Results of the foresiGHt Trial Support the Efficacy and Safety of Once-Weekly Lonapegsomatropin in Adults with Growth Hormone Deficiency

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Presented on behalf of the 116 foresiGHt investigators

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Adult Growth Hormone Deficiency (GHD)

Adult GHD can either be persistence of pediatric GHD into adulthood or newly developed during adulthood

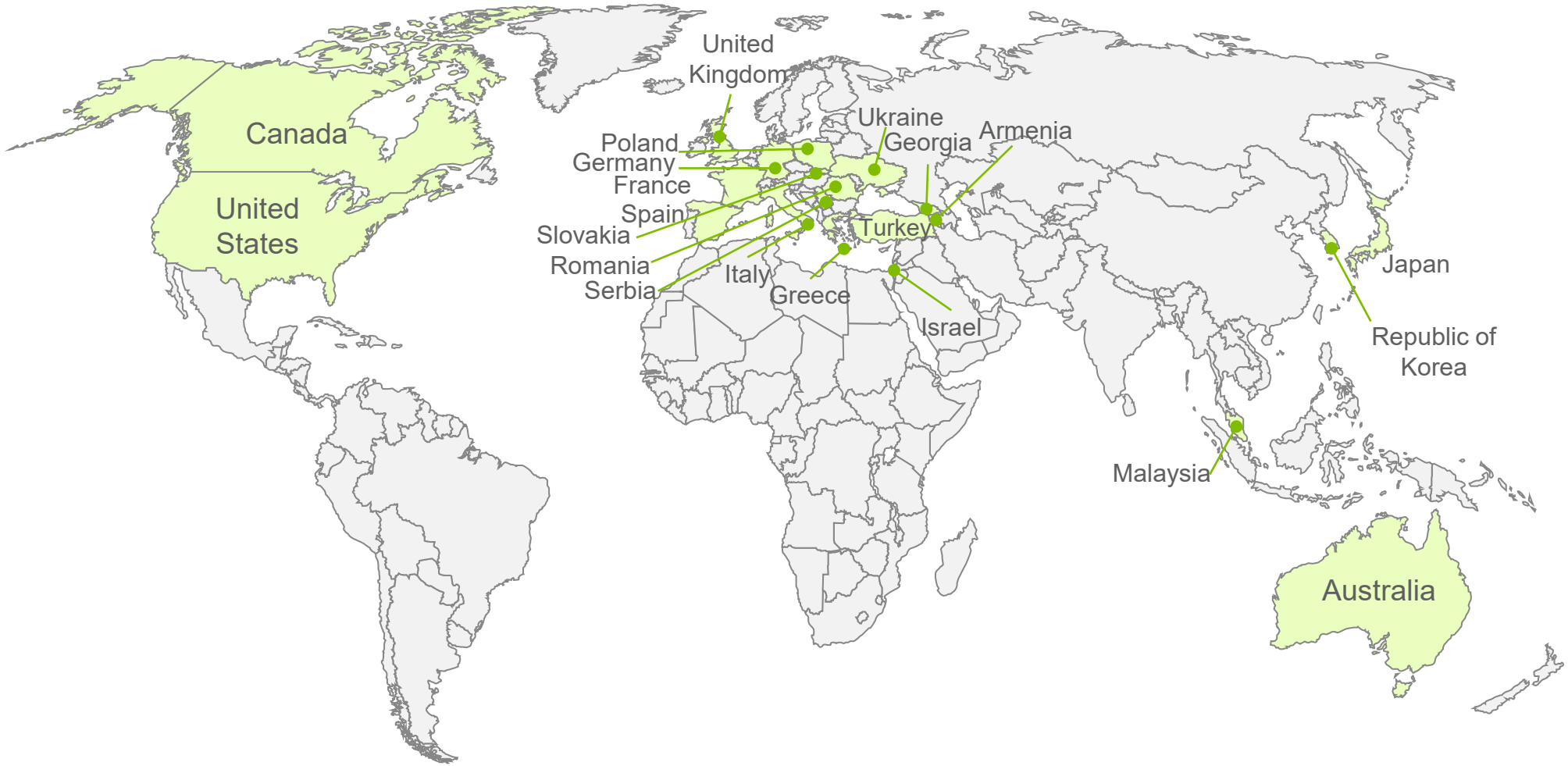
Causes: hypothalamic/pituitary tumors, surgery/radiation, trauma/vascular injury, infiltrative/infectious/inflammatory disorders, congenital defects, idiopathic disease

Associated with low bone density, increased body fat, reduced muscle mass, decreased strength, abnormal lipids, low energy, and poor concentration[1,2, 3]

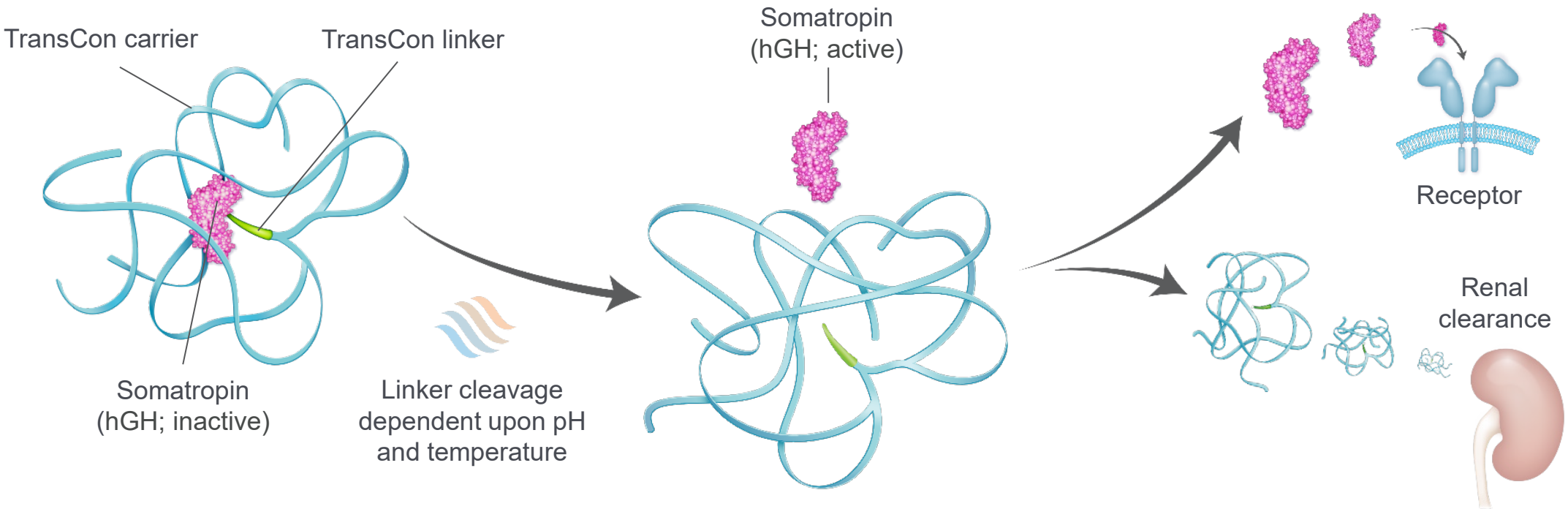
Growth hormone (GH) replacement therapy with daily somatropin injections has been associated with improved body composition, improved lipids and other cardiovascular risk markers, increased bone mineral density, and improved quality of life[1, 2, 4]

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. Feldt-Rasmussen U,et al. Clinical Management. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; May 23, 2022. 4. Leong GM, Johannsson G. *Horm Res.* 2003;60(suppl 1):78-85.

The foresiGHt trial was conducted at 116 sites in 21 countries on 4 continents



Lonapegsomatropin (TransCon hGH) design



- Lonapegsomatropin is a once-weekly prodrug of somatropin designed to provide sustained release of active, unmodified somatropin[1,2]
- The unmodified, unbound somatropin released from lonapegsomatropin has the identical 191 amino-acid sequence and size (22 kDa) as endogenous growth hormone[1, 3]

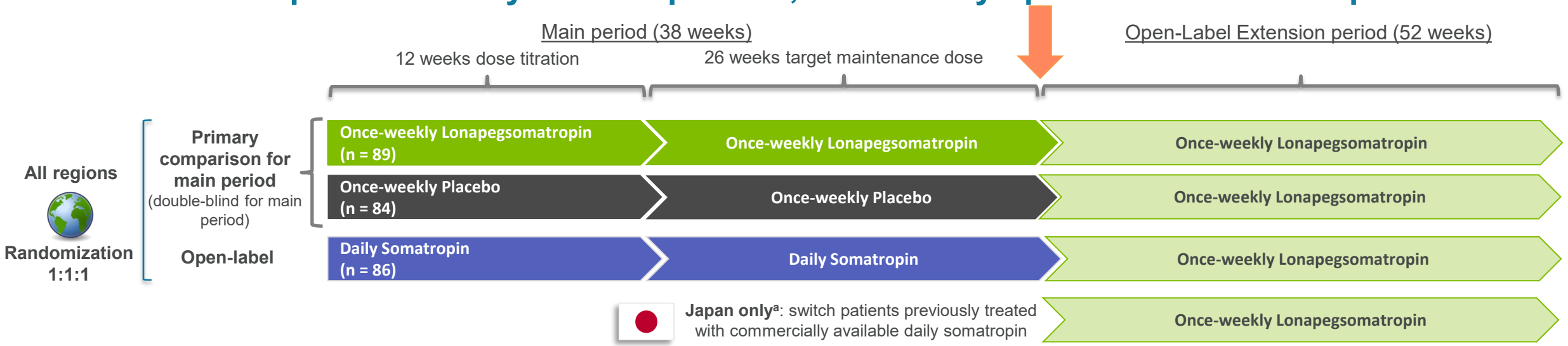
Approved for children in the US[4] since August 2021 and the EU[5] since Jan 2022

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. Blum WF, et al. *Endocr Connect*. 2018;7(6):R212-R222. 4. SKYTROFA® (lonapegsomatropin-tcgd) [package insert]. Palo Alto, CA: Ascendis Pharma, Inc; 2024. 5. SKYTROFA. SmPC. EPAR product information. EMA. 2023.

The phase 3 foresiGHt trial of lonapegsomatropin in adults with growth hormone deficiency

Double-blind, placebo-controlled main period with open-label daily somatropin arm, followed by open-label extension period



Key Eligibility Criteria

- Adults with GHD
- Aged 23-80 years
- GH treatment-naïve or no GH therapy in past 12 months
- IGF-I SDS ≤ -1.0 at screening

Primary Objective

Demonstrate efficacy compared to placebo

Primary Efficacy Endpoint

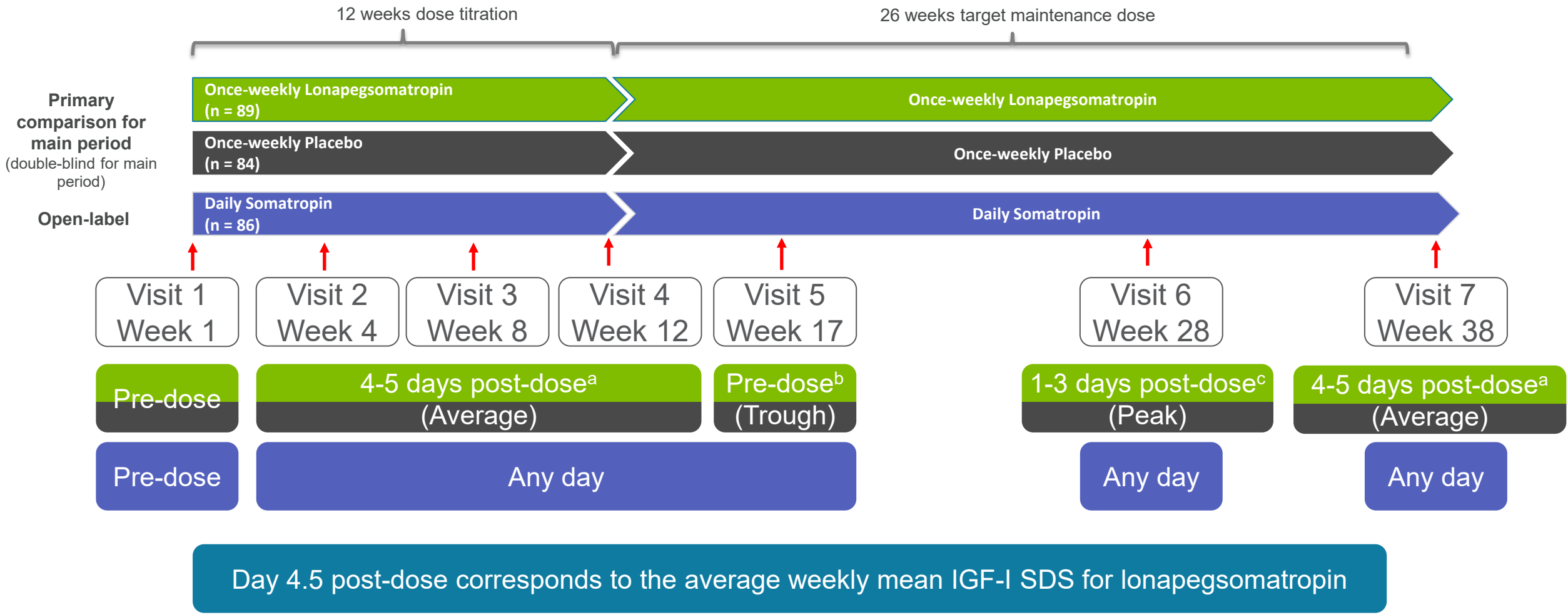
Change from baseline in trunk % fat at Week 38

Secondary Efficacy Endpoints

Change from baseline in total body lean mass and trunk fat mass at Week 38

[a]13 participants from the Japan only arm have enrolled in the open-label extension

Timing of visits in foresiGHt main period (38 weeks)



[a]corresponds to average mean IGF-I SDS level during the week
[b]corresponds to trough IGF-I SDS level at Week 17 for lonapegsomatropin (144-168 ±3 hours post-dose)
[c]corresponds to peak IGF-I SDS level at Week 28 for lonapegsomatropin (24-73 ±3 hours post-dose)

Dosing was uptitrated over 12 weeks until fixed maintenance dose was reached

Lonapegsomatropin dosing table (hGH/w)			
Week (w)	**Dose Group 1 (oral estrogen intake [any age] or <30 years old) (n = 91)**	**Dose Group 2 (≥30 to ≤60 years old; no oral estrogen intake) (n = 134)**	**Dose Group 3 (>60 years old; no oral estrogen intake) (n = 34)**
1-4	2.1 mg	1.4 mg	0.7 mg
5-8	3.6 mg	2.1 mg	1.4 mg
9-12	5.2 mg	3.0 mg	2.1 mg
13-38 (Maintenance Period)	6.3 mg	4.3 mg	3.0 mg

- Fixed, non-weight-based dosing (not titrated to a certain IGF-I response)
- Dose reductions permitted in case of persistent AEs or other safety parameters attributable to GH
- Dose reduction per protocol for average weekly IGF-I SDS ≥2.0

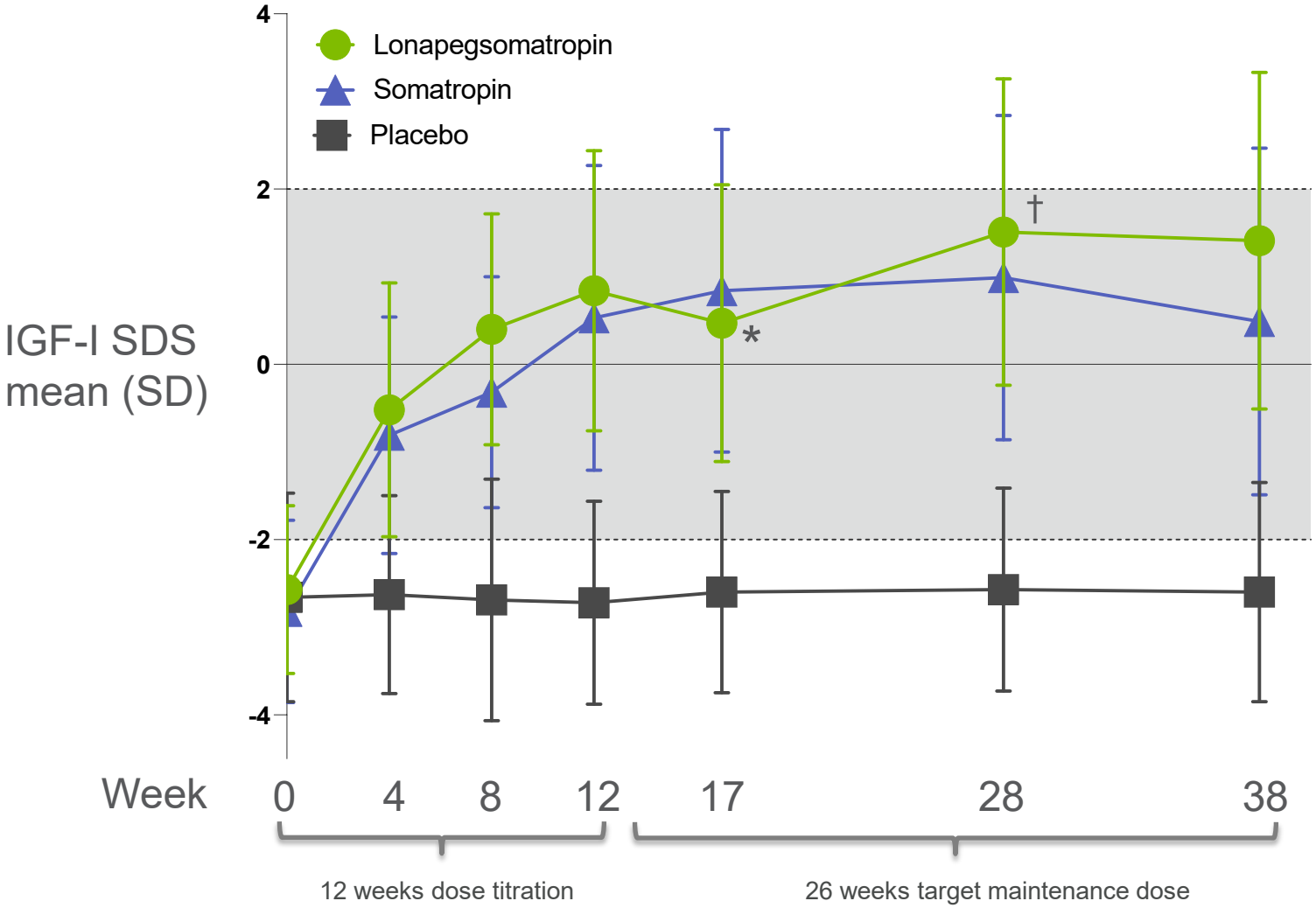
Baseline demographics and characteristics were similar between treatment arms

ITT Population	Lonapegsomatropin (n = 89)	Placebo (n = 84)	Somatropin (n = 86)	Total (N = 259)
Age, mean (SD)	43.0 (13.4)	44.1 (14.7)	41.3 (14.3)	42.8 (14.2)
>60 years, n (%)	12 (13.5%)	11 (13.1%)	11 (12.8%)	34 (13.1%)
Female, n (%)	42 (47.2%)	39 (46.4%)	38 (44.2%)	119 (45.9%)
on oral estrogen, n (%)	21 (23.6%)	16 (19.0%)	18 (20.9%)	55 (21.2%)
Diabetes mellitus, n (%)	5 (5.6%)	4 (4.8%)	2 (2.3%)	11 (4.2%)
GHD onset				
Adulthood, n (%)	50 (56.2%)	46 (54.8%)	49 (57.0%)	145 (56.0%)
Childhood, n (%)	39 (43.8%)	38 (45.2%)	37 (43.0%)	114 (44.0%)

Baseline demographics and characteristics were similar between treatment arms

ITT Population	Lonapegsomatropin (n = 89)	Placebo (n = 84)	Somatropin (n = 86)	Total (N = 259)
Trunk percent fat (DXA), mean (SD)	39.7 (7.4)	40.5 (8.8)	39.3 (7.8)	39.8 (8.0)
BMI (kg/m^2), mean (SD)	27.0 (5.0)	28.5 (6.5)	28.6 (7.2)	28.0 (6.3)
IGF-I SDS, mean (SD)	-2.6 (1.0)	-2.7 (1.2)	-2.8 (1.0)	-2.7 (1.1)
Additional pituitary hormone deficiencies				
GHD and additional pituitary hormone deficiencies, n (%)	83 (93.3%)	78 (92.9%)	83 (96.5%)	244 (94.2%)
GHD only, n (%)	5 (5.6%)	5 (6.0%)	3 (3.5%)	13 (5.0%)

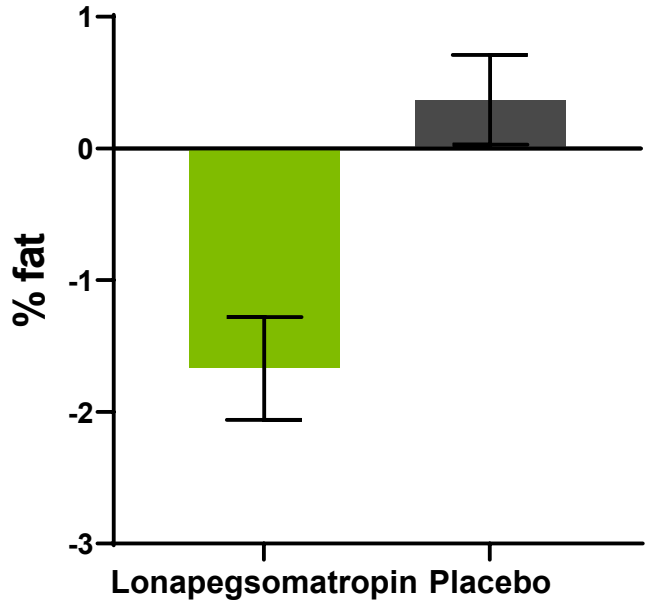
Lonapegsomatropin and somatropin increased mean average IGF-I SDS to within the reference range



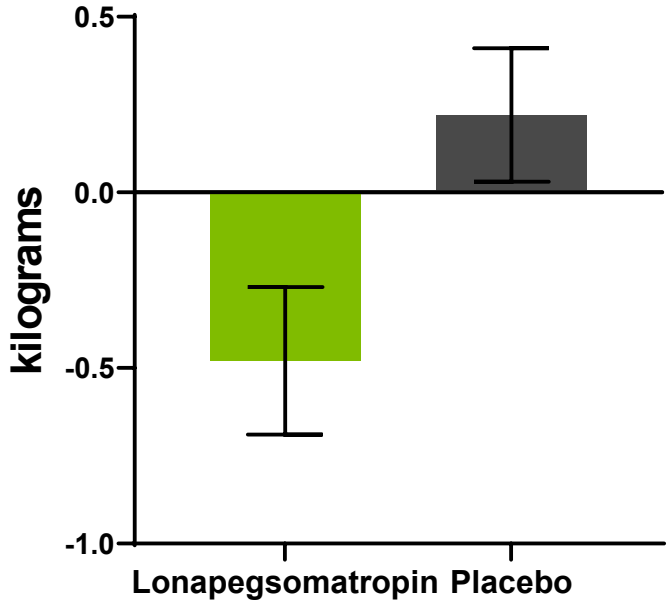
*trough IGF-1 SDS; †peak IGF-1 SDS

Lonapegsomatropin demonstrated superiority over placebo on change from baseline in body composition endpoints at week 38

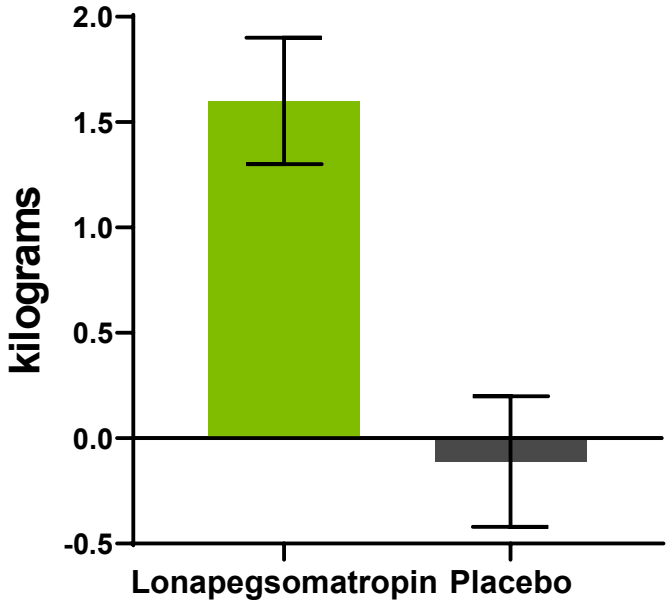
Primary Efficacy Endpoint
Trunk % Fat



Secondary Efficacy Endpoint
Trunk Fat Mass



Secondary Efficacy Endpoint
Total Body Lean Mass



LS mean difference [95% CI] Lonapegsomatropin minus placebo	**-2.04** [-2.94, -1.14] *P* < .0001	**-0.7** [-1.20, -0.21] *P* = .005	**1.7** [0.95, 2.46] *P* < .0001

Error bars represent standard error; The difference in change from baseline at Week 38 was estimated using ANCOVA model including treatment arm, region, baseline age group, gender, concomitant oral estrogen at screening in female subjects and AGHD onset and baseline value of the endpoint as a covariate

Treatment adherence was high in all groups

Safety Population	Lonapegsomatropin (n = 89)	Placebo (n = 84)	Somatropin (n = 85)
Duration of GH treatment (weeks), mean (SD)	37.5 (5.8)	37.5 (5.1)	37.2 (5.1)
Total number of injections, mean (SD)	36.7 (6.1)	36.5 (5.9)	250.2 (43.8)
Total amount of GH (mg), mean (SD)	135.7 (48.9)	0	135.3 (48.1)
Adherence >90%, n (%)	81 (91.0%)	79 (94.0%)	76 (89.4%)

Adherence was assessed by patient diaries

- Mean weekly (SD) dose during the maintenance period (week 13-38) was 4.2 (1.4) mg for lonapegsomatropin and 4.2 (1.4) mg for somatropin
- Lonapegsomatropin provided a similar amount of GH as somatropin over the course of the trial, but with fewer injections

Safety profile was similar between lonapegsomatropin and somatropin

TEAEs occurring in ≥5% of total participants in safety population	Lonapegsomatropin (n = 89)	Placebo (n = 84)	Somatropin (n = 86)
Participants with at least one TEAE	64 (71.9%)	55 (65.5%)	63 (73.3%)
Covid 19	7 (7.9%)	11 (13.1%)	6 (7.0%)
Arthralgia	8 (9.0%)	8 (9.5%)	7 (8.1%)
Nasopharyngitis	5 (5.6%)	11 (13.1%)	6 (7.0%)
Headache	7 (7.9%)	9 (10.7%)	5 (5.8%)
Upper respiratory tract infection	2 (2.2%)	8 (9.5%)	4 (4.7%)
Injection site reaction	4 (4.5%)	4 (4.8%)	5 (5.8%)

- Injection site reaction incidence was low and similar for lonapegsomatropin, somatropin, and placebo
- No deaths occurred in the safety population
- HbA1c levels remained stable in all treatment arms
  - No participants in the lonapegsomatropin arm developed new onset diabetes mellitus
- No TEAEs assessed as related to study drug led to treatment discontinuation

[a]Injection site reactions is a combined term that includes PTs of injection site erythema, bruising, pain, hematoma, hemorrhage, pruritus, and atrophy. All injection site reactions were mild or moderate in severity.

Author's Conclusions

- Lonapegsomatropin has a safety profile comparable to daily GH, superior efficacy compared to placebo, and was well-tolerated
- The wide geographic range, demographics, and high rate of multiple pituitary hormone deficiencies suggest that this was a representative adult GHD patient population
- Once-weekly dosing may be more convenient compared with daily GH for adults with GHD

Acknowledgements

The authors and Ascendis Pharma thank the participants, study site nurses, research coordinators, and other site personnel, and the 116 investigators who participated in this clinical trial.

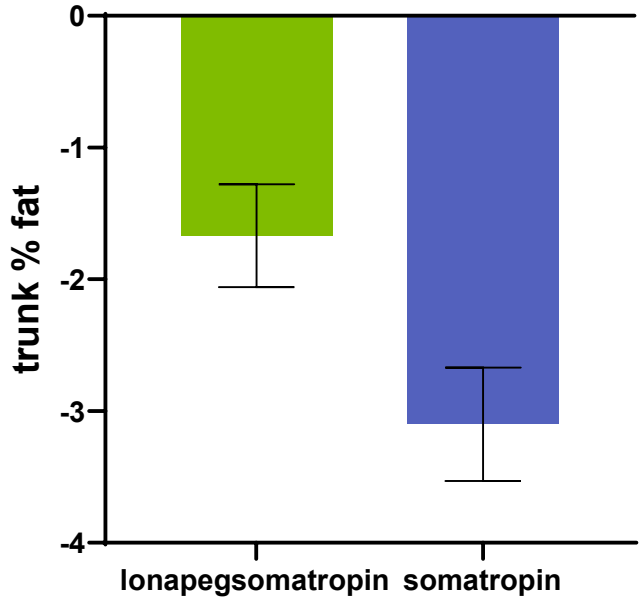
Thank you!

Backup Slides

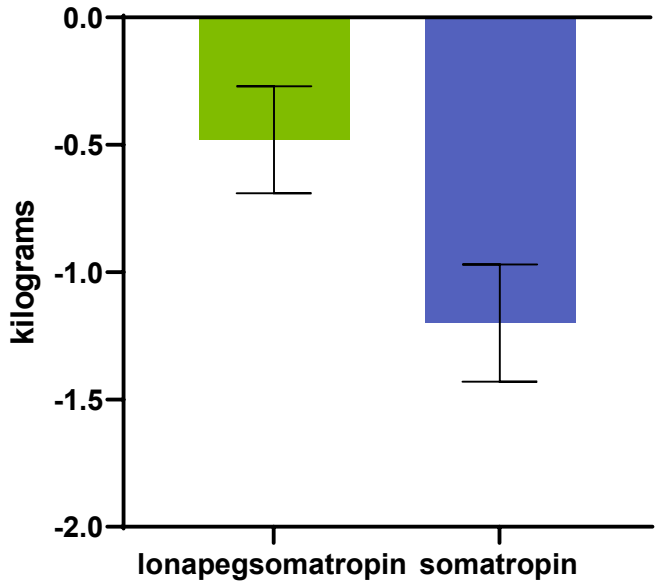
Exploratory efficacy: lonapegsomatropin vs daily somatropin (ITT population)

Change from baseline at Week 38

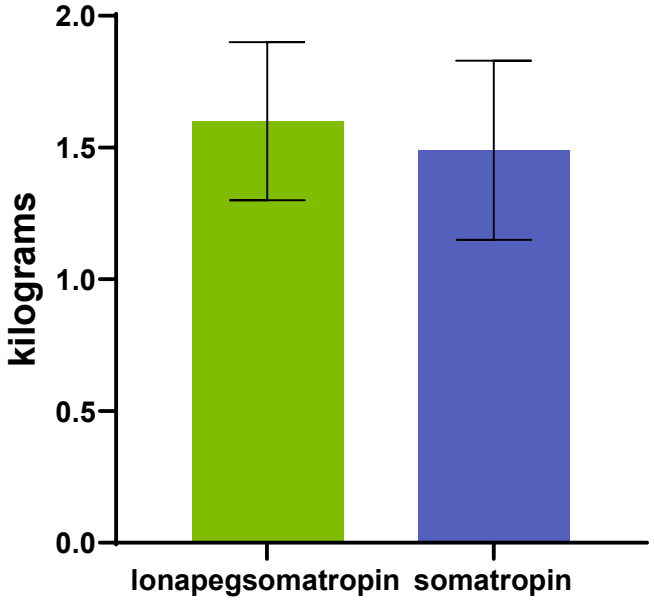
Trunk % Fat



Trunk Fat Mass



Total Body Lean Mass



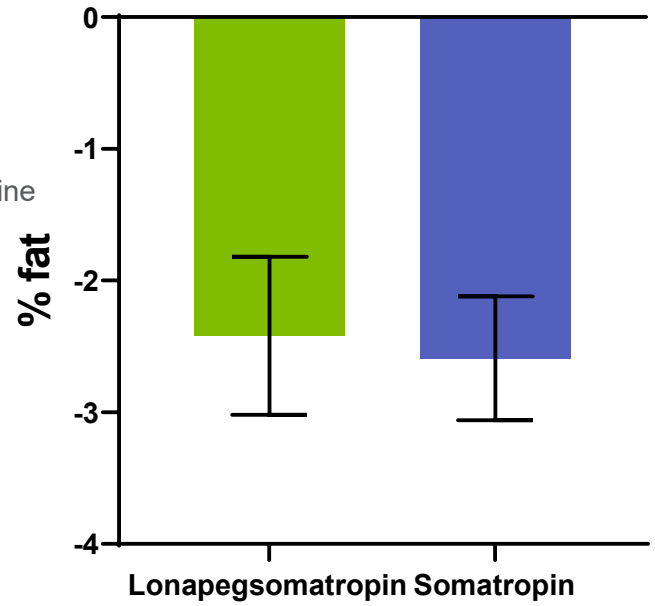
Lonapegsomatropin, n = 89; somatropin, n = 86. Error bars represent standard error; The difference in change from baseline at Week 38 was estimated using ANCOVA model including treatment arm, region, baseline age group, gender, concomitant oral estrogen at screening in female subjects and AGHD onset and baseline value of the endpoint as a covariate

Similar changes in body composition between lonapegsomatropin and somatropin in subset of participants with comparable IGF-I SDS

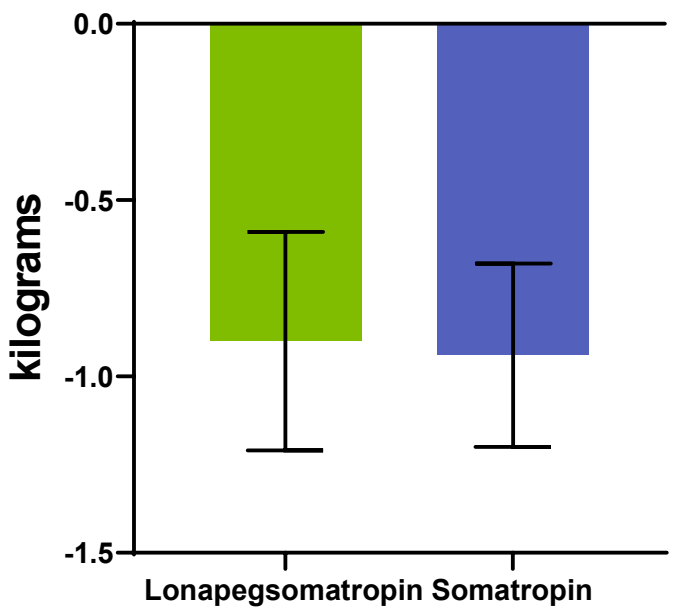
Hypothesis-generating post hoc analysis in subset of participants with average IGF-1 SDS ≤1.75 at Week 38

Change from baseline at Week 38

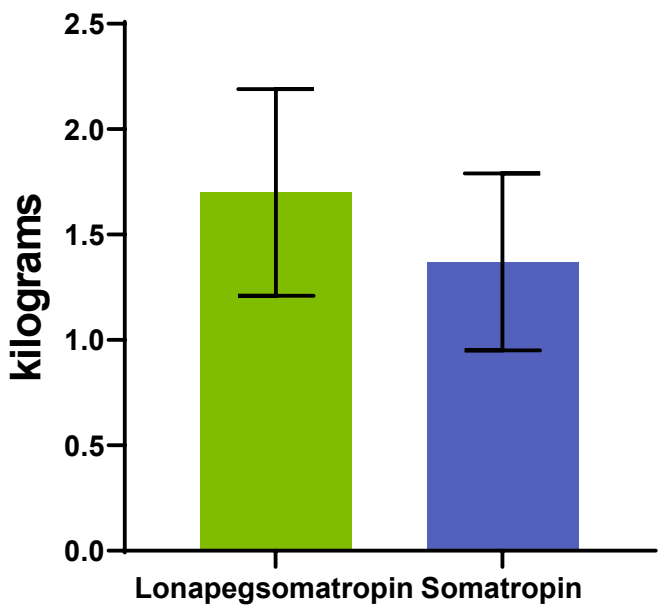
Trunk % Fat



Trunk Fat Mass



Total Body Lean Mass



Lonapegsomatropin, n = 37; somatropin, n = 55. Error bars represent standard error; The difference in change from baseline at Week 38 was estimated using ANCOVA model including treatment arm, region, baseline age group, gender, concomitant oral estrogen at screening in female subjects and AGHD onset and baseline value of the endpoint as a covariate

High retention of participants in foresiGHt

ITT Population	Lonapegsomatropin (n = 89)	Placebo (n = 84)	Somatropin (n = 86)	Total (N = 259)
Early withdrawal from trial, n (%)	3 (3.4%)	3 (3.6%)	3 (3.5%)	9 (3.5%)
Lost to Follow-up	0 (0)	1 (1.2)	0 (0)	1 (0.4)
Withdrawal by Subject	2 (2.2)	1 (1.2)	2 (2.3)	5 (1.9)
Physician Decision[a]	0 (0)	0 (0)	1 (1.2)	1 (0.4)
Adverse Event[b]	1 (1.1)	0 (0)	0 (0)	1 (0.4)
Other [c]	0 (0)	1 (1.2)	0 (0)	1 (0.4)

Most participants completed the 38-week main period (248, 95.8%) and the majority enrolled into the 52-week open-label extension study (220, 84.9%)

[a]Decision made taking into account all reported AEs (edema, myalgia, arthralgia) and patient's willingness, risk/benefit balance. [b]Epilepsy. [c]Patient changed country of residence.

Dosing was uptitrated over 12 weeks until fixed maintenance dose was reached

Daily Somatropin dosing table (hGH/day)			
Week (w)	**Dose Group 1 (oral estrogen intake [any age] or <30 years old) (n = 30)**	**Dose Group 2 (≥30 to ≤60 years old; no oral estrogen intake) (n = 44)**	**Dose Group 3 (>60 years old; no oral estrogen intake) (n = 11)**
1-4	0.3 mg	0.2 mg	0.1 mg
5-8	0.525 mg	0.3 mg	0.2 mg
9-12	0.75 mg	0.425 mg	0.3 mg
13-38 (Maintenance Period)	0.9 mg	0.625 mg	0.425 mg

- Fixed, non-weight-based dosing (not titrated to a certain IGF-I response)
- Dose reductions permitted in case of persistent AEs or other safety parameters attributable to GH
- Dose reduction per protocol for average weekly IGF-I SDS ≥2.0

Randomization Strata

- Dose group
- In the “≥30 to ≤60 years old (no oral estrogen)” dose group, randomization was further stratified by sex
- Diabetes mellitus status

Similar changes in body composition between lonapegsomatropin and somatropin in subset of participants with comparable average IGF-I SDS

Hypothesis-generating post hoc analysis in subset of participants with average IGF-1 SDS ≤1.75 at Week 38

Change from baseline at Week 38	Lonapegsomatropin (n = 37)	Somatropin (n = 55)
Trunk % fat, LS Mean (SE)	-2.42 (0.60)	-2.59 (0.47)
Total body lean mass (kg), LS Mean (SE)	+1.70 (0.49)	+1.37 (0.42)
Trunk fat mass (kg), LS Mean (SE)	-0.90 (0.31)	-0.94 (0.26)
IGF-I SDS at Week 38, mean (SD)	-0.14 (1.37)	-0.48 (1.59)

The difference in change from baseline at Week 38 was estimated using ANCOVA model including treatment arm, region, baseline age group, gender, concomitant oral estrogen at screening in female subjects and AGHD onset and baseline value of the endpoint as a covariate

Lonapegsomatropin demonstrated superiority over placebo in primary and secondary efficacy endpoints

Change from Baseline at Week 38 in ITT Population	Lonapegsomatropin (n = 89)	Placebo (n = 84)	LS Mean Difference [95% CI]	P value
Trunk % fat	-1.67	+0.37	-2.04 [-2.94,-1.14]	<0.0001
Trunk Fat Mass (kg)	-0.48	+0.22	-0.70 [-1.20,-0.21]	0.0053
Total Body Lean Mass (kg)	+1.60	-0.10	1.70 [0.95,2.46]	<0.0001

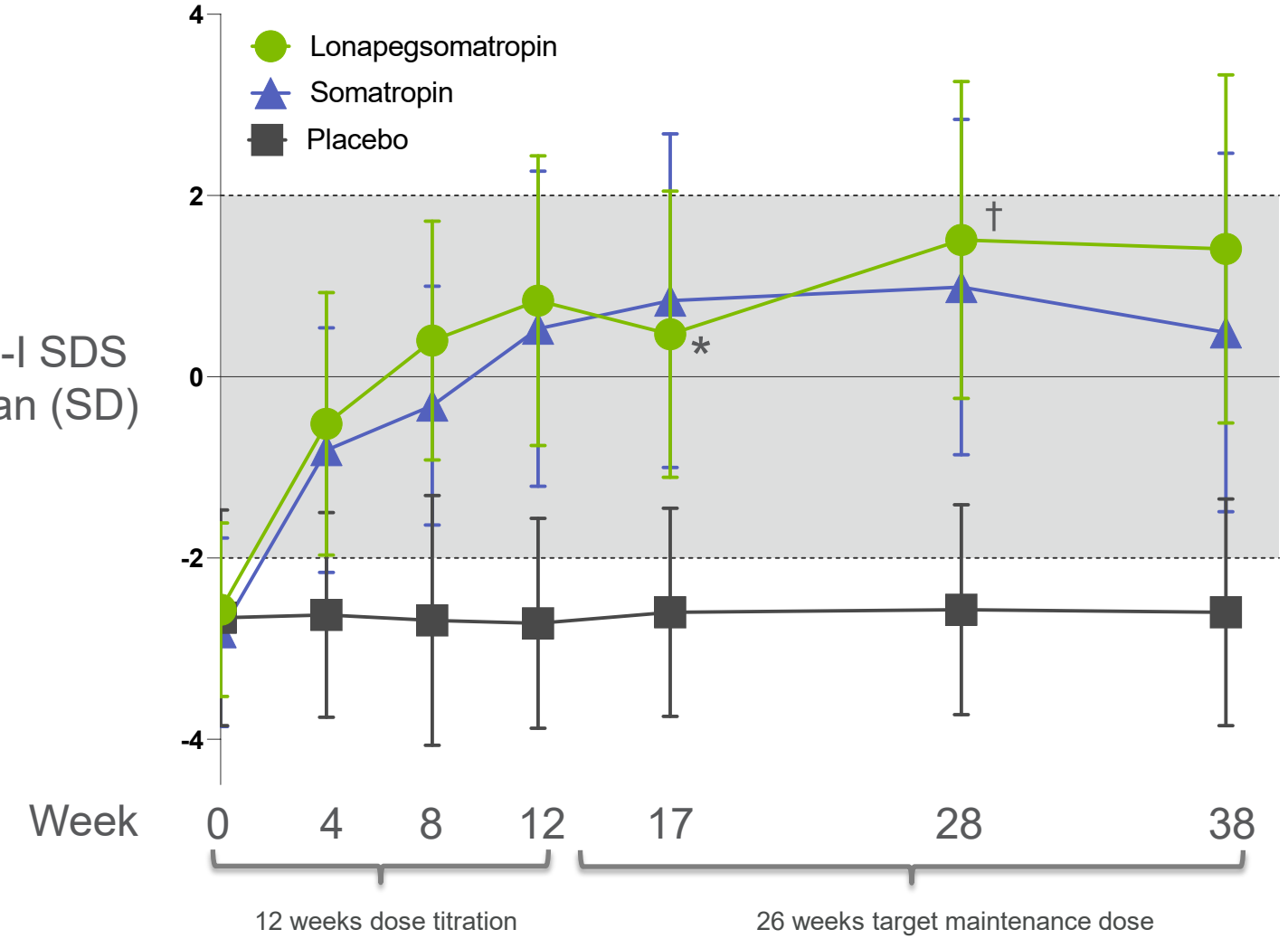
ITT, intention to treat.

The difference in change from baseline at Week 38 was estimated using ANCOVA model including treatment arm, region, baseline age group, gender, concomitant oral estrogen at screening in female subjects and AGHD onset and baseline value of the endpoint as a covariate

Safety profile was similar between lonapegsomatropin and somatropin

Safety Population	Lonapegsomatropin (n = 89)	Placebo (n = 84)	Somatropin (n = 86)
TEAEs	64 (71.9%)	55 (65.5%)	63 (73.3%)
Related TEAEs	22 (24.7%)	11 (13.1%)	19 (22.1%)
Serious TEAEs	4 (4.5%)	1 (1.2%)	6 (7.0%)
Serious and Related TEAE	1 (1.1%)	0	1 (1.2%)
TEAE that Led to Study Drug Discontinuation	1 (1.1%)	0	1 (1.2%)
TEAE Leading to Any Action on Study Drug	8 (9.0%)	1 (1.2%)	11 (12.8%)

Lonapegsomatropin and somatropin increased mean average IGF-I SDS to within reference range



IGF-I for lonapegsomatropin and placebo:

- At most visits, 4-5 days post-dose, corresponding to the weekly **average** IGF-I SDS
- At Week 17, 144-168 ±3 hours post-dose, corresponding to **trough** IGF-I SDS level
- At Week 28, 24-73 ±3 hours post-dose, corresponding to **peak** IGF-I SDS level

*trough IGF-1 SDS; †peak IGF-1 SDS