Somavaratan, a Long-acting Recombinant Human Growth Hormone, for the Treatment of Adults with Growth Hormone Deficiency: Results of VITAL, an Open-label, Dose-finding, International, Phase 2 Study (NCT02526420)

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SWEDISH

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Disclosures

- KCJY: Investigator for Pfizer, Inc.; Opko; Novo Nordisk; and Versartis, Inc. Medical advisory board member for Pfizer, Inc.; Novo Nordisk; Sandoz; and Versartis, Inc.

- BMKB: Received research grants from Novo Nordisk; Opko; and Versartis, Inc., and has acted as consultant to Novo Nordisk; Pfizer; and Versartis, Inc.
- DR, SAY, RWC, BB, EH: Employees of Versartis, Inc.
- TR: Employee of CRO, Versartis, Inc.
- MK-H: Consultant, Versartis, Inc.
- TSB: Investigator for ACON; Abbott Laboratories; Ascensia; Boehringer Ingelheim; BD; Companion Medical; Dexcom; Elcelyx; Glysens; Insulet; Jansen Pharmaceuticals; Lexicon Pharmaceuticals, Inc.; Lifescan; Eli Lilly & Company; Medtronic Minimed; Merck & Co.; Novo Nordisk; Sanofi; Senseonics; Versartis, Inc.; and Yofimeter. Ad hoc consultant to Ascensia, Astra Zeneca, BD, Calibra, Eli Lilly & Company, Medtronic Minimed, Novo Nordisk, and Sanofi. Speaker for Abbott Laboratories, Insulet, Medtronic Minimed, Novo Nordisk, and Sanofi
- KH: Medical advisory board member for Pfizer, Inc., and Versartis, Inc. Speaker bureau member for Ipsen; Novartis Pharmaceuticals; and Pfizer, Inc. Investigator for Novo Nordisk and Versartis, Inc.
- LK: Medical Advisory board member for Pfizer, Inc., and Versartis, Inc. Investigator for Versartis, Inc.
- KM: Investigator for Novo Nordisk and Pfizer, Inc.
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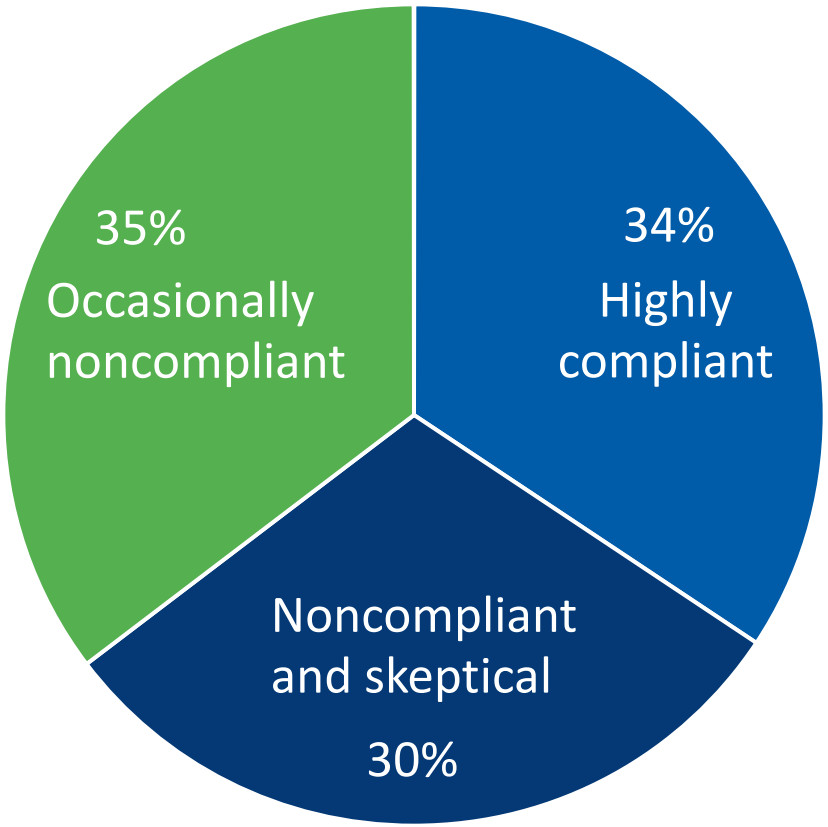
- SN: Investigator for Novo Nordisk and Versartis, Inc.
- DJT: Medical advisory board member for Eisai and Genzyme Corporation; Educational Seminar, Eli Lilly & Company; Principal Investigator for Eisai; Janssen- Cilag; Novo Nordisk; and Versartis, Inc.
- WWW: Investigator for Novo Nordisk and Versartis, Inc. Medical advisory board member for Ipsen; Chiasma; and Versartis, Inc.
- MB: Investigator for Pfizer, Inc.; OPKO; Genexine; and IDS. Speaker for Pfizer, Inc.; Sandoz; and Diasorin. Ad hoc consultant for Versartis, Inc.; OPKO; Sandoz; and Genexine.
- CJS: Medical advisory board member and investigator for Versartis, Inc.
- KSD: Nothing to disclose

Daily administration of GH injections can affect compliance



- Questionnaire on daily GH to 158 adult GHD patients
- High level of noncompliance
- Even in “highly compliant” segment, up to 21 doses missed over 3 months
- Discomfort with injection was one factor strongly correlated with noncompliance

Rosenfeld RG, Bakker B. *Endocr Pract*. 2008;14:143-154.

Growth Hormone Research Society perspective on the development of long-acting GH (LAGH) preparations

Report from the GRS Workshop on long-acting GH:

- LAGHs have different pharmacodynamic properties
- Offer convenience
- Potential for increased adherence and improved outcomes
- LAGH may be an advance over daily GH, with detailed study needed

Today we will show results from the phase 2 study of somavaratan (VRS-317) in AGHD

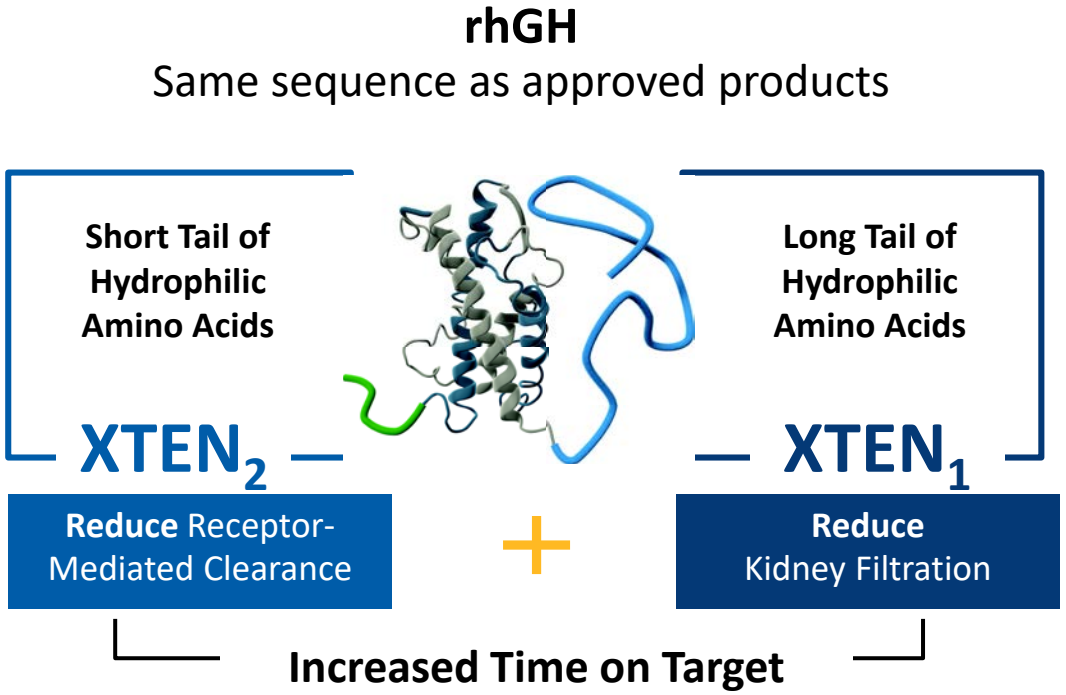
Table 1 Long-acting GH preparations.

	Company	Product
Depot formulations		
	Genentech	Nutropin Depot
	LG Life Sciences, Ltd.	LB3002
	Altus Pharmaceuticals	ALTU-238
	Critical Pharmaceuticals	CP016
PEGylated formulations		
	Ambrx	ARX201
	Novo Nordisk A/S	NNCI126-0083
	Pfizer	PEG-GH PHA-794428
	Bolder BioTechnology	BBT-031
	GeneScience Pharmaceuticals Co., Ltd.	Jintrolong
Pro-drug formulations		
	Ascendis	TransCon PEG GH (ACP-001)
Non-covalent albumin binding GH compound(s)		
	Novo Nordisk A/S	NNC0195-0092
GH fusion proteins		
	Asterion	ProFuse GH
	Genexine and Handok	GX-H9
	Hanmi Pharmaceutical Co.	LAPSrhGH/HM10560A
	OPKO Health and Pfizer	MOD-4023
	Teva	TV-1106
	Versartis	VRS-317

Christiansen JS, et al. *Eur J Endocrinol.* 2016:174:C1-C8.

Somavaratan: A novel, long-acting form of rhGH

- Rapid absorption with long serum half-life due to delayed clearance[1,2]
- A phase 1 PK/PD study of single-dose administration in AGHD demonstrated:[2]
  - Extended elimination half-life
  - Durable IGF-I response



- Drug peak and AUC exposure proportional to dose[2,3]

IGF-I = insulin-like growth factor 1; PK/PD = pharmacokinetic/pharmacodynamic; rhGH = recombinant human growth hormone.

1. Cleland JL, et al. *J Pharm Sci.* 2012;101:2744-54; 2. Yuen, et al. *J Clin Endocrinol Metab*. 2013;98:2595-603; 3. Moore WV, et al. *J Clin Endocrinol Metab.* 2016;101:1091-1097.

Phase 2 somavaratan study objectives

Versartis International Trial in Adults with Long-acting Growth Hormone (VITAL)

- **Evaluate:**
  - ***Starting dose***
  - ***Dose titration plan***
  - ***Safety***

- **Determine** IGF-I response with **30-day dosing**

Methods: Patient selection

Key Criteria

Inclusion

- Aged 23 to 70 years
- Adult GHD diagnosed according to established guidelines[1]
- Body-mass index of 19.0–35.0 kg/m^2
- Stable pituitary condition and hormone replacement
- rhGH therapy washed out ≥ 14 days

Exclusion

- History of:
  - Diabetes mellitus or inadequate glucose control
  - Malignancy
  - Migraines
- Current significant medical condition
- Untreated adrenal insufficiency or free thyroxine outside the normal reference range

1. Ho KK, et al. *Eur J Endocrinol.* 2007;157:695-700.

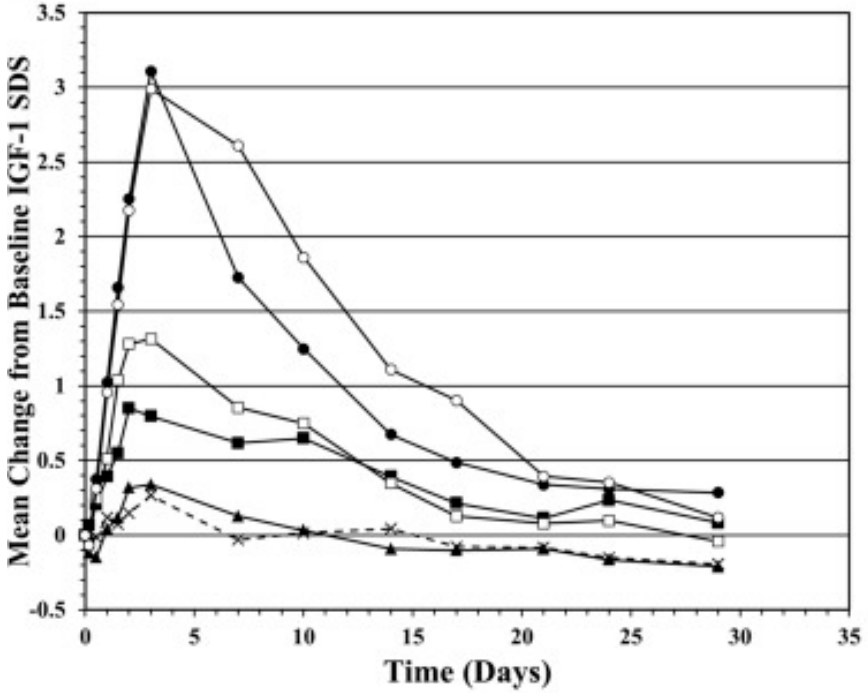
Dosing cohorts

- Patients were allocated into 3 starting dose cohorts based on age and oral estrogen use

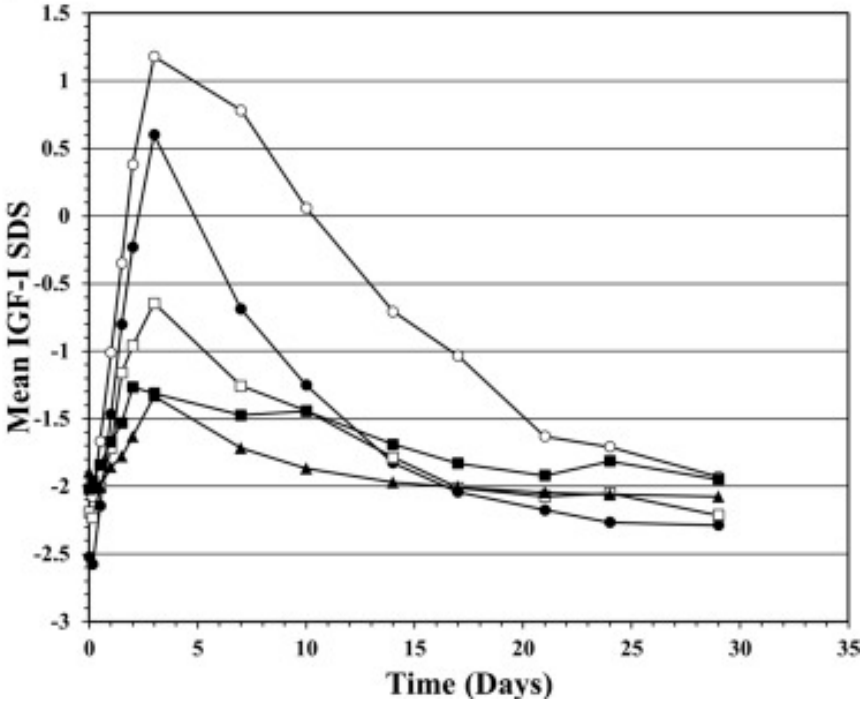
Cohort A	Cohort B	Cohort C
• Age ≥ 35 years • 0.6 mg/kg/month	• Age < 35 years • 0.8 mg/kg/month	• Females on oral estrogen, regardless of age • 1.0 mg/kg/month

Dosing based on a single ascending dose study in adults

Mean change in IGF-I SDS



Normalization of IGF-I SDS

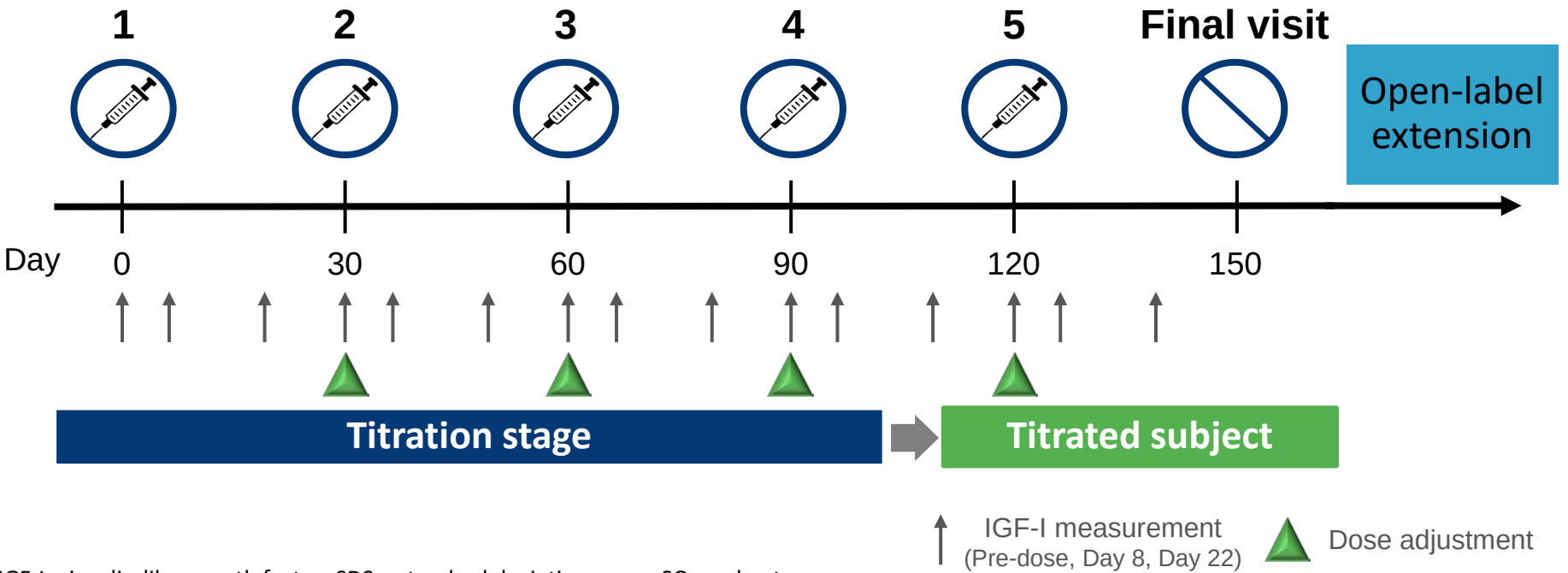


X Placebo ▲ 0.05 mg/kg ■ 0.10 mg/kg □ 0.20 mg/kg ● 0.40 mg/kg ○ 0.80 mg/kg

Yuen KCJ, et al. *J Clin Endocrinol Metab.* 2013;98:2595-2603.

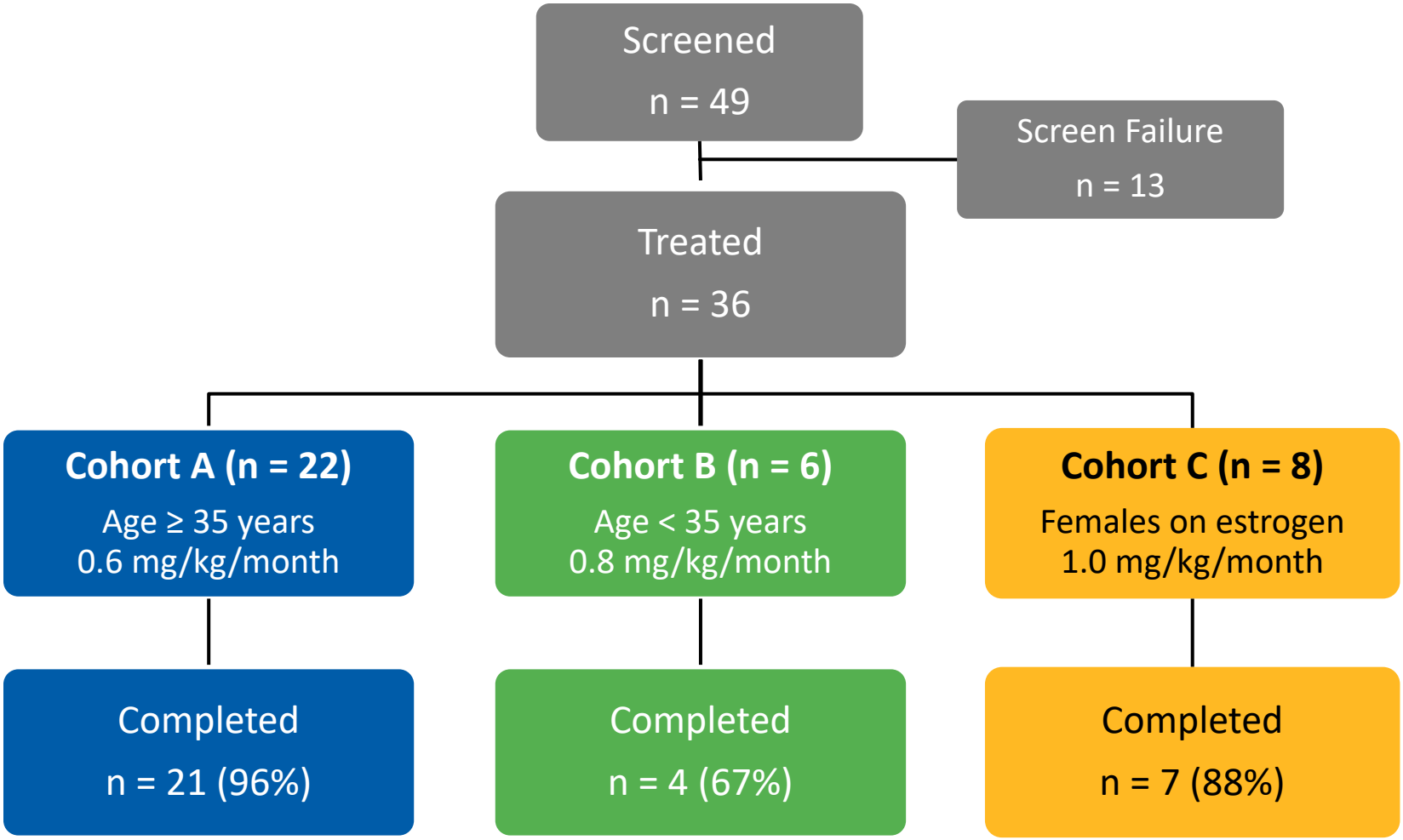
Study design

- Patients received 5 monthly SQ doses of somavaratan in clinic
- Target IGF-I SDS (mean of pre-dose and Day 8): 0 to 1.5
- 4 dose adjustments were permitted until 2 consecutive means were within the target range



IGF-I = insulin-like growth factor; SDS = standard deviation score; SQ = subcutaneous.

Results: Patient disposition



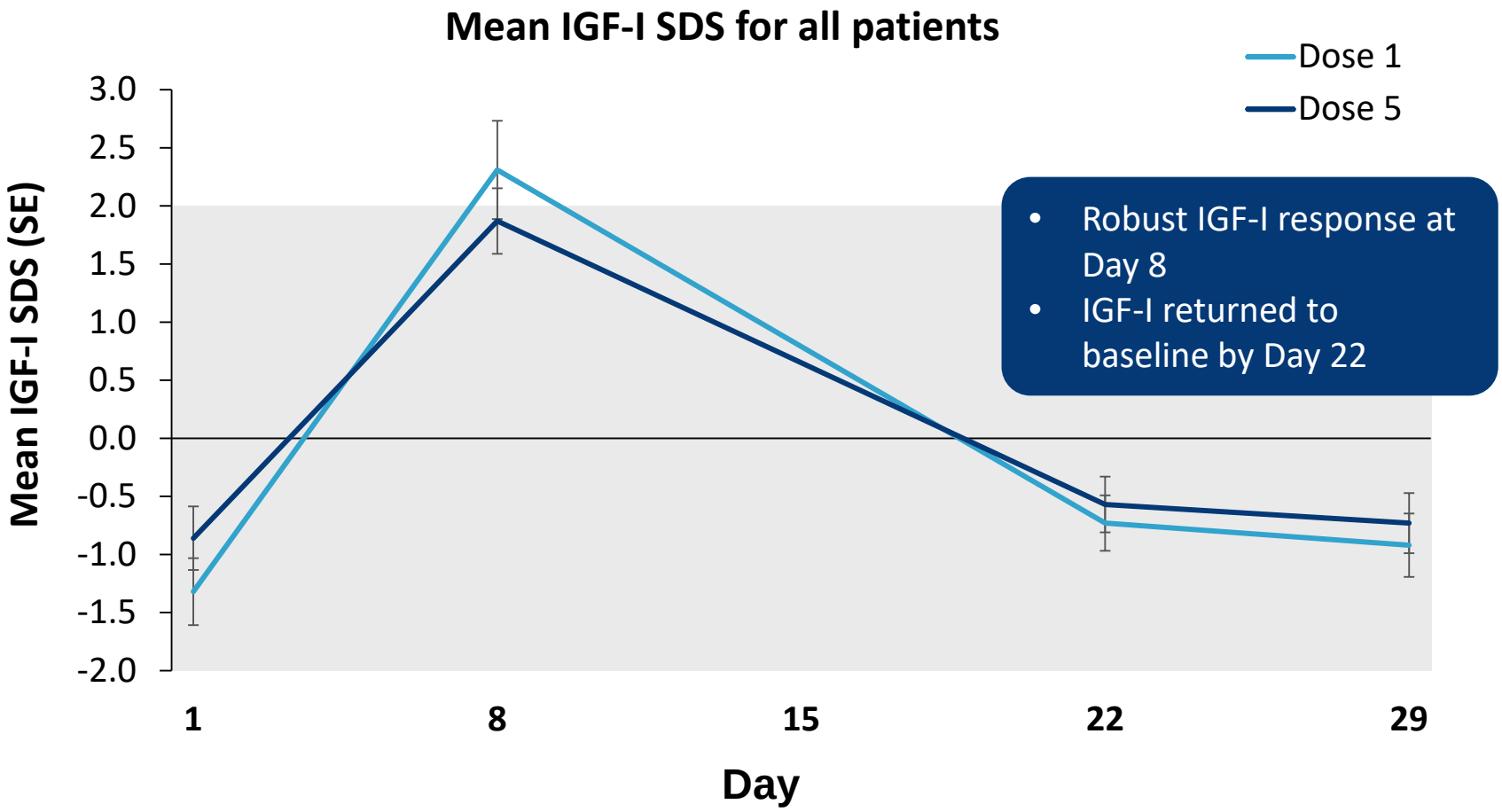
Patient baseline characteristics (N=36)

CHARACTERISTIC	COHORT A (n = 22)	B (n = 6)	C (n = 8)
Age, years	54 ± 10	30 ± 2	38 ± 10
Male, n (%)	14 (64)	4 (67)	0
BMI, kg/m^2	29 ± 4	27 ± 5	27 ± 4
Weight, kg	87 ± 17	79 ± 19	76 ± 14
Baseline IGF-I SDS	-0.53 ± 1.32	-2.89 ± -2.89	-2.29 ± 1.69

Data presented as mean ± SD.

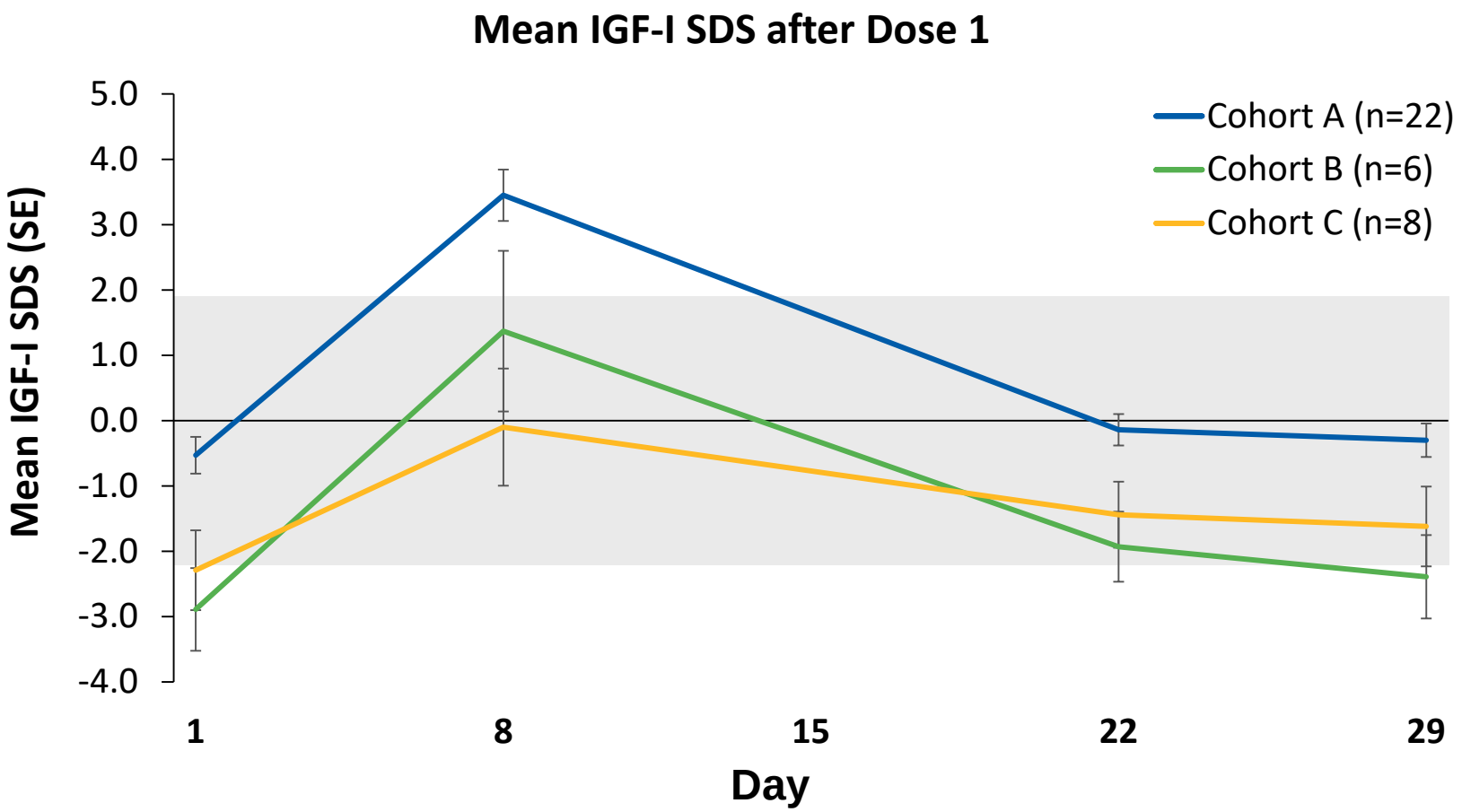
BMI = body-mass index; IGF-I = insulin-like growth factor 1; SDS = standard deviation score; min, max = minimum, maximum.

IGF-I response to the first and fifth injection across 30 days



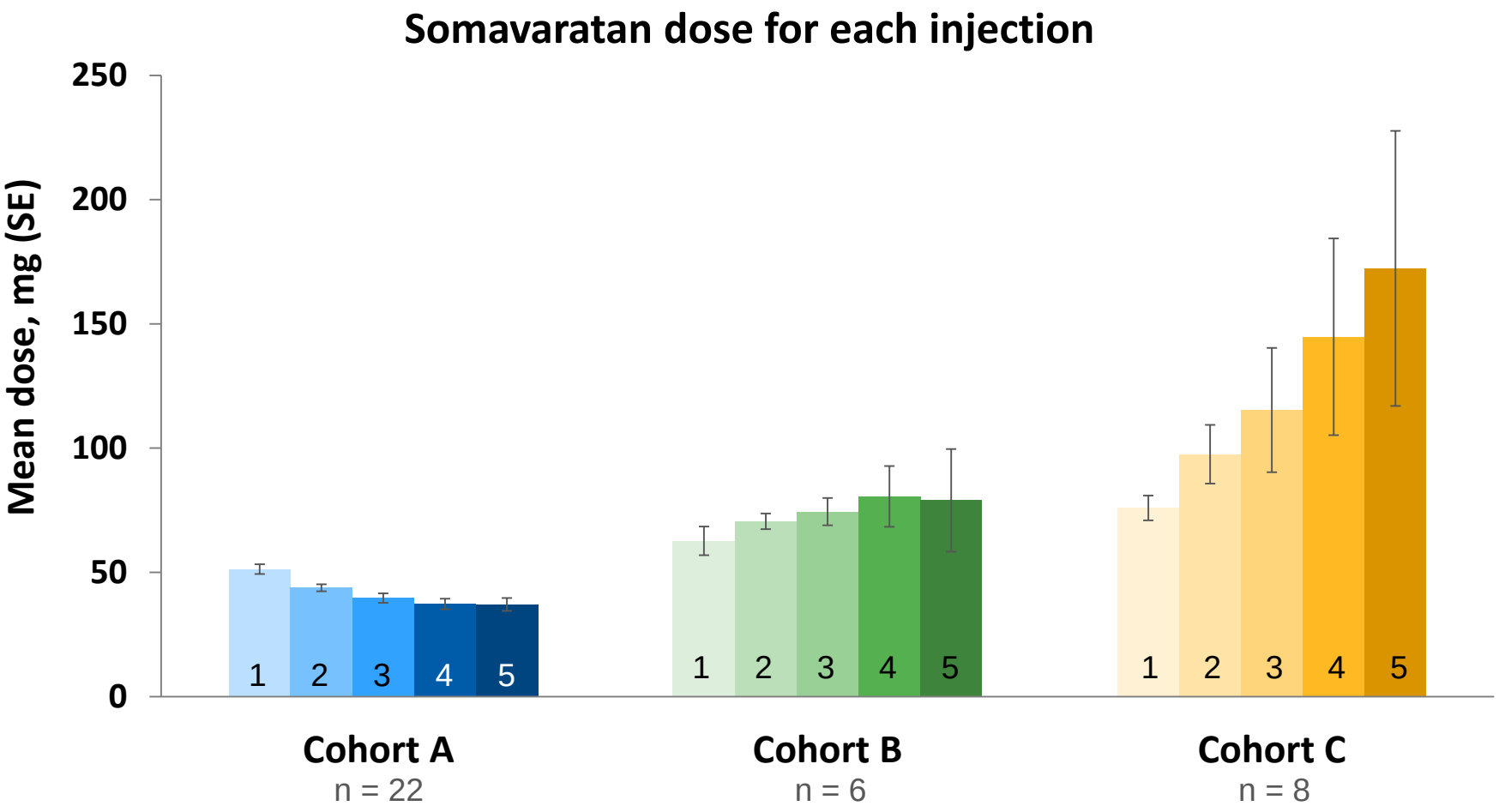
Dose 1, n:	36	36	36	35
Dose 5, n:	33	33	32	31

IGF-I response by cohort

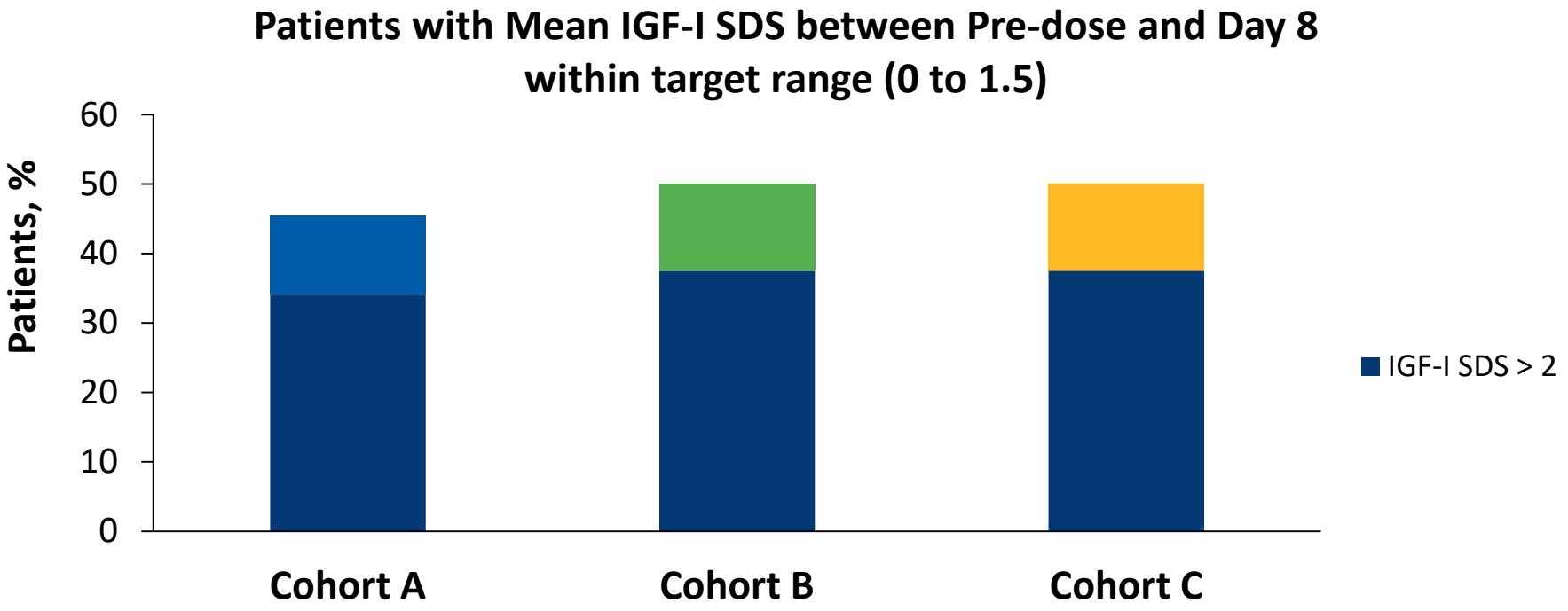


- In each cohort, IGF-I returned to baseline by Day 22
- More frequent administration needed

Somavaratan starting dose and titration



Target IGF-I SDS after Dose 5



DOSE, mg (min, max)	COHORT A (n = 22)	B (n = 6)	C (n = 8)	OVERALL (N = 36)
Start	51.3 (31.5, 60.0)	62.7 (45.2, 80.0)	75.9 (55.0, 95.4)	58.7 (31.5, 95.4)
End	37.1 (13.4, 61.8)	79.0 (41.5, 137.8)	172.3 (50.0, 400.0)	70.9 (13.4, 400.0)

Treatment-related adverse events (AEs) occurring in > 1 subject

	n (%)			
	COHORT			
AEs	A (n = 22)	B (n = 6)	C (n = 8)	OVERALL (n = 36)
All AEs n (%)	7 (32)	5 (83)	3 (38)	**15 (42)**
Headache	3 (14)	1 (17)	0	**4 (11)**
Fatigue	2 (9)	0	0	**2 (6)**
Injection site pain	2 (9)	1 (17)	1 (13)	**4 (11)**
Injection site erythema	1 (5)	1 (17)	0	**2 (6)**
Injection site pruritus	0	1 (17)	1 (13)	**2 (6)**

- Nearly all patients experienced ≥ 1 AE, with 55% presenting no related AEs
- No related SAEs were reported
- Related AEs were generally mild, transient, and consistent with the safety profile of daily rhGH

AE = adverse event; rhGH = recombinant human growth hormone; SAE = serious adverse event.

Summary and conclusions

- Somavaratan was safe in adults
- Somavaratan induced a robust IGF-I response in adult patients with GHD
- IGF-I levels returned to pre-dose levels by day 22
- This study provided the needed information to optimize somavaratan treatment in AGHD, including the:
  - Starting dose
  - Titration plan
  - Dosing frequency
- Lower starting somavaratan doses administered twice-monthly are being investigated in the extension study* and will be used in a phase 3 study

*NCT02719990, protocol 15VR8

Acknowledgements

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- Nurses and study coordinators
- Versartis for study funding
- JB Ashtin for editorial assistance

Backup Slides

Glucose and hemoglobin A1c

MONTH 5 RESULTS	COHORT A (n = 22)	B (n = 6)	C (n = 8)	OVERALL (n = 36)
Fasting plasma glucose				
Low	1 (4.5)	0	0	**1 (2.8)**
Normal	19 (86.4)	5 (83.3)	6 (75.0)	**30 (83.3)**
High	1 (4.5)	1 (16.7)	0	**2 (5.6)**
Missing	1 (4.5)	0	2 (25.0)	**3 (8.3)**
Hemoglobin A1c				
Normal	21 (95.5)	6 (100)	7 (87.5)	**31 (94.4)**
High	0	0	0	**0**
Missing	1 (4.5)	0	1 (12.5)	**2 (5.6)**

Data are n (%).

Somavaratan dose titration

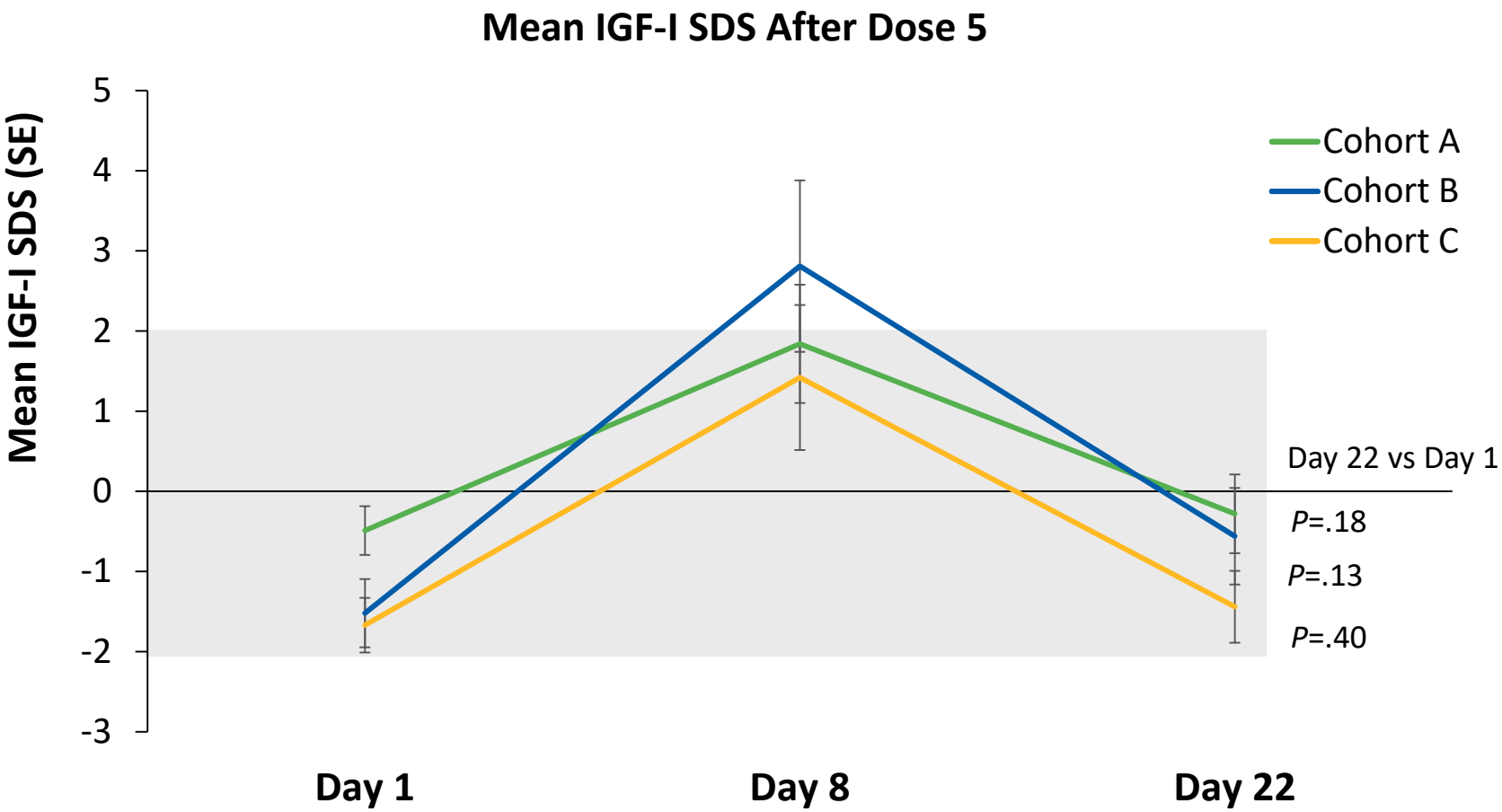
- Used the SDS of the mean of IGF-I values from pre-dose and Day 8 (7 days after dosing)
- Adjusted until 2 consecutive means of pre-dose and Day 8 target IGF-I SDS were within the target range

Prespecified Dose Titration

MEAN IGF-I SDS	COHORT A	B	C
Upward Dose Titration*, % Dose Increase			
–0.50 to –0.01	10	15	20
–0.51 to –2.00	20	30	30
< –2.00	30	45	50
Downward Dose Titration, % Dose Decrease			
1.51 to 2.00	10	5	5
2.01 to 3.00	20	10	10
> 3.00	30	20	20

*Maximum allowable dose is 5.0 mg/kg

IGF-I SDS returned to pre-dose levels by Day 22



	Day 1	Day 8	Day 22
Cohort A, n:	22	4	7
Cohort B, n:	22	4	7
Cohort C, n:	21	4	7

IGF-I SDS = insulin-like growth factor 1 standard deviation score.

Dose effect on IGF-I response

- Subjects who received higher total doses tended to have higher IGF-I responses

Regression of Total Dose (mg) and IGF-I SDS 7 Days After Dose 1

COHORT	*r*	MODEL r^2
A	0.652	**0.425**
B	0.844	**0.713**
C	0.339	**0.115**
Total	0.148	**0.022**

IGF-I = insulin-like growth factor 1; SDS = standard deviation score.

Treatment-emergent adverse events

Adverse Events (AEs)	COHORT A (n = 22)	B (n = 6)	C (n = 8)	OVERALL (n = 36)
All AEs, n	90	35	43	**168**
Patients who experienced AEs, n (%)	21 (96)	5 (100)	8 (100)	**35 (97)**
Severity, n (%)				
Mild	6 (27)	3 (50)	3 (38)	**12 (33)**
Moderate	13 (59)	3 (50)	5 (63)	**21 (58)**
Severe	1 (5)	0	0	**1 (3)**
Life threatening	1 (5)	0	0	**1 (3)**
Serious AEs, n (%)	3 (14)	0	0	**3 (8)**
Death, n (%)	0	0	0	**0**

- Nearly all patients experienced ≥ 1 AE
- Most AEs were mild or moderate in intensity