A Phase 3 Efficacy and Safety Study of Ravulizumab in Adult Patients With Neuromyelitis Optica Spectrum Disorder: Study Design and Methodology

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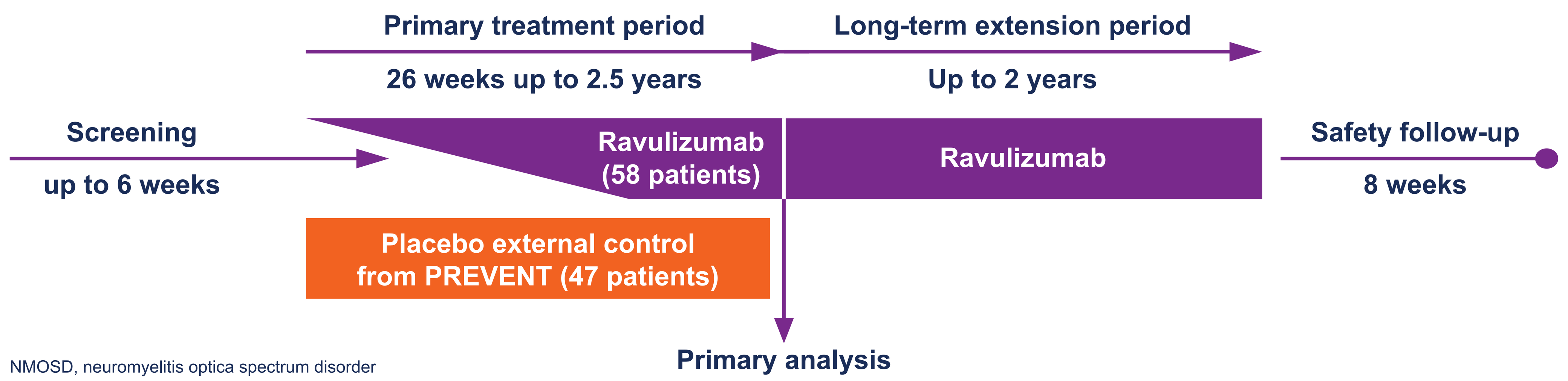
BACKGROUND

- Eculizumab is a first-generation complement component 5 (C5) inhibitor approved for the treatment of adults with aquaporin-4 antibody-positive (AQP4+) neuromyelitis optica spectrum disorder (NMOSD).[1]
- Data from the phase 3, randomized, placebo-controlled PREVENT study and its open-label extension have demonstrated that long-term eculizumab treatment is well-tolerated, reduces relapse risk and stabilizes disability outcomes.[2,3]
- Ravulizumab, which binds to the same C5 epitope, has a longer half-life than eculizumab.[4] This longer half-life enables a decrease in infusion frequency relative to eculizumab (every 8 weeks vs every 2 weeks).
- In view of the evolving treatment landscape for this rare-disease patient population, we designed the CHAMPION NMOSD trial, an innovative phase 3 trial with no concurrent placebo exposure, to assess the efficacy and safety of ravulizumab in adults with AQP4+ NMOSD.

STUDY DESIGN

- The CHAMPION NMOSD trial is a phase 3, global, open-label, multicenter, externally controlled study (ALXN1210-NMO-307; NCT04201262) (**Figure 1**) using the placebo group from the PREVENT trial (eculizumab vs placebo in NMOSD; 2014–2018; NCT01892345) as an external comparator.
  - Given the serious long-term clinical impact of NMOSD attacks, use of a concurrent placebo comparator was precluded for ethical reasons due to the availability of eculizumab and the expected approval of additional medications in the near future, because it would have necessitated assigning patients to placebo when an effective treatment existed.[5]
  - A noninferiority efficacy trial against existing approved treatment was also considered, but it would not be practical to recruit the very large sample size required to power the study adequately in this rare disease.
  - Given the limits noted above, the study was designed to use the placebo group from the PREVENT trial as an external comparator.
    - Similar to the approach in this trial, single-arm trials with external comparator groups have been used to evaluate the efficacy and safety of experimental drugs in rare and severe diseases, including pivotal trials that resulted in regulatory approvals.[6]
- To ensure scientific validity of the PREVENT placebo group as an external comparator and to align with published regulatory guidance, consistency with PREVENT will be maintained by including similar patient populations, procedures for relapse adjudication, key endpoints and permitted concomitant medications.
  - To maintain consistency, key inclusion criteria for the CHAMPION NMOSD trial (**Table 1**) are largely in line with those from PREVENT. The 2015 IPND NMOSD diagnostic criteria were followed when determining trial eligibility.[7]
  - Newly published data regarding future relapse risk were available at the time of trial design, including those demonstrating no marked difference in the risk of future relapse between patients who had one versus two attacks in the previous 2 years.[8] Based on this current understanding of relapse risk, the inclusion criterion regarding historical relapse rate was adapted to require ≥ 1 relapse in the 12 months prior to screening rather than the criterion used in PREVENT (≥ 2 relapses in 12 months prior to screening, or ≥ 3 relapses in 24 months prior to screening with ≥ 1 of the 3 relapses in 12 months prior to screening).
  - Given that the clinical trial participants have not been randomized to the treatment arm in the CHAMPION NMOSD trial, there may be differences in key baseline characteristics between the ravulizumab arm in the current study and the placebo arm from the PREVENT study.
  - In both trials, an independent committee, utilizing the same review process of available clinical and imaging data in each trial, was put in place for adjudication of all investigator-reported relapses to confirm that the protocol-defined criteria of a relapse were met.[2]

Figure 1. The CHAMPION NMOSD trial design



NMOSD, neuromyelitis optica spectrum disorder

Table 1. Key inclusion and exclusion criteria for the CHAMPION NMOSD trial

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Treatment with mitoxantrone or rituximab during the 3 months before screening
Diagnosis of NMOSD according to the 2015 criteria[7]	Treatment with intravenous immunoglobulin during the 3 weeks before screening
Anti-AQP4 Ab-positive	Previous or current treatment with complement inhibitor
≥ 1 relapse in 12 months prior to screening	Unresolved clinically significant or untreated meningococcal disease/systemic bacterial or other infection
EDSS score ≤ 7	Previous participation in the PREVENT trial
Stable supportive IST (if applicable)	
Vaccination against *Neisseria meningitidis* in the 3 years prior to ravulizumab initiation, or prophylactic antibiotics until 2 weeks after vaccination	

AQP4+, aquaporin-4 antibody-positive; EDSS, Expanded Disability Status Scale; IST, immunosuppressive therapy; NMOSD, neuromyelitis optica spectrum disorder

Table 2. Key endpoints for the CHAMPION NMOSD trial[a]

Endpoint	Definition
Primary endpoint	Time to first adjudicated on-trial relapse and relapse risk reduction
Secondary endpoints	Adjudicated on-trial annualized relapse rate
	Clinically important change from baseline in HAI score
	Change from baseline in EQ-5D index score
	Change from baseline in EQ-VAS score
	Clinically important worsening from baseline in EDSS score
Safety endpoints	Incidences of TEAEs, TESAEs, and TEAEs leading to discontinuation of study drug

[a]If the primary endpoint is statistically significantly in favor of ravulizumab, the secondary endpoints will be evaluated according to the rank order listed in this table.
EDSS, Expanded Disability Status Scale; EQ-5D, EuroQol 5 Dimensions; EQ-VAS, EuroQol Visual Analog Scale; HAI, Hauser Ambulation Index; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

  - Study endpoints (**Table 2**) for the CHAMPION NMOSD trial are similar to those for the PREVENT study. They include time to first adjudicated on-trial relapse and relapse risk reduction as the primary endpoint, and adjudicated on-trial annualized relapse rate as the first key secondary endpoint.
    - Additional secondary endpoints include the Hauser Ambulation Index (HAI), the EuroQol 5 Dimensions (EQ-5D) and the Expanded Disability Status Scale (EDSS).
- To account for potential differences in patient characteristics between the ravulizumab group and the external placebo group that might confound the treatment effect, sensitivity analyses using propensity scores (PSs) are prespecified.[9]
  - The PS (the predicted probability of being in the ravulizumab treatment group) is derived from a model in which baseline characteristics that are thought to be associated with outcomes are included as predictors of treatment group in a logistic regression model.
    - By incorporating the PS into analyses of the clinical trial endpoints, the treatment groups are balanced with respect to the variables in the PS model.
    - A limitation of the PS is that the treatment groups are balanced only with respect to the variables included in the model that provided the predicted probabilities.
  - To determine how strong an unknown confounder would have to be to cancel the observed treatment effect, the E-value[10] will also be calculated.
    - A large E-value (> 1) implies that considerable unmeasured confounding would be needed to account for the treatment effect.
    - A small E-value (~ 1) implies that little unmeasured confounding would be needed to account for the treatment effect.
- The CHAMPION NMOSD trial comprises a screening period, a primary treatment period, a long-term extension period and a safety follow-up period (**Figure 1**).
- The trial has fully enrolled.
- The ongoing primary treatment period will end when the last-enrolled patient reaches week 50, unless two patients have an adjudicated relapse before that time.
- The total duration of treatment for each patient will last up to approximately 4.5 years. The duration of the primary treatment period for each patient is expected to be between 26 weeks and approximately 2.5 years, depending on when they initially enrolled in the trial.

CONCLUSIONS

- **The CHAMPION NMOSD trial (ALXN1210-NMO-307) is an ongoing, phase 3, global, open-label, multicenter, externally controlled study using the placebo arm of PREVENT as an external comparator to assess the efficacy and safety of the C5 inhibitor ravulizumab in patients with AQP4+ NMOSD.**
- **The study is designed to be consistent with PREVENT and will use robust statistical methods to ensure that an appropriate comparison can be made between the ravulizumab arm and the PREVENT placebo arm.**

PREVIOUS PRESENTATION

This poster was presented at the 7th annual Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2022; February 24-26, 2022; West Palm Beach, Florida, USA.

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DISCLOSURES

SJP – a patent # 8 889 102 (application #12-678350) - Neuromyelitis optica autoantibodies as a marker for neoplasia, and a patent # 9 891 219B2 (application #12-573942) - Methods for treating neuromyelitis optica (NMO) by administration of eculizumab to an individual that is aquaporin-4 (AQP4)-IgG autoantibody positive. He has a patent pending for GFAP, Septin 5, MAP1B, KLHL11, PDE10A IgGs as markers of neurological autoimmunity and paraneoplastic disorders. He has consulted for Alexion, Astellas, Euroimmune, Genentech/Roche, Medimmune/Horizon, Prime Therapeutics and Sage Therapeutics. He has received research support from Alexion, Genentech/Roche, Grifols and Medimmune/Horizon; and from Autoimmune Encephalitis Alliance, Guthy-Jackson Charitable Foundation and NIH. KA, MY and YM – employees of Alexion, AstraZeneca Rare Disease and hold stock in AstraZeneca.

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