Efficacy and Safety of Remibrutinib Compared to Teriflunomide in Participants With Relapsing Multiple Sclerosis

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Main Information

Primary registry identifying number
LBCTR2023015151

Protocol number
CLOU064C12301

MOH registration number

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency

Primary sponsor
Novartis Pharma AG

Primary sponsor: Country of origin
Novartis Pharma AG

Date of registration in primary registry
13/09/2023

Date of registration in national regulatory agency

Public title
Efficacy and Safety of Remibrutinib Compared to Teriflunomide in Participants With Relapsing Multiple Sclerosis

Acronym

Scientific title
A Randomized, Double-blind, Double-dummy, Parallel-group Study, Comparing the Efficacy and Safety of Remibrutinib Versus Teriflunomide in Participants With Relapsing Multiple Sclerosis, Followed by Extended Treatment With Open-label Remibrutinib

Acronym

Brief summary of the study: English
To compare the efficacy and safety of remibrutinib versus teriflunomide in patients with relapsing multiple sclerosis

Brief summary of the study: Arabic
مقارنة فعالية وسلامة دواء ريميبروتينيب مقابل دواء تيريفلونوميد لدى مشاركين مصابين بالتصلّب المتعدد الانتكاسي

Health conditions/problem studied: Specify
Relapsing Multiple Sclerosis

Interventions: Specify
Drug: Remibrutinib
tablet taken orally
Other Name: LOU064

Drug: Teriflunomide
capsule taken orally

Key inclusion and exclusion criteria: Inclusion criteria
- 18 to 55 years of age
- Diagnosis of RMS according to the 2017 McDonald diagnostic criteria

- At least: 1 documented relapse within the previous year. OR 2 documented relapses within the previous 2 years, OR 1 active Gadolinium (Gd) - enhancing lesion in the 12 months.
- EDSS score of 0 to 5.5 (inclusive)
- Neurologically stable within 1 month

Inclusion to Extension part:
- Patients who complete the Core Part of the study on double-blind study treatment and conduct the Accelerated Elimination Procedure (AEP)

Other inclusion and exclusion criteria may apply

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

55

Key inclusion and exclusion criteria: Exclusion criteria

- Diagnosis of primary progressive multiple sclerosis (PPMS)
- Disease duration of more than 10 years in participants with EDSS score of 2 or less at screening
- History of clinically significant CNS disease other than MS
- Ongoing substance abuse (drug or alcohol)
- History of malignancy of any organ system (other than complete resection of localized basal cell carcinoma of the skin or in situ cervical cancer),
- Participants with history of confirmed Progressive Multifocal Leukoencephalopathy (PML) or Neurological symptoms consistent with PML
- Suicidal ideation or behavior
- Evidence of clinically significant cardiovascular, neurological, psychiatric, pulmonary , renal, hepatic, endocrine, metabolic, hematological disorders or gastrointestinal disease that can interfere with interpretation of the study results or protocol adherence
- Participants who have had a splenectomy
- Active clinically significant systemic bacterial, viral, parasitic or fungal infections
- Positive results for syphilis or tuberculosis testing
- Uncontrolled disease states, such as asthma, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids
- Active, chronic disease of the immune system (including stable disease treated with immune therapy (e.g. Leflunomide, Methotrexate)) other than MS (e.g. rheumatoid arthritis, systemic lupus erythematosus, etc.) with the exception of well- controlled diabetes or thyroid disorder.
- Participants with a known immunodeficiency syndrome (AIDS, hereditary immune deficiency, drug induced immune deficiency), or tested positive for HIV antibody
- History or current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or participants with moderate or severe hepatic impairment (Child-Pugh class C) or any chronic liver or biliary disease.
- History of severe renal disease or creatinine level
- Participants at risk of developing or having reactivation of hepatitis
- Hematology parameters at screening:

    Hemoglobin: < 10 g/dl (<100g/L)
    Platelets: < 100000/mm3 (<100 x 109/L)
    Absolute lymphocyte count < 800/mm3 (<0.8 x 109/L)
    White blood cells: <3 000/mm3 (<3.0 x 109/L)
    Neutrophils: < 1 500/mm3 (<1.5 x 109/L)
    B-cell count < 50% lower limit of normal (LLN) or total IgG & total IgM < LLN (only required for participants who had a history of receiving B-cell therapies, such as rituximab, ocrelizumab or ofatumumab, prior to screening)
- History or current diagnosis of significant ECG abnormalities
- Resting QTcF ≥450 msec (male) or ≥460 msec (female) at pre-treatment (prior to randomization)
- Use of other investigational drugs
- Requirement for anticoagulant medication or use of dual anti-platelet therapy Significant bleeding risk or coagulation disorders,
- History of gastrointestinal bleeding
- Major surgery within 8 weeks prior to screening
- History of hypersensitivity to any of the study drugs or excipients
- Pregnant or nursing (lactating) female participants, prior to randomization
- Women of childbearing potential not using highly effective contraception
- Sexually active males not agreeing to use condom
- Have received any live or live-attenuated vaccines within 6 weeks of randomization or requirement to receive these vaccinations during study
- Use of strong CYP3A4 inhibitors or strong CYP3A4 inducers within two weeks prior to randomization

Other inclusion and exclusion criteria may apply

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope
Therapy

Trial scope: Specify scope
N/A

Study design: Allocation
Randomized controlled trial

Study design: Masking
Blinded (masking used)

Study design: Control
Active

Study phase
3

Study design: Purpose
Treatment

Study design: Specify purpose
N/A

Study design: Assignment
Parallel

Study design: Specify assignment
N/A

IMP has market authorization
No

IMP has market authorization: Specify

Name of IMP
Remibrutinib

Year of authorization

Month of authorization

Type of IMP
Immunological

Pharmaceutical class
Bruton's Tyrosine Kinase (BTK) Inhibitor

Therapeutic indication
Relapsing Multiple Sclerosis

Therapeutic benefit
Treatment

Study model
N/A

Study model: Explain model
N/A

Study model: Specify model
N/A

Time perspective
N/A

Time perspective: Explain time perspective
N/A

Time perspective: Specify perspective
N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention

Biospecimen description

Samples with DNA**

Samples will be shipped to Q2 solutions central lab

Target sample size

16

Actual enrollment target size

Date of first enrollment: Type

Anticipated

Date of first enrollment: Date

01/04/2023

Date of study closure: Type

Anticipated

Date of study closure: Date

23/11/2029

Recruitment status

Pending

Recruitment status: Specify

Date of completion

IPD sharing statement plan

Yes

IPD sharing statement description

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com

Additional data URL

https://clinicaltrials.gov/ct2/show/record/NCT05147220?term=CLOU064C12301&draw=2&rank=1

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
Clinicaltrials.gov	NCT05147220

Sources of Monetary or Material Support

Name
Novartis Pharma AG

Secondary Sponsors

Name
NA

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Halim Abboud	Beirut	Lebanon	009613535711	halimabboud@hotmail.com	Hotel Dieu De France
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Public	Shawkat Beayni	Al Chouf	Lebanon	009613700357	shwakat.beayni@gmail.com	Ain Wazein Medical Village
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Public	Samia Khoury	Beirut	Lebanon	009611350000 ext. 7422	sk88@aub.edu.lb	American University of Beirut Medical Center

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Hotel Dieu De France	Halim Abboud	Neurology	Approved
Ain Wazein Medical Village	Shawkat Beayni	Neurology	Approved
Saint George Hospital University Medical Center	Aline Mourad	Neurology	Approved
Makassed General Hospital	Hania Jarkass	Neurology	Approved
American University of Beirut Medical Center	Samia Khoury	Neurology	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Hotel Dieu de France	03/10/2022	Sami Richa	cue@usj.edu.lb	+9611421229
Ain w Zein Medical Village	11/11/2022	Khaled Abdel Baki	Khaled.abdelbaki@awmedicalvillage.org	+9615509001 ext 2115
Saint George Hospital University Medical Center	15/12/2022	Michel Daher	mndaher@stgeorgehospital.org	+9611441733
Makassed General Hospital	30/11/2022	Mariam Rajab	Research.makassed@hotmail.com	+9611636941
American University of Beirut Medical Center	06/04/2023	Rami Mahfouz	rm11@aub.edu.lb	+9611350000 ext 5445

Countries of Recruitment

Name
Argentina
Belgium
Bulgaria
China
Croatia
Guatemala
India
Italy
Latvia
Malaysia
Netherlands
Poland
Russian Federation
Slovakia
Spain
Switzerland
United Kingdom
United States of America

Health Conditions or Problems Studied

Condition	Code	Keyword
Relapsing Multiple Sclerosis	Multiple sclerosis (G35)	Relapsing Multiple Sclerosis

Interventions

Intervention	Description	Keyword
Consenting, IMP administration, Laboratory testing, Imaging	Consenting, IMP administration, Laboratory testing, Imaging	Consenting, IMP administration, Laboratory testing, Imaging

Primary Outcomes

Name	Time Points	Measure
Annualized relapse rate (ARR) of confirmed relapses	Baseline up to 30 month	ARR is the average number of confirmed MS relapses in a year

Key Secondary Outcomes

Name	Time Points	Measure
Time to 3-month confirmed disability progression (3mCDP) on Expanded Disability Status Scale (EDSS)	Baseline up to 30 month	Time to 3-month confirmed disability progression (3mCDP) is defined as an increase in Expanded Disability Status Scale (EDSS) which is sustained for at least 3 months
Time to 6-month confirmed disability progression (6mCDP) on EDSS	Baseline up to 30 month	Time to 6-month confirmed disability progression (6mCDP) is defined as an increase in Expanded Disability Status Scale (EDSS) which is sustained for at least 6 months
Annualized rate of new or enlarging T2 lesion	Baseline up to 30 month	Number of new/newly enlarged T2 lesions per year
Neurofilament light chain (Nfl)	Baseline up to 30 months	Neurofilament light chain (NfL) concentration in serum
Number of Gd-enhancing T1 lesions per MRI scan	Baseline up to 30 month	Average number of Gd-enhancing T1 lesions per scan
Percentage of participants with No Evidence of Disease Activity-3 (NEDA-3)	Baseline up to 30 month	Percentage of participants with No Evidence of Disease Activity-3 (NEDA-3), as assessed by absence of confirmed MS relapses, 6mCDP and new/enlarging T2 lesions on MRI
Time to first confirmed relapse	Baseline up to 30 month	Change in the Expanded Disability Status Scale (EDSS), an increase of at least 0.5 points on the EDSS (total) score, or an increase of at least 1 point on at least two functional scores (FSs), or an increase of at least 2 points on at least one FS, excluding changes involving bowel/bladder or cerebral FS, compared to the previous available rating
Time to 6-month confirmed disability improvement (6mCDI) on EDSS	Baseline up to 30 month	Decrease in Expanded Disability Status Scale Score (EDSS) which is sustained for at least 6 months
Change from baseline in the Symbol Digit Modalities Test (SDMT)	Baseline up to 30 month	Symbol Digit Modalities Test (SDMT), an array of symbols paired with empty spaces, measures processing in speed; participants verbally match the number for each symbol as rapidly as possible. The score is the number of correctly coded items in 90 seconds. Higher scores indicate improvement. Lower scores indicate worsening
Time to 6-month confirmed worsening by at least 20% in the Timed 25-foot walk test (T25FW)	Baseline, up to 30 month	The patient walking speed to cover 25 foot distance is recorded in seconds. Longer time indicates poorer lower limb function. 20% worsening is defined as 20% increase from baseline T25FW score
Time to 6-month confirmed worsening by at least 20% in the Timed 9-hole peg test (9HPT)	Baseline up to 30 month	The patient's right and left arm function to peg 9 holes measured in seconds. Longer time indicates poorer upper limb function. 20% worsening is defined as 20% increase from baseline 9HPT score in at least one hand (average of two trials per hand)
Time to composite 6-month confirmed disability Progression (CDP)	Baseline up to 30 month	The composite involves CDP and worsening by at least 20% in T25FW and 9HPT

Change from Baseline in T2 lesion volume	Baseline up to 30 month	Change from baseline in total T2 lesion volume
Change from baseline in Fatigue Symptoms and Impacts Questionnaire - Relapsing Multiple Sclerosis (FSIQ-RMS)	Baseline up to 30 month	20-item, self-administered questionnaire. Global score ranges from 0 to 100 where higher score represents greater fatigue
Change from baseline in Generalized Anxiety Disorder Scale (GAD-7)	Baseline up to 30 month	7-item, self-administered scale. It has a global score ranging from 0-21. Higher score means higher severity of anxiety symptoms
Change from baseline in Patient Health Questionnaire-9 (PHQ-9)	Baseline up to 30 month	9-item, self-administered scale. Scores can range from 0 to 27. PHQ-9 scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively
Change from baseline in Brief Pain Inventory- short form (BPI -SF)	Baseline up to 30 month	15-item, self-administered questionnaire to assess the severity of pain and the impact of pain on daily functions. Includes seven-item interference scale. It has a 10-point response option, ranging from 0 (does not interfere) to 10 (completely interferes). Global score ranges from 0 to 10, where lower scores represent lower pain
Change from baseline in Health Utilities Index (HUI-III)	Baseline up to 30 month	15-item, self-administered index that measures eight health-related quality of life areas including vision, hearing, speech, ambulation/mobility, pain, dexterity, emotion, and cognition
Change from baseline in Multiple Sclerosis Impact Scale (MSIS-29)	Baseline up to 30 month	29-item, self-administered questionnaire that includes 2 domains, physical and psychological. Responses are captured on a 4-point scale ranging from "not at all" (1) to "extremely" (4), where higher scores reflect greater impact on day to day life
Number of participants with Adverse events and Serious adverse events(SAE)	Baseline up to 30 month	Adverse events and SAEs including clinically significant , laboratory data, vital signs, electrocardiogram (ECG), Columbia Suicide Severity Rating
Pharmacokinetics of remibrutinib	Month 1, Month 6	Blood concentrations of remibrutinib
Number of participants with Adverse events and Serious adverse events (SAE)	Day 1 Extension up to 5 years	Adverse events and SAEs including clinically significant, laboratory data, vital signs, electrocardiogram (ECG), Columbia Suicide Severity Rating
Annualized relapse rate (ARR) of confirmed relapses [Extension Part]	Day 1 Extension up to 5 years	ARR is the average number of confirmed MS relapses in a year
Annualized rate of new or enlarging T2 lesion [Extension Part]	Day 1 Extension up to 5 years	Number of new/newly enlarged T2 lesions per year
Time to 6-month confirmed disability progression (6mCDP) on EDSS [Extension Part]	Day 1 Extension up to 5 years	Time to 6-month confirmed disability progression (6mCDP) is defined as an increase in Expanded Disability Status Scale (EDSS) which is sustained for at least 6 months
Change from baseline in the Symbol Digit Modalities Test (SDMT) [Extension Part]	Day 1 Extension up to 5 years	Symbol Digit Modalities Test (SDMT), an array of symbols paired with empty spaces, measures processing in speed; participants verbally match the number for each symbol as rapidly as possible. The score is the number of correctly coded items in 90 seconds. Higher scores indicate improvement. Lower scores indicate worsening
Neurofilament light chain (NfL) [Extension Part]	Day 1 Extension up to 5 years	Neurofilament light chain (NfL) concentration in serum
Change from baseline in Fatigue Symptoms and Impacts Questionnaire - Relapsing Multiple Sclerosis (FSIQ-RMS) [Extension Part]	Day 1 Extension up to 5 years	20-item, self-administered questionnaire. Global score ranges from 0 to 100 where higher score represents greater fatigue
Change from baseline in Generalized Anxiety Disorder Scale (GAD-7) [Extension Part]	Day 1 Extension up to 5 years	7-item, self-administered scale. It has a global score ranging from 0-21. Higher score means higher severity of anxiety symptoms
Change from baseline in Patient Health Questionnaire-9 (PHQ-9) [Extension Part]	Day 1 Extension up to 5 years	9-item, self-administered scale. Scores can range from 0 to 27. PHQ-9 scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively

Change from baseline in Brief Pain Inventory- short form (BPI -SF) [Extension Part]	Day 1 Extension up to 5 years	15-item, self-administered questionnaire to assess the severity of pain and the impact of pain on daily functions. Includes seven-item interference scale. It has a 10-point response option, ranging from 0 (does not interfere) to 10 (completely interferes). Global score ranges from 0 to 10, where lower scores represent lower pain
Change from baseline in Health Utilities Index (HUI-III) [Extension Part]	Day 1 Extension up to 5 years	15-item, self-administered index that measures eight health-related quality of life areas including vision, hearing, speech, ambulation/mobility, pain, dexterity, emotion, and cognition
Change from baseline in Multiple Sclerosis Impact Scale (MSIS-29) [Extension Part]	Day 1 Extension up to 5 years	29-item, self-administered questionnaire that includes 2 domains, physical and psychological. Responses are captured on a 4-point scale ranging from "not at all" (1) to "extremely" (4), where higher scores reflect greater impact on day to day life

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files