A Randomized Controlled Trial of Vosoritide in Infants and Toddlers with Achondroplasia

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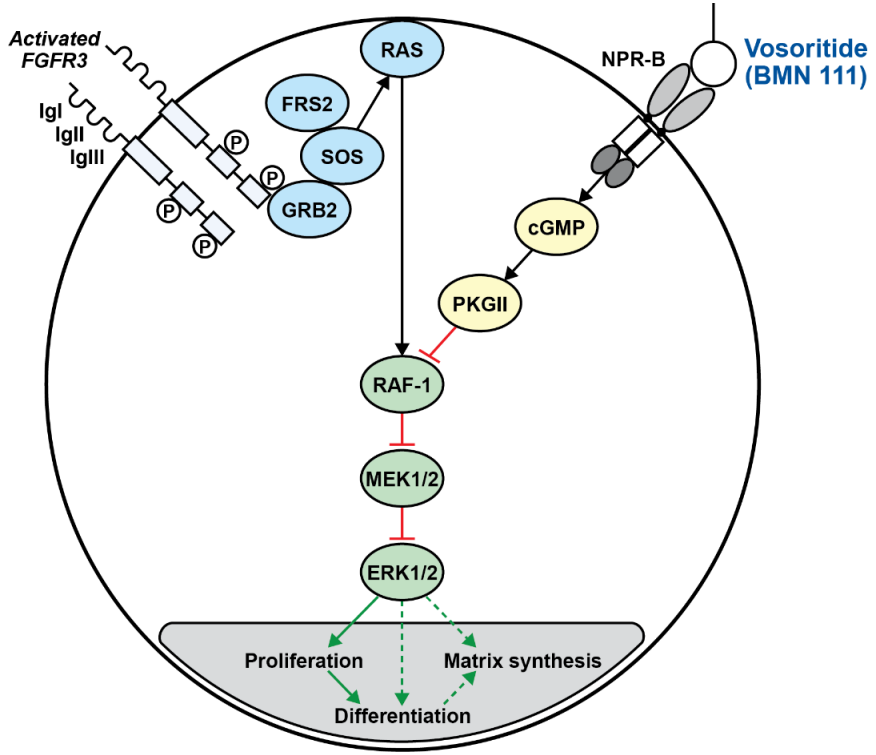
Achondroplasia (ACH) Disease Overview

- Achondroplasia (ACH) is the most common form of disproportionate short stature (approx. 1:25,000 live births)[1,2]
- Caused by a pathogenic variant in *FGFR3* that constitutively activates the downstream inhibitory signaling pathway in chondrocytes, leading to impaired endochondral bone growth[1]
- Complications of ACH impact multiple systems and occur throughout the lifespan[3]
  - Complications include cervicomedullary compression, sleep apnea, genu varum, spinal stenosis

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Vosoritide: Targeted Therapy for ACH

- CNP down-regulates aberrant FGFR3 signaling in chondrocytes by inhibiting the MAPK-ERK pathway[1,2]
- Vosoritide is based on naturally-occurring CNP engineered to resist degradation and increase the half-life[3]



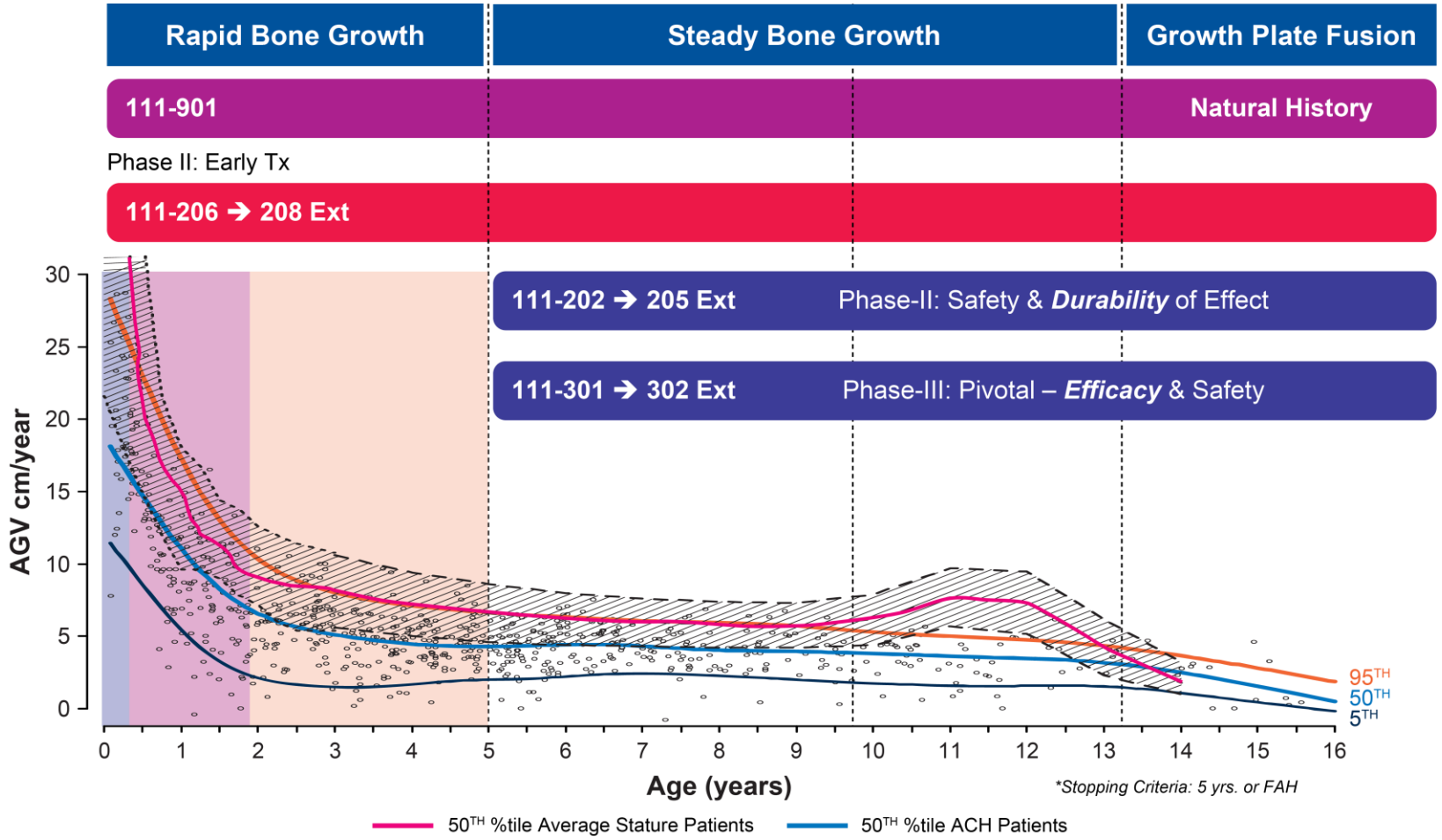
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Vosoritide: Targeted Therapy for ACH

- An open-label, 52-week phase 2 trial (BMN 111-202) and its extension study (BMN 111-205) in children with ACH showed that vosoritide treatment resulted in sustained increases in annualized growth velocity (AGV)1
- A phase 3 randomized placebo-controlled trial (BMN 111-301) in children with ACH showed treatment with vosoritide resulted in a statistically significant improvement in AGV after
  52 weeks compared to placebo2; AGV improvement sustained after 2 years of vosoritide treatment in extension study (BMN 111-302)3
- Vosoritide is approved for use in children with ACH aged ≥5 years in the US, aged ≥2 years in the EU, Brazil, and Australia, and from birth in Japan, until closure of epiphyses

1. Savarirayan R et al. C-type natriuretic peptide analogue therapy in children with achondroplasia. *N Engl J Med 2019*;381:25-35. 2. Savarirayan R et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *Lancet 2020*; 396:684-692. 3. Savarirayan R et al. Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study. *Genet Med 2021*; 23:2443–2447

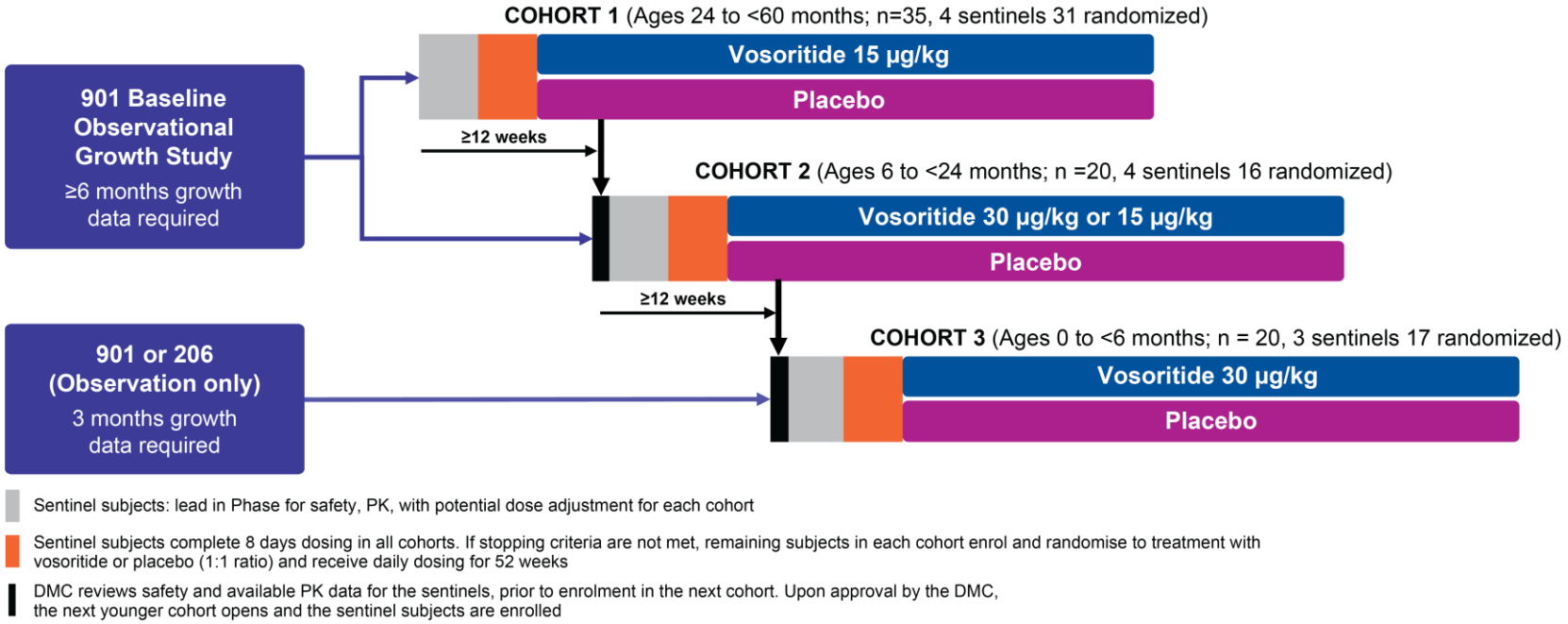
Vosoritide Clinical Development Program in Context of Growth Pattern in Children with ACH



ACH growth curve adapted from Hoover-Fong J et al. *Am J Clin Nutr* 2008

BMN 111-206 Study in Children with ACH Aged 0–5 Years

- Primary Objectives:
  - Evaluate safety and tolerability of vosoritide in children with achondroplasia
  - Evaluate the effect of vosoritide on change from baseline in height/body length Z-scores
- Secondary Objectives include Height, AGV, Upper to Lower body segment ratio



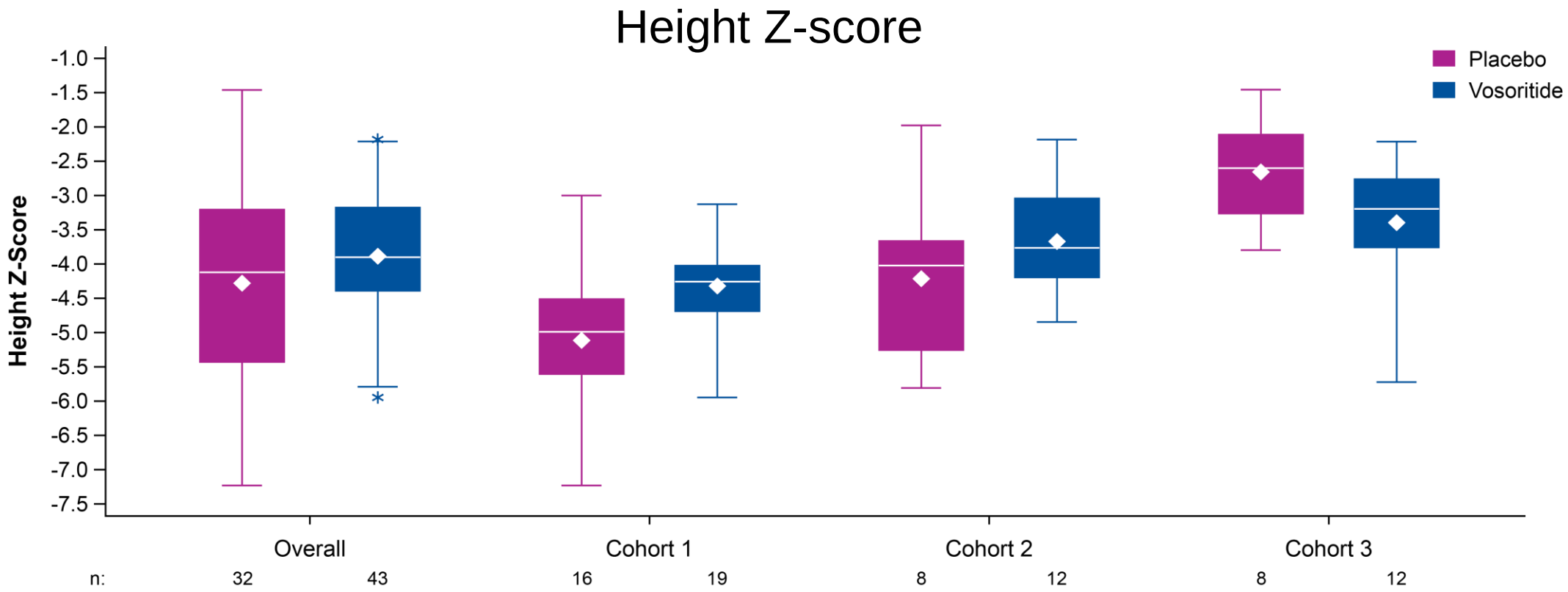
Statistical Methods

- Randomization by Age Strata
  - Cohort 1: age stratification ≥ 24 to < 36, ≥ 36 to < 60 months
  - Cohort 2: age stratification ≥ 6 to < 15, ≥ 15 to < 24 months
  - Cohort 3: age stratification 0 to < 6 months
- Populations Analyzed
  - All enrolled (randomized + sentinels)
  - All randomized (randomized only)
- Comparative Analysis vs Placebo using ANCOVA model
  - Baseline covariates: Sex, Age, Age Stratum, AGV + baseline for each endpoint
  - No formal statistical hypothesis for efficacy comparisons and no type 1 error control
  - ITT principle (imputation of missing data, n=2)
- Pre-specified Subgroup Analyses by cohort

Subject Demographics

	Overall		Cohort 1		Cohort 2		Cohort 3	
	Vosoritide (N=43)	**Placebo (N=32)**	**Vosoritide (N=19)**	**Placebo (N=16)**	**Vosoritide (N=12)**	**Placebo (N=8)**	**Vosoritide (N=12)**	**Placebo (N=8)**
Age on Day 1, Months								
Mean (SD)	24.47 (17.66)	27.82 (19.25)	41.48 (11.07)	44.33 (11.54)	16.59 (5.11)	16.87 (6.21)	5.41 (0.53)	5.76 (0.59)
Median	21.82	26.43	40.02	40.39	16.54	18.56	5.62	5.91
Q1, Q3	5.91, 36.86	7.67, 40.39	30.19, 51.06	34.55, 56.36	11.63, 21.42	10.46, 22.16	4.86, 5.86	5.72, 5.95
Sex, n(%)								
Male	25 (58.1)	13 (40.6)	10 (52.6)	7 (43.8)	9 (75.0)	5 (62.5)	6 (50.0)	1 (12.5)
Female	18 (41.9)	19 (59.4)	9 (47.4)	9 (56.3)	3 (25.0)	3 (37.5)	6 (50.0)	7 (87.5)
Race*								
White	29 (67.4)	25 (78.1)	12 (63.2)	13 (81.3)	9 (75.0)	6 (75.0)	8 (66.7)	6 (75.0)
Asian	11 (25.6)	6 (18.8)	6 (31.6)	3 (18.8)	2 (16.7)	1 (12.5)	3 (25.0)	2 (25.0)
Japanese	4 (9.3)	4 (12.5)	2 (10.5)	3 (18.8)	1 (8.3)	1 (12.5)	1 (8.3)	0

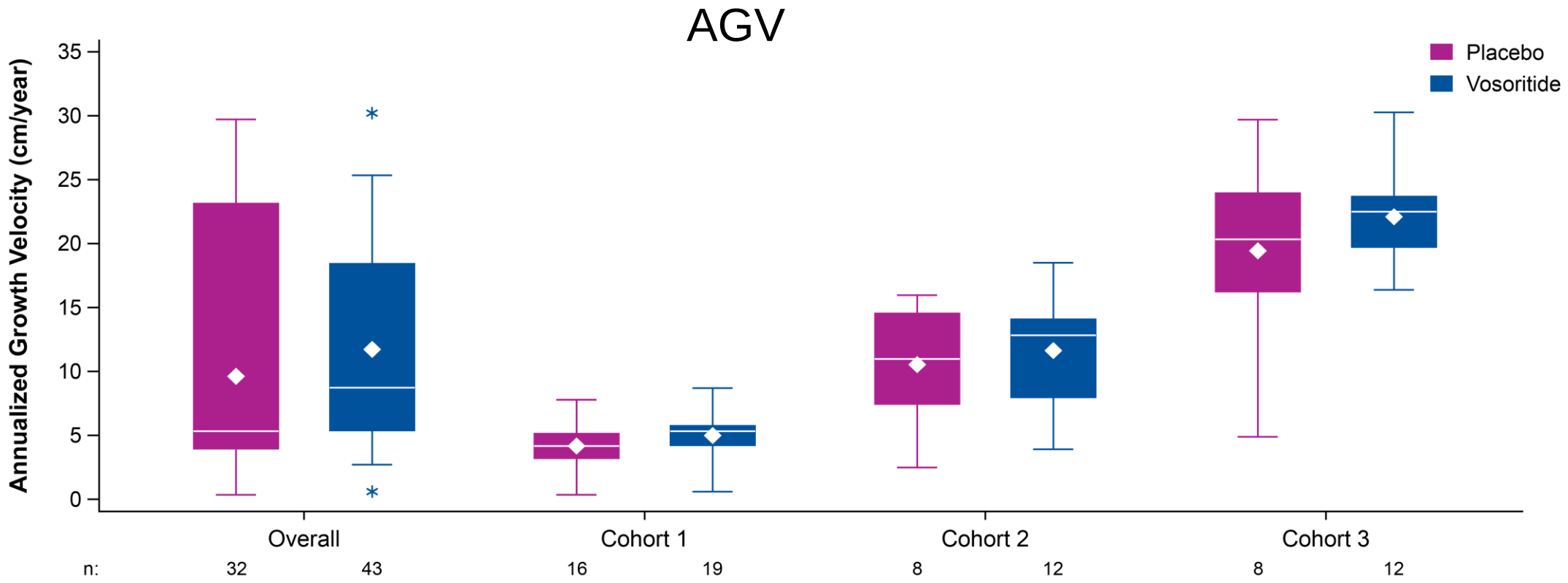
Baseline Growth Characteristics



Cohort 1: Ages 24 to <60 months
Cohort 2: Ages 6 to <24 months
Cohort 3: Ages 0 to <6 months

Box plot displays the 25th and 75th percentiles (box edges), the median (midline), the mean (diamond symbol) and the 2.5th and 97.5th percentiles (whiskers). Asterisks represent outliers.

Baseline Growth Characteristics



Cohort 1: Ages 24 to <60 months
Cohort 2: Ages 6 to <24 months
Cohort 3: Ages 0 to <6 months

Overview of SAEs

SOC and PT	Sentinel (N=11)	Vosoritide (N=32)	Placebo (N=32)	All Vosoritide Treated (N=43)
Subjects with any SAE, n (%)	**0**	**3 (9.4)**	**6 (18.8)**	**3 (7.0)**
Infections and infestations, n (%)	0	2 (6.3)	3 (9.4)	2 (4.7)
Pneumonia	0	1 (3.1)	0	1 (2.3)
Respiratory syncytial virus bronchiolitis	0	1 (3.1)	0	1 (2.3)
Gastroenteritis	0	0	1 (3.1)	0
Otitis media	0	0	1 (3.1)	0
Parainfluenzae virus infection	0	0	1 (3.1)	0
General disorders and administration site conditions, n (%)	0	1 (3.1)	0	1 (2.3)
Sudden death (respiratory arrest)	0	1 (3.1)	0	1 (2.3)
Investigations, n (%)	0	1 (3.1)	0	1 (2.3)
Oxygen saturation decreased	0	1 (3.1)	0	1 (2.3)
Gastrointestinal disorders, n (%)	0	0	1 (3.1)	0
Vomiting	0	0	1 (3.1)	0
Injury, poisoning and procedural complications, n (%)	0	0	1 (3.1)	0
Skull fracture	0	0	1 (3.1)	0
Nervous system disorders, n (%)	0	0	1 (3.1)	0
Petit mal epilepsy	0	0	1 (3.1)	0
Psychiatric disorders, n (%)	0	0	1 (3.1)	0
Autism spectrum disorder	0	0	1 (3.1)	0
Respiratory Disorders n (%)	0	0	1 (3.1)	0
Respiratory distress	0	0	1 (3.1)	0

Incidence of TEAE by SOC by Cohort

	Cohort 1		Cohort 2		Cohort 3	
SOC	**Vosoritide (n=19)**	**Placebo (N=16)**	**Vosoritide (n=12)**	**Placebo (N=8)**	**Vosoritide (n=12)**	**Placebo (N=8)**
General disorders and administration site conditions	16 (84.2)	10 (62.5)	10 (83.3)	6 (75.0)	12 (100.0)	8 (100.0)
Infections and infestations	17 (89.5)	15 (93.8)	11 (91.7)	8 (100.0)	9 (75.0)	7 (87.5)
Gastrointestinal disorders	11 (57.9)	12 (75.0)	6 (50.0)	7 (87.5)	8 (66.7)	7 (87.5)
Respiratory, thoracic and mediastinal disorders	13 (68.4)	8 (50.0)	5 (41.7)	5 (62.5)	7 (58.3)	6 (75.0)
Skin and subcutaneous tissue disorders	6 (31.6)	6 (37.5)	4 (33.3)	2 (25.0)	6 (50.0)	4 (50.0)
Injury, poisoning and procedural complications	10 (52.6)	7 (43.8)	3 (25.0)	2 (25.0)	1 (8.3)	2 (25.0)
Ear and labyrinth disorders	4 (21.1)	7 (43.8)	3 (25.0)	4 (50.0)	4 (33.3)	1 (12.5)
Musculoskeletal and connective tissue disorders	5 (26.3)	3 (18.8)	1 (8.3)	1 (12.5)	2 (16.7)	3 (37.5)
Immune system disorders	3 (15.8)	0	0	1 (12.5)	2 (16.7)	1 (12.5)
Investigations	2 (10.5)	2 (12.5)	1 (8.3)	1 (12.5)	1 (8.3)	0
Nervous system disorders	2 (10.5)	5 (31.3)	1 (8.3)	0	1 (8.3)	3 (37.5)
Psychiatric disorders	0	0	1 (8.3)	1 (12.5)	1 (8.3)	0
Vascular disorders	0	0	1 (8.3)	1 (12.5)	1 (8.3)	0
Blood and lymphatic system disorders	1 (5.3)	0	0	0	0	1 (12.5)
Eye disorders	1 (5.3)	0	0	0	0	0
Metabolism and nutrition disorders	0	2 (12.5)	0	0	1 (8.3)	1 (12.5)
Reproductive system and breast disorders	1 (5.3)	0	0	0	0	0
Cardiac disorders	0	1 (6.3)	0	0	0	0
Endocrine disorders	0	0	0	0	0	1 (12.5)

Incidence of TEAE Reported with > 5% Higher Frequency in Vosoritide vs Placebo

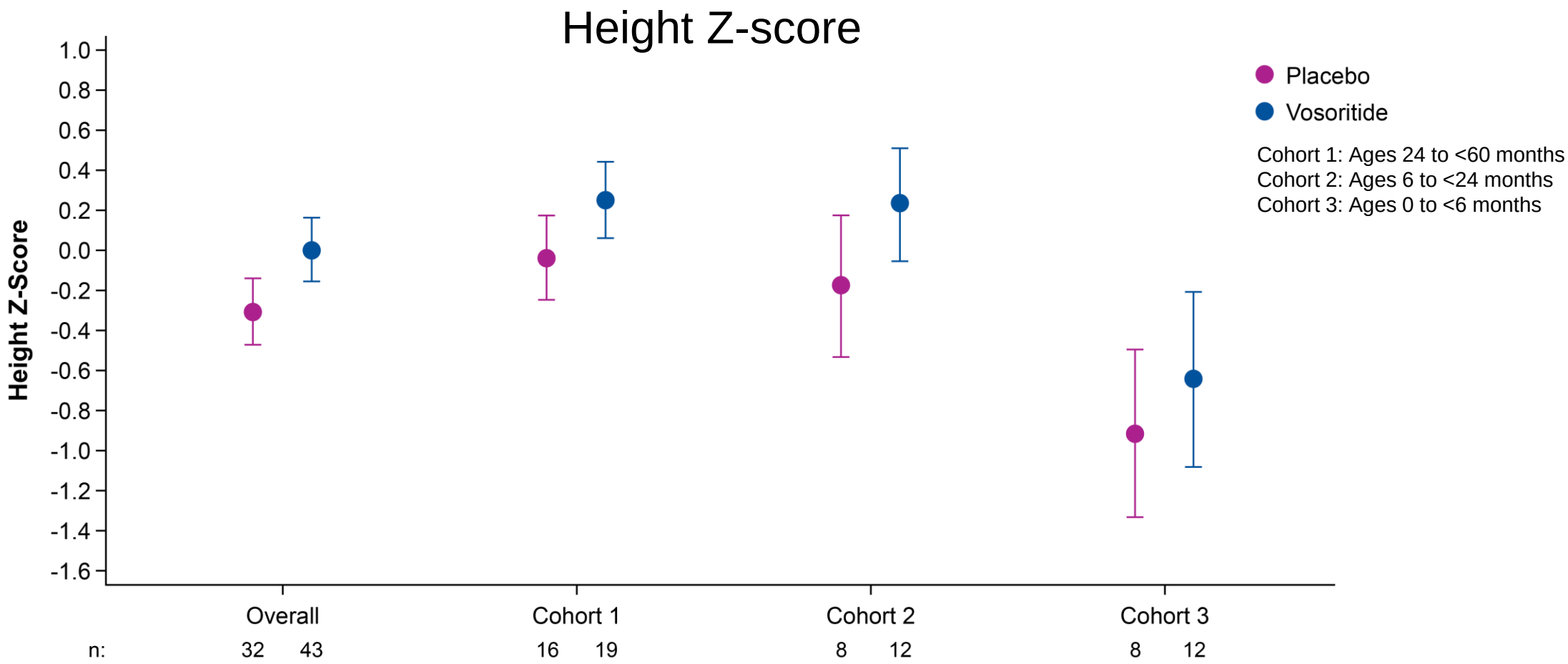
	Placebo (N=32)		Vosoritide (N=43)	
Preferred Term	**Incidence n (%)**	**Events m (rate)**	**Incidence n (%)**	**Events m (rate)**
Injection site reaction	13 (40.6)	154 (4.8)	34 (79.1)	3057 (71.5)
Injection site erythema	13 (40.6)	1738 (54.3)	33 (76.7)	5100 (119.4)
Injection site swelling	2 (6.3)	3 (0.1)	8 (18.6)	36 (0.8)
Injection site urticaria	1 (3.1)	1 (0.0)	6 (14.0)	22 (0.5)
Injection site induration	0	0	5 (11.6)	14 (0.3)
Viral Infection	4 (12.5)	8 (0.2)	8 (18.6)	28 (0.7)
Fall	3 (9.4)	5 (0.2)	7 (16.3)	9 (0.2)
Arthropod bite	2 (6.3)	2 (0.1)	6 (14.0)	7 (0.2)
Constipation	2 (6.3)	4 (0.1)	5 (11.6)	7(0.2)
Dermatitis Diaper	1 (3.1)	1 (0.0)	4 (9.3)	5 (0.1)
Lower respiratory tract infection	1 (3.1)	3 (0.1)	4 (9.3)	4 (0.1)
Rhinitis	0	0	4 (9.3)	8 (0.2)
Sleep apnea syndrome	0	0	3 (7.0)	3 (0.1)
Viral upper respiratory tract infection	0	0	3 (7.0)	3 (0.1)
Epistaxis	0	0	3 (7.0)	3 (0.1)

Improvement in Growth with Vosoritide vs Placebo

- Vosoritide (n=43), compared to placebo (n=32) (All Enrolled):
  - increased height Z-score by 0.30 SD (95% CI 0.07, 0.54)
  - increased AGV by 0.92cm/year (95% CI 0.24, 1.59)
  - did not significantly change upper-to-lower body segment ratio, which changed by -0.06 (95% CI -0.15, 0.03)

- Vosoritide (n=32), compared to placebo (n=32) (All Randomized):
  - increased height Z-score by 0.25 SD (95% CI -0.02, 0.53)

Positive Change in Height Z-Score in Children Treated with Vosoritide in All Cohorts



- Increased variability at youngest age group reflects rapidly changing growth pattern in young children

Height Gain

All Enrolled Analysis population

	Height Gain (cm) After One Year					
	Placebo			Vosoritide		
	Cohort 1 24-60 months (n=16)	Cohort 2 6-24 months (n=8)	Cohort 3 0-6 months (n=8)	Cohort 1 24-60 months (n=19)	Cohort 2 6-24 months (n=12)	Cohort 3 0-6 months (n=12)
Average Stature*	7.06	10.69	15.05	6.98	10.33	15.65
ACH **	5.51	8.01	10.32	6.38	9.04	11.29
% Height gain ACH vs Average Stature***	78.04	74.96	68.55	91.45	87.50	72.16

*Estimated using the CDC chart for average stature: Mean average stature height gain derived as mean of the median height gain over one year for average stature subjects of the same age and sex for each subject in the Vosoritide/Placebo arm
**LS Mean change from baseline from the ANCOVA model in the 111-206 all enrolled analysis population
***Height gain ACH versus average stature is calculated as LS mean change from baseline/Mean average stature height gain x 100%

MRI: Face and Sinus Volumes and Foramen Magnum Area

	Cohort 1 24-60 months		Cohort 2 6-24 months		Cohort 3 0-6 months	
	Vosoritide (n=19)	**Placebo (N=16)**	**Vosoritide (n=12)**	**Placebo (N=8)**	**Vosoritide (n=12)**	**Placebo (N=8)**
Face volume (cm^3)						
Baseline, N	16	13	12	8	11	8
Mean ± SD	582.41 ± 88.15	573.83 ± 91.02	451.48 ± 61.45	450.79 ± 71.20	340.37 ± 38.68	357.53 ± 51.16
Week 52, N	14	8	7	7	9	6
Mean ± SD % change at week 52	6.32 ± 7.82	11.85 ± 4.96	20.56 ± 10.48	15.08 ± 5.66	43.49 ± 10.33	33.74 ± 12.66
Sinus volume (cm^3)						
Baseline, N	19	16	12	8	12	8
Mean ± SD	9.48 ± 4.20	8.90 ± 3.91	4.35 ± 3.46	5.38 ± 4.48	2.33 ± 1.62	2.78 ± 2.20
Week 52, N	17	11	8	7	10	6
Mean ± SD % change at week 52	52.01 ± 82.95	100.90 ± 177.15	44.91 ± 78.80	80.91 ± 160.39	128.81 ± 128.18	48.49 ± 191.74
Foramen magnum area (cm^2)						
Baseline, N	19	16	12	8	12	8
Mean ± SD	0.14 ± 0.02	0.14 ± 0.02	0.14 ± 0.03	0.13 ± 0.03	0.09 ± 0.03	0.09 ± 0.03
Week 52, N	17	12	8	7	10	6
Mean ± SD % change at week 52	−7.26 ± 21.86	0.93 ± 16.07	0.76 ± 14.82	4.00 ± 11.99	43.89 ± 74.44	24.74 ± 26.07

Conclusions

- Daily injections of vosoritide were well tolerated with no treatment limiting adverse events with the safety profile consistent with that in treated children over 5 years of age
- Most common adverse events observed were mild and self-limiting injection site reactions
  - No clinically relevant differences in safety profile of vosoritide between cohorts (doses)
- SAEs more frequent in Placebo group (18%) compared to Vosoritide-treated group (7%). All SAEs including fatal event in treatment group were unrelated to treatment
- In children with ACH 0-5 years of age, improvement in height Z-score of + 0.30 (95% CI 0.07; 0.54) SDS was seen with vosoritide vs placebo after 52 weeks, and was consistent with improvement observed after one year treatment in children over 5 years of age[1]
- There was no significant change in body proportions

1. Savarirayan R et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *Lancet 2020*; 396:684-692

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