# Myostatin Dynamics in Health and Disease: Pharmacologic Effects of SRK-015, a Highly Selective Monoclonal Antibody Inhibitor of Myostatin Activation

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## Abstract

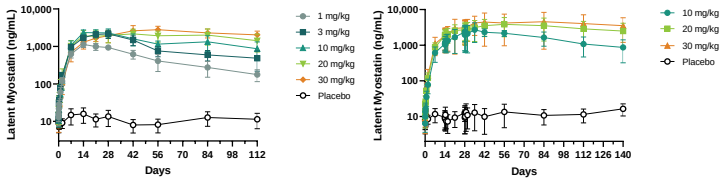
Myostatin, an important negative regulator of muscle mass (particularly that of fast-twitch fibers), is synthesized as an inactive precursor, requiring two proteolytic cleavage steps to release the active growth factor. Understanding myostatin production and activation in health and disease may provide important insight into the potential effects of anti-myostatin therapeutics.

Scholar Rock is currently developing and investigating SRK-015, a monoclonal antibody that selectively binds and inhibits the activation of latent myostatin, for the treatment of spinal muscular atrophy (SMA). The safety and efficacy of SRK-015 in SMA are currently being evaluated in an ongoing Phase 2 trial (TOPAZ). To further characterize the relationship between levels of serum latent myostatin, disease state, and response to SRK-015, we measured serum latent myostatin concentrations in healthy animals and humans, a mouse model of SMA, and patients with SMA. Latent myostatin accumulated in serum following administration of SRK-015 (or its parent antibody in mouse experiments) by up to 100-fold in healthy animals and a mouse model of SMA as well as in healthy humans and patients with SMA. Following treatment at higher doses, these increases in serum latent myostatin concentrations persisted for longer periods of time. The latent myostatin increases are believed to be due to binding of SRK-015 to its target, resulting in movement of the antibody-antigen complex from the muscle into systemic circulation until eventual clearance. These data provide a better understanding of the dynamics of latent myostatin in the serum of animals and humans in health and disease and further guide the clinical investigation of SRK-015's therapeutic potential in SMA.

## Introduction

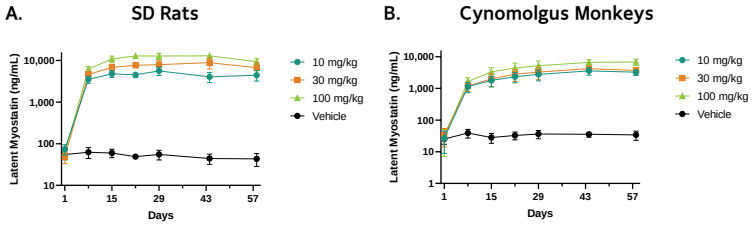
- Several recent reports have indicated that serum myostatin concentrations are decreased in animals and patients with neuromuscular diseases, raising the possibility that myostatin inhibition is unlikely to be effective in these populations (1,2).
- To understand the relationship between myostatin levels and disease in both patients with SMA and a mouse model of SMA, we measured serum latent myostatin levels in healthy volunteers and SMA patients, as well as in healthy animals and the SMNΔ7 mouse.
  - We and others have shown that the proform (precursor form) of the active myostatin, latent myostatin, is the predominant myostatin form present in serum (3,4).
- Assessment of serum latent myostatin is a measure of target engagement, as binding to SRK-015 results in accumulation of latent myostatin as the bound target assumes the half-life of the antibody and accumulates in circulation and in target tissues (5,6).
- To accurately measure serum latent myostatin levels, we developed a bioanalytical method capable of quantifying latent myostatin over a wide range of concentrations (7).

## Figure 1: SRK-015 robustly engages its target in healthy volunteers



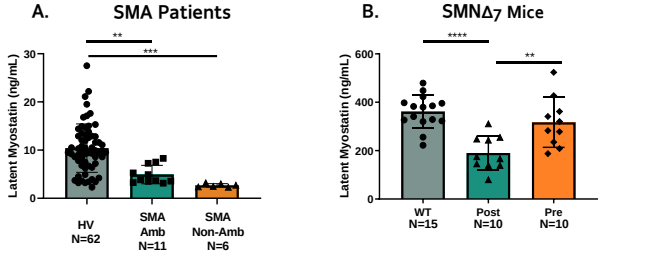

Target engagement by SRK-015 is reflected in marked increases in serum latent myostatin. Healthy volunteers were administered intravenously (IV) a single (A) or multiple (B) doses of SRK-015 or placebo and serum latent myostatin levels assessed at the indicated timepoints. For the multiple ascending dose study patients were dosed every two weeks for three doses. Latent myostatin levels increase in a dose-dependent but not dose-proportional manner. (N=6-10 per group)

## Figure 2: SRK-015 displays robust target engagement in healthy animals



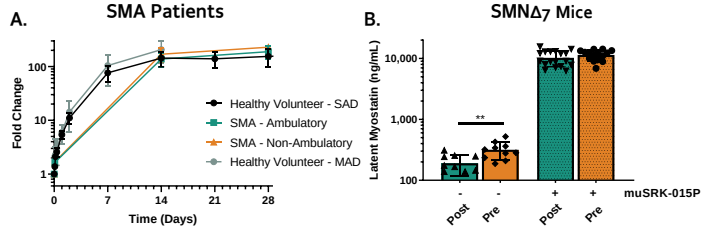

Latent myostatin levels increase in healthy rats (A) and monkeys (B) following four weekly doses with the indicated dose levels of SRK-015 administered IV. Latent myostatin levels increase in a dose-dependent but not dose-proportional manner. (N=12/group for cynos; N=12-18/group).

## Figure 3: Circulating latent myostatin is reduced in SMA patients and mice




Basal latent myostatin levels were assessed in healthy volunteers, ambulatory SMA patients, and non-ambulatory SMA patients (A). The SMA patients were receiving nusinersen. One group of SMNΔ7 mice were treated with 0.1 mg/kg/day with the small molecule SMN upregulator SMN-C1 for 24 days, then administered 3 mg/kg/day until day 56 (post-symptomatic treatment). A second group of SMNΔ7 mice were treated with 3 mg/kg/day SMN-C1 from day 1 until day 56 (pre-symptomatic treatment) (B).

## Figure 4: SRK-015 engages latent myostatin to an equivalent degree regardless of diseases status




Regardless of disease state, SRK-015 engages latent myostatin, resulting in robust increases of serum latent myostatin in both SMA patients and SMNΔ7 mice. (A) Healthy volunteers and SMA patients (receiving nusinersen) were administered a single IV dose of 20 mg/kg SRK-015. Latent myostatin was measured at the indicated timepoints post dosing. SMNΔ7 mice were treated with SMN-C1 (as described in Figure 3) and administered IP doses of muSRK-015P beginning at day 24. muSRK-015P is the parental clone of SRK-015 on a mouse IgG1. Latent myostatin was measured following 4 weekly doses of antibody. These data indicate that, despite lower circulating levels, the muscle of SMA patients and mice nevertheless produces significant levels of latent myostatin.

## Table 1: Baseline serum latent myostatin levels in humans and animals

| Population | | Latent Myo (ng/mL) | St Dev | N |
|---|---|---|---|---|
| Human | Healthy | 10.6 | 5.3 | 46 |
| | SMA | 4.1 | 1.9 | 17 |
| Mouse | WT | 360.6 | 68.4 | 15 |
| | SNMΔ7 + SMNC-1 | 266.9 | 101.4 | 34 |
| Rat | Adult | 52.9 | 18.9 | 606 |
| Cynomolgus | Adult | 28.8 | 17.4 | 49 |

## Conclusions

- SRK-015 administration results in robust and sustained target engagement in healthy volunteers, rats and cynomolgus monkeys, as assessed by increases in serum latent myostatin.
- Baseline circulating latent myostatin levels are reduced in SMA patients and SMNΔ7 mice, compared to healthy controls.
- SRK-015 treatment results in equivalent increases in serum latent myostatin regardless of disease state and baseline levels.
  - These data indicate that muscles of SMA patients and SMNΔ7 mice produce myostatin at levels equivalent to healthy controls.
  - Circulating myostatin levels may be a reflection of overall muscle mass, rather than the level of myostatin expression.
- Serum latent myostatin may serve as a robust and highly translational biomarker to capture the effects of myostatin inhibitors in the clinic; however the relationship to efficacy remains to be established.

## References

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**Disclaimer:** SRK-015 is an investigational drug candidate being developed and studied for SMA and other indications. The effectiveness and safety of SRK-015 has not been established and SRK-015 has not been approved by the FDA or other regulatory agency.



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