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Response to PALKO from Alexion:

We would like to thank PALKO for the possibility to respond to the draft recommendation of "Ravulitsumabi neuromyelitis optica - kirjon häiriön (NMOSD) hoidossa". According to the draft recommendation, ravulizumab is not proposed to be part of the national range of services in the treatment of neuromyelitis optica spectrum disorder (NMOSD).

Alexion finds the PALKO draft recommendation for use of Ultomiris in NMOSD surprising, particularly PALKO's view of significant uncertainty in the clinical impact/benefits of Ultomiris in relation to the adverse events and the lack of a clear stopping criteria.

The PALKO recommendations should be based on the best available clinical and economic information at the time of approval. We would like to bring attention to recently published data (including 228 week long-term extension data) such that PALKO can utilize the latest available evidence in making the final recommendation. Furthermore, we also respond to specific comments made in the draft.

Ultomiris received marketing authorization in the EU on July 2, 2019 and is currently approved for use in four indications. In May 2023, Ultomiris was approved as treatment of adult patients with NMOSD who are anti-aquaporin 4 (AQP4) antibody-positive. According to the public assessment report, the Committee for Medicinal Products for Human Use (CHMP) concludes that the efficacy of ravulizumab has been sufficiently demonstrated to support its use, with the overall benefit/risk ratio of Ultomiris being positive (CHMP assessment report Procedure No. EMEA/H/C/004954/II/0032). Alexion would like to stress that there are over 26 000 patient years of exposure globally across the four approved indications (Alexion safety database including both clinical trial and real-world data). Alexion estimate that more than 1300 patients were treated with Ultomiris for NMOSD worldwide (data from 2024).

NMOSD is an ultra-rare disease with high disease burden

PALKO states that the treatment of ravulizumab is long term and that it is unclear how to determine criteria for continuing or stopping treatment. NMOSD is an ultra-rare condition characterized by attacks that typically result in stepwise accumulation of disability as they are often severe and lead to substantial, and often permanent, neurological deficit (Wingerchuck et al 2015). Consequently, management must be life-long. The EMA assessment report notes: *"Treatment of NMOSD is comprised of both acute treatment of relapses and long-term relapse prevention therapy. Acute treatment of NMOSD relapses consists primarily of high-dose corticosteroids and plasmapheresis. The goal of long-term treatment is to prevent the occurrence of relapses."*

NMOSD has a significant disease burden. A recent Danish study showed that patients with AQP4-Ab+ NMOSD have a median life expectancy of 64 years, compared to 83 years in the general population (Papp et al 2024_1). These patients have more than twice the risk of death (HR 2.22; Papp et al 2024_1). After the disease starts, many patients lose their ability to work, which quickly worsens their financial situation and increases costs for families and society (Papp et al 2024_2).

Design of the clinical data package

PALKO states that the evidence is based on an open label external placebo-controlled study. However, the CHAMPION-NMO study demonstrates statistically significant, clinically meaningful results in preventing relapses (Pittock et al 2023). In keeping with this, the EMA assessment report determined: The study design of CHAMPION-gMG (Pittock et al 2023) is in line with CHMP guidance / scientific advice as stated in the EMA assessment report: "*The clinical program as well as the design and outcomes of study ALXN1210-NMO-307 were discussed during a scientific advice in October 2019 (EMA/CHMP/SAWP/545125/2019) and during a follow-up procedure in February 2020 (EMEA/H/SA/3331/5/FU/1/2020/II). The MAH has overall followed the recommendations received.*" In addition, it is important to note that use of a placebo arm as control was considered ethically unacceptable when other therapies for NMOSD were to be available during the conduct of the study, including eculizumab. In addition, the comparison to eculizumab under a non-inferiority hypothesis is unfeasible in terms of required sample size in a rare condition. All considered, it was concluded in the EMA assessment report that a single arm uncontrolled study could be considered acceptable in these exceptional circumstances.

Efficacy and safety of ravulizumab in NMOSD

PALKO states that there is significant uncertainty in the clinical impact of ravulizumab and that there was no subgroup identified who would have more or less benefits of ravulizumab treatment. The study CHAMPION NMO study demonstrates statistically significant, clinically relevant results in effectively preventing relapses (Pittock et al 2023). In line with this, the EMA assessment report concludes that *"The study met its primary objective by demonstrating the efficacy of ravulizumab for the treatment of adult patients with NMOSD. No patients in the ravulizumab group had an adjudicated On-trial Relapse during the Primary Treatment Period of Study ALXN1210-NMO-307, compared with 20 patients (42.6%) in the placebo group from Study ECU-NMO-301 (Table 29)." "The hazard ratio (95% CI) for ravulizumab compared with placebo was 0.014 (0.000, 0.103), representing a 98.6% reduction in the risk of relapse. At Week 48, all patients in the ravulizumab group were relapse free (versus 63.2% in placebo-treated patients). This effect was sustained through the end of the Primary Treatment Period, at which point all patients in the ravulizumab group remained relapse free. The median (min, max) analysis follow-up time was 73.50 (11.00,117.71) weeks for the ravulizumab group and 36.00 (1.86, 117.71) weeks for the placebo group. "*

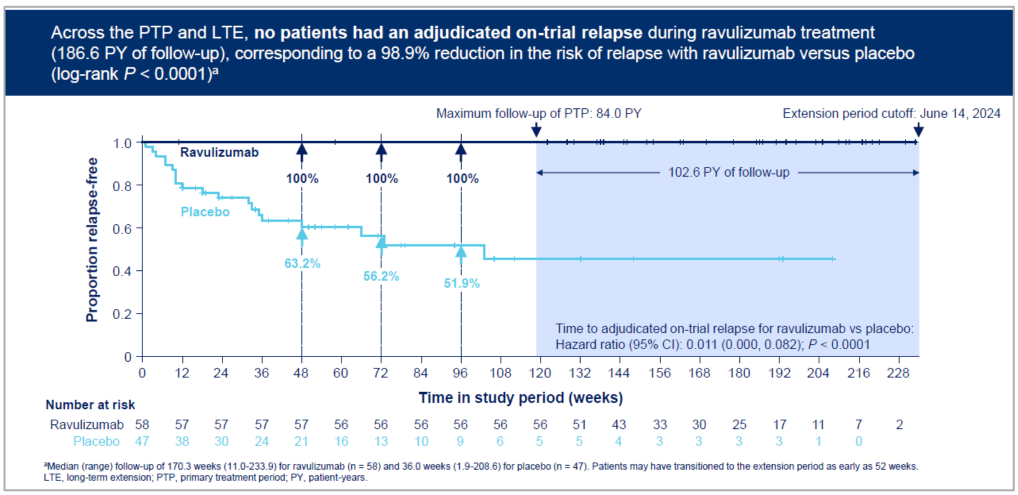
A variety of pre-specified subgroups were analyzed, including region, age group, gender, race, concomitant baseline immunosuppressive therapy (IST), and prior rituximab use. The effect of ravulizumab was consistent across all subgroups, including those with prior rituximab exposure. Alongside robust relapse prevention, the EMA assessment also noted that ravulizumab was generally well tolerated.

Additionally, Alexion conducted a network meta-analysis (NMA) comparing the efficacy of Ultomiris with that of Soliris, inebilizumab, and satralizumab in treating adult AQP4+ NMOSD, based on current clinical trial evidence (Clardy et al 2024). Using validated methods, the analysis revealed that as monotherapy, Ultomiris was significantly more effective than inebilizumab and satralizumab in both time to first relapse and annualized relapse rate (ARR). In combination with IST, Ultomiris also proved more effective than satralizumab in time to first relapse. Among patients treated with either monotherapy or combination therapy (as in the CHAMPION-NMOSD and PREVENT trials), Ultomiris was associated with a lower risk of first relapse and fewer total relapses compared to satralizumab.

Taken together, these results clearly demonstrate the substantial clinical benefit of Ultomiris.

Long term efficacy of Ultomiris in NMOSD

Recent data presented from a 228-week open-label extension (OLE) confirm the long-term benefits of Ultomiris in NMOSD. No patients had an adjudicated on-trial relapse during ravulizumab treatment (186.6 PY of follow-up), corresponding to a 98.9% reduction in the risk of relapse with ravulizumab versus placebo (log-rank P < 0.0001) (Pittock et al 2025, Appendix 1).



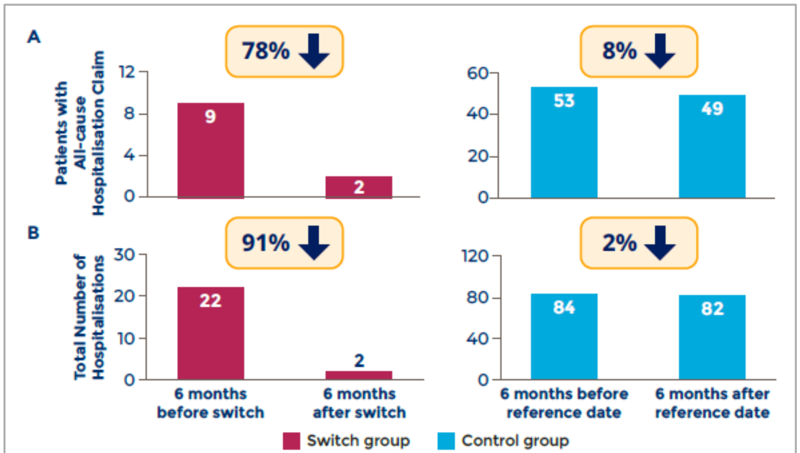
Real world data on complement inhibition in NMOSD

Real-world data collected by Alexion in the Global NMO SPOTLIGHT Registry supports the efficacy and safety of complement inhibition in NMOSD. In the most recent analysis of 30 patients treated with eculizumab or ravulizumab for a median of 40.2 (Q1, Q3: 24.0, 49.7) and 1.0 (0.7, 1.3) months, respectively, 10 patients experienced relapses (0.5 ARR) during one year before the treatment and 2 patients (0.02 ARR) during the treatment. No new safety signals were observed during the treatment and no patient experienced a meningococcal infection (Obeidat AZ, et al. 2024). Real-world data on complement inhibition (eculizumab) has also been reported in the Japanese post-marketing study including 155 patients (151 formed the effectiveness set) with median treatment duration of 52.1 weeks (0.1-174.3). From eculizumab initiation 7 patients experienced relapses (0.06 ARR), compared with 95 (0.57 ARR) in the two years before the complement inhibitor initiation. Safety profile was consistent with that observed in the clinical trial setting and no meningococcal infections were observed (Nakahara J, et al. 2024).

Economic value, price and cost effectiveness

Understanding the treatment cost and economic value of Ultomiris remains essential in healthcare resource allocation.

A recent study compared the number of hospitalizations, duration of hospital stay, comorbidities, and hospital expenses in the six months before and after AQP4+ NMOSD patients switched from rituximab to eculizumab. The analysis showed a marked reduction in hospitalizations, days spent in hospital, and associated comorbidities in the eculizumab group, underscoring that complement C5 inhibition can lower healthcare resource utilization (Lee et al 2023, Appendix 1).



- In the switch group, the number of patients with an all-cause hospitalisation claim decreased from 9 (45%) prior to the treatment switch to 2 (10%) post-treatment switch from RTX to ECU (p=0.013) (**Figure 3A**)
  - Total number of hospitalisations decreased from 22 (1.1 per patient) prior to treatment switch to 2 (0.1 per patient) post-treatment switch (**Figure 3B**)
  - One of the 2 patients with hospitalisations post-treatment switch had discontinued ECU ~7.5 weeks before the hospitalisation event; the other patient's hospitalisation was due to a surgical procedure. Both patients resumed their ECU treatment some time after the hospitalisation ended
  - Median duration of hospitalisation decreased from 8.5 weeks to 2.5 weeks before and after treatment switch to ECU, respectively (p<0.001)
- In the control group, the number of patients with all-cause hospitalisations (n=53, 10% vs n=49, 9%) (**Figure 3A**), the number of hospitalisations (84 vs 82) (**Figure 3B**), and median duration of hospitalisations (4.0 vs 4.0 weeks) remained stable from before vs after the reference date

Ultomiris has been evaluated by HTA bodies and is now reimbursed in most major EU countries. Most recently, reimbursement was granted in Australia (PBAC recommendation).

Alexion estimates that there are only approximately 5-10 NMOSD patients that are eligible for Ultomiris in Finland. These patients are refractory with remaining symptoms despite receiving the currently available treatments in Finland (including rituxiumab). Ultomiris is thus very limited with the number of patients being very low.

The prices mentioned in the draft PALKO report are significantly higher than the actual prices in Finland. It is important to keep in mind that Ultomiris is included in hospital tenders (with new even lower tender prices from 1 January 2026). The actual net price paid by hospitals and the Finnish healthcare system is therefore significantly lower than the first-year care cost of €379,000 stated in the PALKO report. Furthermore, the net price offered in Finland and other countries is confidential.

Conclusion:

Alexion is requesting PALKO to conditionally recommend the use of Ultomiris in NMOSD. Since its approval in the EU, ravulizumab has demonstrated significant clinical efficacy and a positive safety profile in multiple studies. The CHAMPION NMO study (including 228 week OLE results) shows robust improvements in preventing relapses, underscoring its therapeutic value in this very serious condition. Ultomiris is included in hospital tenders with significant confidential discounts including new tender prices from 1 January 2026. In addition to these new confidential prices, Alexion is willing to further negotiate a risk sharing agreement to allow Ultomiris to be conditionally recommended for use in NMOSD.

Given the rarity and complexity of NMOSD Ultomiris provides an essential advancement in treatment options that align with both clinical effectiveness and economic feasibility. We encourage PALKO to integrate the comprehensive clinical and economic evidence presented into their final recommendation, facilitating improved patient care and healthcare outcomes for NMOSD patients in Finland.

Abbreviations

AQP4: Anti-aquaporin-4 antibody
CHMP: Committee for Medicinal Products for Human Use
EMA: European Medicines Agency
HTA: Health technology assessment
IST: Immuno-Suppressive Therapy
MAH: market authorization holder
NMA: network meta-analysis
MCID: Minimal Clinical Important Difference
MGC: Myasthenia Gravis Composite
NMOSD; neuromyelitis optica spectrum disorder
CI: confidence interval
C5: complement component 5
AE: Adverse Event
QALY: Quality-Adjusted Life Year

References

Ultomiris EMA assessment report NMOSD: Ultomiris, INN-ravulizumab

PBAC recommendation: RAVULIZUMAB | Medicine Status Website

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Papp V, Magyari M, Möller, S, Sellebjerg F, Battistini JL, MD, Svendsen KB, MD,. Søndergaard HB, Nilsson AC, Illes Z. Mortality of the Danish Nationwide AQP4 Antibody- Seropositive Neuromyelitis Optica Spectrum Disorder Patient Cohort. Neurology® 2024;102 (reference Papp et al 2024_1)
Papp V, Wandall-Holm M, Bacher Svendsen K, Frederiksen J, Sellebjerg F, Illes Z, Magyari M. Socioeconomic burden of AQP4-antibody seropositive NMOSD: a nationwide registry-based study. J Neurol Neurosurg Psychiatry 2024;**0**:1–4 (reference Papp et al 2024_2)

Pittock SJ, Barnett M, Bennett JL, Berthele A, de Sèze J, Levy M, Nakashima I, Oreja-Guevara C, Palace J, Paul F, Pozzilli C, Yountz M, Allen K, Mashhoon Y. Ravulizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. Ann Neurol. 2023 Jun;93(6):1053-1068

Appendixes:

Appenix_1:
Pittock et al 2025. Efficacy and safety of ravulizumab in adults with AQP4-Ab+ NMOSD: interim analysis from the ongoing phase 3 CHAMPION-NMOSD trial. April 5-9, San Diego, CA | AAN 2025

Appendix_2:
Lee et al 2023. Switching from rituximab to eculizumab in patients with AQP4+ NMOSD in the United States: Impact on hospitalisations and comorbidities. ECTRIMS-ACTRIMS Meeting (MSMilan2023), 11–13 October 2023, Milan, Italy