

Lonigutamab, a Novel Anti-IGF-1R, Has a Limited Impact on Circulating IGF-1 Levels

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THYROID BIOLOGY AND DISEASE

POSTER

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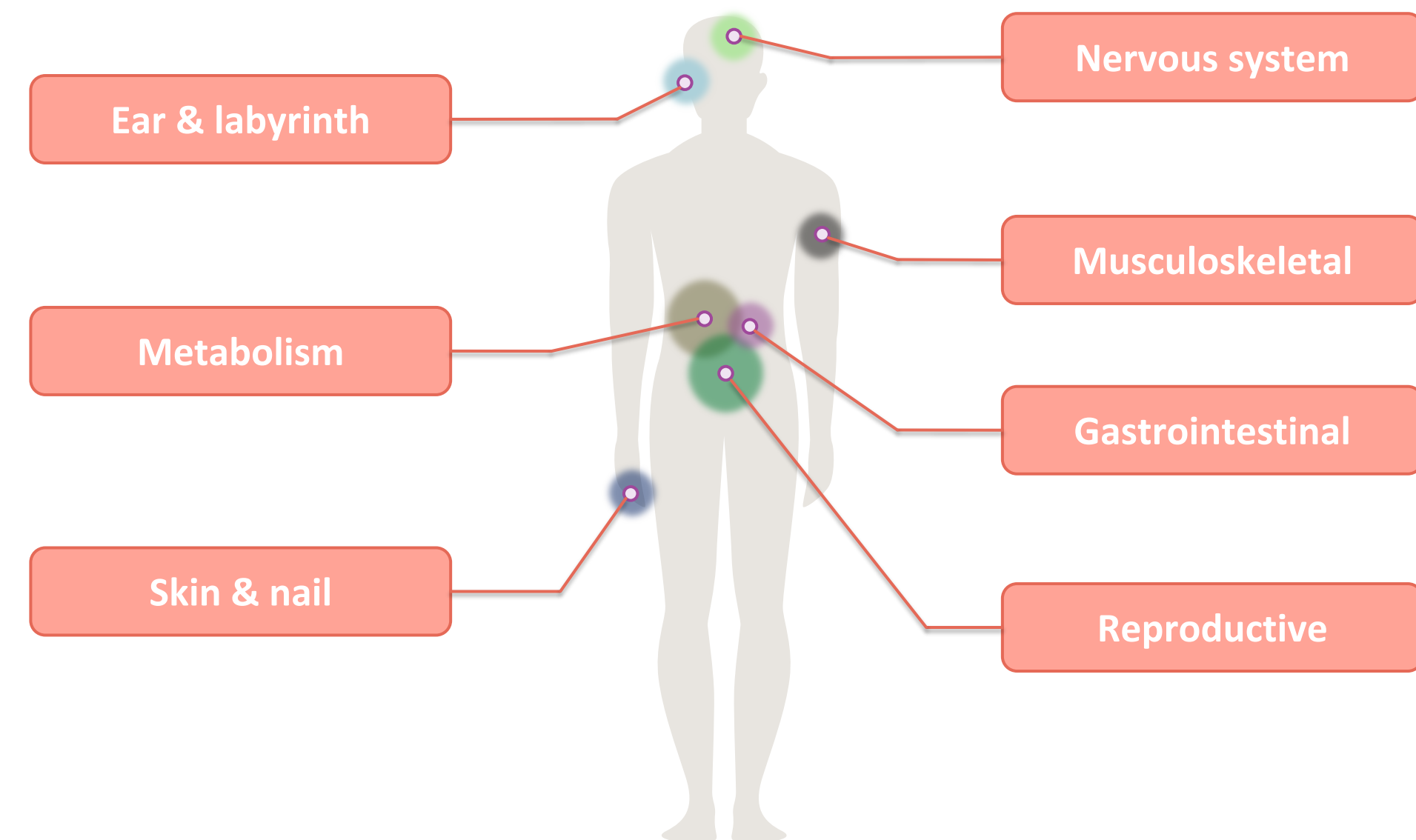


ENDO 2025 Annual Meeting
San Francisco, CA, USA
July 12–15, 2025

Background

- Thyroid eye disease (TED) is a chronic, debilitating, and vision-threatening condition characterized by aberrant stimulation of the insulin-like growth factor 1 receptor (IGF-1R) pathway^{1,2}
- IGF-1R is a clinically validated therapeutic target in TED^{1,3}; however, monoclonal antibodies that directly compete with IGF-1 for receptor binding reportedly increase serum IGF-1 levels by 250% to 700%^{4,5}
- Since IGF-1 has pleiotropic effects on numerous body systems, elevated IGF-1 levels may contribute to the adverse event profile associated with competitive anti-IGF-1Rs (Figure 1)⁶
- Limiting the increase in IGF-1 levels may help to reduce treatment-limiting side effects seen with competitive anti-IGF-1Rs (eg, hyperglycemia, menstrual disorders),⁷⁻¹⁰ thereby potentially yielding an improved safety profile for patients with TED

Figure 1. Possible Adverse Events Observed with Anti-IGF-1R Therapy in TED⁶

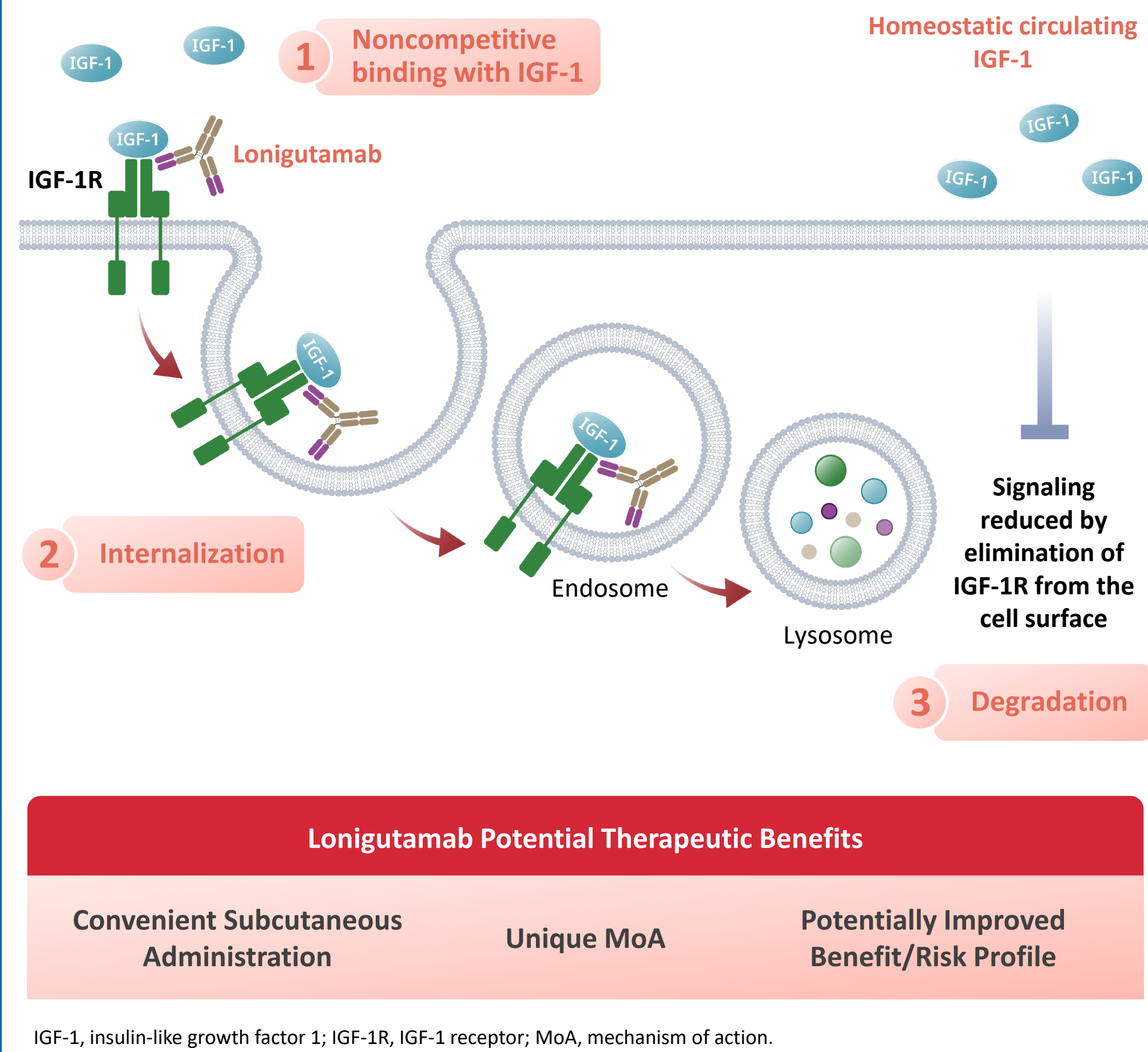


Anti-IGF-1Rs that directly compete with IGF-1 binding increase circulating IGF-1 levels by 250% to 700%^{4,5}

IGF-1, insulin-like growth factor 1; IGF-1R, IGF-1 receptor; TED, thyroid eye disease.

- Lonigutamab is a novel, high-affinity, subcutaneously administered, anti-IGF-1R monoclonal antibody being evaluated for the treatment of TED (Figure 2)^{11,12}
 - Lonigutamab binds IGF-1R peripheral to the IGF-1 binding site. This noncompetitive binding to IGF-1R elicits rapid internalization and degradation of the receptor, thus eliminating it from the cell surface
- In a prior analysis of lonigutamab pharmacokinetics (PK)/pharmacodynamics (PD) in healthy volunteers (HVs), lonigutamab demonstrated dose-dependent PK consistent with target-mediated drug disposition (TMDD)¹³
 - The TMDD threshold, above which receptor internalization was saturated in the majority of patients, occurred around 3 µg/mL¹³
- In a phase 1/2 study in patients with TED, lonigutamab showed preliminary clinical efficacy across multiple manifestations of the disease when minimal exposure was maintained above receptor saturation¹⁴

Figure 2. Lonigutamab Mechanism of Action



IGF-1, insulin-like growth factor 1; IGF-1R, IGF-1 receptor; MoA, mechanism of action.

Objective

This study tests the hypothesis that lonigutamab has a limited impact on circulating IGF-1 at target-saturating levels¹³ relative to the increases in IGF-1 levels previously reported with competitive IGF-1R inhibitors.

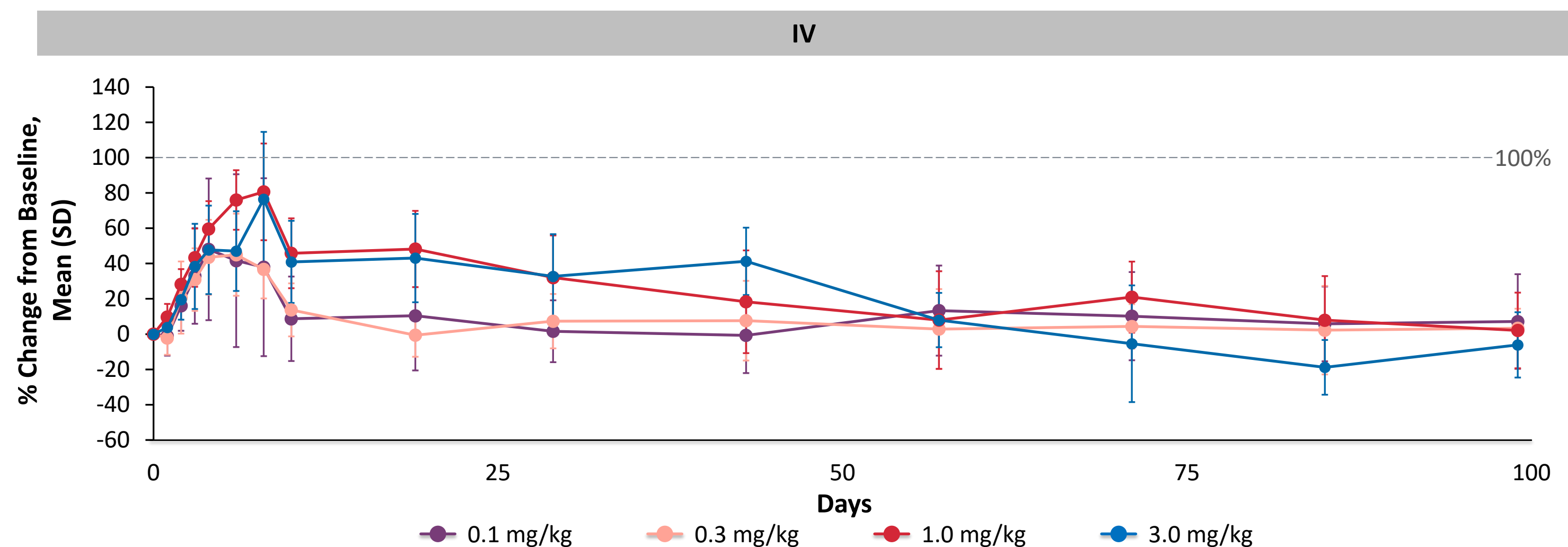
Methods

- Phase 1, single-ascending-dose (SAD) study in HVs
 - In cohorts 1 to 4, participants received a single intravenous (IV) infusion of lonigutamab over a period of approximately 60 minutes at the following dose levels: 0.1, 0.3, 1.0, and 3.0 mg/kg
 - In cohorts 5 to 8, participants received a single subcutaneous (SC) injection of lonigutamab at the following dose levels: 20, 40, 125, and 250 mg
- Phase 1, multiple-dose (MD) study in HVs
 - Participants received 3 weekly SC injections of lonigutamab: 75 mg loading dose on day 1, followed by weekly doses of 37.5 mg on days 8 and 15
- IGF-1 levels
 - Quantified by enzyme-linked immunosorbent assay (R&D Systems Quantikine Immunoassay) pre-dose, daily, and at regular intervals thereafter

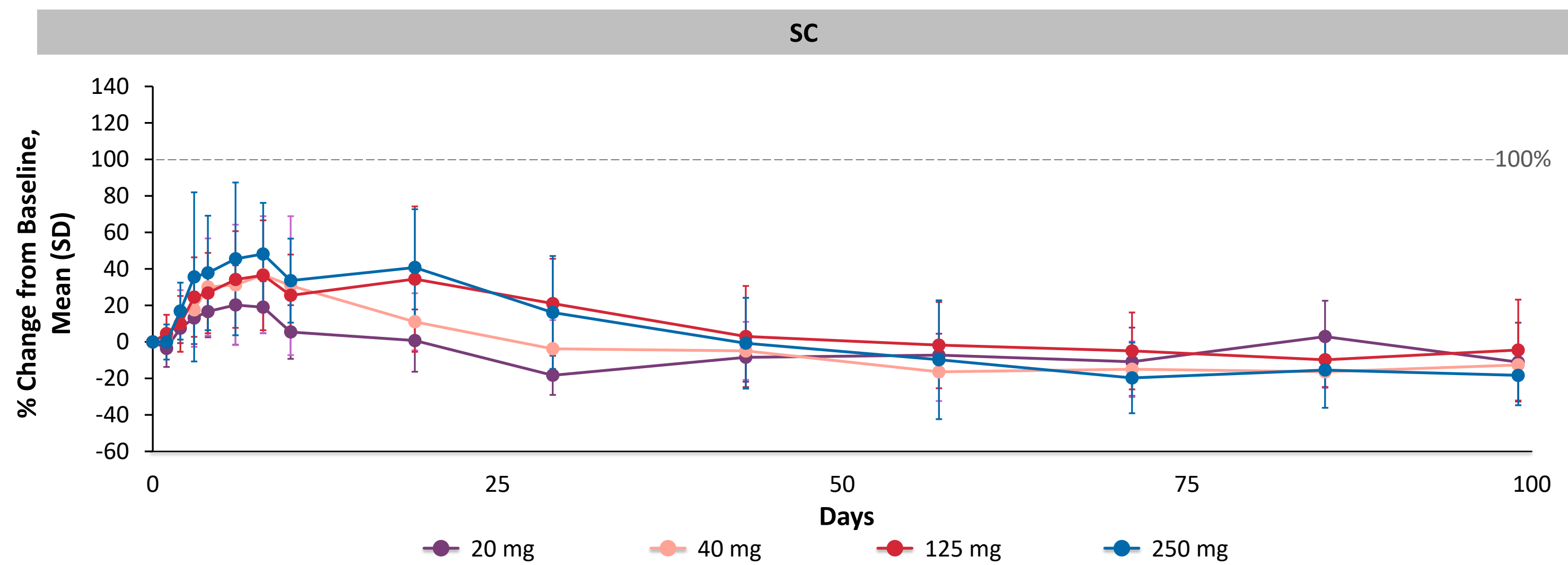
Results

- In total, the SAD study included 47 lonigutamab-treated HVs; most HVs were male (76.6%) and Black/African American (51.1%), with an age range of 19 to 55 years. Safety findings have been previously reported¹³
- Lonigutamab demonstrated limited and transient increases in IGF-1 levels
 - Peak mean IGF-1 concentrations were observed between days 4 and 8, with an approximate 20% to 80% increase from baseline across cohorts (Figure 3), during which lonigutamab levels were maintained above target saturation (ie, at doses hypothesized to be therapeutic).¹³ IGF-1 levels returned to baseline between days 10 and 57, corresponding to a decrease in target saturation and PK

Figure 3. Mean Percent Change from Baseline in Serum IGF-1 Levels with Lonigutamab (SAD Study)



Cohort	Dose	n	Maximum IGF-1 % Change, Mean (SD)	Day of Maximum % Increase
1	0.1 mg/kg	6	48.1 (40.1)	4
2	0.3 mg/kg	6	45.0 (23.3)	6
3	1.0 mg/kg	6	80.6 (27.4)	8
4	3.0 mg/kg	5	76.5 (38.1)	8

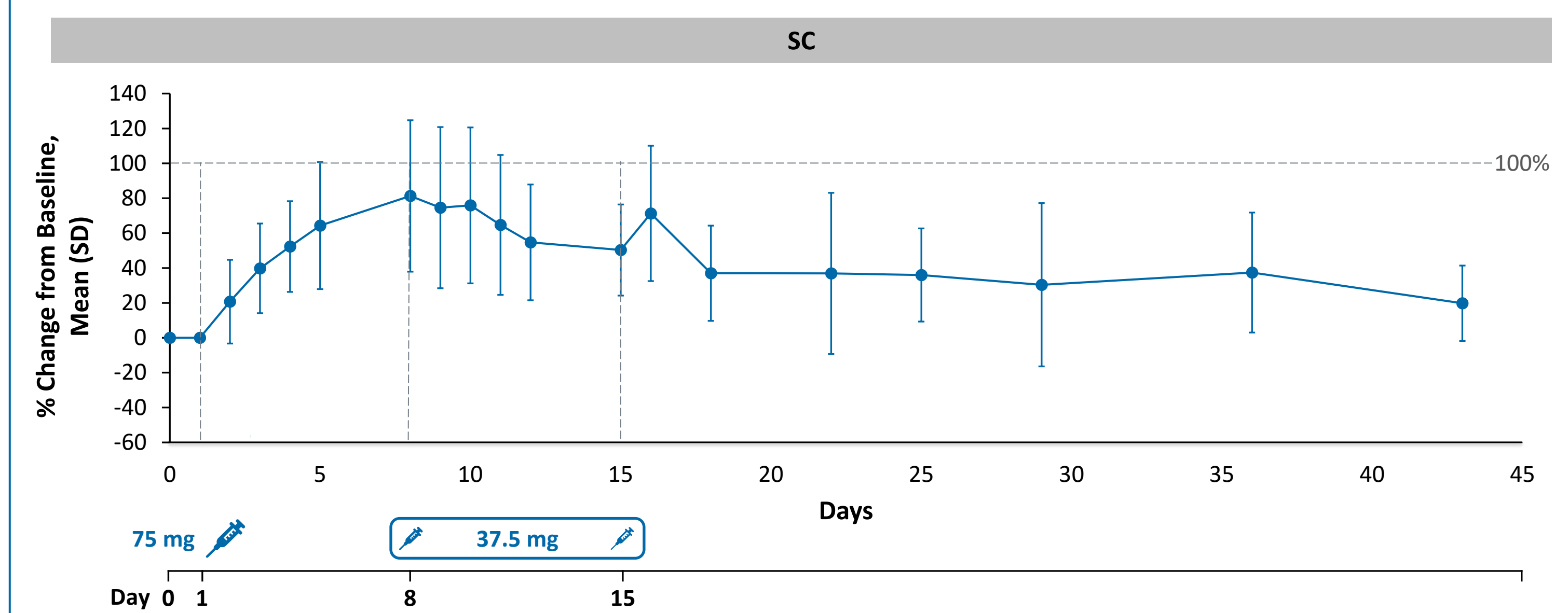


Cohort	Dose	n	Maximum IGF-1 % Change, Mean (SD)	Day of Maximum % Increase
5	20 mg	6	20.2 (21.7)	6
6	40 mg	6	36.8 (32.1)	8
7	125 mg	6	36.5 (30.1)	8
8	250 mg	6	48.2 (28.0)	8

IGF-1, insulin-like growth factor 1; IV, intravenous; SAD, single-ascending dose; SC, subcutaneous; SD, standard deviation.

- The MD study included 6 HVs; most HVs were male (66.7%) and White (83.3%), with an age range of 25 to 52 years. No notable safety findings were observed
- Similar to the SAD study, serum IGF-1 levels increased modestly after the first lonigutamab dose, reaching a maximum mean increase from baseline of 81.3% (standard deviation [43.4]) on day 8 (Figure 4)
- The IGF-1 elevation was transient
 - IGF-1 mean serum concentrations were approximately 37% and 20% above baseline on days 36 and 43 (end of study), respectively

Figure 4. Mean Percent Change from Baseline in Serum IGF-1 Levels with Lonigutamab (MD Study)



Dashed vertical lines indicate day of injection. IGF-1, insulin-like growth factor 1; MD, multiple dose; SC, subcutaneous; SD, standard deviation.

Conclusions

- Lonigutamab, a high-affinity, next-generation, anti-IGF-1R monoclonal antibody, exhibited a limited elevation of serum IGF-1 levels in HVs relative to previously published increases in IGF-1 levels reported with competitive IGF-1R inhibitors
 - Lonigutamab-induced IGF-1 elevations were transient and peaked at an approximately 80% increase from baseline at the highest doses tested
- HV studies showed no notable or dose-dependent safety observations
- These findings provide clinical support of lonigutamab's unique noncompetitive mechanism of action, which enables internalization and degradation of IGF-1R as well as IGF-1
- The observed limited increase in IGF-1 levels with lonigutamab may translate into an improved safety profile while maintaining the therapeutic benefit of IGF-1R pathway inhibition
- Further investigation of lonigutamab as a therapeutic option in TED is warranted

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Acknowledgments

Writing and editorial support were provided by Elisabetta Lauretti, PhD, of Red Nucleus, and funded by ACELYRIN, INC., a wholly owned subsidiary of Alumis Inc. The study was funded by ACELYRIN, INC., a wholly owned subsidiary of Alumis Inc.