Long-term Safety and Efficacy of Lonapegsomatropin in Adults With Growth Hormone Deficiency: Results From a 52-Week Open-Label Extension Trial

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Disclosures

Disclosure of potentially relevant conflicts for Julie M. Silverstein

- Received consulting fees from Xeris and Chiesi, has served on advisory boards for Camurus, and has served as a research investigator for Ascendis Pharma LLC, Fractyl Health Inc., Camurus, Bayer, Sparrow, Recordati, and AbbVie.

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Introduction

GH deficiency in adults can either be persistence of pediatric GH deficiency into adulthood or newly developed during adulthood

GH deficiency is associated with increased body fat, reduced muscle mass and strength, low bone density, dyslipidemia, fatigue, impaired cognition, elevated cardiovascular risk, and reduced quality of life in adults[1,2]

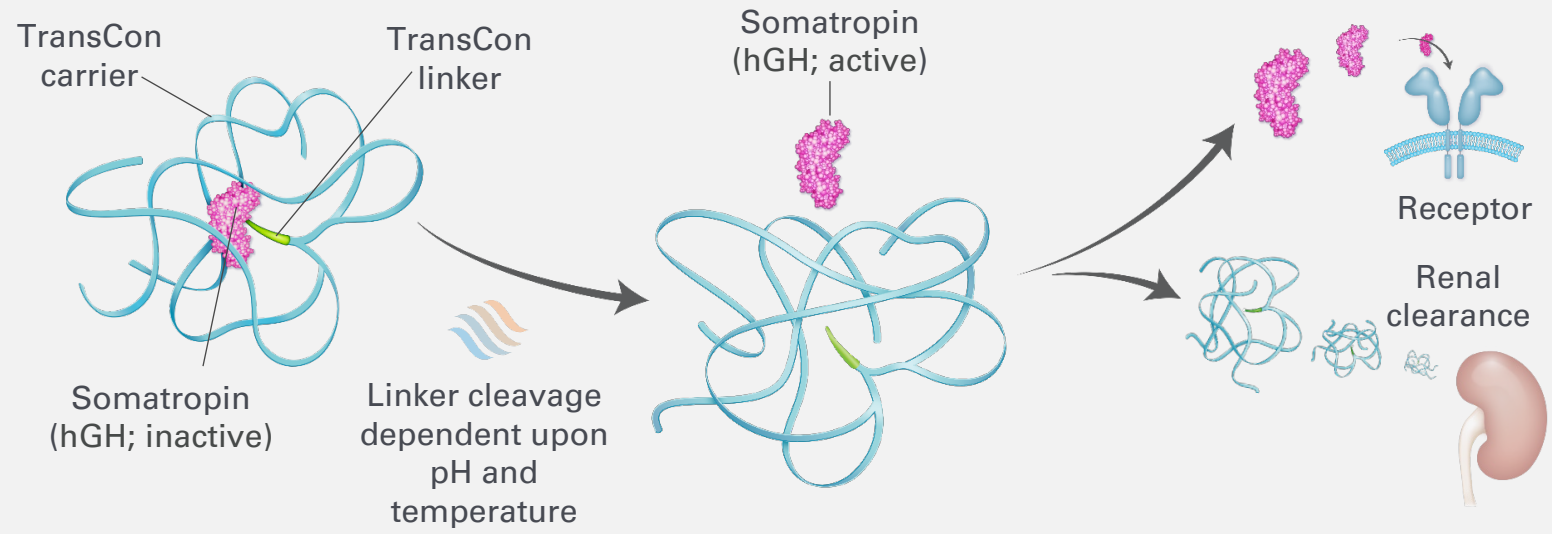
Treatment for GH deficiency includes daily somatropin injections, which may adversely affect adherence in children and adults[3]

Suboptimal adherence and persistence to daily somatropin has been associated with less favorable clinical outcomes, underscoring the need for less burdensome treatments[4,5]

GH, growth hormone.

1. Yuen KCJ, et al. *Endocr Pract*. 2019;25(11):1191-1232. 2. Molitch ME, et al. *J Clin Endocrinol Metab*. 2011;96(6):1587-1609. 3. Rosenfeld RG, et al. *Endocr Pract*. 2008; 14(2): 143-154. 4.Feldt-Rasmussen U, et al. *Endotext*. South Darmouth (MA) 2000. 5. Loftus J, et al. *Front Endocrinol*. 2022; 13: 1014743.

Lonapegsomatropin (TransCon® hGH) Design



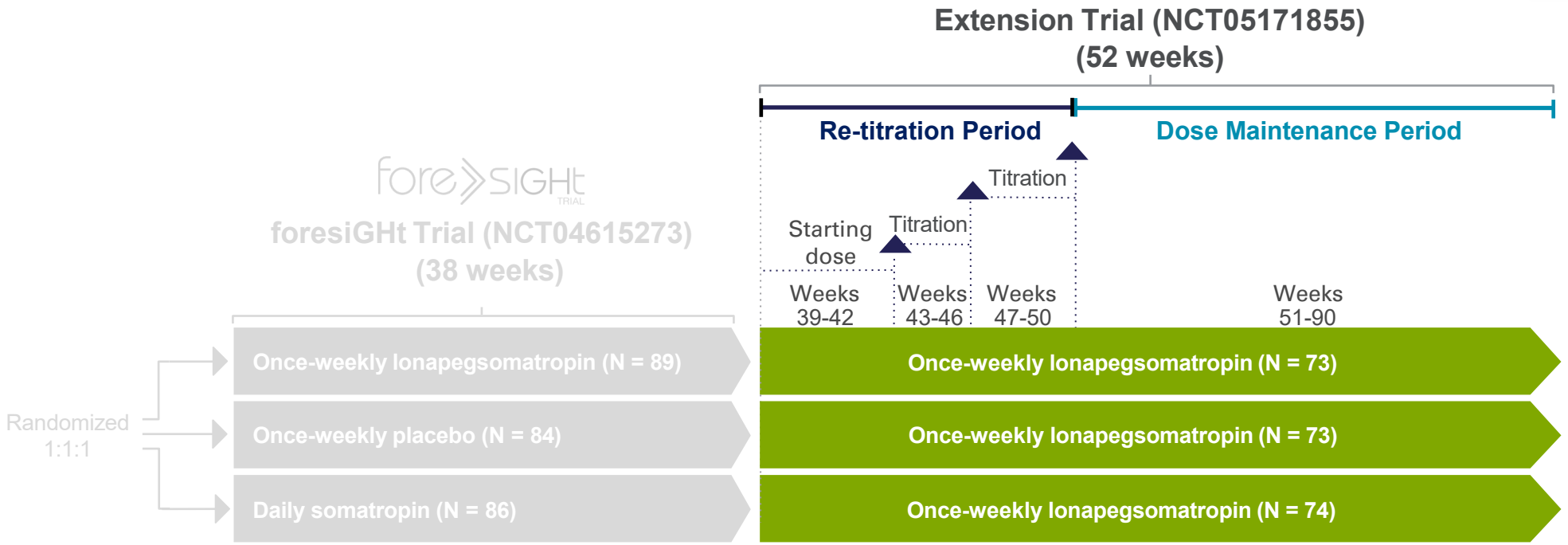
Lonapegsomatropin is a prodrug of somatropin administered once weekly, designed to provide sustained release of active, unmodified somatropin[1,2]

Lonapegsomatropin is approved in the US and EU for pediatric GH deficiency and was approved in the US for adults with GH deficiency in July 2025 based on the phase 3 foresiGHt trial[3]

GH, hormone; hGH, human growth hormone.

1. Sprogøe K, et al. *Endocr Connect*. 2017;6(8):R171-R181.2. Thornton PS, et al. *J Clin Endocrinol Metab.* 2021;106(11):3184-3195. 3. Biller B, et al. *J Clin Endocrinol Metab*. 2025; doi: 10.1210/clinem/dgaf680

Extension trial to the foresiGHt trial



Trial Population

- Of the 248 participants that completed treatment in the foresiGHt trial:
  - 220 (88.7%) continued into the extension trial for up to 90 weeks
  - 202 (91.8%) participants completed 52 weeks of treatment in the extension trial

Regions

- North America, Europe, Asia, and Oceania

Objective

- Evaluate the long-term safety of once-weekly lonapegsomatropin in adults with GH deficiency previously treated in the foresiGHt trial

Safety Endpoints

- AEs, laboratory values, vital signs, immunogenicity, 12-lead ECGs, fundoscopy

AE, adverse event; ECG, electrocardiogram; GH, growth hormone.

Baseline demographics and characteristics at the start of the extension trial

Safety Analysis Population	Lonapegsomatropin/ Lonapegsomatropin (N = 73)	Placebo/ Lonapegsomatropin (N = 73)	Somatropin/ Lonapegsomatropin (N = 74)	Total (N = 220)
Age, mean (SD)	43.6 (13.1)	44.2 (14.3)	41.6 (13.8)	43.4 (13.8)
> 60 years, n (%)	10 (13.7)	9 (12.3)	8 (10.8)	27 (12.3)
Female, n (%)	37 (50.7)	32 (43.8)	31 (41.9)	100 (45.5)
GH deficiency onset				
Adulthood, n (%)	42 (57.5)	38 (52.1)	42 (56.8)	122 (55.5)
Childhood, n (%)	31 (42.5)	35 (47.9)	32 (43.2)	98 (44.5)
BMI, mean (SD) (kg/m^2)	27.0 (5.0)	28.6 (6.7)	28.7 (6.7)	28.1 (6.2)
Etiology of GH deficiency[a]				
Hypothalamic-pituitary surgery	30 (41.1)	27 (37.0)	24 (32.4)	81 (36.8)
Pituitary tumor	20 (27.4)	23 (31.5)	23 (31.1)	66 (30.0)
Structural hypothalamic-pituitary defect	12 (16.4)	18 (24.7)	10 (13.5)	40 (18.2)
Idiopathic	11 (15.1)	8 (11.0)	12 (16.2)	31 (14.1)
Genetic[b]	6 (8.2)	4 (5.5)	7 (9.5)	17 (7.7)
Cranial irradiation	2 (2.7)	5 (6.8)	6 (8.1)	13 (5.9)
Traumatic brain injury	1 (1.4)	1 (1.4)	2 (2.7)	4 (1.8)
Other[c]	6 (8.2)	8 (11.0)	8 (10.8)	22 (10.0)

[a]Categories not mutually exclusive.
[b]Genetic mutations were in *PROP1*, *PROKR2*, and *GH-N*.
[c]Other included: lymphocytic hypophysitis, Langerhans cell histiocytosis, pituitary apoplexy, pituitary gland necrosis, and Sheehan syndrome.
BMI, body mass index; GH, growth hormone; SD, standard deviation.

Lonapegsomatropin was well tolerated for up to 90 weeks

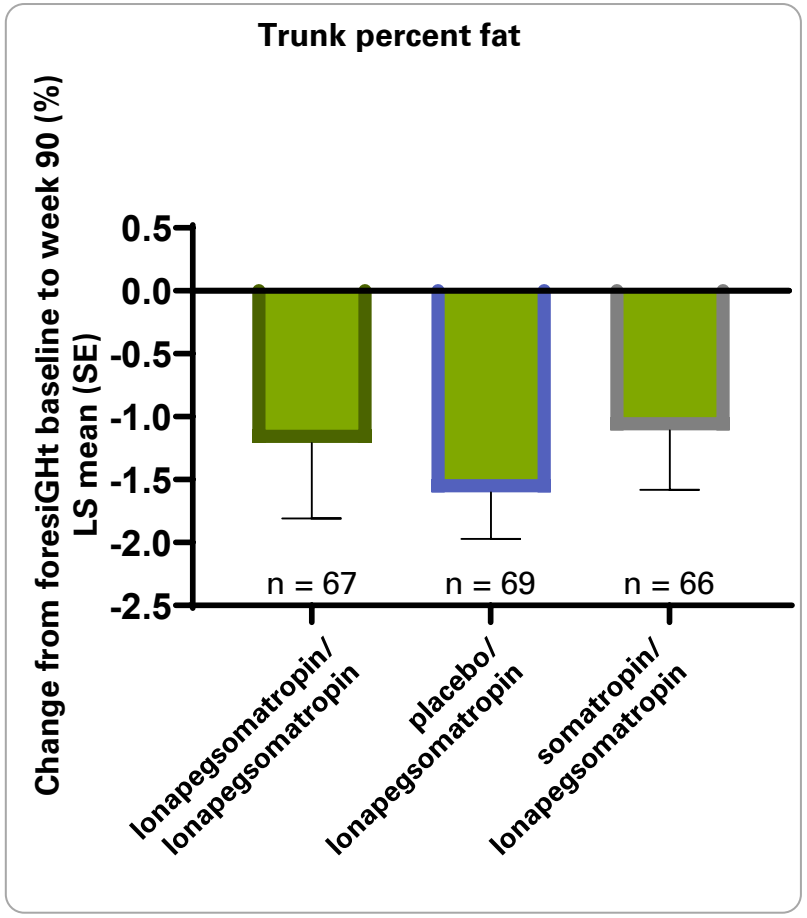
foreSIGHt TRIAL EXTENSION

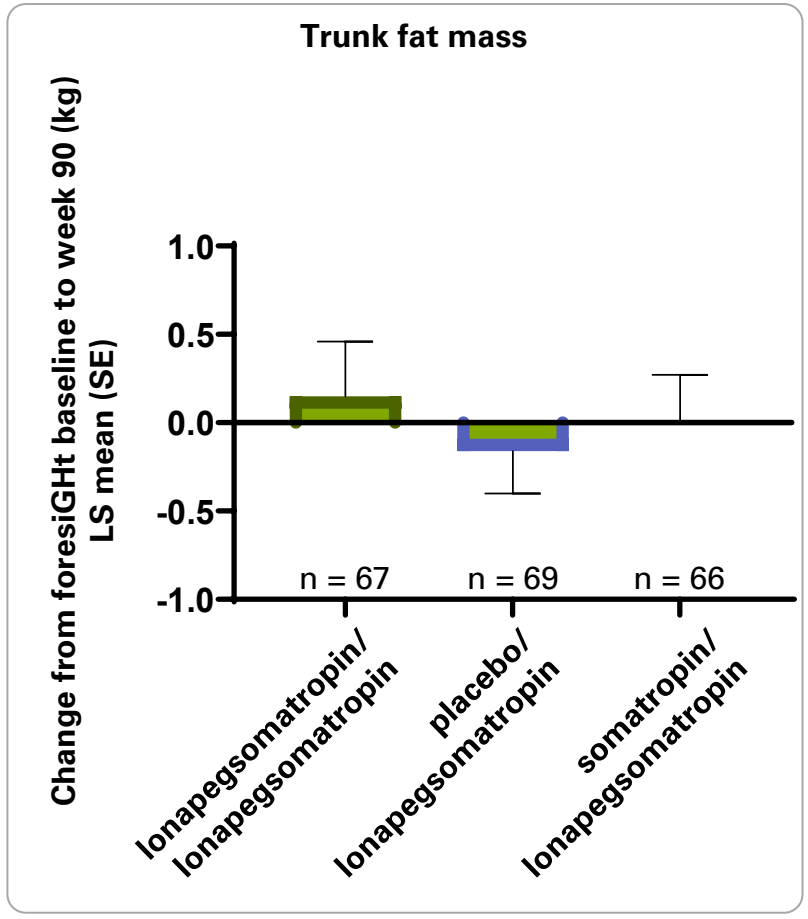
AEs occurring in ≥ 5% of all participants, n (%)	Lonapegsomatropin-treated participants across the foresiGHt and extension trials (N = 236)
Nasopharyngitis	23 (9.7)
Upper respiratory tract infection	22 (9.3)
Headache	19 (8.1)
COVID-19	17 (7.2)
Arthralgia	15 (6.4)
Injection site reactions[a]	12 (5.1)

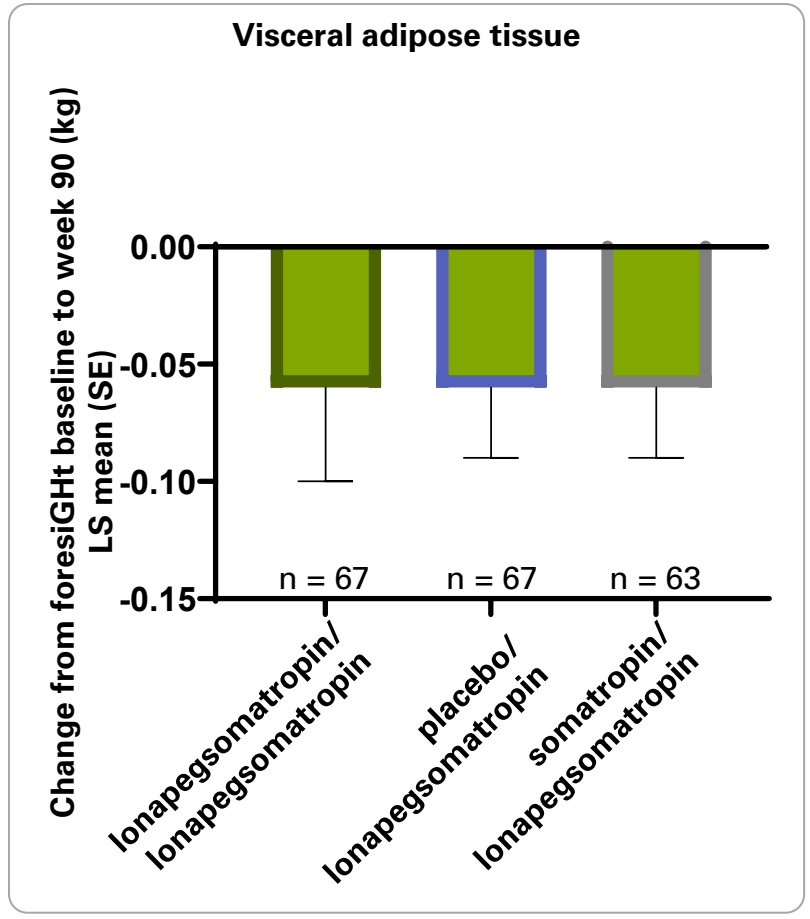
- Most AEs in lonapegsomatropin-treated participants were mild or moderate
- There was a low incidence (3.8%) of treatment discontinuations due to AEs
- Injection site reactions were infrequent (5.1%) and were mild or moderate

[a]Combined term (injection site atrophy, erythema, hemorrhage, pain, and cellulitis), all assessed as treatment-related by the investigator.
AE, adverse event.

Body composition outcomes were improved from foresiGHt baseline through week 90







Note. The difference in change from foresiGHt baseline at week 90 was estimated using an ANCOVA model including treatment arm, region, baseline age group, sex, concomitant oral estrogen at screening (yes vs no), GH deficiency onset (adult vs childhood), and baseline value of the endpoint as covariates.

ANCOVA, analysis of covariance; GH, growth hormone; LS, least squares; SE, standard error.

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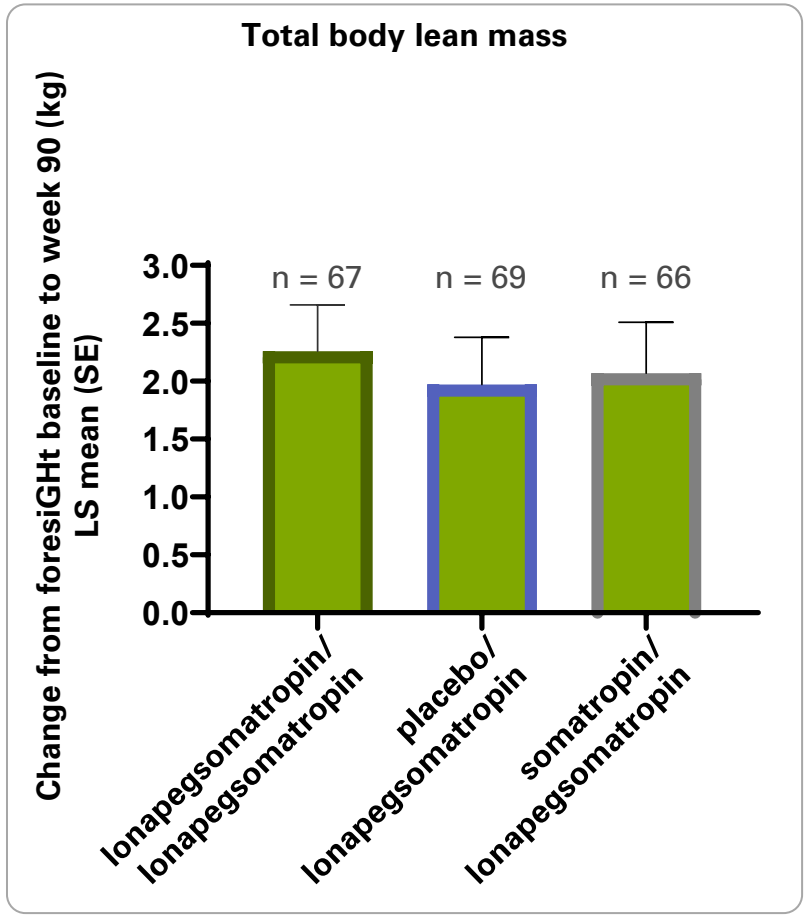

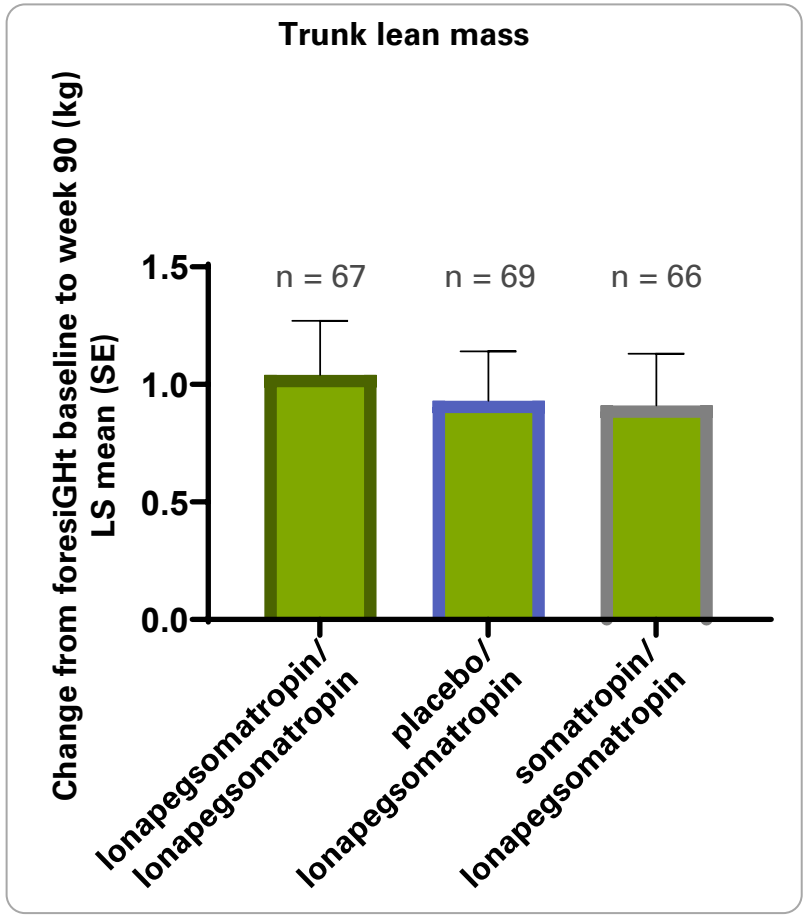

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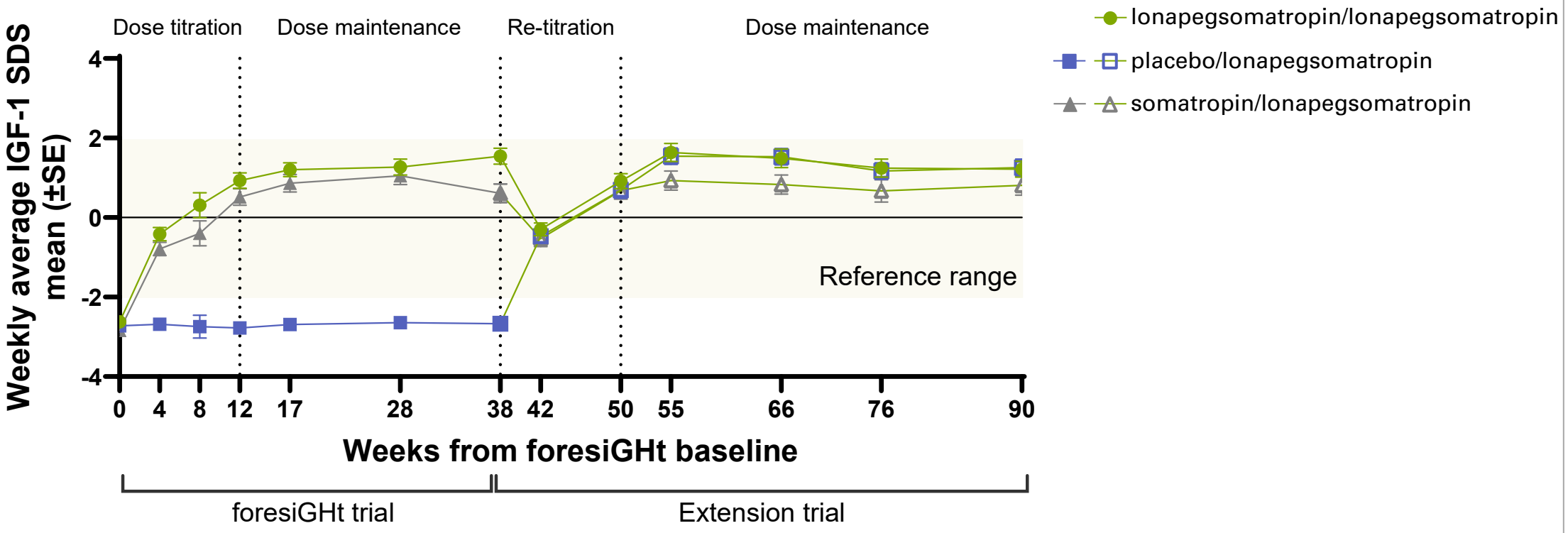
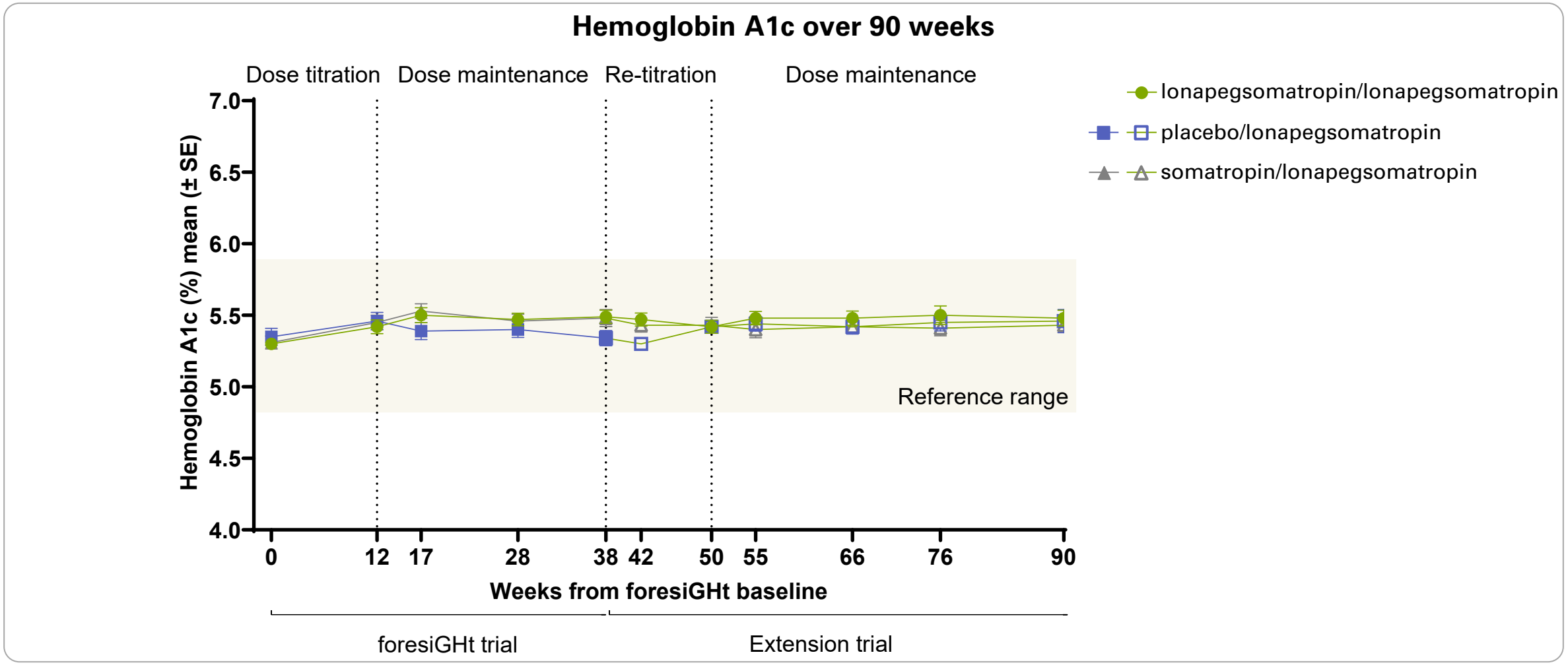
Weekly average IGF-1 SDS was maintained within the reference range through week 90



Note. Estimated weekly average IGF-1 SDS was calculated using the algorithm described by Lin, et al[1].
1. Lin Z, et al. *J Endocr Soc*. 2022; 6(1):bvab168. doi:10.1210/jendso/bvab168.
IGF-1, insulin-like growth factor 1; SDS, standard deviation score; SE, standard error.

Mean hemoglobin A1c remained stable through week 90



SE, standard error.

Low incidence of antibodies during the foresiGHt and extension trials

Treatment-emergent antibodies	Lonapegsomatropin-treated participants across the foresiGHt and extension trials (N = 236)
anti-hGH antibodies, n (%)	8 (3.4)
anti-lonapegsomatropin antibodies, n (%)	8 (3.4)
anti-PEG binding antibodies, n (%)	2 (0.9)

- Antibodies were low titer and transiently detected
- No neutralizing antibodies were detected

Note. Percent is based on the number of participants who had post-baseline assessments.
hGH, human growth hormone; PEG, polyethylene glycol.

Lonapegsomatropin was associated with improvements in TRIM-AGHD scores through week 90

foreSIGHt TRIAL EXTENSION

	Responder Analysis of TRIM-AGHD Total Score[a]		
	Lonapegsomatropin/ Lonapegsomatropin (N = 73)	**Placebo/ Lonapegsomatropin (N = 73)**	**Somatropin/ Lonapegsomatropin (N = 74)**
Number of responders at week 90[b] % (95% CI)	30/69 43.5% (31.8, 55.2)	28/69 40.6% (29.0, 52.2)	24/67 35.8% (24.3, 47.3)
Among responders, change from foresiGHt baseline to week 90 in TRIM-AGHD, mean (SE)	-21.5 (1.79)	-19.4 (1.23)	-22.7 (2.07)

Decreased TRIM-AGHD scores following lonapegsomatropin treatment indicated a reduced burden of GH deficiency

PRO, patient-reported outcome; SE, standard error; TRIM-AGHD, treatment-related impact measure-adult growth hormone deficiency.

[a]Participants were classified as responders if the change in TRIM-AGHD total score from the start of the foresiGHt trial decreased by ≥ 10 points, consistent with the established minimal important difference.[1]
[b]The number of participants meeting the responder threshold/number of participants with non-missing TRIM-AGHD total score at week 90.

1. Brod M et al. *Pharmacoecon Open*. 2018; 3: 71-80.

Conclusions

Lonapegsomatropin was generally well tolerated and demonstrated efficacy over 52 weeks in the open-label extension, and up to 90 weeks across the foresiGHt and extension trials

- A high percentage (88.7%) of participants rolled over from the foresiGHt trial and > 90% of these participants completed 52 weeks of treatment in the open-label extension
- Body composition parameters showed overall improvement from the foresiGHt trial baseline through the end of the extension trial
- These findings support the long-term safety and efficacy profile of once-weekly lonapegsomatropin for adults with GH deficiency

GH, growth hormone.

Ascendis Pharma and the authors thank the participants, caregivers, study sites, and investigators who participated in this clinical trial.

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