

The Monarch Study

Factsheet for Healthcare Providers



Protocol Title: A Phase 3, Randomized, Double-blind, Efficacy and Safety Study Comparing Orelabrutinib to Placebo in Patients with Non-active Secondary Progressive Multiple Sclerosis

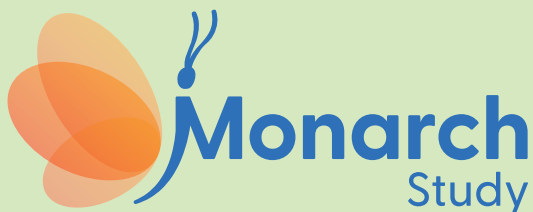
Protocol Number: ZB020-03-002
Clinicaltrials.gov Number: 07299019
Phase of Development: Phase 3

Investigational Treatment

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) marked by demyelination and progressive neurological dysfunction. Many patients with MS eventually develop secondary progressive multiple sclerosis (SPMS), a phase characterized by gradual neurological decline with or without ongoing relapses. Treatment options for SPMS remain limited; although several disease-modifying therapies are approved for relapsing forms of MS, there are no therapies specifically approved for non-active SPMS.

In MS, BTK levels are higher in areas of active and ongoing inflammation, especially within microglia in the CNS. This suggests that BTK inhibition may offer a promising approach in the treatment of naSPMS. With multiple BTK inhibitors under investigation for the treatment of multiple sclerosis, it is important to note that each BTK inhibitor may differ in their selectivity, mode of binding, target occupancy, inhibitory potency, and CNS penetrance.

The investigational drug, orelabrutinib, is an oral, brain-penetrant BTK inhibitor with high selectivity that irreversibly blocks BTK signaling and abnormal B-cell activation. By targeting both peripheral B cells and CNS-resident microglia, orelabrutinib may modulate the compartmentalized CNS inflammation and chronic innate immune activation that drive naSPMS progression, which may help slow the accumulation of disability in those with naSPMS.



Study Objectives

Primary Objective:

- To evaluate the efficacy of orelabrutinib compared with placebo in delaying disability progression in naSPMS, as evidenced by 24-week confirmed disability progression (CDP) on the Expanded Disability Status Scale (EDSS) score

Secondary Objectives:

- To evaluate the efficacy of orelabrutinib compared with placebo on disability progression, clinical endpoints, magnetic resonance imaging lesions, cognitive performance, and quality of life
- To evaluate the safety and tolerability of orelabrutinib
- To assess the pharmacokinetics of orelabrutinib

Study Duration

Participation in the Monarch Study includes:

- **Screening period:** Up to 4 weeks
- **Treatment period:** Approximately 24 to 60 months, depending on when a participant joins the study
- **Follow-up:** 4 weeks after the last dose of the study drug

Study Overview

The Monarch Study is a phase 3, randomized, double-blind efficacy and safety study comparing orelabrutinib to placebo in participants with non-active SPMS.

After a screening period of up to 4 weeks, eligible participants will enter the double-blind treatment period and be randomized 2:1 to receive orelabrutinib or placebo, both of which are provided in tablet form. The study will be unblinded when the total number of CDP events reaches the study target and all participants still on treatment in the double-blind treatment period have reached a minimum treatment duration of 12 months.

Participants with 24-week confirmed disability progression as assessed by EDSS may be eligible for open-label treatment with orelabrutinib.

All participants will have a safety follow-up visit approximately 4 weeks after the last dose of the study drug.

Key Eligibility Criteria

To be eligible for the Monarch Study, participants must:

- Be 18 to 60 years of age
- Have a previous diagnosis of RRMS according to 2024 McDonald Criteria
- Have a current diagnosis of SPMS in accordance with clinical course criteria revised in 2013
- Have documented evidence of disability progression independent of clinical relapse observed during the 24 months before screening
- Have an absence of clinical relapse for at least 24 months
- Have an absence of gadolinium-enhancing T1 lesions in the 12 months prior to screening (if MRI is available)
- Have an EDSS score between 3.0 and 6.5 points at screening

Other inclusion and exclusion criteria apply.

Potential Risks to Participants

Not all of the risks or side effects of orelabrutinib are known. As with all medicines, orelabrutinib can cause side effects in some participants, including but not limited to:

- Hepatotoxicity
- Hemorrhage
- Cytopenia
- Infection
- Malignancy
- Hypertension
- Arrhythmia

Potential Benefits to Participants

Participants may not receive a direct benefit from taking part in the Monarch Study. Participation is likely to lead to a better understanding of the effectiveness and safety of orelabrutinib as a potential treatment for naSPMS.

For more information about the Monarch Study, please contact:

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