Confirming pharmacokinetic properties of satralizumab using a bodyweight tiered dosing regimen in LUMINESCE, a phase 3 study for generalized Myasthenia Gravis (gMG)

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Background and Objective

- Satralizumab (SA) is a humanized IgG2 monoclonal recycling IL-6 receptor antagonist antibody.
- SA is approved for treatment of neuromyelitis optica spectrum disorder (NMOSD) and is being evaluated in additional indications.
- The safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of SA in patients with gMG has been evaluated in the LUMINESCE trial [1].
- A model-informed bodyweight (BW)-tiered dosing regimen was implemented based on the PK properties in order to maximize the target engagement (receptor occupancy, RO) across the body weight range.
- The current analysis aimed to confirm the SA PK properties in the gMG population including development and impact of anti-drug antibodies (ADA) as well as rescue therapy on SA PK.

Methods

Study design: The trial included 188 patients and the study design is shown in Figure 1. Patients could receive rescue therapy (intravenous immunoglobulin (IVIg) and plasma exchange (PE)).
Dosing regimen: 120 mg for patients with BW ≤100 kg, 180 mg for BW > 100 kg administered as a sub-cutaneous (SC) injection on weeks 0, 2, 4, and every 4 weeks (Q4W) thereafter.
Sampling: PK and ADA were sampled pre-dose at each visit during the DB and for the first 24 weeks of the OLE, and every 12 weeks thereafter.

PopPK analysis: The PK analysis was based on a previous model in NMOSD patients (legacy) [2]. This was a model with first order subcutaneous absorption and parallel linear and Michaelis-Menten elimination.
Covariate relationships in the legacy model: BW on CL,Q, VC, and VP with fixed allometric scaling coefficients. ADA on CL and Bioavailability (Fsc).
ADA effects were re-evaluated as well as impact of rescue treatment.

ADA analysis: A logistic regression analysis was performed to investigate the factors influencing the appearance of ADA, including exposure (steady-state Ctrough (Ctr)), BW and background therapy.

Results

Study data: The study parameters have been summarized in Table 1.

PopPK analysis: PK in gMG patients was similar to NMOSD for ADA negative subjects while the impact of ADA was weaker, consistent with lower ADA titers and later onset in the gMG patients. The ADA effect on Fsc was excluded with all other parameters fixed. The VPC is shown in Figure 2. As expected, PE and IVIg had a significant impact on CL during the treatment which was either greater than or equal to the total satralizumab CL. The effect of IVIg declined exponentially with time (half-life ~9 days) after the end of treatment.

ADA analysis: Low exposure was the main predictor for the appearance of ADA, Figure 3. The BW-tiered dosing regimen provided additional insights to the correlation between exposure, BW and risk of developing ADA. Median RO was predicted to be >95% across the dose interval for the entire BW range, regardless of ADA status, Figure 4.

Table 1. Summary of Study Parameters

Patients receiving SA in DB or OLE	168
Patients receiving 120 mg as 1st dose	147 (88%)
Patients receiving 180 mg as 1st dose	21 (12%)
Patients with ADA+ samples	67 (40%)
Patients receiving IVIg	6 (4%)
Patients receiving PE	2 (1%)
Treatment duration (Median, wks)	44
Number of PK & ADA Samples included in analysis	1606

Figure 1. LUMINESCE study design

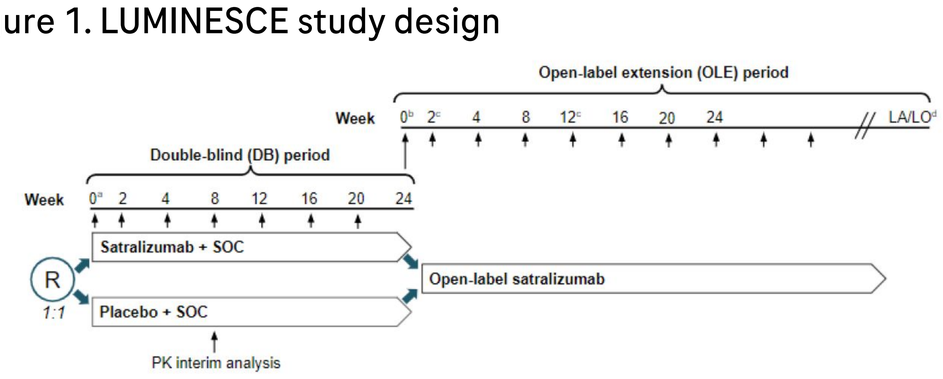


Figure 2. Visual Predictive Check confirming the appropriateness of the legacy PK model with gMG data

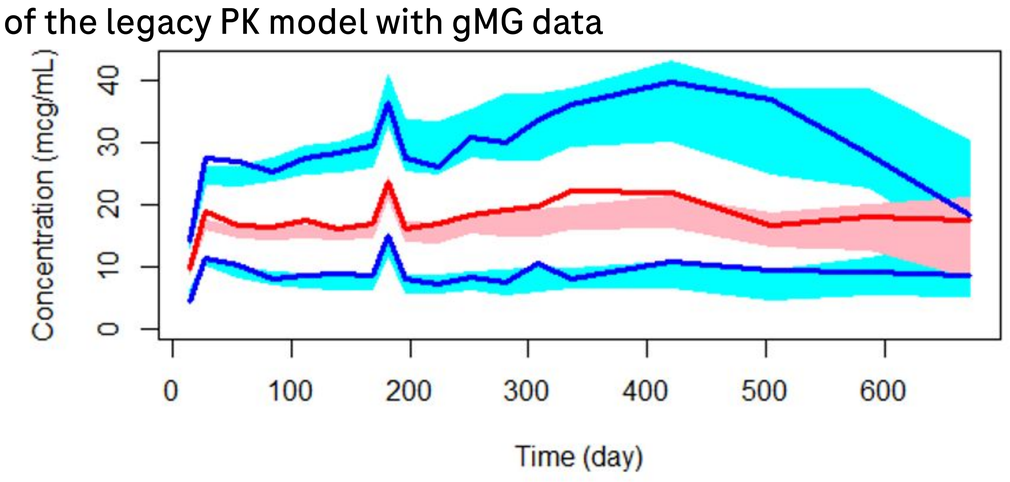


Figure 3. Figure 3. Logistic regression showing how the probability of developing ADAs related to steady-state Ctr

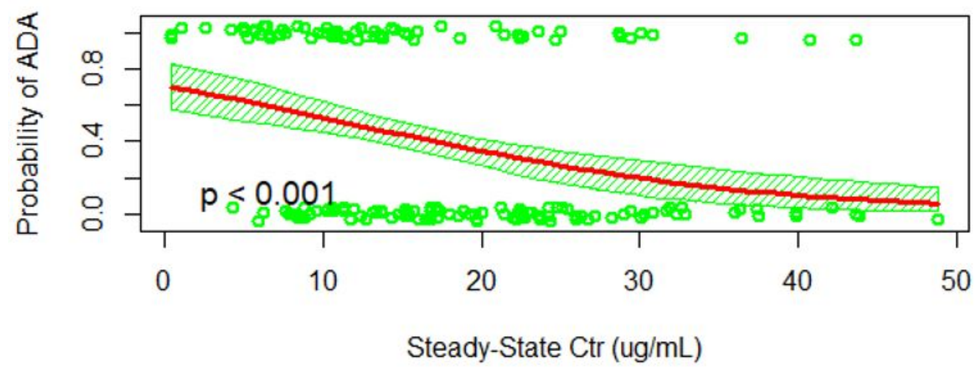
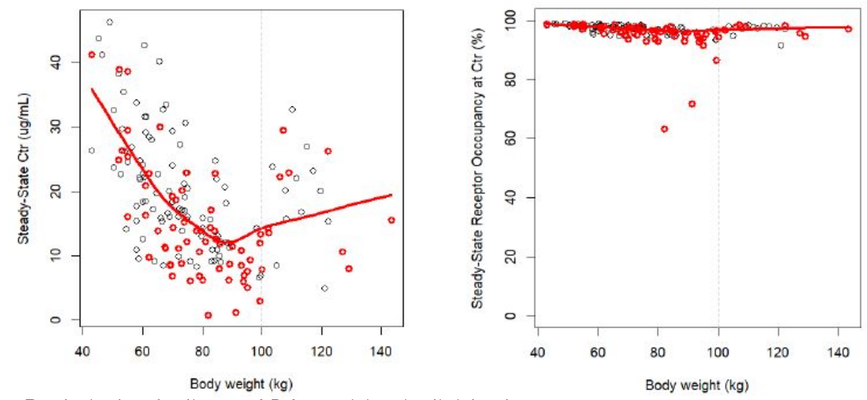


Figure 4. Predicted steady-state Ctr (left) and RO (right) vs BW



Red circles Indicate ADA positive individuals

Conclusion

- PK properties were confirmed to be similar to the previous indication (NMOSD) with only a minor adjustment related to the ADA impact on bioavailabilty
- The impact of IVIg and PE rescue treatment on clearance was quantified in the PK model and it supports the per-protocol recommendation to re-load satralizumab following PE.
- The BW-tiered regimen was confirmed to achieve the targeted RO (>95%) in the gMG population, irrespective of ADA status.

References:
[1] Safety and efficacy of satralizumab in patients with generalised myasthenia gravis (LUMINESCE): a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. Habib, Ali A et al. The Lancet Neurology, Volume 24, Issue 2, 117 - 127
[2] PAGE 29 (2021) Abstr 9665 [www.page-meeting.org/?abstract=9665]