Full Study Title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Obexelimab, in Patients with Relapsing Multiple Sclerosis
Plain Language Title: A Phase 2 Study of Obexelimab in Patients with Relapsing Multiple Sclerosis
EU Trial Number: 2024-512707-40-00

Definitions for underlined terms can be found in the glossary at the end of this document.

Rationale: MS Is a potentially disabling autoimmune disease that affects the central nervous system (brain and spinal cord). B cells play an important role in the autoimmune disease mechanism. Obexelimab, an experimental study drug, is an antibody developed for the treatment of such autoimmune disorders. The drug acts by binding to the B cell surface and decreases B cell activity.The purpose of this study is to evaluate the safety and effectiveness of obexelimab, on MS. In the RCP (Part A), obexelimab or placebo will be administered at random. Two thirds of the patients will receive obexelimab and one third will receive placebo, once weekly for 12 weeks. After week 12, all patients will receive obexelimab in the OLP (Part B), for an additional 12 weeks.

Objectives Questions researchers want to answer during the trial	**Endpoints** How the researchers plan to answer their questions during the trial
Primary To study the effect of weekly subcutaneous (SC) injections of obexelimab in patients with RMS. **Secondary Efficacy** To study the effect of weekly SC injections of obexelimab on measures of disease activity in patients with RMS **Secondary Safety** To study the safety and effectiveness of weekly SC injections of obexelimab in patients with RMS.	**Primary** • Cumulative number of new MS-specific lesions over week 8 and week 12 as measured by brain MRI. **Key Secondary Efficacy Endpoints** • Additional changes in MS-specific lesions over weeks 8 and 12 • Levels of a marker in the blood potentially associated with MS (NfL)**Secondary Safety** • Incidence of adverse events (AEs), serious adverse events (SAEs), and any adverse events of special interest (AESI)

Trial Design: This is a randomized, double-blind, placebo-controlled research study to evaluate the safety and effectiveness of obexelimab in patients with relapsing MS. At least 93 patients will be enrolled at approximately 50 sites in 15 countries.

Trial Population:

- Eligible patients are males and females between the ages of 18-60 and have a diagnosis of RMS.
- Patients must meet the 2017 revision of the McDonald diagnostic criteria.
- Patients must have an EDSS of less than or equal to 5.5.
- Patients must have documentation of at least 1 relapse within the previous year; or 2 or greater relapses in the past 2 years; or 1 or greater active Gd-enhancing brain lesion on an MRI scan within the past 6 months.
- Patients must not have received a B cell depleting agent in the past or other immunomodulatory agents in the past 6 months, or systemic corticosteroids in the past month.
- Patients must not have received an investigational treatment or direct medical intervention on another clinical study within 12 weeks prior to randomization
- Patients must have no evidence of active tuberculosis, hepatitis B infection, active hepatitis C virus, or HIV infection.

Interventions:

	Part A (RCP)		**Part B (OLP)**
Trial Treatment	Obexelimab 250 mg (66% of patients)	Placebo (33% of patients)	Obexelimab 250 mg (all patients)
Administration	Two 1-mL SC injections		
Schedule	Weekly for 12 wks		Weekly for additional 12 wks

Overall Design: In **Part A**, Eligible patients will receive a SC injection of obexelimab or placebo weekly, beginning on Day 1. Patients will return to the study site for monthly in-clinic visits for administration of obexelimab or placebo and to carry out study assessments. Patients may administer obexelimab or placebo at home every 7 days in between the monthly in-clinic visits or return to the clinic weekly for their injection. Following **Part A**, patients will enter **Part B**, an OLP period and return to the clinic and receive active study drug (obexelimab) at the same frequency stated above. Including screening, follow-up, and OLP, the maximum length of participation for an individual patient is 36 wks (28-day screening period, 12-wk randomized treatment with obexelimab or placebo, 12-wk OLP, and 8-wk follow-up).

Patients will be asked if they will consent to having 3 Lumbar Punctures (LP) performed during the study to collect Cerebral Spinal Fluid (CSF) to learn what happens to the CSR following obexelimab administration. It is anticipated that approximately 9-10 patients will agree to this procedure.

Ethical Considerations: Part A of this study is a randomized, double-blind, placebo-controlled clinical study. This is considered the most scientific study design to determine whether the effects observed are due to obexelimab, as well as, to demonstrate the safety of a new medical treatment for RMS. Patients **may** experience some **benefits,** their health **may stay the same,** or their health may **get worse**. Patients should consider the following **risks:**

	When **obexelimab** is given by SC injection may include:	Associated with study **test procedures** may include:
Most Common	Injection site redness • Dizziness • Headache • Nausea • Back pain	• Pain, bruising, or feeling faint from blood sampling • Skin irritation from electrocardiogram (ECG) leads • Headache or backache from LP procedure.
Less Common	None	• Pain & tingling in legs from LP procedure. • Nausea, vomiting or headache from contrast dye used in MRI.

Glossary of Terms

Term	Abbreviation	Definition
Adverse events	AE	Any undesirable experience associated with the use of an investigational product (IP) whether or not considered related to the IP
Adverse events of special interest	AESI	A serious or nonserious event of scientific and medical concern specific to the IP that may warrant further investigation in order to characterize and understand it. For this study, malignancies will be considered AESI.
B Cells		A type of white blood cell
Blinded		A masked study drug in which the recipient does not know if he or she is receiving the actual drug versus a placebo.
Cerebral Spinal Fluid	CSF	A clear, colorless fluid found within the tissue that surrounds the brain and spinal cord.
Double-Blind		A condition in which neither the recipient nor the administrator knows if the recipient is receiving the actual drug.
Expanded Disability Status Scale	EDSS	A way to measure how much someone is affected by their Multiple Sclerosis.
Gadolinium	Gd	Gadolinium enhancement is used to depict the early inflammatory phase of MS lesions
Lesions		Areas of damage or scarring in the central nervous system
Lumbar Puncture	LP	A procedure in which a needle is inserted into the spinal column to collect cerebral spinal fluid. Also known as a spinal tap.
Magnetic Resonance Imaging Scan	MRI scan	A test that uses magnets, radio waves, and a computer to make pictures of body tissues and structures.
McDonald diagnostic criteria		A set of guidelines that incorporate clinical and laboratory evaluations, as well as MRI data to establish a diagnosis of MS.
Open Label Period	OLP	Upon completing the double-blind placebo-controlled period (Part A) patients begin taking the active study drug for an additional 12 weeks (Part B).
Placebo		A sham substance or treatment that does not contain any active ingredients and has no therapeutic value.
Placebo-Controlled Trial		A trial in which there are 2 (or more) groups. One group gets the active treatment, and the other gets the placebo. Everything else is the same between the 2 groups, so that any difference in their outcome can be attributed to the active treatment.
Relapsing Multiple Sclerosis	RMS	A common course of MS with clearly defined attacks of new or increasing neurologic symptoms.
Randomized/Randomization/ Randomized, double-blind, placebo-controlled research study		The process by which patients in clinical trials are assigned by chance, like flipping a coin, to separate groups (study drug or placebo). Neither the researcher nor the participant chooses which treatment or intervention the participant will receive.
Serious Adverse Events	SAE	Any medical occurrence that results in death, puts the patient at risk of death, requires inpatient hospitalization or prolongation of existing hospitalization, results in substantial disruption of a person's ability to conduct normal life functions, results in a birth defect, other important medical events
Subcutaneous Injection	SC injection	An injection that is administered under the skin. Study drug in this trial is delivered by SC injection.