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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Uplizna (inebilizumab)
Treatment of neuromyelitis optica spectrum disorders
EU/3/17/1856
Sponsor: Viela Bio B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance	Inebilizumab
Other name	--
International Non-Proprietary Name	Inebilizumab
Tradename	Uplizna
Initial orphan condition	Treatment of neuromyelitis optica spectrum disorders
Sponsor's details:	Viela Bio B.V. Schiphol Boulevard 359 1118 BJ Schiphol Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	AstraZeneca AB
COMP opinion	16 February 2017
EC decision	20 March 2017
EC registration number	EU/3/17/1856
Post-designation procedural history	
Transfer of sponsorship	Transfer from AstraZeneca AB to Quality Regulatory Clinical Ireland Ltd – EC decision of 27 September 2018 2nd transfer from Quality Regulatory Clinical Ireland Ltd to Viela Bio B.V. – EC decision of 24 November 2020
Marketing authorisation	
Rapporteur / Co-rapporteur	K. Moll Harboe / F. Ventura
Applicant	Viela Bio B.V.
Application submission	23 November 2020
Procedure start	24 December 2020
Procedure number	EMA/H/C/005818
Invented name	Uplizna
Proposed therapeutic indication	Uplizna is indicated as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin 4 immunoglobulin G (AQP4-IgG) seropositive. Further information on Uplizna can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Uplizna
CHMP opinion	11 November 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	D. Matusevicius / A. Magrelli
Sponsor's report submission	19 February 2021
COMP discussion and adoption of list of questions	3-5 November 2021
Oral explanation	8 December 2021

COMP opinion (adoption via written procedure)	20 December 2021
Appeal to the COMP opinion procedural history	
COMP rapporteur	M. Hoffmann / T. Leest
Appeal submission	1 February 2022
Appeal oral explanation	16 February 2022
COMP final opinion (adoption via written procedure)	3 March 2022

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2017 was based on the following grounds:

"The sponsor AstraZeneca AB submitted on 25 October 2016 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing inebilizumab for treatment of Neuromyelitis Optica Spectrum Disorders (NMOSD) (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention treat the condition with the medicinal product containing inebilizumab was considered justified based on pre-clinical in vivo data showing a depletion in the majority of tissue B cells and autoantibody-producing plasma cells, a reduction in pathogenic autoantibody titers, and a suppression of autoimmune CNS inflammation;
- the condition is chronically debilitating and life-threatening due to neurological impairment such as paraplegia, sensory loss, bladder dysfunction, peripheral pain, and increased 5-year mortality;
- the condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing inebilizumab, as an orphan medicinal product for the orphan indication: treatment of neuromyelitis optica spectrum disorders."

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The proposed condition represents a group of severe autoimmune inflammatory demyelinating disorders that are typically characterized by optic neuritis and transverse myelitis. The 2015 consensus defines describes 5 core clinical characteristics: optic neuritis, acute myelitis, postrema syndrome, narcolepsy or acute diencephalic clinical syndrome with typical MRI findings, symptomatic cerebral syndrome with MRI findings. In general, at least 2 core characteristics (for the NMOSD without

autoantibodies) or 1 core characteristic and presence of autoantibodies are required (Wingerchuk, Neurology 2015; 85:1-13).

The approved therapeutic indication "Uplizna is indicated as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive" falls within the scope of the designated orphan condition "treatment of neuromyelitis optica spectrum disorders".

Intention to diagnose, prevent or treat

Based on the CHMP review of data on quality, safety and efficacy, the CHMP recommends the granting of the marketing authorisation for Uplizna on 11 November 2021.

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any changes in the seriousness of the disease since designation. Since the original orphan designation for inebilizumab, Soliris (eculizumab) was approved for the treatment of Neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease. Further, Enspryng (satralizumab) was authorised as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive. The impact of this approval on the morbidity and mortality of NMOSD has not yet been determined and reported in the literature.

The COMP has previously considered that the condition is chronically debilitating due to neurological impairment such as paraplegia, sensory loss, bladder dysfunction, and central visual loss accompanied by ocular pain and life-threatening with the 5-year mortality reported as high as 30%. The seriousness of NMOSD is acknowledged.

Number of people affected or at risk

The sponsor has conducted a literature search and identified publications for the EU countries including Denmark (Asgari et al, 2011; Papp et al, 2019), and Austria (Aboul-Enein et al, 2013) are presented in Table 1.

Table 1. Prevalence of NMOSD from Literature

	Study Years (Prevalence Period)	**Age, Range, Years**	**Prevalence per 100,000 Population**	
			NMOSD	**NMO/ NMOSD**
UK				
(Cossburn et al, 2012)	2010 (Point)	All ages	1.54 [a]	1.96
(Jacob et al, 2013)	2010 (Point)	16+	0.45	0.72
EU Countries				
(Aboul-Enein et al, 2013) (Austria)	2008-2011 (NR)	All ages	NA	0.71
(Asgari et al, 2011) (Denmark)	1998-2008 (11 years)	15+	4.4 [b]	NA
(Jonsson et al, 2019) (Sweden)	1987-2013	NR	1.04	NA

	Study Years (Prevalence Period)	Age, Range, Years	Prevalence per 100,000 Population	
			NMOSD	NMO/ NMOSD
(Papp et al, 2018) (Denmark)	2007-2014 (8 years)	Adults	1.09 [c]	N/A

NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; NA = not applicable; NR = not reported; UK = United Kingdom.

[a] Calculated as a proportion of a reported NMO/NMOSD prevalence.

[b] Monophasic NMO only.

[c] NMOSD defined per 2015 criteria including laboratory confirmed AQP4-IgG positivity

The available EU studies have provided prevalence rates (Table 1) between 0.45 and 4.4 per 100,000 for NMOSD (Aboul-Enein et al, 2013; Asgari et al, 2011; Papp et al, 2018; Cossburn et al, 2012; Jacob et al, 2013). A re-analysis of the data from the Denmark study has reported the prevalence of AQP4-antibody-positive NMOSD at 1.68/100,000 (Asgari et al, 2019).

Table 2 presents the reported data on NMOSD incidence. Incidence rate estimates range from 0.016 to 0.4 per 100,000 person-years and cover all ages, in both the adult and paediatric populations (Aboul-Enein et al, 2013; Absoud et al, 2013; Asgari et al, 2011; Papp et al, 2018; Jacob et al, 2013; Ketelslegers et al, 2012).

Table 2. Incidence of NMOSD from Literature

Author, Year	Study Years	Age, Range, Years	Incidence per 100,000 person-years	
			NMOSD	NMO/ NMOSD
UK				
(Jacob et al, 2013)	2010 (Point)	16+	NA	0.08
UK/Ireland				
(Absoud et al, 2013)	2009-2010	1-15	0.016 [a]	NA
Other Countries				
(Aboul-Enein et al, 2013) (Austria)	2008-2011	All ages	NA	0.054
(Asgari et al, 2011) (Denmark)	1998-2008	15+	0.4	NA
(Papp et al, 2018) (Denmark)	2007-2014	Adults	0.070	NA
(Ketelslegers et al, 2012) (The Netherlands)	2007-2010	0-18	0.02 [a]	NA

NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; NA = not applicable; UK = United Kingdom.

Calculated as a proportion of a reported NMO/NMOSD prevalence.

In summary, the collective evidence from EU studies continues to suggest that the population at risk for NMOSD remains 0.44 per 10,000 people, and consequently this meets the requirements for orphan designation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Currently there are two products which have been authorised for this condition:

- Soliris is indicated (among others) in adults for the treatment of "*Neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease*".
- Enspryng is indicated: "*as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients from 12 years who are antiaquaporin 4 (AQP4) seropositive*".

There are currently no pan-European guidelines for the treatment of the condition. A review of the treatment of the condition was published in 2016: Kessler R et al, Curr Treat Options Neurol. 2016 January; 18(1): 2.

The proposed therapeutic indication for Uplizna is *"monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive."*

The therapeutic indication for Soliris is narrower as it only covers patients with a "relapsing course of the disease", while Uplizna can be used in non-relapsing patients. Therefore, Soliris would not be considered a satisfactory method to treat the exact same patient population as Uplizna.

On the other hand, Enspryng has a full overlap with the Uplizna target patient population, wider in fact as it covers adolescent patients as well. Therefore, Enspryng is considered a satisfactory method for the target patient population of Uplizna and has to be considered for the evaluation of a possible significant benefit of Uplizna.

Significant benefit

The sponsor received Scientific Advice (SA) in 2013 (EMEA/H/SA/2664/1/2013/III) and in 2015 (EMEA/H/SA/2664/1/FU/1/2015/II). However, no specific questions were raised on the maintenance of orphan designation.

The sponsor argued the existence of a significant benefit over Soliris in the maintenance report; but did not do the same versus Enspryng. It is acknowledged that Enspryng was only approved relatively recently (authorisation granted in June 2021); however, the recent authorisation of an orphan product does not mean that the recently authorised product should not be taken into account when evaluating whether a candidate orphan product (for the same target population) brings any significant benefit vis-à-vis the already authorised treatments in the Union. Therefore, a justification of the significant benefit of Uplizna over Enspryng would be needed and a question was adopted by the COMP for this purpose.

4. COMP list of issues

- Significant benefit:

The sponsor is requested to further elaborate on the significant benefit of their product within the context of the target population defined by their therapeutic indication and the population of an authorised products with a similar therapeutic indication namely Enspryng (satralizumab). Clinical data derived from studies conducted with the sponsor's product should be used to support the basis of a clinically relevant advantage and/or major contribution to patient care compared with the currently authorised product.

Comments on sponsor's response to the COMP list of issues

The sponsor provided a written response and participated in an oral explanation.

In their written response the sponsor further elaborated on the indirect comparison to satralizumab which has been recently authorised in Europe and it was highlighted that there were several difficulties in making an indirect comparison due to problems of accessibility to data for satralizumab.

In their oral explanation the sponsor made several claims in support of the existence of a clinically relevant advantage, as well as a major contribution to patient care.

The sponsor sought to substantiate the existence of a clinically relevant advantage by indirectly comparing their product against satralizumab on the basis of published data and data on file for inebilizumab. The sponsor had neither conducted a matching-adjusted indirect comparison (MAIC) nor provided a comprehensive overview about the demographics and disease characteristics of the trial populations. The limitations of a descriptive naïve comparison and the importance of providing relevant information about the characteristics of the trial populations had been highlighted to the sponsor during the preparatory period before the oral explanation. In the absence of comprehensive information on the compared patient populations and in the absence of any population adjustment, the indirect comparison of inebilizumab and satralizumab may not be considered sufficiently robust for the purpose of establishing the claim of better efficacy.

Regarding the sponsor's claim of better efficacy of satralizumab on disability as measured by the Expanded Disability Status Scale (EDSS) over a 4-year period, it was noted by COMP that the sponsor had used a dichotomised endpoint (worsening in EDSS) whereas the SAkuraStar trial for satralizumab had used a continuous endpoint (change in EDSS score from baseline). During the oral explanation, the sponsor explained that they had also performed an analysis of the continuous change in EDSS score from baseline resulting in a better point estimate than what was seen in the SAkuraStar trial. However, only limited details of what amounted to a descriptive comparison were shared by the sponsor with regards to this analysis. Furthermore, the COMP raised concerns that the results from the satralizumab trial were presented in seropositive and seronegative patients whereas the results for the sponsor's product were presented in seropositive patients only. During the oral explanation the sponsor argued that serostatus would not impact the disability outcome; however, no rationale for this was provided. In addition to general concerns about the robustness of the presented indirect comparison, the COMP specifically did not consider that the sponsor provided convincing evidence to demonstrate better disability outcomes for inebilizumab as compared to satralizumab.

During the oral explanation, the sponsor presented Kaplan-Meier figures on the time until attack / relapse for patients treated with inebilizumab or satralizumab in order to argue that long-term treatment consistently showed that a greater proportion remains attack-free under inebilizumab as compared to satralizumab. The sponsor highlighted point estimates of an estimated attack-free rate of 83% under inebilizumab at week 208 versus an estimated relapse-free rate of 73% at week 192 under satralizumab monotherapy. The estimates were based on small sample sizes and no confidence intervals were provided. The Kaplan-Meier figures for inebilizumab and satralizumab were taken from two different publications (Rensel et al. (2021) and Kleiter et al. (2021)) and the sponsor provided no information to what extent relevant aspects of the studies were comparable (e.g. included patient

populations, follow-up duration, outcome assessment). The level of evidence presented on this aspect was therefore considered insufficient to support the sponsor's claim for better long-term attack-free rates under inebilizumab as compared to satralizumab.

In view of the above, the COMP considers that the sponsor did not provide conclusive evidence of the existence a clinically relevant advantage of inebilizumab over satralizumab.

Furthermore, the sponsor argued that their product could offer a major contribution to patient care based on the frequency and route of administration. The sponsor claimed that a twice-yearly intravenous administration would be preferred by patients over the monthly subcutaneous self- or hospital-administered injection required for satralizumab. To support this claim, the sponsor presented results from one patient preference survey in 329 Japanese patients. This was based on data on file and few details on the study (e.g. how patients were recruited or what were the primary objectives) were provided. It was noted by the COMP that the response categories were not designed to specifically compare only monthly subcutaneous administration with satralizumab versus intravenous administration every six months for inebilizumab. For example, two categories for monthly subcutaneous administration were included (at home or at the hospital). If the number of responders for the two subcutaneous administrations were added together this represented a similar or even larger proportion than the proportion who preferred intravenous administration. This was the only data/study submitted and discussed in support of the argument of major contribution to patient care. A more comprehensive overview of NMOSD patient preferences as well as a discussion on how the results from the Japanese study would translate to the EU was missing. Claims regarding a reduction in the use of healthcare services such as NMOSD-related hospitalisations were made; however, no information was provided on NMOSD-related hospitalisations under satralizumab treatment to ascertain the existence of these supposed beneficial outcomes for the patients which would further support the claim of major contribution to patient care.

Further to the above, the COMP considered that it could not recommend maintaining the orphan designation.

5. COMP position adopted on 20 December 2021

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of neuromyelitis optica spectrum disorders (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening due to neurological impairment such as paraplegia, sensory loss, bladder dysfunction, peripheral pain, and increased 5-year mortality;
- although a satisfactory method for the treatment of the condition has been authorised in the European Union, the assumption that Uplizna may be of potential significant benefit to those affected by the orphan condition does not hold, since the sponsor could not establish the existence of a clinically relevant advantage over the authorised satisfactory method of treatment. In addition, although the sponsor claimed that their product could offer a major contribution to patient care through a different dosing schedule and route of administration, insufficient and inconclusive data has been submitted to support this claim versus the currently authorised satisfactory method of treatment.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are not satisfied.

The Committee for Orphan Medicinal Products has recommended that Uplizna, inebilizumab for treatment of neuromyelitis optica spectrum disorders (EU/3/17/1856) is removed from the Community Register of Orphan Medicinal Products.

6. Appeal to the negative opinion adopted on 20 December 2021

Grounds for appeal

The sponsor presented detailed grounds for appeal (EMA/OD/0000079956) on 1 February 2022.

Please refer to the sponsor's appeal documents in the case *Input from Industry* folder.

The detailed grounds for appeal were further addressed by the sponsor at an oral explanation before the COMP on 16 February 2022.

Comments on the grounds of appeal

The sponsor challenged the COMP's position on significant benefit linked to the sponsor's claim of a clinically relevant advantage due to improved efficacy; and linked to the sponsor claim of major contribution to patient care.

In their grounds for appeal the sponsor aimed to address the main issues which led to the negative opinion. As a general note, the sponsor has provided mainly new data/analyses in support of establishing significant benefit based on improved efficacy of Uplizna (inebilizumab) vs Enspryng (satralizumab). The sponsor provided indirect comparative efficacy analyses on the time to first attack (primary efficacy endpoint), attack-free rates and impact on disability accumulation. The sponsor states to have taken into consideration relevant and possible adjustments to match trial populations. The sponsor noted that it had examined all publicly available data sources of Enspryng (satrilizumab) in order to prepare these comparisons.

The sponsor provided details of patients' baseline and disease characteristics and emphasized that the study populations, enrolment criteria, and trial designs are overall comparable between the pivotal randomized placebo-controlled monotherapy trials N-MOmentum (inebilizumab) and SAkuraStar (satralizumab). Both studies used time to first attack as a primary endpoint and enrolled patients with a similar level of baseline disease severity, including the mean or median age of first attack, annualised attack rate, and mean or median EDSS. One marked difference between the two studies, however, was the different duration of their respective randomised-controlled periods (RCP). To capture the number of events needed to show statistical significance, considerably more patients were randomised in N-MOmentum (N=213, AQP4+; 93% of total trial population) to permit a shorter placebo exposure period with an RCP of 6 months, while fewer patients were randomised in SAkuraStar (N=64, AQP4+; 67% of total trial population) with a longer placebo exposure period and an RCP of 18 months.

Matching-adjusted indirect comparison (MAIC) for the primary efficacy endpoint of time to first attack

For the purpose of the matching-adjusted indirect comparison (MAIC), for the primary efficacy endpoint of time to first attack, the sponsor describes to have used a Cox regression analysis which identified 3 variables (sex, race, and region) as statistically significantly different ($p < 0.05$) between the two AQP4+ study populations. These factors were the basis for the MAIC adjustments. It is noted that the comparison of rates between two populations, as done by the sponsor, corresponds to the results from a Chi-squared test. The sponsor concludes that the efficacy benefit observed with inebilizumab versus satralizumab is substantial, after conducting the MAIC, with an estimated hazard ratio (HR) of 0.67. While the COMP acknowledged the positive trend of this point estimate, they emphasised that the 95% confidence interval (CI) of (0.237, 3.170) covers 1, i.e. "no difference", with

an upper limit of above 3. This implies a great level of uncertainty for this estimate, meaning that it cannot be excluded that inebilizumab and satralizumab are not different with regard to preventing attacks, or that inebilizumab may even be inferior to satralizumab in this regard.

During the COMP plenary, the sponsor was invited to elaborate on the claimed improved efficacy of ineblizumab over satralizumab in terms of an absolute risk reduction of having an attack. It was pointed out by the sponsor that the difference between the adjusted HRs from the Cox Proportional Hazards Model was 0.1 (0.086). However, it is noted by COMP that results from a Cox Proportional Hazards Model don't allow drawing conclusions about an absolute risk reduction; in particular, a difference between two HRs cannot be interpreted as absolute risk reduction.

A further (separate) limitation in the interpretation of this estimate is the different durations of the randomized controlled phases (RCP) of the N-MOmentum and SAkuraStar trials, i.e. 6 months vs. 18 months. Considering that NMO does not have linear disease activity but cluster activity, the significantly different durations of the randomized- placebo controlled phases may constitute a bias in the analysis of attack-rate. The COMP would have liked to see hazard ratios for different periods on the SAkuraStar trial, e.g. in particular after 6 months, which were however not available. The sponsor emphasized that the estimates are HRs from a Cox Proportional Hazards Model which assumes proportional hazards over time and that there are no grounds to believe that the treatment effect will change over time for Ineblizumab or Satralizumab.

Table 3. Primary Endpoint: Time to First Attack Estimates – RCP, AQP4+ Population

	Inebilizumab vs Placebo	**Satralizumab vs Placebo**	**Inebilizumab vs Satralizumab**
Hazard ratio (95% CI) N / N	**0.227** (0.121, 0.423) 161 / 52	**0.26**[1] (0.11, 0.63) 41 / 23	**0.870**[2] (0.296, 2.559)
MAIC Hazard ratio (Sex, Geography, Race) (95% CI or SE) N / N	**0.174** (0.067, 0.451) 39 / 27	**0.26** (0.449) 41 / 23	**0.666** (0.237, 3.170)
1. Enspryng EPAR; 2. Network meta-analysis			

Additional sensitivity analyses were provided by the sponsor which adjusted for additional sets of parameters in the comparison of the respective AQP4+ populations of the N-MOmentum and SAkuraStar trials, i.e. region + sex: HR of 0.71 (95% CI 0.235-3.203); race + sex: HR of 0.77 (95% CI 0.273-2.754); prior attacks + region + sex: HR of 0.674 (95% CI 0.227-3.309); and prior attacks + race + sex: HR of 0.796 (95% CI 0.270-2.780). These additional sensitivity analyses, with regard to a comparative reduction in attack-rate, are consistent with the point estimate from the primary MAIC. They suggest a positive trend for inebilizumab to reduce the attack-rate but are still associated with substantial uncertainty. Again, the upper value of the 95% CI contains values far exceeding 1, indicating that the treatment effect for inebilizumab could also be similar or inferior to satralizumab.

In addition, the sponsor provided Kaplan-Meier analyses of attack-free rates. Considering that NMOSD is a life-long condition, the COMP was especially interested in the analysis for the 192-week timepoint. The analysis compared any patient that received inebilizumab to any patient that received satralizumab over time within the NMOmentum and SAkuraStar- trials. At Week 192, inebilizumab had an estimated 78% risk reduction in relapse while satralizumab had an estimated 73% risk reduction of relapse. However, while both trials were RCTs, the calibration against control is lost for the comparison

at week 192 due to the fact that both studies permitted the placebo patients to cross-over to active drug during the RCP after a protocol defined attack (treated + control patients who crossed over). In addition, no CIs were available for satralizumab for this time point.

Apart from methodological uncertainties and concerns over the proposed point estimates being true values, the COMP also pointed out that the clinical relevance of a putative 5% lower risk for relapse has not been contextualized sufficiently by the sponsor and their experts, for the respective target populations. The question on a clinically relevant advantage between different products becomes considerably more complex when both products have reasonably good efficacy and a possible additional gain in efficacy with one product would, at best, be modest.

Considering all the above, a positive conclusion on improved efficacy and a clinically relevant advantage of Uplizna over Enspryng could not be drawn.

Disability impact

The sponsor now presents data from a continuous analysis (instead of the EMA preferred categorical analysis for which no data is available for satralizumab) of Expanded Disability Status Scale (EDSS) and modified Rankin Scale (mRS) to permit comparison of inebilizumab with satralizumab in terms of disability status / dependence in the daily activities. Because results are not available for satralizumab in the AQP4+ population, the comparison was conducted on the 1) unadjusted ITT populations and 2) adjusted ITT population (i.e. NMOmentum ITT population being MAIC adjusted to the AQP4 Status of SAkuraStar to reflect similar ITT populations). As a reminder, in N-MOmentum AQP4+ patients accounted for 93% of the ITT population vs only 67% of the SAkuraStar ITT population.

The continuous analysis reveals inebilizumab was associated with greater numerical benefit on both EDSS and mRS measures (analysis with unadjusted ITT Population*). After adjusting for AQP4+ status, satralizumab was associated with a numerical benefit on EDSS but the numerical worsening on mRS remained in comparison with an improvement in the inebilizumab treated population:

Table 4. Change from Baseline in EDSS and mRS at Week 28 (Continuous Analysis) – RCP, ITT Population (Inebilizumab Adjusted AQP4 Status to SAkuraStar) **–** *adjusted from the sponsors appeal grounds*

	N-MOmentum (Inebilizumab) Adjusted ITT Population[3]		**SAkuraStar (Satralizumab) ITT Population[4,5]**	
Change from Baseline[1,2]	**EDSS**	**mRS**	**EDSS**	**mRS**
LS Mean (95% CI)				
Treatment	-0.11 (-0.27 - 0.06)	-0.04 (-0.20, 0.12)	-0.34 (-0.62, -0.05)	-0.03 (-0.29, 0.23)
Placebo	0.02 (-0.25, 0.30)	0.14 (-0.14, 0.41)	-0.17 (-0.52, 0.19)	-0.19 (-0.52, 0.13)
LS mean difference 95% CI	-0.13 (-0.22)* (-0.44, 0.18)	-0.18 (-0.16)* (-0.49, 0.13)	-0.17 (-0.50, 0.16)	0.17 (-0.14, 0.47)
P-value	0.407	0.252	0.31	0.29

1. Week 28 for N-MOmentum; Week 24 for SAkuraStar
2. Post hoc analysis for N-MOmentum (inebilizumab)
3. Adjusted to satralizumab population of AQP4 Status MAIC Adjusted for Inebilizumab
4. Satralizumab data sourced from Canadian clinical review report
5. Traboulsee et al, 2020.

* change from Baseline in EDSS and mRS (Continuous Analysis) – RCP, unadjusted ITT Population

Overall, the COMP considers that these comparative analyses show a somewhat mixed picture (depending on adjustment factors and EDSS vs mRS scales). Furthermore, the observation time of 28

weeks was considered very limited to allow meaningful conclusions on relative disability impact. Furthermore, and linked to the prior point, also the relative changes in the scores were very small and their relative translations into clinical relevant effects were not clear to the COMP. Study populations of the NMOmentum and SAkuraStar trials were overall at rather early disease stages and disability in NMO is directly linked to the attacks, as compared to other diseases such as multiple sclerosis where disability progresses also independently of attacks.

Patient care

No new relevant data has been presented by the sponsor on this aspect.

The patient representative attending the oral hearing pointed out that in general hospital administration of the NMOSD medicine would rather be preferable than home self-administration, mainly due to the fact that this may allow for a more frequent access to their respective health care professional. The patient representative pointed out that she only gets appointments with her neurologist about once a year to review her health status which she considered being too infrequent.

Furthermore, the patient representative noted that there could be a potential advantage in taking a drug which does not require such frequent safety monitoring, as is the case for Enspryng, at least within the first year.

The COMP acknowledged these points but emphasized the lack of relevant and conclusive data in support of a claim of major contribution to patient care. The claim of a supposed self-evident significant benefit of a product with a less frequent administration by a health care professional and less safety monitoring as compared to authorized products was not considered acceptable by the COMP, as this assumption was not supported by any data showing meaningful benefits for patients.

In general, the observations of the sponsor in connection to the claim of major contribution to patient care (e.g., in connection to dosing and adherence; reduced hospitalisations; avoidance of CYP-related drug-drug interactions) were not supported by any data demonstrating clinical benefits for patients.

Conclusion

In conclusion, the additional analyses do not alter the COMP's position in that the assumption that Uplizna may be of significant benefit over Enspryng does not hold.

While the COMP acknowledged the positive trend in the attack-rate from the MAIC, the level of uncertainty over this estimate being a true value of the estimand of the increased efficacy of inebilizumab over satralizumab, was considered too high.

With regard to the disability impact, the COMP considers that the comparative analyses provided by the sponsor do not allow a clear conclusion.

With regards to the claim of improved patient care, the COMP acknowledged the points made by the patient representative but emphasized the lack of relevant and conclusive data in support of a claim of major contribution to patient care.

7. COMP final position on review of criteria for orphan designation adopted on 3 March 2022

Based on the assessment of the detailed grounds for appeal and the explanations presented by the sponsor during the oral explanation, the COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of neuromyelitis optica spectrum disorders (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening due to neurological impairment such as paraplegia, sensory loss, bladder dysfunction, peripheral pain, and increased 5-year mortality;
- in the context of the first opinion, the COMP accepted that no comparison was required between Uplizna and Soliris for the purpose of the maintenance of the orphan designation of Uplizna, as Soliris is not authorised for all patients for which Uplizna is intended. However, a comparison was required between Uplizna and Enspryng, as the two products are intended for a similar adult patient population. In the context of this comparison, the sponsor sought to establish the existence of a significant benefit of Uplizna over Enspryng on the basis of two (alternative) claims; first, on the basis of the claim of a clinically relevant advantage of Uplizna over Enspryng; second, on the basis of the claim that Uplizna amounts to a major contribution to patient care. These claims were not accepted due to the lack of conclusive evidence in support of those claims;
- in the context of the appeal, the sponsor presented additional evidence and/or arguments to the COMP to further substantiate the claims of clinically relevant advantage and of major contribution to patient care;
- the additional indirect comparisons of two different placebo-controlled trials submitted by the sponsor in the context of the appeal, in support of the claim of a clinically relevant advantage of Uplizna over Enspryng, were associated with substantial methodological uncertainties. In particular, the point estimate of the hazard ratio comparing Uplizna versus Enspryng for time to first attack favored Uplizna. However, the corresponding 95% confidence interval indicated large uncertainty, and this means that it could not be excluded that the efficacy of Uplizna is similar or inferior to that of Enspryng. Furthermore, the sponsor was not able to reliably establish clinical relevance of the numerical difference, which was considered small in the setting of an indirect comparison. On account of the lack of conclusive evidence in support of the claim of a clinically relevant advantage, the COMP concluded that this claim could not be established;
- the additional arguments submitted by the sponsor in the context of the appeal, in support of the claim of major contribution to patient care, did not contain any data demonstrating the existence of clinical benefits for patients taking Uplizna (as opposed to Enspryng). On account of the lack of further data in support of the claim of a major contribution to patient care, the COMP concluded that this claim could not be established;
- therefore, the COMP considered that the submitted evidence and/or arguments in the context of the appeal did not suffice to establish that Uplizna provides a significant benefit over Enspryng.

The COMP, having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;

- the criteria for designation as set out in Article 3(1)(b) are not satisfied.

The COMP recommends that Uplizna, inebilizumab, for treatment of neuromyelitis optica spectrum disorders (EU/3/17/1856) is removed from the Community Register of Orphan Medicinal Products.