SYNOPSIS

Study Title:

A Phase 2, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of ALXN2050 in Adult Participants with Generalized Myasthenia Gravis

Study Number: ALXN2050-MG-201

Regulatory Agency Identifier Number(s):

IND	154567
EudraCT	2021-001229-26
EU CT	2022-502905-14
ClinicalTrials.gov	NCT05218096

Study Phase: 2

Name of Study Intervention(s): ACH-0145228, ALXN2050, vemircopan

Name of Sponsor/Company: Alexion Pharmaceuticals Inc.

Number of Study Center(s) and Countries:

This study was initiated at 60 sites globally. Participants were enrolled and randomized at 38 sites across 8 countries: Canada (3), Germany (4), Italy (7), South Korea (2), Serbia (2), Spain (5), Taiwan (2), and the United States (13).

Publications (if any): None

Study Period:

This report is for the study period from 14 Apr 2022 (first participant's informed consent date) through 03 Apr 2024 (last participant's last visit date/date of last observation from last participant).

Rationale: ALXN2050 is a potent, reversible, small molecule inhibitor of complement FD, which is a key component of the AP. The complement system is involved in the pathophysiology of AChR antibody-positive gMG, and its inhibition has been proven to generate clinical benefit. ALXN2050 is an oral molecule that has the potential to provide a unique option to patients with gMG who suffer from debilitating and often incapacitating symptoms.

Objectives, Endpoints, Estimands, and Statistical Methods

The following table reflect the endpoints that are discussed in this abbreviated CSR.

Objectives	Endpoints	Statistical Analyses
Primary		
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on improvement in the MG-ADL total score	Proportion of participants with an MG-ADL total score reduction of ≥ 2 points in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy	The differences in proportions, along with 2-sided 90% CIs using Chan and Zhang method (Chan and Zhang, 1999), were presented between the ALXN2050 180 mg bid group and the placebo group. P-value using the Barnard's unconditional exact test to determine whether there was a difference in the proportions of responders between the 2 treatment groups was presented. A trend analysis to detect whether there was an increasing trend in the proportions of responders in the primary endpoint was presented, along with the p-value using the Cochran-Armitage test. No imputation was implemented.
Secondary		
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on improvement in the QMG total score	Change from baseline in QMG total score at Week 8	An MMRM was used to estimate the treatment effect using all available data up to Week 8, irrespective of whether participants received rescue therapy. Missing data were not imputed for the analysis. The MMRM included change from baseline at each prespecified timepoint (Weeks 1, 2, 3, 4, 5, 6, 7, and 8) as the response variable; treatment group, study visit, and treatment-by-study visit interaction as fixed categorical effects; and the baseline QMG total score as a covariate. A descriptive summary was provided by study visit.

Objectives	Endpoints	Statistical Analyses
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on additional endpoints involving the MG-ADL total score	Change from baseline in MG-ADL total score at Week 8	An MMRM was used to estimate the treatment effect using all available data up to Week 8, irrespective of whether participants received rescue therapy. Missing data were not imputed for the analysis. A descriptive summary was provided by study visit.
PK/PD		
To characterize the PK/PD of ALXN2050 and to establish the PK/PD relationship in participants with gMG	• Observed C_{max} and C_{trough} values over time • Absolute values and change from baseline in plasma Bb concentration and serum AP activity over time	PK/PD analyses are described in detail in Appendix 16.1.9 SAP Amendment 1.0 Section 5.7.1and Section 5.7.2, and further updated in SAP Addendum Version 1.0 Section 1.2.
Safety		
To characterize the overall safety of ALXN2050 compared with placebo in participants with gMG	• Incidence of TEAEs and TESAEs over time • Changes from baseline in laboratory assessments	Safety analyses are described in detail in Appendix 16.1.9 SAP Amendment 1.0, Section 5.6.

Methodology:

This was a Phase 2, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the efficacy and safety of ALXN2050 in adult participants with gMG.

Eligible participants were stratified by MG-ADL total score at baseline (5 to 6 [capped to approximately 10% of total enrollment] versus ≥ 7) and randomized on Day 1 in a 2:1:2 ratio to 1 of 3 treatment groups: ALXN2050 180 mg bid (Group 1), ALXN2050 120 mg bid (Group 2), or placebo (Group 3). Participants randomized to Group 1 and Group 2 received ALXN2050 during the PEP (8 weeks) and the ETP (26 weeks). Participants in Group 3 received placebo treatment during the PEP and at the end of the PEP were rerandomized in a 1:1 ratio to receive either ALXN2050 180 mg bid (Group 3a) or ALXN2050 120 mg bid (Group 3b). During the OLE Period (up to approximately 1.5 years), all participants received ALXN2050 and were to be switched to the optimal dose of ALXN2050 if that dose was identified during the study, as long as the participant had completed the first 34 weeks of treatment. An EOS Visit occurred 30 (±2) days after the last dose of study intervention for all participants.

Participants and Investigators were blinded to treatment.

Number of Participants (Planned and Analyzed):

Planned: 70

Analyzed: 70

Diagnosis and Main Criteria for Inclusion and Exclusion:

This study enrolled male and female adult participants (aged ≥ 18 years) diagnosed with gMG with an MGFA Clinical Classification between Class II to IV at the Screening Visit and a MG-ADL total score ≥ 5 (with at least 50% of the score attributed to non-ocular elements) at the Screening Visit and at randomization (Day 1).

The full list of exclusion criteria are provided in Appendix 16.1.1 Protocol Section 5.2.

Study Intervention(s), Dose, and Mode of Administration:

Oral administration of ALXN2050 (120 mg or 180 mg bid) or placebo.

Duration of Study Intervention:

The study consisted of a Screening Period of up to 4 weeks, a PEP of 8 weeks, an ETP of 26 weeks, and an OLE Period of up to approximately 1.5 years. An EOS Visit was to occur 30 (±2) days after the last dose of study intervention for all participants.

The overall study duration for an individual participant was planned to be approximately 125 weeks (from the Screening Visit through the EOS Visit).

Summary of Results and Conclusions:

Demographic and Other Baseline Characteristics:

Demographic characteristics of Groups 1, 2, and 3 in the FAS were similar in ethnicity, baseline height, baseline BMI, and region. Demographic characteristics that were different descriptively among Groups 1, 2, and 3 were mean age at first dose of study intervention (49.0, 55.9, and 58.2 years, respectively), percentages of females (64.3%, 71.4%, and 35.7%, respectively), and body weight (78.1 kg, 70.9 kg, and 85.2 kg, respectively).

Baseline MG-ADL total scores and QMG total scores were similar among Groups 1, 2, and 3. The mean age at MG diagnosis was 40.4 , 41.5, and 52.3 years in Groups 1, 2, and 3, respectively, and the mean years from diagnosis to informed consent in the study was 9.1, 15.0, and 6.5 years, respectively in Group 1, 2, and 3. The rate of MG exacerbations/100 participant years and rate of MG crisis were higher in Group 3 than in Groups 1 and 2. In general, other baseline disease characteristics were similar among the treatment groups.

Exposure:

During the PEP, the exposure to study intervention was similar in Groups 1, 2, and 3 (median was 8.0 weeks for each). The percentage of participants with a treatment duration of ≥ 8 weeks was 96.4%, 100%, and 92.9% in Groups 1, 2, and 3, respectively.

During the ALXN2050 Treatment Period, the median duration of study intervention for Groups 1, 2, 3a and 3b ranged from 33.0 to 38.5 weeks. The percentage of participants with a treatment duration of ≥ 34 weeks was 60.7%, 50.0%, 53.8%, and 46.2% in Groups 1, 2, 3a, and 3b, respectively.

Efficacy Results:

Data were planned to be analyzed in 3 steps:

- Analysis 1 (Week 8) after the last randomized participant completed the PEP or discontinued study intervention during the PEP.
- Analysis 2 (Week 34) after the last randomized participant completed the ETP or discontinued study intervention before the end of the ETP.
- Analysis 3 (Final Analysis) at the end of the study when all participants completed the study or discontinued study intervention before the end of the study.

Based on Analysis 1 (Week 8) that showed a lack of efficacy in participants randomized to ALXN2050 arms compared with the placebo arm, Alexion decided to terminate Study ALXN2050-MG-201. A subset of the planned analysis is presented in this abbreviated CSR.

Primary Efficacy Endpoint:

The primary efficacy endpoint of the study was the proportion of participants with an MG-ADL total score reduction of ≥ 2 points in any 4 consecutive weeks during the PEP (the first 8 weeks of treatment) and who did not receive rescue therapy.

The difference in the proportion of participants with an MG-ADL total score reduction of ≥ 2 points between Group 1 (ALXN2050 180 mg bid) and Group 3 (placebo) (primary analysis of the primary endpoint), Group 2 (ALXN2050 120 mg) and Group 3 (secondary analysis of the primary endpoint), and between Group 1 and Group 2 (secondary analysis of the primary endpoint) did not reach statistical significance

The numbers (%) of participants with a response were 16/28 (57.1%), 8/14 (57.1%), and 18/28 (64.3%) in Groups 1, 2, and 3, respectively. The difference in proportion versus placebo was -7.1% for each of the ALXN2050 treatment groups during the PEP.

There was no trend detected for differences in the response rate across the 3 treatment groups.

Secondary Efficacy Endpoints

At Week 8, the difference in LS mean of the change from PEP baseline in the MG-ADL total score between Group 1 and Group 3, between Group 2 and Group 3, and between Group 1 and Group 2 did not reach statistical significance, based on the MMRM analysis. Similarly, at Week 8, the difference in LS mean of the change from PEP baseline in the QMG total score between Group 1 and Group 3, between Group 2 and Group 3, and between Group 1 and Group 2 did not reach statistical significance, based on the MMRM analysis.

Safety Results:

Safety data are presented for safety variables during:

- the PEP including Group 1 (ALXN2050 180 mg bid), Group 2 (ALXN2050 120 mg bid, All ALXN2050 group (Group 1 and Group 2), and Group 3 (placebo) using the SS.

- the ALXN2050 Treatment Period including the applicable aggregated PEP, ETP, and OLE Period, ie, Group 1, Group 2, Group 3a (placebo switch to ALXN2050 180 mg bid), Group 3b (placebo switch to ALXN2050 120 mg bid), and the All ALXN2050 group (Group 1, Group 2, Group 3a, and Group 3b) using the ALXN2050 Treated Set.

During the PEP, the incidence of TEAEs was similar among the treatment groups: 59.5% of participants in the All ALXN2050 group (64.3% of participants in Group 1 and 50.0% of participants in Group 2) and 64.3% of participants in Group 3 experienced at least 1 TEAE.

- During the PEP, the most frequently reported TEAEs (≥ 5% participants in the All ALXN2050 group by PT) were headache (8 [19.0%]), diarrhea (6 [14.3%]), and nausea (4 [9.5%]). In Group 3, 5 participants (17.9%) experienced headache, whereas 8 participants (28.6%) and no participants experienced headache in Group 1 and Group 2, respectively. Other TEAEs experienced by ≥ 5% participants in Group 3 were nasopharyngitis (3 [10.7%] participants), and cough, influenza like illness, pruritus, and swelling face (2 [7.1%] participants each), whereas no participants in Groups 1 and 2 had these TEAEs.
- During the PEP, the maximum severity of the majority of TEAEs experienced by the participants was Grade 1 or Grade 2. Five participants experienced at least 1 Grade 3 event, 1 (3.6%) in Group 1, 2 (14.3%) in Group 2 and 2 (7.1%) in Group 3. There were no Grade 4 or 5 TEAEs reported.
- During the PEP, the percentages of participants with any TEAE considered to be related to study intervention by the Investigator were 19.0% in the All ALXN2050 group, and 10.7% in Group 3. In the All ALXN2050 group, the most frequently experienced TEAEs considered to be related to study intervention were headache (7.1%), diarrhea (9.5%), nausea (7.1%), and abdominal pain upper (4.8%), all in Group 1. Headache (7.1%) was also reported in Group 3. No most frequently reported, related TEAE was observed in Group 2.
- During the PEP, 2 (4.8%) participants in the All ALXN2050 group (1 [3.6%] participant in Group 1 and 1 [7.1%] participant in Group 2) and 3 (10.7%) participants in Group 3 experienced at least 1 TESAE. The TESAE reported for the Group 1 participant, herpes simplex meningitis, was considered to be related to study intervention. Three participants experienced TESAEs that led to study intervention discontinuation (herpes simplex meningitis) or interruption (acute respiratory failure and acute kidney injury).
- During the PEP, 1 (3.6%) participant in Group 1 had a TESAE, herpes simplex meningitis, which led to discontinuation of study intervention; no participants in Group 2 or Group 3 were discontinued from study intervention due to AEs.

No deaths were reported during the PEP.

During the ALXN2050 Treatment Period (applicable aggregated ALXN2050 treated PEP, ETP, and OLE Period until discontinuation or study termination), the incidence of TEAEs was similar among the treatment groups: 75.0% of participants in Group 1, 71.4% in Group 2, 69.2% in

Group 3a (placebo switch to ALXN2050 180 mg bid) and 76.9% in Group 3b (placebo switch to ALXN2050 120 mg bid) experienced at least 1 TEAE.

- The most frequently reported TEAEs (≥5% participants by PT) in the participants treated with ALXN2050 were headache (17.6%, 34.4 events per 100 PY), diarrhea (13.2%, 19.99 events per 100 PY), COVID-19 (10.3%, 16.3 events per 100 PY), upper respiratory tract infection (10.3%, 16.3 events per 100 PY), nausea (8.8%, 10.9 events per 100 PY), arthralgia (5.9%, 7.2 events per 100 PY), and myasthenia gravis (5.9%, 9.1 events per 100 PY).
- The maximum severity of the majority of TEAEs experienced by participants treated with ALXN2050 was Grade 1 or Grade 2 (in 26.5% of participants for each grade). The numbers (percentages) of participants reporting Grade 3, Grade 4, and Grade 5 events were 11 (16.2%), 2 (2.9%), and 1 (1.5%), respectively.
- The most frequently experienced related TEAEs experienced by participants treated with ALXN2050 were headache, diarrhea, nausea, and abdominal pain upper (all in Group 1, headache also in Group 2). All of the related TEAEs were experienced during the PEP, except for headache, which was reported by a Group 2 participant after the PEP. The majority of related TEAEs were each reported by 1 participant.
- During the ALXN2050 Treatment Period, 14/68 (20.6%) participants in the All ALXN2050 group experienced 20 TESAEs: 6 TESAEs experienced by 5 (24.7%) participants in Group 1, 9 TESAEs experienced by 4 (28.6%) participants in Group 2, 3 TESAEs experienced by 3 (23.1%) participants in Group 3a, and 2 TESAEs experienced by 2 (15.4%) participants in Group 3b.
  - Two of the TESAEs that occurred during the OLE Period, hepatic failure (Group 3a) and hepatic enzyme increased (Group 1) were considered to be related to study intervention. These 2 TESAEs, and 2 additional TESAEs (substance-induced psychotic disorder and myocardial infarction experienced by participants in Group 2 and Group 3 b, respectively) resulted in discontinuation of study intervention. Salmonella sepsis experienced by 1 participant in Group 2 resulted in interruption of study intervention.
- One participant died during the study. The participant who was in Group 3a (placebo switch to 180 mg bid) experienced a TESAE of hepatic failure during the OLE Period, on Days 249 to 267 of ALXN2050 treatment. It was considered by the Investigator to be related to study intervention. Autopsy results were suggestive of acute necrotic-hemorrhagic hepatic disease on chronic hepatic condition related to CMV (acute reactivation of CMV infection on chronic hepatic CMV infection, with concurrent EBV infection).
- During the ALXN2050 Treatment Period, 6/68 (8.8%) participants in the All ALXN2050 group had TEAEs that led to discontinuation of study intervention: myocardial infarction, hepatic failure, herpes simplex meningitis, hepatic enzyme increased, sensory disturbance, and substance-induced psychotic disorder. All these events were TESAEs except sensory disturbance. Hepatic failure, herpes simplex meningitis, and hepatic enzyme increased were considered to be related to study

intervention. Discontinuation of study intervention due to herpes simplex meningitis occurred during the PEP.

- No meningococcal infections were observed during the study.

Other safety

- There were no clinically significant trends observed over time in clinical chemistry, coagulation, hematology, urinalysis, or liver function parameters assessed during the study. Shifts from baseline (normal) to postbaseline (low or high) were not clinically significant.
- During the PEP, 6 participants had clinical laboratory abnormalities that were reported as TEAEs. In Group 1, ALT increased and AST increased were experienced by 2 participants, and activated partial thromboplastin time prolonged, prothrombin time prolonged, and hematuria, were each experienced by 1 participant. Hypernatremia and ketonuria were reported in Group 2 and hypokalemia was reported in Group 3, each experienced by 1 participant.
- During the PEP, none of the clinical laboratory abnormalities that were reported as TEAEs were TESAEs, above Grade 1 in severity, or led to discontinuation of the study intervention. All TEAEs resolved. ALT and AST increased were experienced by 2 participants; in 1 participant, they were considered to be related to the study intervention and in the other participant, the events were unrelated but resulted in interruption of the study intervention.
- There were no clinically meaningful findings in vital sign measurements, physical examination assessments and ECG results. Results and observations were similar in the treatment groups during the study over different time periods. During the PEP, 1 participant in Group 3 experienced an unrelated TESAE of hypertension. Two participants experienced unrelated TEAEs of palpitations.
- One pregnancy was reported during the study. The participant was in Group 3b (placebo switch to ALXN2050 120 mg bid at the start of the ETP, 15 Sep 2022). The pregnancy was discovered on 25 Sep 2023, Day 433, by a serum pregnancy test. The last dose of study intervention was on 17 Sep 2023. Fetal ultrasounds during 30 Oct, 22 Nov, and 20 Dec were normal. A spontaneous delivery occurred on 01 Apr 2024 at 35 weeks gestation, with no complications, no abnormalities, and no need for ICU admission. The baby was 2.8 kg, 52 cm, and had APGAR scores of 9 and 10.
- The C-SSRS was used to monitor suicidal ideation, suicidal behavior, and/or self-injurious behavior. During the PEP, 1 participant in Group 2 had suicidal ideation (wish to be dead) that was not present during the past 12 months or during their lifetime. Suicidal ideation in this participant occurred intermittently during the PEP and ETP.

Pharmacokinetic Results:

Mean ALXN2050 concentrations in the 180 mg bid group (Group 1) were consistently greater than the exposures in the 120 mg bid group (Group 2). Placebo participants switched to 180 mg

bid (Group 3a) or 120 mg bid (Group 3b) at Study Day 57 achieved similar steady state exposures as Group 1 and 2, respectively.

Pharmacodynamic Results:

Mean serum AP hemolytic activity was reduced below 10% starting 2 hours postdose of treatment with ALXN2050 for both Groups 1 and 2, and the same trend was observed for placebo (Group 3) switch participants (Groups 3a and 3b). By Week 8, mean reductions were maintained below 10% at trough in Group 1 but not Group 2.

Plasma Bb fragment concentrations were reduced after initiation of treatment with ALXN2050, and the same trend was observed for placebo switch participants.

Conclusions:

The study did not meet its primary efficacy endpoint and the study was early terminated by the Sponsor. ALXN2050 monotherapy of up to 180 mg BID in participants with gMG was safe and well tolerated.