary vaccinations prior to enrollment into the study. You should NOT take certain types of vaccines, i.e. any live vaccine during the study or in the 6 weeks prior to starting the study. Please ask your study doctor for further guidance.

Lactose Intolerance: The study treatment you will be given might contain 85 mg of lactose per tablet. This very small amount of lactose per tablet is unlikely to cause symptoms in patients with lactose intolerance. If you have one of the rare hereditary problems of galactose intolerance, total lactase deficiency and glucose-galactose malabsorption please ask your study doctor for further guidance. Lactose is a source of glucose and galactose. The study treatment may also contain traces of cow's milk proteins. If you are allergic to cow's milk, talk to your study doctor for further guidance.

ECGs: As part of this study, you will have ECGs performed. Some people may experience redness and pain at the site of the ECG electrode placement.

Blood collection risks: As part of this study, you will have blood samples drawn. The risks of collecting blood may include: fainting, pain, and/or bruising. Rarely, there may be a small blood clot or infection at the site of the needle puncture.

Imaging risks: For the participants of the MRI cohort from the pre-selected MRI cohort sites: Brain MRI uses a magnetic field and releases radio waves. There are no known harmful effects from the strong magnetic field used for MRI. The magnet may affect pacemakers, joint or limb replacement and other medical devices that contain iron. You will be asked to remove any metallic objects before entering the MRI facility. MRI scanners can be noisy at times. This is normal and not harmful. You will be given earplugs to wear. Lying on the MRI table without moving may be uncomfortable. Some patients may experience claustrophobia or discomfort being in a confined space. Your MRI scans for this study would usually be expected to take 40-45 minutes to get the images needed for the study and you will be able to take any anti-anxiety medication after discussion with your study doctor if you usually need this to have an MRI. You will be given an injection of a contrast agent (gadolinium) during the MRI examination. Gadolinium (sometimes shortened to "Gd") is a contrast agent/dye that is injected into your vein before the last set of images are taken and it may cause side effects, such as mild headache, nausea and local burning sensation. Very rarely (less than one in a thousand), patients are allergic to gadolinium (including anaphylactoid reactions). Tell your study doctor if you know or think you may be allergic to gadolinium. There is a risk that repeated gadolinium administration, especially in younger participants, may lead to a cumulative build-up of trace amounts of gadolinium deposition in the central nervous system, which may be associated with a higher level of longer-term consequences, and may also carry an increased risk of other contrast reactions (including Nephrogenic Systemic Fibrosis (NSF) although data on the long-term effects are currently limited. To date, no causal association between use of gadolinium contrast and any long-term neurological symptoms has yet been established. NSF is a severe reaction that may be caused by gadolinium-based contrast medium in patients with severely reduced kidney function. It is a disease that causes thickening and hardening of the skin and may involve other organs. The risk of NSF following exposure to gadolinium-based contrast agents is increased in patients with severe kidney insufficiency or in the period after a liver transplant. To date, there are no known cases of NSF in patients with normal kidney function. Your kidney function will be assessed during the screening period to check if you are eligible for the study. Patients with severe kidney disease are not eligible to join the study. The brain MRI will be done in a similar way to how you may have had an MRI done previously to diagnose and monitor your MS.

You may also ask the local imaging facility any questions that you have.

Risks of Accelerated Elimination Procedure (AEP) and the drugs used for it: AEP has the potential to result in the return of disease activity (including relapse) as you will be off study treatment. The common adverse events for the medications used in the AEP are dark stool and constipation for activated charcoal; constipation, abdominal pain, flatulence, nausea, vomiting and diarrhoea for cholestyramine. Your doctor may change the dose or frequency of these medications to manage these adverse events.

17. WHAT DO I NEED TO KNOW ABOUT BIRTH CONTROL AND PREGNANCY AND BREAST FEEDING?

Studies done in pregnant animals have shown that study treatment can harm an unborn baby. In a study in pregnant rabbits, remibrutinib caused birth defects in the fetus when given at doses that were higher than you may receive. It is not fully understood what this means for humans as the risk of birth defects in humans is not known at this stage. Teriflunomide may cause serious birth defects when administered during pregnancy. Teriflunomide is contraindicated in pregnancy.

If you are female and are able to have a baby (i.e. have reproductive potential), you must use the right type of birth control. The study doctor will discuss the birth control methods

approved for the study and the period of time birth control will be needed (see appendix 2). Highly effective methods of contraception should be used while taking study medication and be continued for at least **4 weeks** after stopping study medication, and use of contraception should also be continued until it is verified that plasma concentrations of teriflunomide have dropped below a specific level described in the teriflunomide patient information. If you become pregnant, you must tell the study doctor immediately. The study treatment will be stopped. Additionally, if you become pregnant during the Core Part of study you will be advised to undergo the accelerated elimination procedure (AEP) and to verify that the plasma teriflunomide concentration has dropped below a specific level as described in the teriflunomide patient information. This procedure reduces the teriflunomide level in your body. Since neither you nor your study doctor know what study drug you are receiving in the core part of the study this procedure will be advised for all patients who become pregnant in the core part of the study.

Females of reproductive potential who wish to become pregnant during the study should discontinue the study treatment and undergo an accelerated elimination procedure (if not already completed). Highly effective contraception should be used for at least 4 weeks after study drug discontinuation and until teriflunomide blood levels have been checked and are low enough. After study treatment is stopped, you will be asked to read and sign another consent form to let the study doctor ask about your pregnancy.

If you are a male participant you must agree to use a condom while taking study treatment and for at least 4 weeks after stopping double-blind study treatment (including completion of AEP). Use of condom should also be continued until it is confirmed that plasma concentrations of teriflunomide are low enough (as described in the teriflunomide patient information). You must also agree not to donate sperm during this time. If you wish to father a child during the core part of the study, you should discontinue study treatment and undergo the AEP. If you wish to father a child during the extension part of the study, you must have undergone AEP following the core part EOS visit. In both cases effective contraception should be continued for at least 4 weeks and until teriflunomide blood levels have been checked and they are low enough (as described in the teriflunomide patient information).

Also, if you are male, you and your female partner should use effective birth control since you may be treated with teriflunomide during the core part of the study. Teriflunomide remains in your blood after you stop taking it, so continue using effective birth control until teriflunomide blood levels have been checked and they are low enough (as described in the teriflunomide patient information). **If your partner becomes pregnant, you must tell the study doctor immediately, and your partner will be asked to read and sign another consent form to let the study doctor collect information about her pregnancy.**

In order to take part in this study it is compulsory that you use an appropriate birth control method because it is not yet known if the study treatment may affect the unborn child.

18. WHAT ARE MY RESPONSIBILITIES AND ARE THERE ANY COSTS FOR ME IF I AGREE TO JOIN THE STUDY?

You will not be paid for being in the study, however you will be reimbursed reasonable travel expenses for getting to and from the hospital including standard class rail travel and bus travel so please keep your receipts. If you are travelling by car, you will be reimbursed at 45p/mile, so please keep a note of your mileage. Car parking fees will be reimbursed so please keep your receipts.

You will not have to pay for the study treatment(s).

For visits lasting longer than 3 hours you will be reimbursed up to £15 for light refreshments.

If you agree to participate in this study, you have the following responsibilities:

You will need to:

Related to study appointments/visits and procedures:

- Carry with you at all times a card (the same size as a credit card) which the study doctor will give you at your first visit. Cards like this are given to everyone who takes part in this kind of study; they include phone numbers to contact in any emergency
- Follow instructions given to you by the study doctor and study staff
- Attend all of your study appointments. If it is necessary to miss an appointment, you must contact the study doctor or study staff to reschedule your appointment.
- Complete your required study activities as instructed, such as filling in questionnaires or diaries
- For the Month 1 and Month 6 visits of the core part you will need to fast overnight (ideally ≥8 h) before coming to the clinic for assessments. Do not take your study treatment at home for these visits; you will need to take your study treatment at the clinic after giving a "pre-dose" blood sample. You will need to remain fasted for approximately one hour after taking your study medication until a one hour "post dose" blood sample is taken. If you consent for the optional "rich sampling" then you will need to remain fasted for approximately four hours after taking your study medication until the four-hour "post dose" blood sample has been taken at Month 1.

Related to the study treatment:

- It is very important for you to take the study treatment exactly as your study doctor tells you to and should not do anything else with it. Do not miss any doses of study treatment. If you do miss a dose(s) please make a note of the date and time and tell the study staff at your next visit.
- Keep the study treatment in a safe place, away from children and for your use only.
- At the end of the study or if you stop study treatment, you must return all of your unused study treatment and empty containers as instructed

Related to side effects and other medications you may be taking:

- You must tell your study doctor or study staff if you have any unusual symptoms, any side effects, other doctor visits, or planned or unplanned hospital visits /admissions that you have for any reason
- You must tell your study doctor about any medications you currently take or may take during the course of the study, including prescription medicines, over the counter medicines and vitamins and supplements
- If you are taking other medications, they may need to be stopped or the dose reduced to manage side effects. This is to avoid a mix-up of effects between the other medication and the study treatment. Your study doctor will discuss this with you.

19. WHAT OTHER CHOICES ARE AVAILABLE FOR ME?

If you decide not to take part in this study, your study doctor will inform you about other possible treatments for patients with MS. You can ask your study doctor about their potential benefits and risks.

20. WHAT IF I BECOME INJURED BECAUSE I PARTICIPATED IN THIS STUDY?

If you are not happy with the general care and treatment you receive during the study, please speak first to your study doctor or nurse, who will try to resolve the problem. He/she should also tell you about Re:Cognition Health - London standard complaints procedure in case you wish to take the matter further.

England:
Patient advice and liaison services (*PALS*)

The Patient Advice and Liaison Service, known as PALS, has been introduced to ensure that the NHS listens to patients, their relatives, carers and friends, and answers their questions and resolves their concerns as quickly as possible. Your local PALs can be located online: https://www.nhs.uk/Service-Search/Patient%20advice%20and%20liaison%20services%20(PALS)/LocationSearch/363

Local PALs Contact Telephone Number: 020 3447 3042

Scotland:
Patient Advice and Support Service

The Scottish Citizens Advice Bureau (CAB) Service delivers the Patient Advice and Support Service (PASS). The service is independent and provides free, confidential information, advice and support to anyone who uses the NHS in Scotland. It aims to support patients, their carers and families in their dealings with the NHS and in other matters affecting their health. Your local PASS can be located online:
https://www.citizensadvice.org.uk/scotland/

If you develop any health problem or suffer harm during the study, you should contact the study doctor. If you think you may have been harmed by the study medication, or otherwise by taking part in the study, Novartis Pharmaceuticals (the company organising the study) should compensate you according to the Clinical Trial Compensation Guidelines issued by the *Association of the British Pharmaceutical Industry (ABPI)*

You can get a copy of the guidelines from your hospital or visit:-

England	Telephone +44 (0)20 7930 3477 or visit http://www.abpi.org.uk/contact-us/
Scotland	Telephone +44 (0) 131 523 0497 or visit http://www.abpi.org.uk/contact-us/

21. WHAT IS PERSONAL DATA AND WHAT HAPPENS WITH IT?

During this clinical study, the study staff will collect certain information/data about you that is called “Personal Data”.

What is Personal Data and who can see it?

What is Personal Data?	Who can see it?
Examples include: • Your name, full date of birth, sex • Race/Ethnicity • Address and phone number • Medical condition and medical history • Images (such as MRI scan results) • Information from your biological samples (such as blood)	• The study doctor/study staff • Institutional Review Boards/Ethics Committees who are responsible for protecting participants' rights • A few people authorised by the sponsor (such as the sponsor's study monitors and auditors) who need to check that all the data is correct. The study monitors may review data from a location other than the study site. • Vendors (people who work on the study for the sponsor, such as a contract research organisations [CROs] or home nursing vendors, courier for home delivery of study treatment). • Health authorities (government groups who make sure that clinical studies are conducted according to established quality and safety standards)

All of the people are trained to keep your data confidential. They use your personal data to ensure the study was run properly and make sure these data are correct. Your "Personal data" will be kept confidential at the Study Site.

Information on your *race/ethnicity* is collected to check 2 things:

(i) Whether the participants in the study represent the *racial or ethnic* make-up of people with MS.

(ii) Whether the safety and/or efficacy of treatments differ between different *racial or ethnic* groups.

Health authorities may also request this information from the sponsor for the same reasons

What is coded data and who can see it?

The study doctor will replace the parts of "personal data" that can identify you, such as your name and address, with your participant ID. This ensures that all this information about you becomes "coded data", and you cannot be identified.

What is coded data?	Who can see it?
Examples include: • Your sex, age and year of birth • Race/ethnicity • Images and information from your biological samples collected during the study • Genetic data	• The study doctor and study staff • Ethics Committees or Institutional Review Boards. • The sponsor and their staff. • The sponsor's collaborators and partners (such as researchers who work with the sponsor or commercial partners and staff at scientific journals).

	• Vendors (see examples in the previous table). • Health authorities' employees located in different countries around the world. • Another company potentially buying the sponsor or part of the sponsor's business

You will **not** be notified every time the coded data is used or shared.

By using coded data, it is very unlikely that anyone other than the study doctor and study staff or sponsor authorised staff can identify you.

The sponsor only keeps the coded data and is required to combine the data of all study participants. The sponsor may use the combined coded data to:

- assess the safety and efficacy (how well it works) of the study treatment and submit it to Health Authorities for the approval of the study treatment.
- support scientific research including sharing with external partners, such as other researchers, staff at scientific journals and commercial partners for further research purposes or publication of the research results.

Some studies may use artificial intelligence (AI) as part of the study. The Sponsor is committed to using AI in an ethical way. For more information on the use of AI, please speak to your study doctor.

The coded data cannot be used to contact you or affect your care or any other decisions about your life. Your coded data will not become part of your health record.

The people/organisations listed in the table above may be located in countries outside of the United Kingdom ("UK"), but during the transfer, the sponsor will ensure the protection and privacy of the coded data as required by law. Personal data may be transferred outside of the UK, where data protection laws may not be as strict as your home country. If we transfer your personal data to overseas jurisdictions, where required, we will put in place appropriate measures to protect your personal data by: (i) applying the level of protection required under the local data protection/privacy laws applicable; and (ii) acting in accordance with our policies and standards.

If you wish to request additional information in relation to international transfers of personal data and/or obtain a copy of the adequate safeguard put in place, please contact privacy_uk.ireland@novartis.com.

By law, the sponsor must keep all study data for at least 25 years.

The collection and use of personal data and coded data by the sponsor is necessary for scientific research purposes, as well as the sponsor's legitimate interests in performing the study.

Subject to laws and regulations, you have the right to:

- review, correct certain personal data, and obtain a copy at the end of the study;
- oppose the use of the personal data;
- lodge a complaint with the Information Commissioner's Office.

It is not possible to erase your personal data or coded data already collected as the data needs to be complete, correct, available for Health Authority purposes and to ensure the integrity of the study. Please remember that the sponsor does not keep personal data. They

only keep the coded data. If you have any questions regarding personal data, you should contact your study doctor.

For any queries related to coded data, you can contact your study doctor/site staff.

22. ARE THERE ANY SITUATIONS WHERE MY PERSONAL DATA MAY BE SHARED?

In rare instances where a nurse, a study doctor, or a laboratory technician, is exposed to your blood, tissue or body fluids by needle stick, cut or splash to mucosa or damaged skin, it may be necessary to test your blood, tissue, or body fluid sample for certain viral infections including Hepatitis B and C and HIV on your sample already available. This is to make it possible for that person to receive appropriate counselling, monitoring and treatment that they may need. In this instance, the study doctor will tell you the results of these tests and advise you on the next steps. The study doctor will also let your GP know about this. Confidentiality of the results of your tests will be respected at all times. By law, positive test results for such reportable diseases must be shared with public health authorities.

23. WHAT HAPPENS TO MY BIOLOGICAL SAMPLES (SUCH AS BLOOD)?

The biological samples collected will be used in the context of the study to achieve its scientific purpose.

If you no longer want to participate in the study, no further samples will be collected. In order to keep the integrity of the study, the already-collected samples will still be used for the purpose of the study, unless prohibited by local law.

Requests may come from any Health Authority to do more testing on your samples. Most of these requests are to ensure the safety of the study medication. The sponsor will comply with these requests when possible, and, as with all your data, this information will remain confidential.

The sponsor will ship biological samples outside of the UK and may keep biological samples for up to 15 years after the study ends and then destroy them. These samples will be kept in a secured environment and you cannot be identified.

You can request at any time that your samples be destroyed by contacting the study doctor who will need to inform the sponsor.

24. HAS THE STUDY BEEN REVIEWED?

Yes. Sheffield Research Ethics Committee has reviewed and given favourable opinion for this research study. The Sheffield Research Ethics Committee includes healthcare professionals as well as non-medical people. All members of the committee are completely independent from anyone organising the study.

25. WHERE CAN I GET MORE INFORMATION?

If you have more questions about this study, you can contact the study doctor whose name and number are on the front page of this information sheet and on the consent form.

Thank you for taking the time to read this information sheet.

Appendix 1 Summary Table of Assessments

	CORE PART (CP)															
Assessments	**Screen Visit**	**Day 1**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 15**	**Month 21**	**Month 24**	**Month 27**	**Month 30**	**End of Treatment**	**Follow Up Visit**	**Abbreviated Visit (when off treatment)**
Review of Medical History	✓															
Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Body Weight	✓			✓			✓				✓		✓	✓	✓	✓
Physical Examination	✓	✓	✓	✓	✓	✓	✓		✓		✓		✓	✓	✓	✓
Electrocardiogram (ECG)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
electronic Columbia Suicide Severity Rating Scale (eC-SSRS)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Participant Diary		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Contraception Status		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy Test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Exploratory DNA Sampling (if optional consent is given)	□	✓														
Transcriptomics (RNA) sample (if optional consent is given)		✓					✓						✓	✓		
Routine laboratory evaluations including urine sampling	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sampling for coagulation evaluation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Sampling for B-cells	✓	✓		✓	✓		✓				✓		✓	✓		
Sampling for Biomarkers	✓	✓		✓	✓		✓				✓		✓	✓		✓

	CORE PART (CP)															
Assessments	**Screen Visit**	**Day 1**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 15**	**Month 21**	**Month 24**	**Month 27**	**Month 30**	**End of Treatment**	**Follow Up Visit**	**Abbreviated Visit (when off treatment)**
Sampling for IgG, IgM levels		✓		✓	✓		✓				✓		✓	✓		
Pharmacokinetic (PK) blood collection (including 'Rich' sampling where additional optional consent is given)	✓		✓		✓											
Questionnaires (MSIS-29, FSIQ-RMS, PHQ-9, GAD-7, BPI, HUI-III)	□	✓	□	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓
Expanded Disability Status Scale (EDSS)	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Timed 25 Foot Walking Scale (T25FW)	✓	✓			✓		✓		✓		✓		✓	✓		✓
9-Hole Peg Test (9HPT)		✓			✓		✓		✓		✓		✓	✓		✓
Symbol Digit Modalities Test (SDMT)		✓					✓				✓		✓	✓		✓
MRI (MRI Cohort only)				✓	✓						✓		✓	✓		✓
Accelerated Elimination Procedure													✓	✓		✓

	EXTENSION PART (EP)												
Assessments	**Day 1**	**Month 1**	**Month 6**	**Month 12**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Follow-up Visit**
Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Body Weight	✓			✓		✓		✓		✓		✓	✓
Physical Examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Electrocardiogram (ECG)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
electronic Columbia Suicide Severity Rating Scale (eC-SSRS)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Participant Diary		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Contraception Status	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy Test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Routine laboratory evaluations including urine sampling	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sampling for coagulation evaluation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sampling for B-cells	✓		✓	✓		✓		✓		✓		✓	
Sampling for Biomarkers	✓		✓	✓		✓		✓		✓		✓	
Sampling for IgG, IgM levels	✓		✓	✓		✓		✓		✓		✓	
Questionnaires (MSIS-29, FSIQ-RMS, PHQ-9, GAD-7, BPI, HUI-III)	✓		✓	✓		✓		✓		✓		✓	
Expanded Disability Status Scale (EDSS)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Timed 25 Foot Walking Scale (T25FW)	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
9-Hole Peg Test (9HPT)	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Symbol Digit Modalities Test (SDMT)				✓		✓				✓		✓	
MRI (MRI Cohort only)	✓							✓				✓	

Investigator: Dr Emer MacSweeney

Centre number: 2501

Contact for queries

If you have any questions about this study, you can contact:

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+44 (0) 20 3355 3536

Out of hours: Dr Emer MacSweeney on

+44 (0) 7540 802222

Re:Cognition Health - London

45 Queen Anne Street

London

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Efficacy and safety of remibrutinib compared to teriflunomide in participants with relapsing Multiple Sclerosis (MS)

Please initial each box to confirm that you have read, understood and agreed each of the numbered points.

1	I have read and understood this Information Leaflet version 02.04.**03** dated **14-Dec-2022** and I have had the time to consider it and the opportunity to ask questions.	1
2	I understand that taking part in the study is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.	2
3	I have read and understood the information on the use of my personal data and coded data, including my biological samples (such as blood), as described in this document.	3
4	I agree that my confidential medical records can be accessed for the study.	4
5.	I agree to my GP being told that I am taking part in this study and providing requested information relevant to my participation.	5.
6	I agree to take part in the above study.	6

When you have initialed all the above boxes, please complete the first box below (including the date) yourself:

Name of **Patient** (CAPITALS):	
Date:	Signature:
Name of **Doctor** taking consent (CAPITALS):	
Date: Time:	Signature:
Name of **Impartial Witness** (if applicable):	
Date:	Signature:

Patient number:	**Patient's initials:**

Original to be kept in the study Investigator Folder; Second original or a copy of the original to be given to the patient. The Information Sheet and Consent Form are one entire document and must not be separated. The Consent Form should be printed and used as a single page

Investigator: Dr Emer MacSweeney

Centre number: 2501

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Efficacy and safety of remibrutinib compared to teriflunomide in participants with relapsing Multiple Sclerosis (MS)

Appendix 2

You have read the information sheet 02.04.03 dated 14-Dec-2022 however as you are of child bearing potential you are being asked to read this additional information

If you are a woman who could become pregnant:
You will be asked to have a pregnancy test at the screening visit, throughout the study and at end of the study. If you think you may have become pregnant during the study, you must tell the doctor immediately.

As a female participant in the study it is important that you use a highly effective form of birth control method (contraception) if you are sexually active and may become pregnant.

Highly effective methods of birth control have a less than 1% chance of unwanted pregnancy during one year, if used according to the instructions of the manufacturer. Please discuss with your study doctor the most appropriate birth control method for you that also respects your cultural and religious situation.

Examples of highly effective birth control methods are:

- Total abstinence (no sexual relations), when this is in line with your preferred and usual lifestyle choice. Periodic abstinence like calendar, ovulation, temperature method, post-ovulation methods, and withdrawal are not acceptable methods of contraception.
- Female sterilisation, when you have been already surgically sterilised prior to the study by surgical removal of both ovaries – (woman's reproductive system that stores and releases eggs for fertilisation and produces female sex hormones) with or without hysterectomy (removal of the uterus), total hysterectomy, or tubal ligation (getting your “tubes tied”) at least six weeks ago.
- Your male partner has already been sterilised with the appropriate documentation at least 6 months prior to screening. The sterilised male partner should be your sole partner.

- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception.
- In case you are using an oral contraception as a woman, you should be stable on the same pill for a minimum of 3 months before stating study medication.

If you become pregnant or suspect being pregnant during study treatment or within **4 weeks** after completing study treatment you must inform your study doctor and you have to stop ongoing study treatment immediately. You will not be allowed to continue study treatment if you are pregnant. Your study doctor will medically follow your pregnancy until delivery to monitor you and your child`s safety.

If you are a man whose partner could become pregnant:
As a male participant in the study you must agree to use a condom during intercourse and not to father a child during the study and after completing study treatment for the period specified in section 17. Vasectomised men must also use a condom in order to prevent delivery of the drug via seminal fluid.
In addition, it is advised that your female partner uses a highly effective form of birth control method (contraception) if she is sexually active and may become pregnant. In case you father a child while in this study you are asked to report the pregnancy to the study doctor immediately. Consent from your partner will be needed to allow your study doctor to medically follow this pregnancy until delivery to monitor the mother`s and child`s safety.

Please initial each box to confirm that you have read, understood and agreed each of the numbered points.

1	I have read and understood this Appendix 2 to the main Information Sheet version **02.04.03 dated 14-Dec-2022** and I have had the time to consider it and the opportunity to ask questions.	1
2	I agree to my participation in the study	2

When you have initialled all the above boxes, please complete the first box below (including the date) yourself:

Name of **Patient** (CAPITALS):	
Date:	Signature:
Name of **Doctor** taking consent (CAPITALS):	
Date: Time:	Signature:
Name of **Impartial Witness** (if applicable):	
Date:	Signature:

Patient number:	**Patient's initials:**

Original to be kept in the study Investigator Folder; Second original or a copy of the original to be given to the patient. The Information Sheet and Consent Form are one entire document and must not be separated. The Consent Form should be printed and used as a single page,
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Optional consent for additional research using your coded data and biological samples.

Appendix 3

During or after the clinical study, the sponsor may want to use coded data, or biological samples (such as blood) collected during the study for additional research. The purpose of the additional research would be limited to:

- help better understand how the study treatment works;
- learn more about your disease;
- help develop ways to detect, monitor, and treat related human diseases;
- improve the way we conduct clinical studies.

The specific details of such additional research are not known right now but examples of what this might involve are using coded data [and/or biological samples]: to test new approaches or biological markers that are or may be relevant to your disease; and, to compare the benefits and risks of the treatment with data about other treatments. The sponsor alone, or with other scientists or partner companies around the world may use and combine coded data with data from other people to support additional research projects and to help science and public health to advance.

Coded data will remain confidential. The sponsor limits the number of people who can see the coded data. This will help ensure that the coded data will only be used for the purpose of scientific research.

The coded data cannot be used to contact you or affect your care or any other decisions about your life. You will not own any data or discoveries made from the additional research; the sponsor will own these data. The coded data will not become part of your health record.

You are not required to sign this consent if you do not want to participate in this optional additional research.

Please note: if you want to withdraw your consent for additional research, you should write to your study doctor. In this case, the coded data will not be used for additional research anymore but it will still be used for the study purposes.

Optional consent for additional research using your coded data

Please tick one of the boxes below to indicate whether you consent to the use of your biological samples and the use, access, and sharing of your coded data for the purposes described above:

☐ I consent ☐ I do not consent

Name of **Patient** (CAPITALS):	
Date:	Signature:
Name of **Doctor** taking consent (CAPITALS):	
Date: Time:	Signature:
Name of **Impartial Witness** (if applicable):	
Date:	Signature:

Patient number:	**Patient's initials:**

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Optional consent for exploratory biomarker RNA transcriptomics.

Appendix 4

Transcriptomic RNA is studied to see the gene expression pattern in cells. To access transcriptomic RNA, blood samples are collected around 3 times during core part of study (Day 1, M12 and EOT or EOS visits) and samples will be stored for long-term storage. RNA transcriptomic may be assessed based on overall results obtained in this study or other similar MS studies. These analyses will be used to examine the effect of remibrutinib on transient RNA and may support the identification of pathways/markers to understand disease better or response of treatment with remibrutinib.

Please check one of the boxes below: You “agree” or you “do not agree” to take part in the additional biomarker RNA transcriptomic assessments as described in this informed consent, and then sign below the boxes:

☐ I consent ☐ I do not consent

Name of **Patient** (CAPITALS):	
Date:	Signature:
Name of **Doctor** taking consent (CAPITALS):	
Date: Time:	Signature:
Name of **Impartial Witness** (if applicable):	
Date:	Signature:

Patient number:	**Patient's initials:**

Original to be kept in the study Investigator Folder; Second original or a copy of the original to be given to the patient. This Information Sheet and Consent Form are one entire document and must not be separated. The Consent Form should be printed and used as a single page.

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Centre number: 2501

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Optional consent for activities that may be done outside of the study site

Appendix 5

It is possible that some of your study activities may be done outside of the study site where your study doctor is. This means, some of the activities may be done at your home or at another suitable "offsite" location following discussion with your study doctor.
The offsite activities will only be offered to you in case there is a declared public health emergency, and when you are not allowed to or able to visit the study site due to the public health emergency.

Your study doctor will work closely with the other healthcare professionals involved in the offsite activities and maintain responsibility for your treatment in the study. The following may apply:

- You may have offsite visits from other health care professionals, such as a nurse.
- You may visit other locations, such as a local hospital/clinic/laboratory. If you visit a different location, another health care professional, such as a doctor, may see you instead of your study doctor.
- Visits to the study site may be replaced by video calls or other communication methods (for example, secure email) with health care professionals who are working on the study.
- Study materials such as your study treatment, may be sent to your home.

During the course of the study, your study doctor may need to change how often the offsite activities will occur or stop offsite activities completely. You may discuss with your study doctor if you wish to stop offsite activities.

If you need medical attention during an offsite activity that cannot be done by the health care professionals who are with you, you may need an urgent visit to the study doctor or a local emergency room. It may take longer to reach emergency services from an offsite location rather than the study site.

There are no costs to you for any study-related activities done offsite. However, if you have certain expenses related to the offsite visit (such as parking fees, transportation costs), you will be reimbursed for those charges, as appropriate.

Your study doctor will need to share some of your personal data (for example, your address, an email address, phone number) with people who are involved in the offsite activities. The sponsor is not involved in this sharing of personal data and does not have access to your personal data.

Please check one of the boxes below: You “agree” or you “do not agree” to take part in the offsite activities as described in this section of the informed consent and then sign below:

☐ I consent ☐ I do not consent

Name of **Patient** (CAPITALS):	
Date:	Signature:
Name of **Doctor** taking consent (CAPITALS):	
Date: Time:	Signature:
Name of **Impartial Witness** (if applicable):	
Date:	Signature:

Patient number:	**Patient’s initials:**

Original to be kept in the study Investigator Folder; Second original or a copy of the original to be given to the patient. This Information Sheet and Consent Form are one entire document and must not be separated. The Consent Form should be printed and used as a single page.

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Optional consent for "Rich" Pharmacokinetic (PK) Sampling

Appendix 6

'Rich' pharmacokinetic (PK) sampling is done to help understand the pharmacokinetic parameters of remibrutinib (how long study medication remains in the body) in participants with RMS. The 'Rich' PK assessments will be performed in a minimum of 160 randomised participants at the selected study sites.

For 'Rich' PK, blood sampling is required at the study site visit on Day 28 (Month 1) at pre-dose and post-dose at the following times after dosing: 0.5 hour, 1.0 hour, 2.0 hours, 3.0 hours and 4.0 hours; and at the Month 6 study site visit at pre-dose and at 1.0 hour post-dose. If your study site is chosen to perform "rich PK sampling", you will be informed by your study doctor during the study consent process.

For these two site visits of the Core Part you will need to fast overnight before coming to the clinic. You must not take your study treatment at home on the days of these visits; you will need to take your study treatment at the clinic after giving the "pre-dose" blood sample. You will also need to remain fasted until all of the post-dose blood samples have been taken (for approximately four hours after taking your study medication at the Month 1 visit, and for approximately one hour after taking your study medication at the Month 6 visit.

The same risks as for other procedures involving blood collection apply (see section 16).

Please check one of the boxes below: You "agree" or you "do not agree" to take part in the additional ''Rich PK'' sampling assessment as described in this informed consent, and then sign below the boxes:

☐ I consent ☐ I do not consent

Name of **Patient** (CAPITALS):	
Date:	Signature:
Name of **Doctor** taking consent (CAPITALS):	
Date: Time:	Signature:
Name of **Impartial Witness** (if applicable):	
Date:	Signature:

Patient number:	**Patient's initials:**

Original to be kept in the study Investigator Folder; Second original or a copy of the original to be given to the patient. This Information Sheet and Consent Form are one entire document and must not be separated. The Consent Form should be printed and used as a single page.

Investigator: Dr Emer MacSweeney

Centre number: 2501

Contact for queries

If you have any questions about this study, you can contact:

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Optional consent for MRI assessment.

Appendix 7

To further understand the treatment effect and progression of RMS through the human brain, Magnetic Resonance Imaging (MRI) assessments will be performed at some selected study sites and sent to a central imaging vendor for review. If your study site is chosen to perform MRIs, you will be informed by your study doctor during the study consent process. Details of the frequency of the MRI assessments are outlined in Section 8. Details of the possible risks should be discussed with your study site or their designated imaging facility (see section 16).

Please check one of the boxes below: You “agree” or you “do not agree” to take part in the additional MRI assessments as described in this informed consent, and then sign below the boxes:

☐ I consent to the MRI assessments including to receive gadolinium based contrast agent as part of the MRI procedures.

☐ I do not consent

Name of **Patient** (CAPITALS):	
Date:	Signature:
Name of **Doctor** taking consent (CAPITALS):	
Date: Time:	Signature:
Name of **Impartial Witness** (if applicable):	
Date:	Signature:

Patient number:	**Patient's initials:**

Original to be kept in the study Investigator Folder; Second original or a copy of the original to be given to the patient. This Information Sheet and Consent Form are one entire document and must not be separated. The Consent Form should be printed and used as a single page