Synopsis

Name of Alexion/Company: Alexion Pharmaceuticals, Inc. **Name of Finished Product:** Ultomiris® **Name of Active Ingredient:** ALXN1210 (ravulizumab)	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: A Phase 3, Open-label, Multicenter Study of ALXN1210 in Children and Adolescents With Atypical Hemolytic Uremic Syndrome (aHUS)		
Coordinating Investigator: [redacted] Spain.		
Study centers: Patients were enrolled at 20 sites in 8 countries (Belgium, Germany, Italy, Japan, Korea, Spain, United Kingdom, and the United States).		
Publications (reference): Tanaka K, Adams B, Madrid Aris A et al. The long-acting C5 inhibitor, ravulizumab, is efficacious and safe in pediatric patients with atypical hemolytic uremic syndrome previously treated with eculizumab. Pediatr Nephrol 2020, doi:10.1007/s00467-020-04774-2. Ariceta G, Dixon BP, Kim SH et al. The long-acting C5 inhibitor, ravulizumab, is effective and safe in pediatric patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment. Kidney Int. In press 2020. Dixon BP, Madris-Aris AD, Adams B, et al. Two-year efficacy and safety of ravulizumab in adults and children with atypical hemolytic uremic syndrome (aHUS): analysis of two Phase 3 studies. Blood. 2021;138(Supplement 1):769-769.		
Studied period (years): Date first patient treated: 01 Sep 2017 Date last patient last visit: 20 Dec 2022		**Phase of Development:** 3
Objective: Primary: The primary objective of the study was to assess the efficacy of ravulizumab in complement inhibitor treatment naïve pediatric patients (ie, Cohort 1) with atypical hemolytic uremic syndrome (aHUS) to inhibit complement mediated thrombotic microangiopathy (TMA) as characterized by thrombocytopenia, hemolysis, and renal impairment. Secondary**:** The secondary objectives for complement inhibitor treatment-naïve patients (ie, Cohort 1) and eculizumab-experienced patients (ie, Cohort 2) were as follows: • To characterize the safety and tolerability of ravulizumab • To evaluate the efficacy of ravulizumab by additional efficacy measures • To characterize the pharmacokinetics (PK)/pharmacodynamics (PD) of ravulizumab • To evaluate the long-term safety and efficacy of ravulizumab		

Methodology: This was a Phase 3, single-treatment arm, multicenter study to evaluate the safety, efficacy, PK, and PD of ravulizumab administered by intravenous (IV) infusion in approximately 23 to 28 pediatric patients, from birth to < 18 years of age, with diagnosis of aHUS. The study had 2 cohorts. Cohort 1 included complement inhibitor treatment-naïve patients; Cohort 2 included eculizumab-experienced patients. The study consisted of a Screening Period (of up to 7 days for Cohort 1 or up to 28 days for Cohort 2), a 26-week Initial Evaluation Period, and up to a 4.5-year Extension Period.

Patients received a loading dose of ravulizumab on Day 1, followed by weight-based maintenance doses of ravulizumab on Day 15 and every 8 weeks (q8w) thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg, for a total of 26 weeks of study treatment. Loading and maintenance doses were based on body weight.

After the Initial Evaluation Period, patients rolled over into an Extension Period in which all patients continued their weight-based maintenance dose of ravulizumab on Day 183 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg, until the product was registered or approved (in accordance with country specific regulation) or for up to 4.5 years, whichever occurred first. The end of trial was defined as the last patient's last visit or follow-up (whether on site or via phone call) during the Extension Period, whichever was later.

Number of patients (planned): Approximately 23 to 28 pediatric (< 18 years of age) patients with documented aHUS were planned to be enrolled. The minimum number of patients for each age category was as follows:

- Birth to < 2 years: 4 patients
- 2 to < 6 years: 4 patients
- 6 to < 12 years: 4 patients
- 12 to < 18 years: 8 patients

Cohort 2 patients must have been 12 to < 18 years of age, except in Japan where patients < 12 years of age were permitted.

Diagnosis and main criteria for inclusion:

For Cohort 1, eligibility was limited to patients (age < 18 years) weighing ≥ 5 kg including patients with onset of TMA after kidney transplant and patients with onset of TMA postpartum. Patients must have not been previously treated with complement inhibitors and must have had evidence of TMA (including thrombocytopenia, evidence of hemolysis, and kidney injury) based on platelet count, lactate dehydrogenase (LDH) and serum creatinine levels.

For Cohort 2, patients must have been between 12 and < 18 years of age (non-Japanese sites) or < 18 years of age (Japanese sites) weighing ≥ 5 kg who had been treated with eculizumab according to the labelled dosing recommendation for aHUS for at least 90 days prior to screening.

Key exclusion criteria for both cohorts included ADAMTS13 ("a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13") deficiency; Shiga toxin-related hemolytic uremic syndrome; positive direct Coombs test; history of heart, lung, small bowel, pancreas, or liver transplant; kidney diseases other than aHUS; acute antibody-mediated rejection; plasma exchange/plasma infusion ≥ 28 days (Cohort 1 only) and chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for end-stage kidney disease).

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).

Patients received ravulizumab loading doses on Day 1 and maintenance doses on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg administered by IV infusion. For Cohort 2 patients, Day 1 of study treatment occurred 14 days from the patient's last dose of eculizumab. Dosages were based on the patient's body weight, as shown in the following table.

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Doses (mg)	Maintenance Dosing Frequency
≥ 5 to < 10	600[a]	300	q4w
≥ 10 to < 20	600	600	q4w
≥ 20 to < 30	900	2100	q8w
≥ 30 to < 40	1200	2700	q8w
≥ 40 to < 60	2400	3000	q8w
≥ 60 to < 100	2700	3300	q8w
≥ 100	3000	3600	q8w

[a] loading dose of 300 mg in the ≥ 5 to < 10 kg group was used for patients enrolled prior to Protocol Amendment 5 (Global).
Abbreviations: q4w = once every 4 weeks; q8w = once every 8 weeks

Lot numbers: 1000107, 1000108, 1000184, 1000201, 1000252, 1000306, 1000375, 1000398, 1000417, 1000459, 1000144, 1000561, 1000891, 1001173, and 1001845

Reference therapy, dose and mode of administration, batch number: Not applicable

Duration of treatment: Initial Evaluation Period of 26 weeks (183 days) followed by an Extension Period of up to 4.5 years.

Criteria for evaluation:

Efficacy Endpoints:

- Primary efficacy endpoint for complement inhibitor treatment-naïve patients (ie, Cohort 1) only:
  - Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients must meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.
- Secondary endpoints:
  - Time to Complete TMA Response (Cohort 1 only)
  - Complete TMA Response status over time (Cohort 1 only)
  - Dialysis requirement status
  - Observed value and change from baseline in estimated glomerular filtration rate (eGFR)
  - Chronic kidney disease (CKD) stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline
  - Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin)
  - Increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between (Cohort 1 only)
  - Change from baseline in quality of life (QoL), as measured by Pediatric Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Questionnaire (patients ≥ 5 years of age)
  - TMA parameters in patients who discontinue treatment in the Extension Period, but remain in the study

Pharmacokinetic and Pharmacodynamic Endpoints:

- Changes in serum ravulizumab concentration over time
- Changes in serum free C5 concentrations over time
- Changes in serum free C5 and serum ravulizumab concentration in patients who discontinue treatment in the Extension Period, but remain in the study

Safety Endpoints:

- The long-term safety and tolerability of ravulizumab was 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 also assessed.

Statistical Methods:

All data collected were presented using summary tables, figures, and data listings. Planned summaries were presented overall and by age groups when applicable. Per protocol, tabulated summaries do not include a direct comparison between Cohort 1 and Cohort 2.

Analysis Populations: Efficacy analyses were performed on the Full Analysis Set (FAS). The FAS for Cohort 1 was based on a modified intent-to-treat approach. With this approach, confirmation of eligibility in patients may have occurred after receiving study drug. This specifically applied to Inclusion Criterion 2c (confirmed via a central laboratory), Exclusion Criterion 1 (confirmed via a central or local laboratory), and Exclusion Criterion 2 (confirmed via a central or local laboratory). Based on the above, the FAS included all patients who received at least 1 dose of ravulizumab, had at least 1 post-baseline efficacy assessment, met Inclusion Criterion 2c, and did not meet Exclusion Criterion 1 or Exclusion Criterion 2. The FAS for Cohort 2 included all patients who received at least 1 dose of ravulizumab and had at least 1 postbaseline efficacy assessment.

Efficacy Analyses:

Primary endpoint (Cohort 1 only): Complete TMA Response during the 26-week Initial Evaluation Period, the primary analysis consisted of estimating the proportion of complete TMA responders among ravulizumab-treated patients. In order to count as a Complete TMA Response, patients needed to achieve each laboratory measure for 28 consecutive days with all 3 measures overlapping at least once. This was performed by calculating the point estimate and a 95% confidence interval (CI) for the proportion of complete TMA responders in ravulizumab-treated patients. The CI was based on exact confidence limits using the Clopper-Pearson method.

Secondary efficacy analyses:

For Cohort 1 only:

The secondary efficacy endpoint of time to Complete TMA Response, a Kaplan-Meier cumulative distribution curve was generated along with a 2-sided 95% CI. Complete TMA Response was summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each post-baseline time point. A similar approach was used to summarize the number and proportion of patients with an increase from baseline in hemoglobin ≥ 20 g/L, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

For Cohort 1 and Cohort 2:

Kidney function (dialysis requirement status, eGFR, CKD stage) and hematologic parameters (platelets, LDH, hemoglobin) were summarized at baseline and each post-baseline time point. Descriptive statistics for continuous variables (eGFR, platelets, LDH, hemoglobin) were used to summarize the observed value as well as the change from baseline. A mixed model for repeated measures (MMRM) with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates was fit to test whether changes differ from zero at each time point. Dialysis requirement status and CKD stage were summarized over time. Dialysis requirement status was summarized among patients receiving dialysis within 5 days prior to ravulizumab treatment initiation by presenting the number and proportion of those patients receiving and not receiving dialysis at each time point. A 2-sided 95% CI for the proportion of patients receiving dialysis was provided. The CKD stage was summarized over time by presenting the number and proportion of patients that improved (excluding those with Stage 1 at baseline as they cannot improve), worsened (excluding those with Stage 5 at baseline as they cannot worsen), and stayed the same compared to CKD stage at baseline. Stage 5 was considered the worst category, while Stage 1 was considered the best category. A 2-sided 95% CI for the proportion was provided for each category.

Quality of life was assessed in patients ≥ 5 years of age by the Pediatric FACIT-Fatigue Questionnaire (patient-reported for patients who were ≥ 8 years of age at the time of enrollment; caregiver-reported or caregiver assistance for patients who were 5 to < 8 years of age at the time of enrollment). This measure was summarized at baseline and each post-baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. An MMRM with the fixed,

categorical effect of visit and fixed, continuous effect of the test's baseline value as covariates may have been fit to test whether changes differ from zero at each time point.

Safety analyses

Safety analyses included exposure to ravulizumab, all AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements, and were presented using descriptive statistics. No formal hypothesis testing was performed for the safety parameters. For the analysis, the baseline value is defined as the average of the values from the assessments performed prior to the first study drug infusion (these can include results from screening and the Day 1 visit).

Immunogenicity analyses

The number and percentage of patients with positive titers for ADAs to ravulizumab and different titer categories was summarized over time. The proportion of patients ever positive and the proportion of patients ever negative were also summarized.

Pharmacokinetic and pharmacodynamics analyses

Graphs of mean serum ravulizumab concentration-time profiles were constructed. Descriptive statistics were calculated for PK serum concentration data at each sampling time, as appropriate. For PD parameters, effects of ravulizumab were evaluated by assessing the absolute values and changes and percentage changes from baseline in serum free C5 serum concentrations over time, as appropriate. Descriptive statistics were calculated for the PD data at each sampling time, as appropriate.

SUMMARY – CONCLUSIONS

This Final Clinical Study Report (End of Study) addendum presents data from the Primary Evaluation Period (ie, 26-week Initial Evaluation Period) through the end of the Extension Period (ie, end of study; dates ranging from 01 Sep 2017 to 20 Dec 2022). This includes long term data for patients up to 250.7 weeks. All available efficacy, safety, PK, PD, and immunogenicity data through the end of the study visit are presented.

EFFICACY RESULTS FOR COHORT 1:

Initial Evaluation Period

- Fifteen of the 20 (75.0%) patients in the FAS (95% CI: 50.9%, 91.3%) achieved the primary efficacy endpoint, Complete TMA Response, during the 26-week Initial Evaluation Period.
- Seventeen of 19 patients in the FAS achieved platelet count normalization during the Initial Evaluation Period, 18 patients achieved LDH normalization, and 16 patients achieved renal function improvement (defined as ≥ 25% reduction in serum creatinine from baseline) during the Initial Evaluation Period.

Results for secondary endpoints are as follows:

- The median time to Complete TMA Response was 30 days and the earliest response occurred by 15 days following the first dose of ravulizumab.
- Hematologic normalization, defined as normalization of both LDH and platelets, was observed in 18 of the 20 patients (90.0% [95% CI: 68.3%, 98.8%]).
- Seventeen of the 20 patients (85.0% [95% CI: 62.1%, 96.8%) had an increase in hemoglobin of ≥ 20 g/L compared to baseline with a confirmatory result.
- Dialysis was discontinued in 4 of the 6 patients in the FAS who had been receiving dialysis at baseline; all 4 of these patients discontinued dialysis within the first 36 days of exposure to ravulizumab. No patients initiated dialysis after starting treatment with ravulizumab.
- Renal function, as assessed by eGFR, improved from a mean of 27.5 mL/min/1.73 m^2 at baseline to 108.5 mL/min/1.73 m^2 at the end of the Initial Evaluation Period.

Extension Period

Results from the Extension Period demonstrated continued improvement or maintenance of disease:

- Complete TMA Response was achieved by 15/20 patients (75.0%) at Week 26 and 18/20 patients (90.0%) at Week 52 and by the end of the Extension Period (Day 1863).
- After initially achieving Complete TMA Response, some patients had transient periods during which not all components of response continued to be met through the end of the study. However, in general, the individual components of TMA response were maintained during long-term treatment with ravulizumab.
- Overall, patients showed improvement in all hematologic TMA parameters (platelets, LDH, and hemoglobin) during the Initial Evaluation Period which were maintained during long-term treatment with ravulizumab.
- All 7 patients who were receiving kidney dialysis at Baseline had discontinued dialysis by Day 193, with 6 discontinuing dialysis within the first 36 days of ravulizumab treatment. No patients were reported to re-initiate dialysis after starting treatment with ravulizumab through the end of study.
- During the Extension Period, the mean eGFR generally remained > 100 mL/min/1.73 m^2 through Day 1359 of the study. Most patients with available data continued to have improvements in CKD stage or no changes in CKD stage through the end of the study. The improvement noted in mean eGFR observed by Week 26 and sustained through the end of the study.
- All 9 patients (ie, ≥ 5 years of age) with available data at Week 26 (Day 183) and Week 52 (Day 351) had at least a 3-point improvement in FACIT Fatigue score at these respective timepoints. At End of Study, all (2/2) patients with available data had a 3-point improvement from Baseline.

EFFICACY RESULTS FOR COHORT 2:

Initial Evaluation Period

- Hematologic parameters in Cohort 2 patients remained stable throughout the Initial Evaluation Period.
- None of the 10 patients received dialysis after starting treatment with ravulizumab.
- Kidney function, as assessed by eGFR, remained stable at the end of the Initial Evaluation Period compared to Baseline.
- QoL, as measured by the Pediatric FACIT-Fatigue score, was maintained during the Initial Evaluation Period for the 8 treated patients who were ≥ 5 years of age.

Extension Period

Results from additional ravulizumab treatment in the Extension Period through the end of study demonstrated continued maintenance of stable hematologic parameters and kidney function without any evidence of loss of efficacy over time.

PK/PD RESULTS:

- Following ravulizumab body weight-based dosing in complement inhibitor treatment naïve pediatric patients with aHUS, therapeutic steady-state exposures were achieved in both q4w and q8w maintenance dosing intervals.
- Immediate and complete terminal complement inhibition (defined as serum free C5 < 0.5 µg/mL) was observed by the end of the first ravulizumab infusion and sustained throughout the entire study.
- Following weight-based dosing with ravulizumab in eculizumab experienced pediatric patients, complete terminal complement inhibition was maintained throughout the entire study for both the q4w and the q8w dosing interval groups.

SAFETY RESULTS:

- Ravulizumab was well tolerated by patients throughout the study, with no unexpected safety concerns in the 24 complement inhibitor treatment naïve (Cohort 1) and 10 eculizumab experienced (Cohort 2) pediatric patients with aHUS. The observed safety profile is consistent with the known safety profile of ravulizumab.
- In Cohort 1, the most frequently reported (> 20% of all patients) AEs were pyrexia (n = 13; 54.2%), vomiting, diarrhea, and headache (33.3% each); nasopharyngitis (29.2%); abdominal pain and hypertension (25.0% each); and constipation, upper respiratory tract infection, contusion, and cough (20.8% each). In Cohort 2, the most frequently reported AEs were upper respiratory tract infection (n = 4; 40.0%) and pharyngitis and oropharyngeal pain (30.0% each).
- No patients died in the study.
- In Cohort 1, 16 patients experienced SAEs, most common of which were pyrexia (reported in 4 patients); diarrhea (reported in 3 patients); and gastroenteritis viral and abdominal pain (reported in 2 patients each). In Cohort 2, 1 patient experienced 5 SAEs of upper respiratory tract infection (3 events), pneumonia, and bronchitis.
- In Cohort 1, 2 patients discontinued study drug during the Initial Evaluation Period due to SAEs (1 patient due to glomerulonephritis membranoproliferative and 1 patient due to anemia, and hypertensive urgency). In Cohort 2, none of the patients discontinued study drug or withdrew from the study.
- No meningococcal infections (prespecified as AEs of special interest) were reported in the study.
- There were no treatment-emergent ADA positive responses reported in either Cohort 1 or Cohort 2 during long term ravulizumab treatment through the end of the study.

CONCLUSION:

This analysis of final data for the 24 patients enrolled in Cohort 1 demonstrated that ravulizumab provided immediate, complete, and sustained inhibition of terminal complement in this complement inhibitor treatment naïve pediatric aHUS population. Complete TMA Response was achieved in 90.0% of patients, with consistent results observed for individual response components as well as other secondary efficacy endpoints of CKD stage and dialysis requirement. After the Initial Evaluation Period, patients continued to benefit from ravulizumab treatment during the Extension Period and through the remainder of the study. Improvements in all hematologic TMA parameters (platelets, LDH, and hemoglobin) during the Initial Evaluation Period were maintained with extended ravulizumab treatment. Decreased disease burden was also evident based on the reduced need for dialysis, as no patients were reported to re-initiate dialysis after starting treatment with ravulizumab, and improved QoL scores.

Data for the 10 patients enrolled in Cohort 2 show that switching patients from eculizumab to ravulizumab results in complete and sustained inhibition of terminal complement. The efficacy results demonstrate maintenance of TMA parameters and kidney function as well as additional benefits in QoL.

Following body weight-based dosing with ravulizumab, immediate and complete terminal complement inhibition was achieved and sustained throughout the treatment period for complement inhibitor naïve and eculizumab experienced pediatric patients. No treatment emergent immunogenicity responses were observed in either complement inhibitor naïve or eculizumab experienced pediatric patients.

Ravulizumab was well tolerated in both complement inhibitor treatment naïve pediatric patients and eculizumab experienced pediatric patients, with no unexpected safety concerns. The data in this final analysis support the favorable benefit/risk profile of ravulizumab and its use for the treatment of pediatric patients with aHUS regardless of experience with prior complement inhibitor treatment

Date of the report: 11 Jun 2023