2. SYNOPSIS

Name of Alexion/Company: Alexion Pharmaceuticals, Inc. **Name of Finished Product:** NA **Name of Active Ingredient:** Ravulizumab (ALXN1210)	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Complement Inhibitor-Naïve Adult Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH)		
Coordinating Investigator: Dr. Jong Wook Lee, College of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Republic of Korea		
Study centers: Patients were enrolled at 123 sites in 25 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Estonia, France, Germany, Italy, Japan, Malaysia, Mexico, Poland, Republic of Korea, Russia, Singapore, Spain, Sweden, Taiwan, Thailand, Turkey, United Kingdom, and United States).		
Publications (reference): Brodsky RA et al. Characterization of breakthrough hemolysis events observed in the phase III randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. Haematologica. 2021;106(1):230. Ishiyama K et al. Results from multinational phase 3 studies of ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria: subgroup analysis of Japanese patients. International Journal of Hematology. 2020;112:466-76. Kulasekararaj AG et al. Long-term safety and efficacy of ravulizumab in patients with paroxysmal nocturnal hemoglobinuria: 2-year results from two pivotal phase 3 studies. European Journal of Haematology. 2022;109(3):205-14. Lee JW et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019;133(6):530-9. Peffault de Latour R et al. Pharmacokinetic and pharmacodynamic effects of ravulizumab and eculizumab on complement component 5 in adults with paroxysmal nocturnal haemoglobinuria: results of two phase 3 randomised, multicentre studies. British Journal of Haematology. 2020;191(3):476-85 Schrezenmeier H et al. One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria naïve to complement inhibitor therapy: open-label extension of a randomized study. Therapeutic Advances in Hematology. 2020;11:2040620720966137.		
Studied period (years): Date first patient treated: 20 Dec 2016 Date last patient completed the Primary Evaluation Period: 25 Jan 2018 Date last patient completed last visit of the study: 28 Feb 2023		**Phase of development:** 3

Objectives:

Primary (Original Cohort): The primary objective of this study was to assess the noninferiority of ravulizumab compared to eculizumab in adult patients with PNH who had never been treated with a complement inhibitor.

Noninferiority was claimed if after 26 weeks of treatment (1) the lower bound of the 95% confidence interval (CI) for the difference (ravulizumab - eculizumab) in transfusion avoidance (TA) rate was greater than -20%, and (2) the lower bound of the 95% CI for the odds ratio of ravulizumab compared with eculizumab for lactate dehydrogenase normalization (LDH-N) was greater than 0.39.

Secondary (Original Cohort): The secondary objectives of this study were as follows:

- To characterize the safety and tolerability of ravulizumab in this patient population
- To evaluate the efficacy of ravulizumab by additional efficacy measures
- To characterize the pharmacokinetics (PK)/pharmacodynamics (PD) and immunogenicity of ravulizumab
- To evaluate the long-term safety and efficacy of ravulizumab
- To evaluate the safety and efficacy in patients who switch from eculizumab to ravulizumab in the Extension Period
- To quantify identified specific safety concerns during treatment with ALXN1210, including meningococcal infections, serious hemolysis after drug discontinuation in PNH, immunogenicity, serious infections, malignancies and hematologic abnormalities, and during pregnancy and breastfeeding

Secondary (Roll-over Cohort):

- Long-term safety of patients receiving ravulizumab after rolling over into Study ALXN1210-PNH-301

Methodology:

This was a Phase 3, open-label, randomized, active-controlled, multicenter study to evaluate the safety and efficacy of ravulizumab versus eculizumab administered by intravenous (IV) infusion to adult patients with PNH who were naïve to complement inhibitor, including eculizumab (herein referred to as the Original Cohort). In addition, long-term safety of patients who rolled over from other ongoing studies of ravulizumab IV in patients with PNH into the Extension Period of Study ALXN1210-PNH-301 (herein referred to as the Rollover Cohort) was evaluated. This study consisted of a 4-week Screening Period, a 26-week Randomized Treatment Period, and an Extension Period of up to 5 years. This CSR presents comprehensive data from the entire study.

Patients were stratified into 6 groups based on their transfusion history (0, 1 to 14, or > 14 units of packed red blood cells [pRBCs] in the 1 year prior to first dose of study drug) and their screening lactate dehydrogenase (LDH) levels (1.5 to < 3 × upper limit of normal [ULN] or ≥ 3 × ULN). The patients within each of the 6 stratification groups were then randomly assigned in a 1:1 ratio to receive ravulizumab or eculizumab. Enrollment of patients without a history of transfusion in the prior year was capped at 20%.

Prior to randomization and within 5 days prior to study drug administration on Day 1, each patient's hemoglobin was evaluated by either central or local laboratory. If at that time the patient's hemoglobin value met protocol-specified transfusion guidelines (hemoglobin value of ≤ 9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion, or a hemoglobin value of ≤ 7 g/dL regardless of presence of clinical signs or symptoms), the patient was transfused with pRBCs to achieve a hemoglobin level above the protocol-specified transfusion threshold in order to be eligible for randomization. The patient's post-transfusion hemoglobin value was confirmed by the central or local laboratory to be above the protocol-specified transfusion threshold.

Patients randomly assigned to the ravulizumab treatment group received a loading dose of ravulizumab on Day 1, followed by maintenance doses of ravulizumab on Day 15 and every 8 weeks (q8w) thereafter for a total of 26 weeks. Loading and maintenance doses were based on body weight (see table below). Patients randomly assigned to the eculizumab treatment group received an induction dose of 600 mg of eculizumab on Days 1, 8, 15, and 22, followed by a maintenance dose of 900 mg of eculizumab on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment. All doses for both treatments were administered as IV infusions. After completion of all assessments on Day 183 of the Randomized Treatment Period, all patients had the opportunity to enter an Extension Period and receive ravulizumab until product registration or approval (in accordance with country specific regulations) or for up to 5 years, whichever occurred first (In Norway and Denmark, patients participated for a total of 2.5 years). During the Extension Period of the study, a cohort of patients from other ongoing ravulizumab studies, treated with weight-based doses of ravulizumab, rolled over into this study to continue to receive ravulizumab treatment. Roll-over patients received weight-based maintenance doses of ravulizumab.
Number of patients (planned and analyzed): Planned (Original Cohort): 214 patients; 107 patients per treatment group (ravulizumab and eculizumab). Analyzed (Original Cohort): 246 patients; 125 in the ravulizumab treatment group and 121 in the eculizumab treatment group. Planned (Roll-over Cohort): 56 patients. Analyzed (Roll-over Cohort): 26 patients: 24 patients in the adult group and 2 patients in the pediatric group.
Diagnosis and main criteria for inclusion: **Original Cohort:** Male and female patients ≥ 18 years of age with PNH confirmed by documented high-sensitivity flow cytometry, who were naïve to treatment with a complement inhibitor, had 1 or more PNH-related signs or symptoms within 3 months of screening, had LDH value ≥ 1.5 × ULN at screening, and had been vaccinated against meningococcal infection. **Roll-over Cohort:** All patients regardless of age, who were currently receiving ravulizumab IV in an ongoing ravulizumab study treating patients with PNH.

Test product, dose and mode of administration, batch number:

Ravulizumab was supplied as a sterile, preservative-free 10 mg/mL solution in single-use vials, designed for administration via IV infusion by diluting into commercially available saline (0.9% sodium chloride injection).

Ravulizumab loading dose on Day 1 and maintenance doses on Day 15 and q8w thereafter was administered by IV infusion. Dosages were based on the patient's body weight, as shown in the table below:

Body Weight	Ravulizumab Loading Dose (Day 1)	Ravulizumab Maintenance Dose (Days 15, 71, 127)
≥ 30 to < 40 kg[a]	1200 mg	2700 mg
≥ 40 to < 60 kg	2400 mg	3000 mg
≥ 60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg

[a] In the event that a patient dropped below 30 kg during the course of the study, the approved ravulizumab atypical hemolytic uremic syndrome (aHUS) dosing for patients weighing ≥ 20 to < 30 kg was to be used: a loading dose of 900 mg and maintenance dose of 2100 mg.

Lot numbers: 011C16AA, 011C16AC, 1000050, 1000060, 1000083, 1000090, 1000106, 1000110, 1000121, 1000124, 1000141, 1000142, 1000156, 1000170, 1000182, 1000202, 1000223, 1000249, 1000257, 1000307, 1000376, 1000378, 1000399, 1000414, 1000460, 1000510, 1000564, 1000672, 1000800, 1000801, 1001051, 1001138, 1001308, 1001428, 1001505, 1001631, 1001721, 1001765, 1001838, 1002043, and 1002082

Reference therapy, dose and mode of administration, batch number:

Eculizumab was supplied as a sterile, preservative-free 10-mg/mL solution in single-use vials, designed for administration via IV infusion by diluting into commercially available saline (0.9% sodium chloride injection).

Eculizumab was administered according to the approved dosing regimen via IV infusion as follows: 600 mg induction dose on Days 1, 8, 15, and 22; 900 mg maintenance dose on Day 29 and q2w thereafter through Day 169.

Lot numbers: AF3891BB, AF5171BA, AF6933BA, AG0383EB, AG0383EF, and AG4965BC

Duration of treatment:

Primary Evaluation Period: 26 weeks (183 days)

- Ravulizumab treatment group: weight-based loading dose on Day 1 followed by weight-based maintenance doses on Days 15, 71, and 127
- Eculizumab treatment group: 600-mg induction doses on Days 1, 8, 15, and 22 followed by 900 mg maintenance doses on Days 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169

Extension Period:

- Original Cohort: Following the 26-week randomized treatment period, patients had the option to enter into an extension period in which all patients received ravulizumab until the product was registered or approved (in accordance with country-specific regulations) or for up to 5 years, whichever occurred first.
- Roll-over Cohort: patients received ravulizumab until the product was registered or approved (in accordance with country-specific regulations) or for the duration of the current study (end of study [EOS]), whichever occurred first.

Criteria for evaluation:

Original Cohort

Efficacy Endpoints:

- Coprimary
  - Transfusion avoidance, defined as the proportion of patients who remain transfusion-free and do not require a transfusion per protocol-specified guidelines through Day 183 (Week 26)
  - Hemolysis as directly measured by LDH-N from Day 29 (first scheduled evaluation status post initiation of maintenance dosing) through Day 183 (Week 26)
- Key Secondary (tested in a hierarchical manner)
  1. Percentage change in LDH from baseline to Day 183 (Week 26)
  2. Change in quality of life (QoL) assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, Version 4, from baseline to Day 183 (Week 26)
  3. Proportion of patients with breakthrough hemolysis (BTH), defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular event [MAVE] including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy
  4. Proportion of patients with stabilized hemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)
- Other Secondary
  - Change in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, from baseline through Day 183 (Week 26)
  - Time to first occurrence of LDH-N
  - Total number of units of pRBCs transfused through Day 183 (Week 26)
  - Change in clinical manifestations of PNH (fatigue, hemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia, and erectile dysfunction) from baseline through Day 183 (Week 26)
  - Proportion of patients experiencing MAVEs from baseline through Day 183 (Week 26)

Pharmacokinetic and Pharmacodynamic Endpoints:

- Change in serum concentration of ravulizumab and of eculizumab over time
- Change in chicken red blood cell (cRBC) hemolytic activity over time (exploratory)
- Change in free complement component 5 (C5) concentration over time

Safety Endpoints:

- The safety and tolerability of ravulizumab compared with eculizumab during the Primary Evaluation Period were evaluated by physical examinations, vital signs, electrocardiograms (ECGs), laboratory assessments, and incidence of adverse events (AEs) and serious adverse events (SAEs). The proportion of patients who developed antidrug antibodies (ADAs) was assessed.

Roll-over Cohort

Safety Endpoints:

- The long-term safety of Roll-over patients on ravulizumab after their roll over into the Extension Period of Study ALXN1210-PNH-301 was evaluated by the incidence of AEs and SAEs, laboratory assessments, and the proportion of patients who develop ADA.

Statistical methods:

For categorical variables, frequencies and percentages were presented by treatment group and overall. For continuous variables, descriptive statistics (n, mean, median, standard deviation [SD], minimum, and maximum) were presented by treatment group and overall. For all analyses and summaries for the Primary Evaluation Period, the randomization stratification variables refer to the observed transfusion history and LDH levels and pooled stratification variables.

Original Cohort

Efficacy analyses for Primary Evaluation Period:

Coprimary efficacy analyses: For the coprimary endpoint of TA, a between-treatment difference in percentage of patients achieving TA was calculated along with a 95% CI for the difference using the stratified Newcombe CI method. This difference was computed using a weighted combination of the differences between treatment groups within the 6 stratification groups using Mantel-Haenszel weights. Patients who withdrew from the study due to lack of efficacy during the Primary Evaluation Period were considered as nonresponders and counted as requiring transfusions. For patients who withdrew for any other reason during this period, their data up to the time of withdrawal were used to assess TA.

For analysis of the coprimary endpoint of LDH-N, a generalized estimating equation approach was used to provide odds ratios and 95% CI. Day 29 through 183 (Week 26) LDH-N was used as the dependent variable and explanatory variables included an indicator variable for treatment; history of transfusion, which was a categorical variable based on the stratification factor level; and baseline LDH level, which was a continuous variable.

Key secondary efficacy analyses: Percent change in LDH and change in FACIT-Fatigue from baseline to Week 26 were analyzed using a mixed model for repeated measures (MMRM) with the fixed, categorical effects of treatment, the stratification randomization indicators of transfusion history and screening LDH levels, study visit, and study visit by treatment group interaction as well as the continuous, fixed covariate of baseline FACIT-Fatigue (or LDH). For percent change in LDH, the baseline LDH level as a continuous variable was included. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. A difference between the ravulizumab and eculizumab treatment groups along with a 2-sided 95% CI was calculated.

For breakthrough hemolysis (BTH) and stabilized hemoglobin, the same approach used for TA was employed. These key secondary endpoints were tested in a hierarchical manner provided that noninferiority was declared for the coprimary endpoints.

When performing the analyses for the key secondary efficacy endpoints, a closed-testing procedure was used so that the lack of significance of a test precluded assessment of subsequent tests. Estimates and CIs were computed for all these key secondary efficacy endpoints irrespective of whether a lack of significance of a test precluded assessment of subsequent tests.

1. If the upper bound of the 95% CI for the difference between the ravulizumab and eculizumab treatment groups in the percentage change from Baseline to Week 26 in LDH is less than the noninferiority margin (NIM) of 20%, then ravulizumab would be declared noninferior for this parameter and the next parameter would be tested.

2. If the lower bound of the 95% CI for the difference between the ravulizumab and eculizumab treatment groups in change from baseline in FACIT-Fatigue is greater than the NIM of -5, then ravulizumab would be declared noninferior for this parameter and the next parameter would be tested.
3. If the upper bound of the 95% CI for the difference between the ravulizumab and eculizumab treatment groups in the proportion of patients with BTH is less than the NIM of 20%, then ravulizumab would be declared noninferior for this parameter and the next parameter would be tested.
4. If the lower bound of the 95% CI for the difference between the ravulizumab and eculizumab treatment groups in the proportion of patients with stabilized hemoglobin is greater than the NIM of -20%, then ravulizumab would be declared noninferior for this parameter.

If noninferiority was established for all key secondary endpoints, then superiority was assessed using a closed-testing procedure with the following order and using a 2-sided 0.05 test of significance for each parameter.

5. Proportion of patients with BTH through Day 183 (Week 26)
6. Percentage change from baseline to Day 183 (Week 26) in LDH
7. Hemolysis as directly measured by LDH-N from Day 29 through Day 183 (Week 26)
8. Change from baseline to Day 183 (Week 26) in FACIT-Fatigue
9. Proportion of patients with stabilized hemoglobin through Day 183 (Week 26)
10. Transfusion avoidance

Due to the hierarchical testing order being prespecified, no adjustment of the type I error was required. Other secondary efficacy analyses were summarized with only descriptive statistics.

Efficacy analyses at end of study:
Summary tables were presented by treatment sequence (ie, Rav/Rav Treatment Sequence and Ecu/Rav Treatment Sequence). Long-term ravulizumab efficacy analyses were evaluated on the full analysis set (FAS) and included all data until the end of the Extension Period. No formal statistical testing of ravulizumab versus eculizumab efficacy was performed as part of the final end of study (EOS) analyses.

Safety analyses (Primary Evaluation Period):

Safety analyses included exposure, all AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements, and were presented using descriptive statistics by treatment group. No formal hypothesis testing was performed for the safety parameters. For all safety parameters during the Primary Evaluation Period, baseline was the last available assessment prior to administration of the first dose of study drug.

Safety analyses at end of study:
Summaries were presented by period and the Entire Study Period during ravulizumab treatment based on the Ravulizumab Treated Set. Two baselines were defined for the safety analyses: Period 1 Baseline was defined as the last available assessment prior to the first study drug infusion (eculizumab or ravulizumab), except for LDH. For LDH data it was the average of all available assessments (including unscheduled) prior to the first study; Period 2 Baseline was defined as the last available assessment prior to Day 183 study drug infusion, except for LDH. For LDH data it was the average of all pre-dose assessments (including unscheduled) at in the Day 183 (pre-dose) visit window. For the switch cohort Day 183 dosing was the first dose of ravulizumab, thus Period 2 Baseline denotes a pre ravulizumab treatment Baseline.

Immunogenicity analyses:

The number and percentage of patients exhibiting ADA and neutralizing antibodies (NAbs) were summarized by treatment group in the Primary Evaluation Period and by treatment sequence in the

ravulizumab treatment period.

Pharmacokinetic and pharmacodynamics analyses:

Serum ravulizumab and eculizumab concentrations were summarized over time using descriptive statistics. Mean serum ravulizumab and eculizumab concentrations versus nominal time were provided graphically on both linear and semilogarithmic scales. Ravulizumab and eculizumab PK parameters were summarized by descriptive statistics. All evaluable PK data were used to derive PK parameters for ravulizumab and eculizumab. Summary statistics of the absolute values and changes and percentage changes from baseline in total and free C5 serum concentrations and cRBC hemolysis were provided over time by treatment group using the FAS during the Primary Evaluation Period. For the analyses at the End of Study, summary statistics were provided by treatment sequence.

Roll-over Cohort

Efficacy analyses:

By-patient listings were provided based on the Roll-over Safety Set.

Safety analyses:

Summaries were presented for the Entire Study Period, defined as Day 1 of rolling over into Study ALXN1210-PNH-301 through EOS visit. Baseline for the Roll-over Cohort was defined as the last assessment prior to the first infusion of study drug after rolling over into ALXN1210-PNH-301, except for LDH, where the average of all assessments (including unscheduled) prior to first study drug infusion in Study ALXN1210-PNH-301.

Immunogenicity analyses:

The number and percentage of patients exhibiting ADA and NAbs were summarized by population.

Pharmacokinetic and pharmacodynamics analyses:

Serum ravulizumab concentrations were summarized over time using descriptive statistics. Mean serum ravulizumab concentrations versus nominal time were provided graphically on both linear and semilogarithmic scales. Ravulizumab PK parameters were summarized by descriptive statistics. All evaluable PK data were used to derive PK parameters for ravulizumab. Summary statistics of the absolute values and changes and percentage changes from baseline in total and free C5 serum concentrations and cRBC hemolysis were provided over time on the Full Analysis Set for Roll-over Cohort (FASr) population.

SUMMARY – CONCLUSIONS

In total, 246 complement inhibitor-naïve patients diagnosed with PNH were enrolled in the study and treated with ravulizumab (N = 125) or eculizumab (N = 121); 244 patients completed the Primary Evaluation Period, and 2 eculizumab-treated patients prematurely discontinued study drug (1 due to physician decision and 1 due to withdrawal by subject). During the Primary Evaluation Period, all patients in the ravulizumab group received all planned infusions; 1 patient in the eculizumab group missed 1 infusion. This clinical study report presents results from the Primary Evaluation Period (baseline through Day 183 [Week 26]) and from the Extension Period through the end of the study.

EFFICACY RESULTS:

Primary Evaluation Period:

- Both coprimary endpoints, avoidance of pRBC transfusion per protocol-specified guidelines and LDH-N from Day 29 to Day 183, met the primary objective of statistically significant noninferiority of ravulizumab compared to eculizumab. Both coprimary endpoints favored ravulizumab.
  - Transfusion avoidance through Day 183 was achieved by 73.6% of patients in the ravulizumab group and 66.1% of patients in the eculizumab group. The lower bound of the 95% CI of the 6.8% treatment difference (95% CI: -4.66%, 18.14%) was greater than the protocol-specified NIM of -20%.

  - The adjusted prevalence of LDH-N (LDH levels ≤ 1 × ULN from Day 29 through Day 183) was 0.536 for the ravulizumab group and 0.494 for the eculizumab group. The adjusted odds ratio for the comparison of ravulizumab to eculizumab was 1.187 (95% CI: 0.796, 1.769). The lower bound of the 95% CI was greater than the protocol-specified NIM of 0.39.

- Ravulizumab also achieved statistically significant noninferiority compared to eculizumab for all 4 key secondary endpoints. Results for all key secondary endpoints favored ravulizumab.
  - Mean percent change in LDH from baseline to Day 183 was -76.84% for the ravulizumab group and -76.02% for the eculizumab group. The mean difference between treatment groups was -0.83% (95% CI: -5.21%, 3.56%). The upper bound of the 95% CI was less than the protocol-specified NIM of 20%.
  - Mean change in FACIT-Fatigue total score from baseline to Day 183 was 7.07 for the ravulizumab group and 6.40 for the eculizumab group. The mean difference between treatment groups was 0.67 (95% CI: -1.21, 2.55). The lower bound of the 95% CI was greater than the protocol-specified NIM of -5.
  - Breakthrough hemolysis was experienced by 4.0% of patients in the ravulizumab group and 10.7% of patients in the eculizumab group. The difference between treatment groups was -6.7% (95% CI: -14.21%, 0.18%). The upper bound of the 95% CI was less than the protocol-specified NIM of 20%.
  - Hemoglobin stabilization through Day 183 was achieved by 68.0% of patients in the ravulizumab group and 64.5% of patients in the eculizumab group. The difference between treatment groups was 2.9% (95% CI: -8.80%, 14.64%). The lower bound of the 95% CI was greater than the protocol-specified NIM of -20%.
- Because statistically significant noninferiority was achieved for both coprimary and all 4 key secondary endpoints, superiority was assessed following the prespecified hierarchical testing order that began with BTH. The treatment difference for BTH ($p = 0.0558$) did not reach the prespecified significance threshold for superiority, and no further testing was conducted. The incidence of BTH was more than 2-fold higher in the eculizumab group (13 patients with 15 events) than in the ravulizumab group (5 patients with 5 events), and the difference was associated with suboptimal C5 inhibition in eculizumab-treated patients (see PK/PD results).
- Subgroup analyses were performed for the randomization stratification variables of transfusion history and screening LDH levels and for sex, race, region, and age for the coprimary and key secondary endpoints. No sensitive subgroups were identified in these analyses. The point estimates for most subgroups favored ravulizumab.

Through End of Study:

Responses observed during the Primary Evaluation Period were maintained throughout the duration of the study for the coprimary endpoints and all of the secondary efficacy endpoints. Long-term data from the PNH patients who entered the Extension Period of Study ALXN1210-PNH-301, with up to 5.84 years follow-up, demonstrate continued efficacy and the maintenance of disease control as evidenced by control of intravascular hemolysis (LDH normalization) and amelioration of clinical manifestations of PNH disease such as anemia, breakthrough hemolysis, and transfusions.

- The percentage of patients with transfusion avoidance was consistently maintained between the Primary Evaluation Period and the Extension Period for either treatment group. During each year of the Extension Period 66.26% to 75.65% of the patients achieved transfusion avoidance.
- The percentage of patients achieving LDH-N in the Primary Evaluation Period was maintained during the Extension Period in both treatment groups.
- Likewise, the percent change in LDH, the change from baseline in FACIT-Fatigue scores, the incidences of BTH, and the percentage of patients with hemoglobin stabilization observed during the Primary Evaluation Period were maintained during ravulizumab treatment throughout the Extension Period.

PK/PD RESULTS:

Primary Evaluation Period:

- Following initiation of the ravulizumab weight-based dosing regimen, steady-state therapeutic serum concentrations were achieved immediately and maintained throughout the entire 26-week treatment period.
- Immediate and complete inhibition of serum C5 (terminal complement) was observed (with mean free C5 serum concentrations of < 0.5 µg/mL) by the end of the first ravulizumab infusion and sustained throughout the entire 26-week treatment period. In contrast, mean free C5 serum concentrations did not consistently remain < 0.5 µg/mL following eculizumab treatment.
- For ravulizumab, all postbaseline individual free C5 concentrations were < 0.5 µg/mL in all patients. In contrast, free C5 serum concentrations did not consistently remain < 0.5 µg/mL following eculizumab treatment, which may explain the higher number of BTH events in this group.
- Suboptimal C5 inhibition (free C5 ≥ 0.5 µg/mL) was temporally associated with BTH for 0 of 5 BTH events in the ravulizumab group and 7 of 15 BTH events in the eculizumab group, suggesting that immediate, complete, and sustained C5 inhibition following treatment with ravulizumab reduces a patient's risk of BTH.
- In contrast to eculizumab, treatment with ravulizumab consistently resulted in immediate, complete, and sustained C5 inhibition in all patients at all times throughout the treatment period.

Extension Period:

- In the Rav/Rav Treatment Sequence, therapeutic ravulizumab serum concentrations were consistent with the Primary Evaluation Period and were maintained through the entire Extension Period. Similarly, complete inhibition of serum free C5 with mean serum free C5 concentrations of < 0.5 µg/mL during Primary Evaluation Period was maintained throughout the entire study period; 3 patients had a singular event of free serum C5 > 0.5 µg/mL during the Extension Period.
- Following initiation of the ravulizumab weight-based q8w dosing regimen in patients in the Ecu/Rav Treatment Sequence, steady-state therapeutic serum concentrations of ravulizumab were achieved immediately and maintained during the entire Extension Period. Inhibition of serum free C5 was overall maintained throughout the entire study period; 2 patients had a singular event of serum free C5 > 0.5 µg/mL during the Extension Period. One of the 2 events coincided with a BTH event.

SAFETY RESULTS:

Primary Evaluation Period:

- Ravulizumab was safe and well tolerated in this study with a safety profile similar to eculizumab in adult patients with PNH.
- The most frequently reported AE was headache, which was experienced by a similar percentage of patients in both groups (ravulizumab: 36.0%, eculizumab: 33.1%).
- No patients died or discontinued study drug due to AEs in the Primary Evaluation Period.
- The percentage of patients with SAEs was similar in the 2 treatment groups (ravulizumab: 8.8%, eculizumab: 7.4%).
- No meningococcal infections were reported.
- Both, ravulizumab and eculizumab treatment groups exhibited similar incidences of ADA (0.8% of patients in each treatment group developed treatment-emergent ADA), with no apparent impact of ADA on PK, PD, efficacy, or safety.

Ravulizumab Treatment from first dose through End of Study:

- From first dose of ravulizumab through the entire study period, the most frequently reported (> 15% of all patients in the Ravulizumab Treated Set) AEs by Preferred Term during ravulizumab treatment were headache (28.7%), upper respiratory tract infection (24.6%), pyrexia (19.7%), nasopharyngitis (18.9%), COVID-19 (17.2%), and arthralgia (15.2%).

- Eight ravulizumab treated patients died, all during the Extension Period; causes of death were COVID-19, pulmonary sepsis, septic shock, cardiac arrest, aspiration, intracranial infection, sepsis, and meningococcal sepsis. Another 3 patients discontinued the study due to AEs that started during the Extension Period and subsequently died (sepsis, lung adenocarcinoma and acute myeloid leukemia). The Investigator assessed the AE of intracranial infection to be possibly related and the meningococcal sepsis to be related to study drug.
- Eight patients discontinued ravulizumab due to an AE (myelodysplastic syndrome [3 events], cerebrovascular accident, sepsis [2 events], lung adenocarcinoma, and acute myeloid leukemia). The Investigator assessed the AEs to be not related to study drug except for acute myeloid leukemia which the Investigator assessed to be unlikely related to study drug.
- Nine patients had AEs that met the protocol-specified criteria for MAVE (peripheral arterial thrombosis; coronary artery disease; cerebrovascular accident, angina unstable, deep vein thrombosis, acute myocardial infarction, pulmonary embolism and cerebral venous thrombosis)
- One event of meningococcal sepsis with a fatal outcome was reported during the Extension Period.
- Four patients in the Rav/Rav Treatment Sequence and 2 patients in the Ecu/Rav Treatment Sequence had treatment-emergent ADA-positive responses during the during the ravulizumab treatment period. The ADA titers were low in the majority of confirmed patients throughout the entire study in both treatment groups; the results had no apparent impact on PK, PD, efficacy, or safety.

Roll-over Cohort:

- The most frequently reported (> 10% of all patients) AEs by Preferred Term were COVID-19 (n = 9 [34.6%]) and asthenia (n = 4 [15.4%]).
- There were no deaths reported in the Roll-over Cohort.
- No patients withdrew from the study or discontinued study drug due to an AE.
- There were no AEs that met the protocol-specified criteria for MAVE.
- No meningococcal infections were reported.
- None of the patients in the Roll-over Cohort were ADA positive at baseline and no treatment-emergent ADA positive responses were observed during the study.

CONCLUSION:

The favorable benefit/risk profile of ravulizumab in this study supports its use for the treatment of patients with PNH including patients switched from eculizumab to ravulizumab.

Primary Evaluation Period:

For both coprimary endpoints and all 4 key secondary efficacy endpoints, ravulizumab achieved statistically significant noninferiority compared to eculizumab, with treatment differences consistently favoring ravulizumab. Compared to eculizumab, ravulizumab provided improved disease control as evidenced by immediate, complete, and sustained inhibition of terminal complement during the entire 26-week treatment period.

Ravulizumab Treatment:

Disease control achieved during the initial 26-weeks of ravulizumab treatment was maintained in the majority of patients throughout the Extension Period with few cases of free C5 levels above 0.5 μg/mL. The frequency of BTH events over time during ravulizumab treatment in the Extension period was consistent with the known profile of ravulizumab.

Roll-over Cohort:

Disease control in patients in the Roll-over Cohort was maintained during the study with no BTH events

reported.

The totality of the clinical data collected through end of Study ALXN1210-PNH-301 demonstrate that the clinical improvements of PNH clinical symptoms and disease parameters were sustained during long-term ravulizumab treatment and supports a favorable benefit-risk profile for treatment with ravulizumab in patients with PNH.

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