Sponsor: Sanofi **Drug substance(s):** tolebrutinib (SAR442168)	**Study Identifiers:** U1111-1265-6378; NCT05132569; EudraCT Number: 2021-003898-59 **Study code:** EFC17262

Title of the study:

A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of tolebrutinib (SAR442168) in adults with generalized myasthenia gravis (URSA)

Study center(s):

This study was conducted at 26 centers and 9 countries (7 activated, 2 initiated)

Study period:

- First randomization date: 20 December 2021
- Early termination date: 21 February 2023

Study Status: Terminated (prematurely terminated by the Sponsor due to strategic reasons. This decision was not based on any safety issues in the myasthenia gravis program.)

Phase of development: Phase 3

Objectives:

Primary:

Double-blind (DB) period
To evaluate the efficacy of tolebrutinib 60 mg daily compared to placebo as measured by the Myasthenia Gravis-Activities of Daily Living (MG-ADL) score in participants with generalized myasthenia gravis (gMG) who are receiving standard of care (SoC)
Open-label extension (OLE)
To evaluate the long-term safety and tolerability of tolebrutinib 60 mg daily in participants with gMG who are receiving SoC

Secondary:

DB period
To evaluate the efficacy of tolebrutinib 60 mg daily compared to placebo on additional efficacy measurements: Quantitative Myasthenia Gravis (QMG), Myasthenia Gravis Impairment Index (MGII), Myasthenia Gravis Quality of Life 15-item scale (MGQoL15), MG-ADL in participants with gMG who are receiving SoC
To evaluate the safety and tolerability of tolebrutinib 60 mg daily compared to placebo in participants with gMG who are receiving SoC
OLE
To evaluate the long-term efficacy of tolebrutinib 60 mg daily in participants with gMG who are receiving SoC

Methodology:

EFC17262 was a multicenter, randomized, double-blind (DB), placebo-controlled, Phase 3 study to evaluate the efficacy and safety of tolebrutinib 60 mg daily compared with placebo in participants aged 18 to 85 years with moderate-to-severe gMG, who were receiving the SoC. The DB period was followed by an OLE period to evaluate the safety and efficacy of tolebrutinib.

The DB period included a screening period (up to 28 days) and a treatment period of 26 weeks. After screening, eligible participants were randomly assigned (1:1 ratio) to receive 60 mg of a tolebrutinib oral, daily dose or matching placebo. Randomization was stratified by the Myasthenia Gravis Foundation of America (MGFA) class (II, IIIa/IVa, or IIIb/IVb) and region (United States [US], non-US). The primary endpoint was change from baseline in the MG-ADL total score at Week 26.

Participants received the investigational medicinal product (IMP) as an add-on therapy to their SoC, ie, their gMG treatment(s) prior to screening maintained at stable doses throughout the 26-week duration of the DB period. These treatments were required to be at a stable dose for a predefined duration prior to the entry in the study. The SoC consisted of an acetylcholinesterase inhibitor (eg, pyridostigmine), oral corticosteroids (OCS) up to the maximal dose of 20 mg daily, and/or a single immunosuppressive treatment, such as azathioprine, mycophenolate mofetil, tacrolimus, or methotrexate.

However, the use of rescue therapy for gMG worsening was allowed at the discretion of the Investigator if there was at least a 2-point increase of individual non-ocular MG-ADL items compared to the Day 1 MG-ADL score, or new or worsening of respiratory/bulbar symptoms. Rescue therapy could include intravenous immunoglobulin (IVIg), plasma exchange, change in the SoC, OCS dose, or any use of new corticosteroids (CS). If rescue therapy was needed, the Sponsor had to be informed, preferably prior to the administration of treatment, where possible, without compromising the participant's safety. In case of use of rescue therapy during the DB period, the study intervention had to be permanently discontinued.

If a participant prematurely and permanently discontinued treatment with the IMP during the DB period, the participant was asked to perform a premature end-of-treatment (pEOT) visit and to continue to perform DB period visits without IMP. If the participant was not willing to continue with DB study visits without IMP, there was a safety follow-up (FU) period (4 to 8 weeks) after the pEOT.

An interim analysis was planned but the study was prematurely terminated by the Sponsor due to strategic reasons. This decision was not based on any safety issues in the myasthenia gravis program.

All participants who completed the DB period on treatment entered the OLE period. During this study period, all participants received open label tolebrutinib 60 mg daily while continuing to receive the same SoC treatment. However, during the OLE period, SoC treatments could be adjusted (ie, dose change, discontinuation, or addition of other allowed SoC treatments) at the discretion of the Investigator based on the clinical presentation. Rescue therapy medications were also allowed during the OLE period, and participants using rescue therapy were not required to discontinue study intervention. The OLE included a safety FU period (4 to 8 weeks) upon discontinuation of open-label IMP, prematurely or at the premature end of study.

Number of participants:

Approximately 192 participants were planned to be screened to achieve 154 participants randomized to study intervention at a randomization ratio of 1:1 (assuming a screen failure rate of 20%).

A total of 6 participants were randomized and treated.

• Three participants early terminated in the DB period (1 participant withdrew from the study and 2 participants were permanently discontinued due to study early termination by the Sponsor).

• Three participants were included in the OLE period but were permanently discontinued due to study early termination by the Sponsor.

Diagnosis and criteria for inclusion:

• Were aged between 18 and 85 years inclusive, at the time of signing the informed consent.

• Had a diagnosis of gMG at Screening with generalized muscle weakness meeting the clinical criteria for diagnosis of myasthenia gravis, as defined by the MGFA Class II, III, or IV, and likely not in need of a respirator for the duration of the study, as judged by the Investigator.

• Had a positive serologic testing for anti-acetylcholine receptor (AChR) or anti muscle-specific kinase (MuSK) autoantibody at Screening OR were seronegative for both anti-AChR and anti-MuSK autoantibodies.

• Had a score ≥6 on MG-ADL scale at Screening and Day 1 visits with greater than half of the score attributed to non-ocular items.

Study products

Study intervention(s)
Investigational medicinal product
• Formulation: tolebrutinib film-coated tablet.
• Route of administration: oral.
• Dose regimen: 60 mg once daily taken with a meal.
Investigational medicinal product
• Formulation: placebo to match tolebrutinib film-coated tablet.
• Route of administration: oral.
• Dose regimen: once daily taken with a meal.
Noninvestigational medicinal products(s)

Not applicable.

Duration of study intervention:

The DB period included a screening period (up to 28 days), after which eligible participants were randomized to a treatment group, 60 mg oral, daily tolebrutinib or matching placebo. The duration of the treatment period was 26 weeks.

The OLE period included all eligible participants who completed the DB period on treatment. Participants were to receive 60 mg of oral daily tolebrutinib for a duration of up to 2 years.

Post-trial access was to be provided, if required, and approved by local regulations.

Criteria for evaluation:

Primary:

Double-blind (DB) period
Change from baseline MG-ADL total score at Week 26

Open-label extension (OLE)

Adverse events (AEs), serious adverse events (SAEs), AEs leading to permanent study intervention discontinuation, adverse events of special interest (AESIs), potentially clinically significant abnormalities in laboratory tests, electrocardiogram (ECG), and vital signs during the treatment period

Secondary:

DB period

Change from baseline in QMG total score at Week 26

Change from baseline in QMG total score at Week 12 (for the interim analysis only)

Change from baseline in MGII total score at Week 26

Change from baseline in MG-QoL15 total score at Week 26

Proportion of participants with ⩾2-point improvement (reduction) in MG-ADL total score at Week 26 Proportion of participants with ⩾3-point improvement (reduction) in QMG total score at Week 26 AEs, SAEs, AEs leading to permanent study intervention discontinuation, AESIs, potentially clinically significant abnormalities in laboratory tests, ECG, and vital signs during the treatment period OLE Change from baseline in MG-ADL total score over time Change from baseline in QMG total score over time Change from baseline in MGII total score over time Change from baseline in MG-QoL15 total score over time Proportion of participants with ⩾2-point improvement (reduction) in MG-ADL total score at end-of-treatment (EOT) (timeframe: baseline, up to Week 130) Proportion of participants with ⩾3-point clinical improvement (reduction) in QMG total score at EOT (timeframe: baseline, up to Week 130) Proportion of participants achieving any reduction from baseline of daily dose of OCS over time
Statistical methods: The modified intention-to-treat population (mITT) was to include all randomized and treated participants with a baseline value and at least 1 post-baseline value for any efficacy assessment. Participants were to be analyzed as randomized. This was to be the primary efficacy population; however, the study was prematurely terminated by the Sponsor due to strategic reasons and efficacy analyses were not conducted.
Summary Results: A total of 6 participants were randomized and treated. Three participants early terminated in the DB period (1 participant withdrew from the study and 2 participants were permanently discontinued due to early termination by the Sponsor). Three participants were included in the OLE period but were permanently discontinued due to study early termination by the Sponsor. Efficacy analyses were not conducted for the study. Participants in the study had no SAEs that were related to study IMP.
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