Insights into the Potential Pharmacological Effects of Apitegromab in Health and Disease: Data from Preclinical and Clinical Studies

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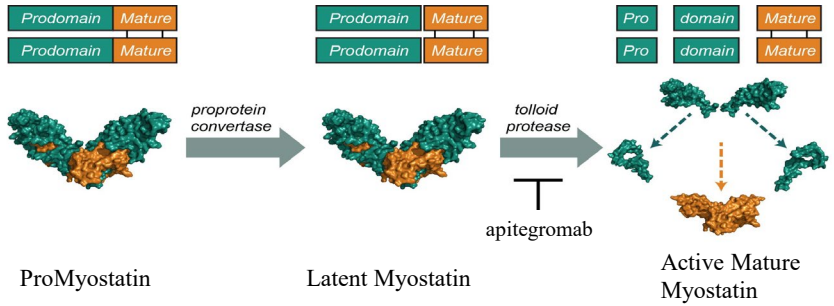
EP.277

Background

Myostatin, an important negative regulator of muscle mass, is synthesized as an inactive precursor, requiring two proteolytic cleavage steps to release the active growth factor. Apitegromab is an investigational, fully human, monoclonal antibody that specifically binds to the proforms of myostatin, which include promyostatin and latent myostatin, thereby inhibiting myostatin activation.[1]

Introduction[2]



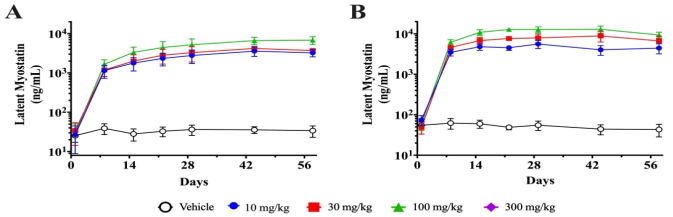
- Activation of myostatin requires two distinct proteolysis events that generate the active mature growth factor; apitegromab inhibits the activity of the tolloid protease. The serum latent myostatin is a surrogate PD marker for target engagement of apitegromab[1,2]
- Apitegromab does not bind to mature myostatin or any form of GDF11, Activin A, or other TGF-β family members[1,2]

Methods

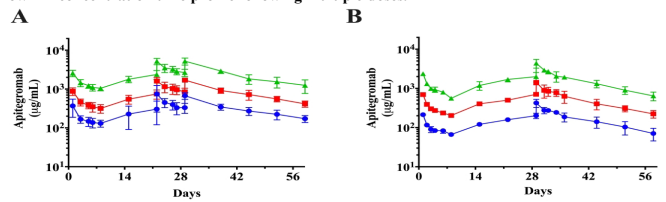
To characterize the relationship between levels of serum latent myostatin and response to apitegromab, we measured serum latent myostatin concentrations in preclinical animal models and healthy humans using a sensitive immunoassay that detects the total levels of serum latent myostatin[3] and further characterized this relationship in patients with Spinal Muscular Atrophy (SMA) during the TOPAZ phase 2 clinical trial (NCT03921528).[4]

Figure 1: Target Engagement and Apitegromab Exposure Confirmed Across the Dosing and Recovery Phases in Preclinical and Clinical Studies[3,5]

Apitegromab was dosed for 4 weeks in cynomolgus monkeys (A) and adult SD rats (B) at 10, 30, and 100 mg/kg, followed by a four-week recovery phase.[5]



Latent myostatin accumulated in the serum following administration of apitegromab by up to 100 fold, shown in concentration time profile following multiple doses.[5]



Serum concentration time profile of apitegromab following multiple doses; QW repeat IV doses

Single and multiple apitegromab doses also resulted in dose-dependent and sustained increases in serum latent myostatin in healthy volunteers in a Phase 1 study, indicating robust target engagement.[3]

Figure 2: TOPAZ Study Design[4]

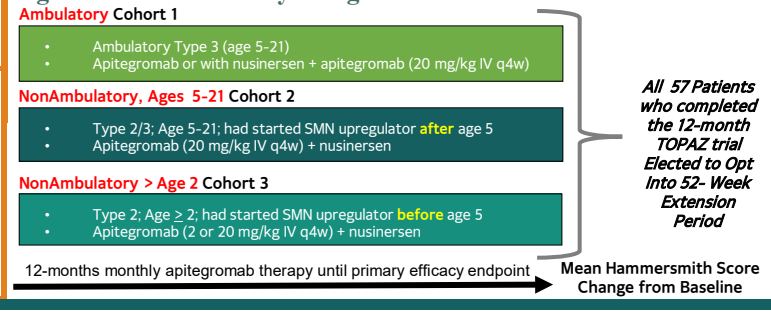
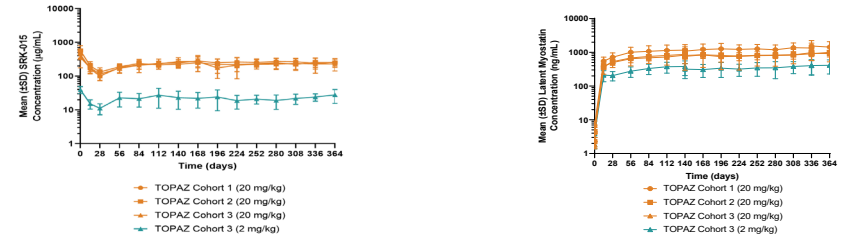


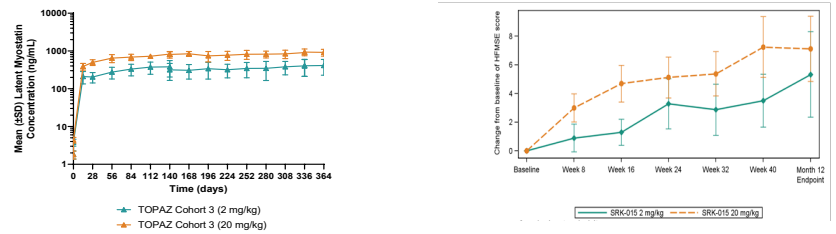
Figure 3: Dose Proportional Apitegromab Exposure and Full Target Engagement Observed in 12-month TOPAZ Study



PK: Dose-proportional and sustained drug exposure following chronic administration of apitegromab

PD: Both 2 and 20 mg/kg doses yielded high levels of target engagement (>100-fold increase from baseline) assessed by serum latent myostatin levels

Figure 4: Dose Response Observed in Serum Latent Myostatin Supports Dose-Dependent Efficacy in NonAmbulatory > 2 Years; Patients with SMA



- **Both 2 and 20 mg/kg doses yielded high levels of target engagement (>100-fold increase from baseline)**
- **High dose offers relatively higher magnitude of target engagement than low dose**
- **The largest fold-change in latent myostatin from baseline was observed in the high dose cohort**
- **Sizeable dose dependent HFMSE increases in patients already on chronic maintenance nusinersen**
- **High dose numerically offered greater HFMSE increases than low dose across all timepoints**
- **Continuous and durable improvements through 12 mo.**
- **A positive trend in serum latent myostatin (Cavg) relationship to efficacy response (HFMSE total score or change from baseline at the 12-month timepoint) was observed**

Safety Five most frequently reported TEAEs* from the TOPAZ trial: headache, pyrexia, URTI, cough, and nasopharyngitis
Incidence and severity of AEs from the TOPAZ trial were consistent with Phase 1 findings and underlying patient population and background therapy

Summary

- This information may clarify latent myostatin dynamics (serum PD marker for target engagement) and apitegromab's potential effects in SMA.
- The data confirmed the ability of apitegromab to engage and saturate the target and additional data on optimal dose to help plan future studies.
- Motor function improvements were observed in the primary efficacy endpoints in the Phase 2 TOPAZ clinical trial
- Dose response in primary endpoint was observed in the TOPAZ trial: greater improvements over baseline in high dose compared to low dose arm
- Supportive PK/PD results; high dose - higher drug exposure and target engagement
- Apitegromab has the potential to be the first muscle-directed therapy to address motor function impairment in patients with SMA.

References 1. Dagbay KB et al. J Biol Chem. 2020; 295(16):5404-5418; 2. Pirruccello-Straub M et al. Sci Rep. 2018; 8(1):2292; 3. Barrett D, et al. Adv Ther. 2021;38(6):3203-3222. 4. Place A et al. Eu J Neurology, 28 (Suppl. 1), 207–334:(EPR-184); 5. Welsh BT, et al. Int J Toxicol. 2021;40(4):322-336.

Acknowledgements
The authors thank the patients, PIs and SCs in the Ph 1 (healthy volunteers) and Ph 2 TOPAZ trial; and the apitegromab preclinical and clinical teams.

Disclaimer: Apitegromab is an investigational drug candidate being developed and studied for SMA. The effectiveness and safety of apitegromab have not been established. Apitegromab has not been approved by the FDA or any other regulatory authority.

*Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug or start prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug.TEAE rates are across all patients in TOPAZ trial; CI, confidence interval; GDF11, Growth differentiation factor 11 also known as BMP11; HFMSE, Hammersmith functional motor scale expanded; IV, intravenous; mg/kg, milligram/kilogram; mo, months; PD, pharmacodynamic; PI, Principal Investigator; PK, pharmacokinetic; q4w, dosed every 4 weeks; RHS, Revised Hammersmith scale; SC, study coordinator; SD, Standard deviation; SE, Standard error; SMA, spinal muscular atrophy; SMN, Survival motor neuron 1; SRK-015, apitegromab; TGF-β, Transforming growth factor β; URTI, upper respiratory tract infection