Amsterdam, 22 May 2025
EMADOC-1700519818-1961531
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Enspryng

Satralizumab

Procedure no: EMA/PAM/0000257150

Note

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

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1. Introduction

On 28 February 2025, the MAH submitted a completed study for Enspryng including a few paediatric subjects in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The marketing authorisation holder (MAH) stated that WN42636 was part of a clinical development program for the treatment of generalized myasthenia gravis (gMG) but the program was halted by the MAH (see below).

2.2. Information on the pharmaceutical formulation used in the study

Satralizumab was supplied by the Sponsor as a prefilled syringe (PFS) assembled with a plunger rod, needle safety device (NSD), and extended finger flange (EFF) filled with 1.0 mL of solution for subcutaneous (SC) injection corresponding to 120 mg. For the 180-mg dose of satralizumab, participants (> 100 kg of weight) were administered the PFS filled with 1.0 mL of solution for SC injection corresponding to 120 mg and a 0.5 ml syringe (60 mg) prepared on site. Satralizumab placebo PFS is identical in composition to satralizumab PFS but does not contain the satralizumab active ingredient. It is identical in appearance and packaging to satralizumab.

A PFS (assembled with an NSD/EFF) filled with 0.5 mL of solution, corresponding to 60 mg satralizumab was used in the open-label extension (OLE) period of the study (after the second OLE dose).

No specific paediatric formulation was used.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final report for:

- Study WN42636 (LUMINESCE): A PHASE III, RANDOMIZED, DOUBLE-BLIND (DB), PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SATRALIZUMAB IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS.

In addition, the study assessed the long-term safety and efficacy of satralizumab during the OLE period.

The study included a 28-day screening period, a 24-week DB treatment period, and approximately 2-year OLE period after the last participant initiated open-label treatment.

Description

The study WN42636 was planned to be the pivotal study for gMG as a new indication for satralizumab. However, upon review of the primary analysis results (DB period), the sponsor decided to halt development of satralizumab in gMG and discontinued further dosing with the study drug (while the OLE period was ongoing).

Results from the study is being submitted to the European Medicines Agency to fulfil the requirements of Article 46 of Regulation (EC) No 1901/2006.

Methods

Study participants

A total of 186 participants (185 adults and 1 adolescent participant [Patient A; see Table 1]) were enrolled in the study. Additional 2 adolescent participants (Patient B and Patient C; see Table 1) were randomized after the last adult participant was enrolled in the study and were therefore not part of the intent to treat (ITT) and modified ITT (mITT) population for the primary analysis. The safety evaluable population comprised all participants randomly assigned to study treatment who received at least one dose of study treatment, including the 2 adolescents enrolled after the last adult participant was randomized.

Table 1. Adolescent patients

	ID	Age (years)	Date of Enrollment[a]	Date of first dose (baseline)	Date of Study Completion
Patient A	[redacted]	[redacted]	6 March 2023	22 March 2023	13 August 2024
Patient B	[redacted]	[redacted]	2 October 2023	30 October 2023	2 September 2024
Patient C	[redacted]	[redacted]	23 October 2023	24 November 2023	2 September 2024

[a] Date when the informed consent form (ICF) was signed.

Key Inclusion Criteria

Participants had to meet the following key criteria for study entry:

– Age ≥12 years at time of signing informed consent form;

– Confirmed diagnosis of gMG meeting the following criteria:

- Documented history of myasthenic weakness;
- MG severity of Myasthenia Gravis Foundation of America (MGFA) Class II, III, or IV at screening;
- The confirmation of the diagnosis had to be documented and supported by positive serologic test for one of the three antibody types: anti-AChR (antibodies against acetylcholine receptor), anti-MuSK (antibodies against muscle-specific kinase), or anti-LRP4 (antibodies against low-density lipoprotein receptor-related protein 4) at screening.

Treatments

Participants received SC satralizumab or the matching volume of placebo at Weeks 0, 2 and 4 (loading doses), and Q4W thereafter, throughout the DB period in addition to background treatments at a stable dose.

In the OLE period, all participants received a SC injection of satralizumab at Weeks 0, 2, and 4, and Q4W thereafter.

Objective

The primary objective was to evaluate the efficacy of satralizumab versus placebo on function in daily life in the AChR+ population.

Outcomes/endpoints

PRO data were collected through use of the following instruments: MG Activities of Daily Living (MG-ADL); Myasthenia Gravis Quality of Life 15 Scale revised (MG-QOL 15r); Quality of Life in Neurological Disorders (Neuro−QoL) Fatigue Subscale; EQ-5D-5L (EuroQoL 5-dimension questionnaire).

ClinRO data was collected through use of the following instruments: quantitative myasthenia gravis (QMG); myasthenia gravis composite (MGC).

Sample size

The sample size of approximately 185 participants (160 AChR + participants and up to 25 AChR - (MuSK + or LRP4 +) were randomized in a 1:1 ratio into two treatment groups. This was predicted to provide approximately 85% power to detect a difference in the mean change from baseline in MG-ADL at Week 24 in AChR + participants between satralizumab and placebo.

The mean change from baseline to Week 24 in placebo group was assumed to be 2.3 points and in the satralizumab group 4.3 points. The standard deviation of the change from baseline was assumed to be 3.97. Approximately 10% of participants were assumed to withdraw during conduct of the study.

Randomisation and blinding (masking)

During the 24-week double blind period, eligible participants were randomized to one of the two treatment groups in a 1:1 allocation and received either 120 mg or 180 mg (in a body weight-tiered dosing regimen) of satralizumab or matching placebo SC treatment at Weeks 0, 2 and 4, and Q4W thereafter until the end of the DB period in addition to background treatments at a stable dose.

Statistical Methods

Serum concentrations of satralizumab (and pharmacodynamic variables (IL-6, sIL-6R)) were determined by validated quantitative sandwich immunoassay.

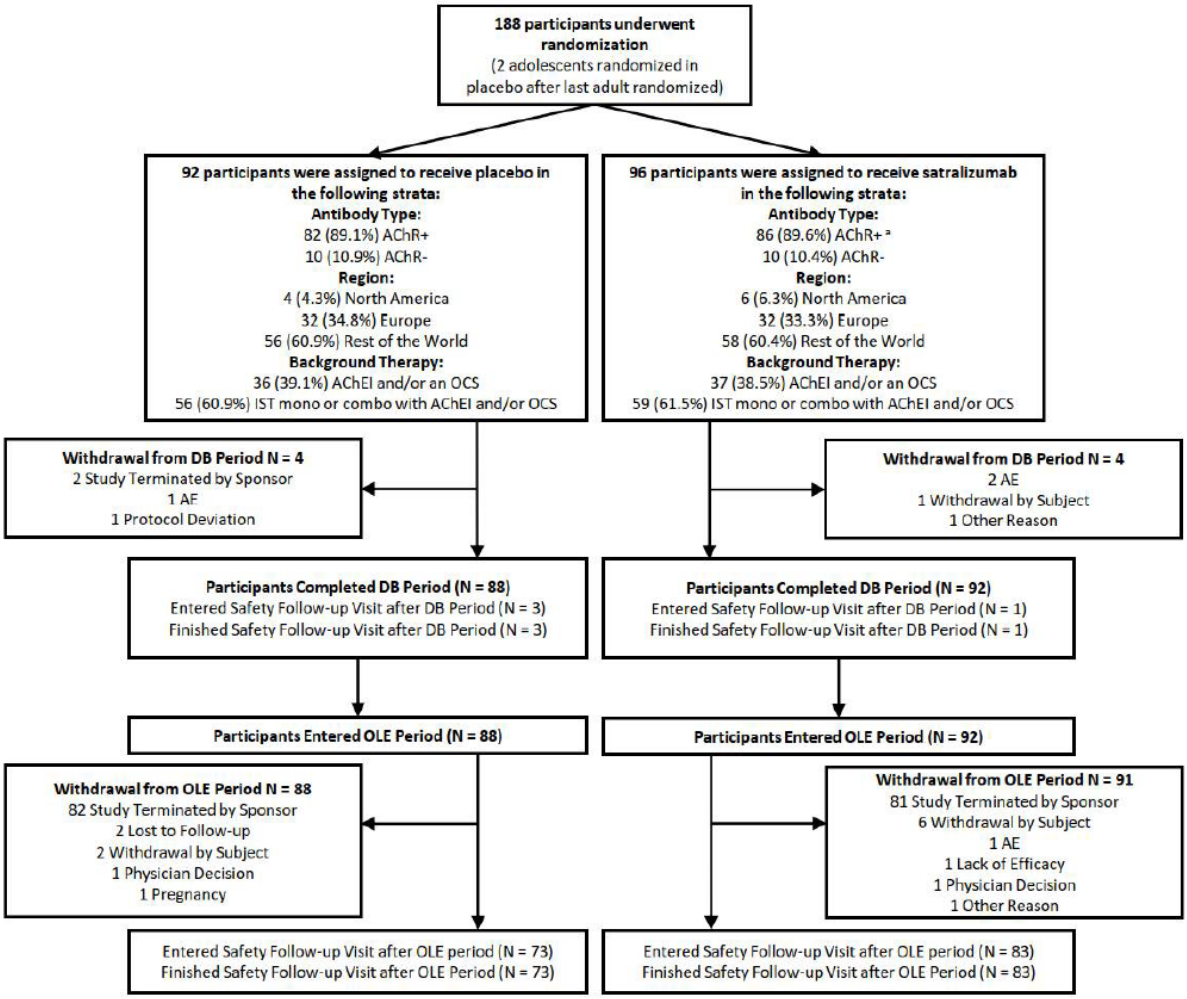
Pharmacokinetic (PK) analysis was performed on all participants in the safety analysis set with at least one valid post-dose concentration result with a dosing record and sampling time. 1 paediatric patient (16-year old, 58 kg) was included in the PK-dataset. Serum samples were collected pre-dose at weeks 0, 2, 4 and every 4 weeks thereafter during the DB and OLE period. Satralizumab concentrations were summarized using descriptive statistics (including geometric mean and coefficient of variance (CV)%, arithmetic mean and SD, median, observed maximums and minimums, and sample size). Non-linear mixed effects modelling was used to estimate population and individual PK parameters and to investigate the influence of covariates such as presence of antidrug antibody (ADA), age, race, gender, and body weight.

Results

Participant flow

The patient disposition is shown in Figure 1.

Figure 1. Patient disposition



a Among the 86 AChR participants assigned to receive satralizumab, in Germany, 2 participants were enrolled based on local historical AChR test results.
AChR = acetylcholine receptor; AChR += AChR-antibody seropositive (participants/population); AE = adverse event; DB = double-blind; OCS = oral corticosteroid; OLE = open-label extension

Recruitment

Due to recruitment difficulties for adolescents related to placebo use in the DB period, the sponsor decided to enroll adolescents directly into the OLE period. The ITT and mITT exclude adolescents joining the study after the last adult participant was randomized. No subgroup analyses were performed in adolescent participants.

Adolescent Population: 2 treated with placebo, 1 with satralizumab

Number analysed

The ITT population included 96 participants in the satralizumab group and 90 participants in the placebo group. The OP (as randomized) included 96 participants in the satralizumab group and 92 participants in the placebo group.

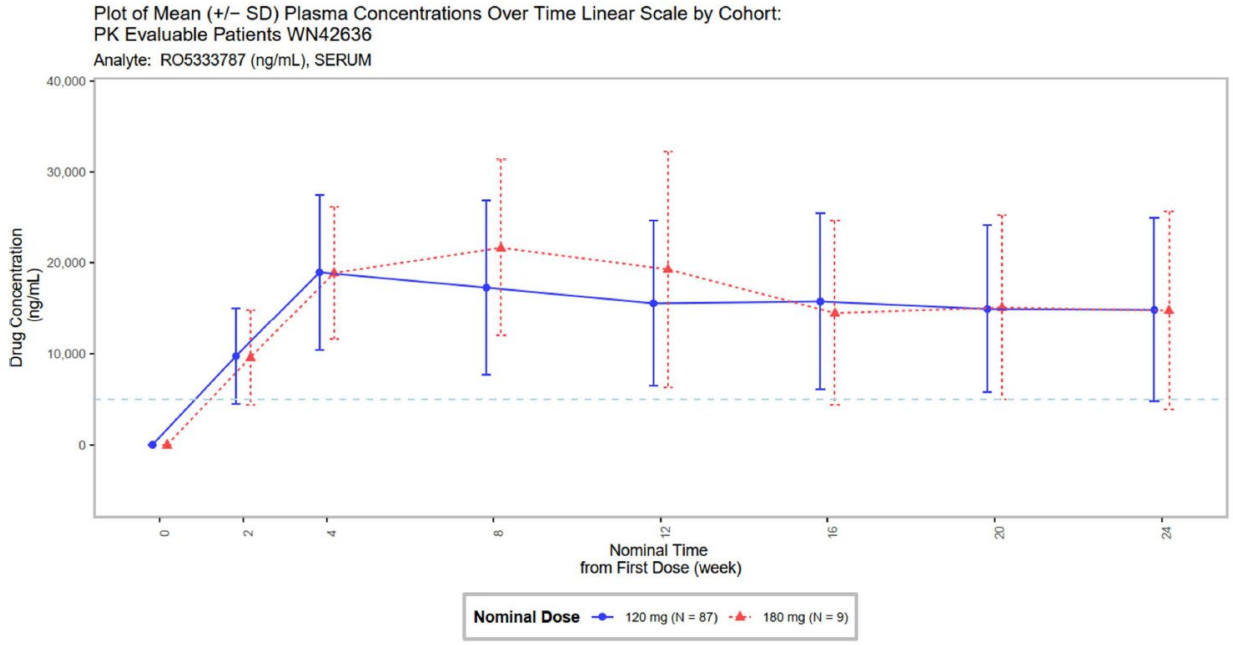
The safety-evaluable population comprised 96 participants in the satralizumab group and 92 participants in the placebo group, all participants who received at least one dose of study treatment. 1 of the 96 participants in the satralizumab group and 2 of the 92 participants in the placebo group were adolescents.

The mITT comprised a total of 96 participants in the satralizumab group and 89 participants in the placebo group who were either AChR+ or AChR - (86 AChR+ and 10 AChR- participants in the satralizumab group; 80 AChR+ and 9 AChR- participants in the placebo group).

Pharmacokinetic results

Observed serum satralizumab concentrations over time during the DB period in the PK evaluable population is shown in Figure 2. Trough concentrations were at approximate steady state during the entire DB period Table 2. The reported observed pre-dose concentrations for the [redacted] adolescent patient ([redacted]) were 10900 – 16700 ng/mL between week 4 – 24 (n=6).

Figure 2. Plot of mean serum satralizumab concentrations over time by dose group during the DB period, PK evaluable population



DB = double blind; PK = pharmacokinetics; SD = standard deviation

Table 2: Summary satralizumab concentration table by dose – DB period

Summary Concentration Table by Dose (from first active dose) - All Satra Treated Period,
Study: WN42636

Treatment Group Visit	n	Number of <LTR/BLQ>s	Mean	SD	CV (%) Mean	Geometric Mean	CV % Geometric Mean	Median	Minimum	Maximum
120 mg (OST)										
Week 0 (OST)	158	158	0	0	NE	NE	NE	0	0	0
Week 2 (OST)	157	0	9890	4870	49.3	8430	74.0	9200	211	23200
Week 4 (OST)	156	1	18800	8120	43.2	NE	NE	18200	0	37400
Week 8 (OST)	156	1	17900	8990	50.3	NE	NE	16500	0	48200
Week 12 (OST)	146	0	16700	9400	56.2	13700	81.9	15600	467	48000
Week 16 (OST)	140	1	16900	9600	56.8	NE	NE	15400	0	48200
Week 20 (OST)	137	1	16200	10000	61.9	NE	NE	14700	0	50700
Week 24 (OST)	132	0	16900	11100	65.3	13000	103.0	14400	362	50400
Week 26 (OST)	81	0	23200	12000	51.8	19700	72.5	21200	920	57600
Week 28 (OST)	81	1	15200	10200	67.0	NE	NE	13800	0	39300
Week 32 (OST)	80	1	15600	10900	69.4	NE	NE	13700	0	53400
Week 36 (OST)	103	0	17200	11100	64.6	13000	104.8	15500	924	51900
Week 40 (OST)	62	0	15900	10900	68.6	11600	121.9	13400	357	46200
Week 44 (OST)	57	0	17800	11500	64.8	14100	88.3	15400	1520	52000
Week 48 (OST)	82	0	19000	12200	64.2	14500	105.1	16800	434	56700
Week 60 (OST)	59	0	20800	12300	59.3	16700	84.8	19000	1640	53400
Week 72 (OST)	43	0	20800	11700	56.4	16500	92.6	19700	1880	43600
Week 84 (OST)	28	0	20600	14000	67.8	15400	105.7	16800	2100	53200
Week 96 (OST)	18	0	20500	14200	69.2	16000	88.4	16600	4230	56500
Week 108 (OST)	7	0	14500	10100	69.9	11400	94.0	15900	3560	32600
180 mg (OST)										
Week 0 (OST)	24	24	0	0	NE	NE	NE	0	0	0
Week 2 (OST)	24	0	9060	4350	48.0	7440	100.5	9400	270	18500
Week 4 (OST)	25	0	18900	6870	36.3	17500	44.7	19900	5260	35900
Week 8 (OST)	24	0	18600	7760	41.8	17000	47.7	18400	5740	40600
Week 12 (OST)	22	0	18400	9000	48.9	16100	65.0	18600	2530	47200
Week 16 (OST)	21	0	16500	7990	48.5	12300	148.8	17300	437	28400
Week 20 (OST)	21	2	17300	8920	51.6	NE	NE	19200	0	35600
Week 24 (OST)	21	2	17400	9450	54.2	NE	NE	17200	0	35900

A previous model developed for NMO, NMOSD and healthy volunteers (Roche Report #1094498) was updated with new data from patients with gMG from Study WN42636 (cut-off date 2023) and used to describe the PK of satralizumab in the population. The final model was a two-compartment model with linear and Michel-Menten elimination. Updates on the model were made on the effect of ADA, PE- and IVIg treatment. Model evaluation diagnostics indicates good description of the population.

The summaries of predicted exposures stratified by covariate group are presents in Table 3. The predicted exposures (C_{trough}, C_{max} and AUC) for the 16-years old paediatric patient falls within the 90% prediction intervals for the rest of the population.

Table 3: Median [Q05 – Q95] predicted steady state exposures by covariates, conditional simulation for final model 330

Individual exposures following 120 mg (WT ≤ 100 kg) or 180 mg (WT > 100 kg) SC Q4W doses (with loading dose at week 0, 2 and 4) were computed by simulation of individual concentration profiles using individual predictions of PK parameters. Time-dependent ADA detection indicator variable (ADA2_T) was assumed to be 0. Subject-specific values of all covariates were used.

Covariate	Level	N	WGT (kg)	C_{trough} (µg/mL)	C_{max} (µg/mL)	AUC (µg/mL day)
All Patients		168	74 [52 - 114]	16.1 [6.39 - 37.3]	27.8 [15.6 - 51.9]	630 [320 - 1280]
Pediatric Patient	Adult	167	74 [52 - 114]	16.1 [6.37 - 37.5]	27.9 [15.6 - 52]	632 [320 - 1280]
	Pediatric	1	58 [58 - 58]	15.4 [15.4 - 15.4]	20.8 [20.8 - 20.8]	528 [528 - 528]
Body Weight Tertile	46.0 kg - 65.8 kg	56	59 [46 - 65.8]	24.7 [10.6 - 41.6]	39.2 [21.5 - 58.5]	934 [484 - 1450]
	67.8 kg - 83.1 kg	56	74 [67.8 - 83.1]	14.4 [6.66 - 27.8]	24.8 [15.9 - 39.2]	581 [326 - 946]
	84.4 kg - 123.0 kg	56	97.1 [84.4 - 123]	12.1 [5.02 - 26.4]	22.4 [12.9 - 39.3]	500 [277 - 941]
Gender	Male	60	88.1 [68.3 - 122]	13.9 [6.63 - 27.1]	24.4 [16 - 39.2]	543 [329 - 941]
	Female	108	67.2 [50.3 - 99.4]	17.5 [6.44 - 39.8]	30.1 [15.6 - 55.5]	693 [320 - 1370]
Race	Missing	5	66 [46.6 - 116]	23.2 [17.1 - 30.5]	33.3 [30.6 - 47.1]	819 [701 - 1090]
	American Indian or Alaska Native	1	72.4 [72.4 - 72.4]	27.3 [27.3 - 27.3]	39.6 [39.6 - 39.6]	965 [965 - 965]
	Asian	57	68.7 [52 - 106]	18.2 [8.19 - 39.7]	29.6 [16.8 - 56.1]	708 [377 - 1380]
	Black or African American	2	75.8 [68.3 - 83.4]	18 [12 - 24.1]	28.5 [23.8 - 33.2]	673 [516 - 829]

Source: Table 13 in popPK report #1130491

Efficacy results

The primary endpoint of difference between the placebo and satralizumab groups in combination with stable background therapy in change from baseline to Week 24 in the total MG-ADL score in the AChR+ population met statistical significance in favor of satralizumab; however, the effect size observed was considered small.

In the satralizumab group, the mean change from baseline to Week 24 in the total MG-ADL score was −3.59 (95% CI: −4.15, −3.02) and in the placebo group was −2.57 (95% CI: −3.25, −1.88). The difference in adjusted mean was −1.02 (95% CI: −1.88, −0.16), p=0.0196.

Safety results

The mean duration of observation was comparable between the satralizumab group (138.6 days) and the placebo group (139.4 days). During the DB period, the proportion of participants who experienced at least one adverse event (AE) was higher in the satralizumab group (89.6%, 86/96 participants) compared to the placebo group (72.8%; 67/92 participants). The most common AEs in both groups were COVID-19, nasopharyngitis, hypertension, and pharyngitis. None of the AEs had a higher frequency (>5% difference) in the satralizumab group compared to the placebo group. The majority of AEs were non-serious and grade 1-2 in severity.

Additional analyses were conducted by comparing results obtained in participants treated with different doses of satralizumab (120 mg vs. 180 mg) determined on the basis of body weight. The safety profile of satralizumab was comparable between the 2 doses.

The safety profile (AEs per 100 patient/year) in the overall satralizumab treatment (OST) period was consistent with the safety profile during the DB period.

None of the AEs reported during the safety follow-up period were considered related to the study drug, and no safety concern was identified.

The safety data collected in Study WN42636 were consistent with the known safety profile of satralizumab. No new safety signals were observed.

2.3.2. Discussion on clinical aspects

The study WN42636 was planned to be the pivotal study for gMG as a new indication for satralizumab. However, upon review of the primary analysis results (DB period), the Sponsor decided to halt development of satralizumab in gMG and discontinued further dosing with the study drug (while the OLE period was ongoing).

Results from the study is being submitted to the European Medicines Agency to fulfil the requirements of Article 46 of Regulation (EC) No 1901/2006. No subgroup analysis could be performed on adolescents due to the limited number.

Pk data from one adolescent (16 years, 58 kg) patient with gMG were available. The exposure for this patient was within the exposure range for the adult population. This is in line with previous observations for adolescents ≥ 40 kg.

3. Rapporteur's overall conclusion and recommendation

The results from study WN42636 were submitted to the European Medicines Agency to fulfil the requirements of Article 46 of Regulation (EC) No 1901/2006. No subgroup analysis could be performed on adolescents due to the limited number. No assessment of the data could be performed due to limited data related to the low number (N=3) of adolescents. The Rapporteur considers the requirements fulfilled.

☒ **Fulfilled: No regulatory action required.**