ForPatients
by Roche

Multiple Sclerosis (MS)Primary Progressive Multiple Sclerosis (PPMS)

A study to evaluate the efficacy and safety of fenebrutinib compared with ocrelizumab in adult patients with primary progressive multiple sclerosis (FENtrepid)

A Study To Evaluate The Efficacy And Safety Of Fenebrutinib Compared With Ocrelizumab In Adult Participants With Primary Progressive Multiple Sclerosis

Trial Status	Trial Runs In	Trial Identifier
Active, not recruiting	28 Countries	NCT04544449 2019-003919-53 2022 502611-10-00 GN41791

The information is taken directly from public registry websites such as ClinicalTrials.gov, EuClinicalTrials.eu, ISRCTN.com, etc., and has not been edited.

Official Title:

A Phase III Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Study to Evaluate the Efficacy and Safety of Fenebrutinib Compared With Ocrelizumab in Adult Patients With Primary Progressive Multiple Sclerosis.

Trial Summary:

A study to evaluate the efficacy and safety of fenebrutinib on disability progression in adult participants with Primary Progressive Multiple Sclerosis (PPMS). All eligible participants will be randomized 1:1 to either daily oral fenebrutinib (and placebo) or intravenous (IV) ocrelizumab (and placebo) in a blinded fashion through an interactive voice or web-based response system (IxRS). 985 participants were enrolled and recruited globally. Participants who discontinue study medication early or discontinue from the study will not be replaced. The Open-Label Extension (OLE) phase is contingent on a positive benefit-risk result in the Primary Analysis of the study.

Hoffmann-La Roche	Phase 3
Sponsor	Phase

NCT04544449 2019-003919-53 2022 502611-10-00 GN41791
Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers
All	#18 Years & # 65 Years	No

1. Why is this study needed?

Multiple sclerosis (MS) is a health condition in which the immune system attacks the protective covering of nerve fibres in the brain and spinal cord. This leads to communication problems between the brain and the rest of the body. Primary progressive multiple sclerosis (PPMS) is a form of MS where disability gradually worsens after symptoms first appear. Better treatments are needed to slow or stop symptoms from getting worse.

This study is testing a medicine called fenebrutinib. It is being developed to treat PPMS. Fenebrutinib is an experimental medicine. This means health authorities (like the U.S. Food and Drug Administration and European Medicines Agency) have not approved fenebrutinib for treating PPMS. Ocrelizumab is approved for treating PPMS in many countries. This study aims to compare the effects of fenebrutinib versus ocrelizumab in people with PPMS.

2. Who can take part in the study?

People of 18 to 65 years of age with PPMS can take part in the study if:

- They were first diagnosed with PPMS, and not another form of MS
- Their symptoms have worsened for at least 1 year without having short periods of time when symptoms improved
- They fit specific disease criteria and scores on a disability scale to do with their PPMS

People who have been given certain treatments or who have certain infections, a history of cancer, or other conditions including a disease of the brain or spinal cord, cannot take part. People who are pregnant, or currently breastfeeding cannot take part in the study.

3. How does this study work?

People will be screened to check if they are able to participate in the study. The screening period can start up to 6 weeks before the start of treatment.

This is a ‘double-dummy’ clinical trial, which means that both groups will be given treatments that look exactly the same. ‘Dummy’ treatments are used so that doctors and patients cannot figure out which treatment each group is receiving. Comparing results from the different groups helps researchers know if any changes seen result from the study medicine or occur by chance.

Everyone who joins this study will be placed into 1 of 2 groups randomly (like flipping a coin) and given either:

- Fenebrutinib given as pills to take twice every day AND ocrelizumab dummy given as a drip into the vein every 6 months, with the first dose given in 2 half-doses, 2 weeks apart, OR
- Fenebrutinib dummy, given as pills to take twice every day AND ocrelizumab given as a drip into the vein every 6 months, with the first dose given in 2 half-doses, 2 weeks apart

Participants will have an equal chance of being placed in either group. A similar number of people will be in each group. The first part of this study is ‘double-blind’. This means that neither the participants in the study nor the team running it will know which treatment is being given until the double-blind period is over. This is done to make sure that the results of the treatment are not affected by what people expected from the received treatment. However, the study doctor can find out which group the participant is in, if the participants' safety is at risk.

The study doctor will see participants regularly. The study doctor will see how well the treatment is working and any unwanted effects participants may have. After about 2 years of treatment, participants may be given the choice to either continue their ‘double-blind’ study treatment, stop study treatment, or be given ‘open-label’ ocrelizumab. ‘Open-label’ means everyone involved, including the participant and the study doctor, will know the study treatment the participant is receiving. The study doctor and the participant will decide together if open-label ocrelizumab should be given, depending on symptoms. The participant will remain blinded to their initial study treatment in the double-blind period, regardless of their choice.

The double-blind period will continue for all participants until all participants are seen for nearly 2 and a half years. After their last dose of treatment in the ‘double-blind’ period, participants will have a follow-up visit at 3 months during which the study doctor will check on the participant’s wellbeing. Those being given ‘doubleblind’ ocrelizumab will have 3 more follow-up visits, 1 every 3 months.

Participants who complete the double-blind treatment may have the option of being given fenebrutinib in the ‘open-label’ period. This will depend on results of the double-blind period, and if the study doctor believes the participant will benefit from fenebrutinib treatment.

Total time of participation in the study will be about 4 and a half years or 7 years, depending on when they join the study and if they have open-label treatment. Participants have the right to stop study treatment and leave the study at any time, if they wish to do so.

4. What are the main results measured in this study?

The main result measured in the study to assess how well each of the medicines have worked is the amount of time between the start of treatment and a worsening of MS that

lasts for 3 months. Worsening of MS can be measured in 1 or more ways. This includes changes in walking speed, hand control and the Expanded Disability Status Scale (EDSS) scores. The EDSS scores measure changes in disability over time.

Other key results measured in the study include:

- The amount of time between the start of treatment and:
  - a worsening of MS that lasts for 6 months
  - a worsening of EDSS score that lasts for 3 or 6 months
  - a worsening of hand control that lasts for 3 months
- How much the brain changes in size after 6 months of treatment
- How much the amount of a sign of nerve damage in the blood changes after 2 years of treatment
- Changes in physical symptoms that people report impacts their daily life
- The number and seriousness of unwanted effects
- How fenebrutinib gets to different parts of the body, and how the body changes and gets rid of it

5. Are there any risks or benefits in taking part in this study?

Taking part in the study may or may not make participants feel better. But the information collected in the study can help other people with similar health conditions in the future. It may not be fully known at the time of the study how safe and how well the study treatment works. The study involves some risks to the participant. But these risks are generally not greater than those related to routine medical care or the natural progression of the health condition. People interested in taking part will be informed about the risks and benefits, as well as any additional procedures or tests they may need to undergo. All details of the study will be described in an informed consent document. This includes information about possible effects and other options of treatment.

Risks associated with the study drugs

Participants may have unwanted effects of the drugs used in this study. These unwanted effects can be mild to severe, even life-threatening, and vary from person to person. During this study, participants will have regular check-ups to see if there are any unwanted effects.

Participants will be told about the known unwanted effects of fenebrutinib and ocrelizumab and possible unwanted effects based on human and laboratory studies or knowledge of similar medicines. The only known unwanted effect of fenebrutinib is a high level of liver markers in the blood. Known unwanted effects of ocrelizumab include an infection of the nose, throat, or sinuses, usually caused by a virus, sore throat and runny nose, or a reaction to being given a drip into a vein.

Known unwanted effects of a drip into a vein include throwing up, wanting to throw up, fever, pain or discomfort in the head, frequent watery stools, shortness of breath, and cough. The study medicine(s) may be harmful to an unborn baby.

Women and men must take precautions to avoid exposing an unborn baby to the study treatment.

What happens if I am unable to take part in this clinical trial?

If this clinical trial is not suitable for you, you will not be able to take part. Your doctor will suggest other clinical trials that you may be able to take part in or other treatments that you can be given. You will not lose access to any of your regular care.

For more information about this clinical trial see the For Expert tab on the specific ForPatient page or follow this link to ClinicalTrials.gov

Trial-identifier: NCT04544449

Inclusion Criteria:

- For sites in Germany and Italy only, enrollment is restricted to participants aged 46-65 years
- A diagnosis of PPMS in accordance to the revised 2017 McDonald Criteria (Thompson et al. 2018).
- Disability progression in the 12 months prior to screening.
- Expanded Disability Status Scale (EDSS) score from 3.0 to 6.5 inclusive at screening.
- Pyramidal functional subscore >=2 at screening.
- For participants currently receiving proton pump inhibitors (PPIs), H2-receptor antagonists (H2RAs), symptomatic treatment for MS (e.g. fampridine, cannabis) and/or physiotherapy: treatment at a stable dose during the screening period prior to the initiation of study treatment and plans to remain at a stable dose for the duration of study treatment.
- Neurologically stable for at least 30 days prior to randomization and baseline assessments.
- Ability to complete the 9-Hole Peg Test (9-HPT) for each hand in <240 seconds.
- Ability to perform Timed 25-Foot Walk Test (T25FWT) in <150 seconds.
- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and refrain from donating eggs.
- For male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and refrain from donating sperm.

OLE Inclusion Criteria:

- Completed the Double-Blind Treatment (DBT) phase of the study (remaining on study treatment; no other Disease-Modifying Therapy (DMT) administered) and who, in the opinion of the investigator, may benefit from treatment with fenebrutinib.
- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and refrain from donating eggs.
- For male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and refrain from donating sperm.

Exclusion Criteria:

- For participants enrolled in Germany and in Italy only: Presence of gadolinium-enhancing lesions on T1-weighted MRI (T1Gd +) lesion on the screening MRI
- Any known or suspected active infection (excluding onychomycosis) at screening, including but not limited to a positive screening test for Hepatitis B and C, an active or latent or inadequately treated infection with tuberculosis (TB), a confirmed or suspected progressive multifocal leukoencephalopathy (PML).
- Participants with a previous history of a serious Infusion-Related Reaction (IRR) (Common Terminology Criteria for Adverse Events [CTCAE] Grade >= 4) and/or any hypersensitivity reaction to ocrelizumab.
- History of cancer including hematologic malignancy and solid tumors within 10 years of screening. Exceptions: Basal/squamous cell carcinoma of skin cured by excision. In situ carcinoma of the cervix successfully treated by curative therapy >1 year prior to screening.
- Known presence of other neurological disorders, that could interfere with the diagnosis of MS or assessments of efficacy or safety during the study, clinically significant cardiovascular, psychiatric, pulmonary, renal, hepatic, endocrine, metabolic or gastrointestinal disease.
- Presence of cirrhosis (Child-Pugh Class A, B, or C)
- Chronic liver disease unless considered stable for >6 months
- Acute liver disease
- Any concomitant disease that may require chronic treatment with systemic corticosteroids, immunosuppressants or specific medication that could impact the primary evaluation of the study.
- History of alcohol or other drug abuse within 12 months prior to screening.
- Female participants who are pregnant or breastfeeding or intending to become pregnant during the study or 6 or 12 months (as applicable from the local label for ocrelizumab) after final dose of study drug.
- Male participants intending to father a child during the study or for 28 days after final dose of study drug.
- Lack of peripheral venous access.
- Any previous treatment with immunomodulatory or immunosuppressive medication without an appropriate washout period.
- Receipt of a live or live-attenuated vaccine within 6 weeks prior to randomization.
- Immunocompromised state, history of primary or secondary (non-drug related) immunodeficiency, or history of transplantation or antirejection therapy
- Known bleeding diathesis, anemia, or history of hospitalization or transfusion for gastrointestinal (GI) bleed
- Any previous treatment with cladribine, mitoxantrone, daclizumab, alemtuzumab, or cyclophosphamide

OLE Exclusion Criteria:

- Chronic liver disease unless considered stable for > 6 months
- Acute liver disease