Free Communications 4: Growth and syndromes

Persistence of Growth Promoting Effects in Infants and Toddlers with Achondroplasia: Results in Children Aged Over 2 Years Old from a Phase II Extension Study with Vosoritide

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Thursday 21 September 2023, 14:55 - 15:55

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DISCLOSURE STATEMENT

Melita Irving

X I have the following potential conflicts of interest to report:

□ Research Contracts
X Consulting
□ Employment in the Industry
□ Stockholder of a healthcare company
□ Owner of a healthcare company
X Other(s) – *speaker honoraria*

No commercial logos or product names to be included please.

□ I declare that I have no potential conflict of interest.

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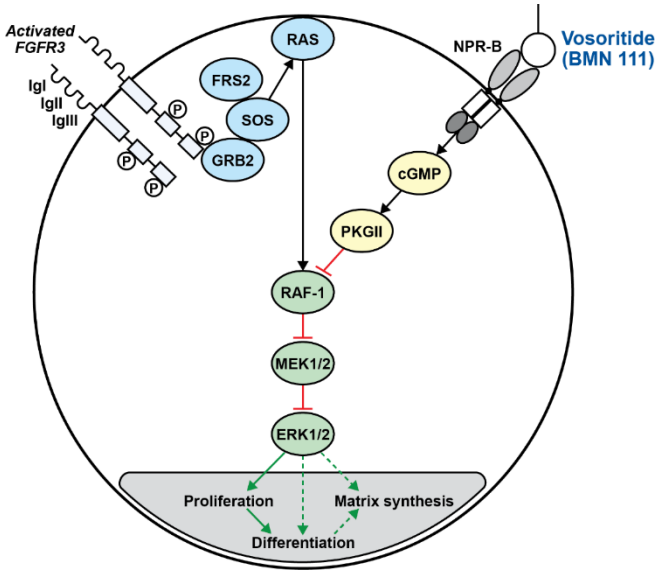
Vosoritide: Targeted therapy for achondroplasia

- Achondroplasia (ACH) is the most common form of disproportionate short stature (approx. **1:25,000 live births**)[1,2]
- ACH is caused by a pathogenic variant in *FGFR3* that **constitutively activates the downstream inhibitory signaling** pathway in chondrocytes, leading to impaired endochondral bone growth and multiple complications[1,2]
- **CNP down-regulates aberrant FGFR3 signaling** in chondrocytes by inhibiting the MAPK-ERK pathway[3,4]
- **Vosoritide is based on naturally-occurring CNP** engineered to resist degradation and increase the half-life[5]



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2. Hoover-Fong J et al. Lifetime impact of achondroplasia: Current evidence and perspectives on the natural history. Bone 2021; 146:115872.
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Increase in growth has been demonstrated with vosoritide in clinical trials in ACH

- An open-label, 52-week phase 2 trial (BMN 111-202) and its extension study (BMN 111-205) in children with ACH aged ≥ 5 years showed that vosoritide treatment resulted in **sustained increases in annualized growth velocity (AGV)** for over 7 years[1,2]

- A phase 3 randomized placebo-controlled trial (BMN 111-301) in children with ACH aged ≥ 5 years showed a **statistically significant improvement in AGV with vosoritide after 52 weeks compared to placebo**[3;] AGV improvement sustained after 3 years of vosoritide treatment in extension study BMN 111-302 [4,5]

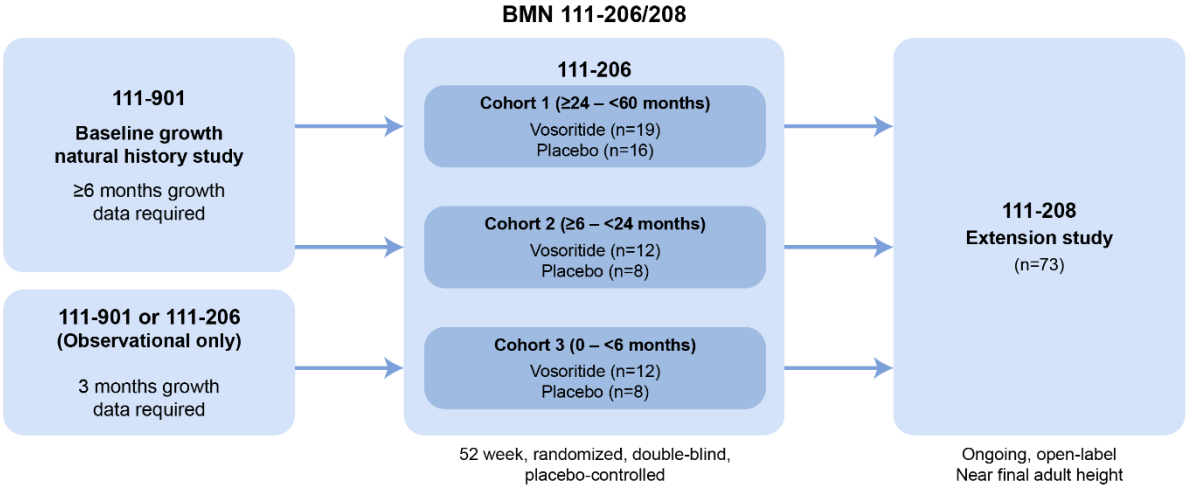
- In children with ACH 0-5 years of age, improvement in height Z-score was seen with vosoritide compared to placebo after 52 weeks (111-206) [6]

- Vosoritide is approved for use in children with ACH and open epiphyses aged ≥5 years in the USA, ≥2 years in EU, Brazil and Australia, and from birth in Japan

1. Savarirayan R et al. C-type natriuretic peptide analogue therapy in children with achondroplasia. *N Engl J Med 2019*;381:25-35. 2. Hoover-Fong J et al. Persistence of Growth Promoting Effects in Children with Achondroplasia Over Seven Years: Update from Phase II Extension Study with Vosoritide, *Genetics in Medicine Open*. 2023;1(1):100223. 3. 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. 4. 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*; 2**3,** 2443–2447. 5. Polgreen L et al. Persistent and stable growth promoting effects of vosoritide in children with achondroplasia for up to 3.5 years: results from an ongoing Phase 3 extension study, *Horm Res Paediatr* (2023) 96 (Suppl. 2). 6. Polgreen L et al. A randomized controlled trial of vosoritide in infants and toddlers with achondroplasia. *Horm Res Paediatr* (2023) 96 (Suppl. 2)

BMN 111-206/208 Study Design

- **111-206:** Phase 2 52-week, randomized, double-blind, placebo-controlled study of children with ACH **aged 0 - < 5 years**
- **111-208:** Phase 2 ongoing open-label extension study
- **Primary objectives**
  - Evaluate safety and tolerability of vosoritide in children with ACH
  - Evaluate effect of vosoritide on height/body length Z-scores
- **Secondary objectives** include evaluating effect of vosoritide on height, AGV, Upper:Lower body segment ratio



CLARITY: Natural history study for comparison with vosoritide data

- **CLARITY**[1] **(AchNH)** is **a multicentre retrospective study of ACH in the USA**

- **1374 participants** with **14123 height assessments** included
  - Molecular or clinical diagnosis of ACH
  - All available medical records for past and present clinical patients
  - Cross sectional and longitudinal patient level height data

- **Age range**
  - Spanning the entire pediatric age-range with some data beyond adult height
  - High data density in pediatric growth period

- **Study quality**
  - Four large US skeletal dysplasia centres with expertise in ACH and anthropometry
  - REDCap database with audit trail
  - Data collected to a common protocol using standardized methodologies

1. Hoover-Fong J et al. Growth in achondroplasia including stature, weight, weight-for-height and head circumference from CLARITY: achondroplasia natural history study-a multi-center retrospective cohort study of achondroplasia in the US. *Orphanet J Rare Dis. 2021:*16(1):522.

Statistical methodology for comparative analyses

Active arm: 111-206/208

- All subjects with at least **one year of follow-up** at data cut-off (December 19th 2022)
- All data **from first dose of vosoritide** in either study 111-206 or 111-208

Two independent external controls

- **AchNH**: natural history controls derived from **CLARITY** (Hoover-Fong J et al. *Orphanet J Rare Dis.* 2021)
- **Observational/Placebo**: untreated data from study **111-901** and from **placebo arms of studies 111-301/111-206**

Two statistical approaches

- **Cross sectional analyses**
  - Subjects from NH source matched to each treated subject by sex and age (+/-1 month). T test to determine treatment gain at follow-up time point adjusted by subtracting the difference at baseline
- **Longitudinal analyses**
  - Subjects from AchNH source matched to each treated subject at baseline by sex, age (+/-1 month), height Z-score (+/- 1SD), height (+/- 5 cm)
  - Subjects from Observational/Placebo data source included in control arm based on age and sufficient follow-up. No matching.
  - ANCOVA models provide LS mean difference for change from baseline at follow-up time point

Three endpoints

- Height Z-score, Height, Upper:Lower Body Ratio (only using the observational/placebo control)

Four time points

- Year 1,2,3 and 4 (only for ≥ 2 years)

Subject disposition

Number of participants							
Age at start of vosoritide	Total	Treatment started in 111-206	Treatment started in 111-208[a]	Comparative Analysis population			
				1 year	2 years	3 years	4 years
≥2 years	34	19	15	34	30	22	9
<2 years	33	23	10	32	25	14	0

- **Age group ≥2 years:** subjects aged 2 - < 5 years at start of vosoritide (in either study 111-206 or 111-208)
- **Age group <2 years:** subjects aged 3 months to <2 years at start of vosoritide (in either study 111-206 or 111-208)

Comparative analysis population comprises only subjects with at least 1 year of treatment follow-up as of December 19th 2022

Subject demographics and growth characteristics at start of vosoritide treatment

	≥2 years (N=34)	<2 years (N=32)
Age (months)		
Mean (SD)	42.30 (10.11)	13.38 (6.75)
Median (Min, Max)	42.46 (25.4, 59.8)	15.39 (4.5, 23.4)
Sex (%)		
Males	19 (55.9)	15 (46.9)
Females	15 (44.1)	17 (53.1)
Height Z-score		
Mean (SD)	-4.72 (1.04)	-3.56 (0.84)
Median (Min, Max)	-4.41 (-6.8, -3.1)	-3.65 (-5.7, -2.1)
Height (cm)		
Mean (SD)	79.72 (4.87)	64.71 (6.76)
Median (Min, Max)	78.38 (69.6, 89.3)	65.30 (54.5, 79.2)
AGV (cm/year)		
Mean (SD)	5.49 (1.78)	14.55 (6.68)
Median (Min, Max)	5.41 (0.6, 10.5)	13.27 (3.9, 30.2)

Overview of adverse events in children ≥2 years at start of treatment (as of February 25th 2023)

	Age at start of vosoritide ≥2 years (N=34; Total exposure: 113.59 person-years)	
Subjects with	**n (%)**	**n (rate per person-year)**
AE	33 (97.1)	858 (7.6)
AEs leading to drug interruption	12 (35.3)	46 (0.4)
AEs leading to study drug discontinuation	0	0
SAE	5 (14.7)	5 (0.0)
Treatment-related AE	8 (23.5)	115 (1.0)
Treatment-related SAEs	0	0
AE of CTCAE grade ≥ 3	2 (5.9)	2 (0.0)
AEs leading to deaths, n (%)	0	0
Injection site reactions CTCAE grade ≥2 or (excluding bruising) lasting >24 hours	5 (14.7)	111 (1.0)
Injection site reactions CTCAE grade ≥2	0	0
Hypotension	1 (2.9)	1 (0.0)
Heart rate change	0	0
Hypersensitivity (SMQ Narrow Terms)	13 (38.2)	23 (0.2)
Avascular necrosis or osteonecrosis	0	0
Slipped capital femoral epiphysis	0	0
Fractures	1 (2.9)	1 (0.0)

Overview of adverse events in children <2 years at start of treatment (as of February 25th 2023)

	Age at start of vosoritide <2 years (N=33; Total exposure: 86.52 person-years)	
Subjects with	**n (%)**	**n (rate per person-year)**
AE	33 (100.0)	857 (9.9)
AEs leading to drug interruption	21 (63.6)	87 (1.0)
AEs leading to study drug discontinuation	1 (3.0)	1 (0.0)
SAE	8 (24.2)	12 (0.1)
Treatment-related AE	9 (27.3)	31 (0.4)
Treatment-related SAEs	0	0
AE of CTCAE grade ≥ 3	6 (18.2)	8 (0.1)
AEs leading to deaths, n (%)	0	0
Injection site reactions CTCAE grade ≥2 or (excluding bruising) lasting >24 hours	9 (27.3)	30 (0.3)
Injection site reactions CTCAE grade ≥2	0	0
Hypotension	1 (3.0)	1 (0.0)
Heart rate change	0	0
Hypersensitivity (SMQ Narrow Terms)	15 (45.5)	25 (0.3)
Avascular necrosis or osteonecrosis	0	0
Slipped capital femoral epiphysis	0	0
Fractures	0	0

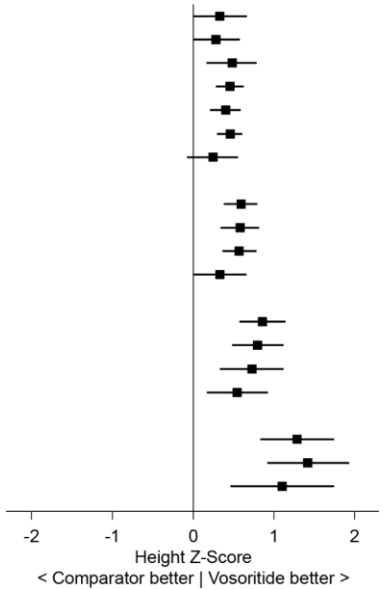
Safety summary of all subjects from first dose of vosoritide

- No significant difference in the nature and pattern of AEs in <2 years vs ≥2 years
- Nature and pattern of injection site reactions were comparable across the age groups and no evidence of long-term sequelae at injection site with daily administration of vosoritide
- Hypotension events were generally mild, asymptomatic, transient and self-limiting with no difference in trends of events reported across the younger and older children
- No events of grade 3 hypersensitivity, anaphylaxis, slipped capital femoral epiphysis, fractures, avascular necrosis or osteonecrosis were reported

In treated children aged ≥2 years, height Z-score consistently increased over 4 years of treatment compared to controls

Age group ≥2 years: Forest plot of differences in mean change from baseline in **height Z score**

Timepoint Studies	Comparator	Number of subjects Vosoritide	 Comparator	Treatment difference
1 year				
Study 111-206 (FAS randomized)	111-206 placebo	15	16	0.33
Study 111-206 (FAS)	111-206 placebo	19	16	0.29
Study 111-206 (FAS randomized)	AchNH longitudinal	15	124	0.48
Study 111-206/111-208	AchNH longitudinal	34	198	0.45
Study 111-206/111-208	AchNH cross-sectional	34	761/701	0.40
Study 111-206/111-208	Obs/Pbo longitudinal	34	72	0.45
Study 111-206/111-208	Obs/Pbo cross-sectional	34	77/134	0.24
2 year				
Study 111-206/111-208	AchNH longitudinal	30	146	0.59
Study 111-206/111-208	AchNH cross-sectional	30	725/614	0.58
Study 111-206/111-208	Obs/Pbo longitudinal	30	55	0.57
Study 111-206/111-208	Obs/Pbo cross-sectional	30	80/163	0.33
3 year				
Study 111-206/111-208	AchNH longitudinal	22	107	0.86
Study 111-206/111-208	AchNH cross-sectional	22	672/484	0.80
Study 111-206/111-208	Obs/Pbo longitudinal	22	21	0.73
Study 111-206/111-208	Obs/Pbo cross-sectional	22	80/167	0.55
4 year				
Study 111-206/111-208	AchNH longitudinal	8	30	1.29
Study 111-206/111-208	AchNH cross-sectional	9	444/254	1.42
Study 111-206/111-208	Obs/Pbo cross-sectional	9	79/109	1.10



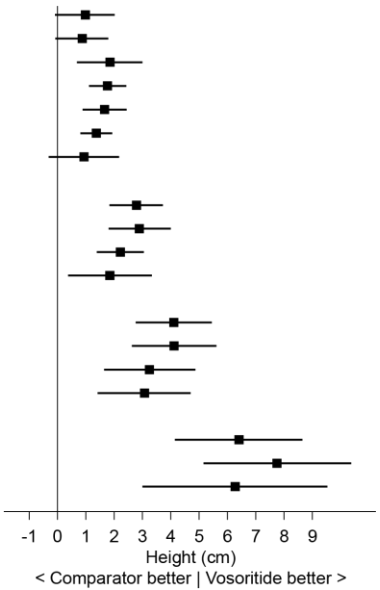
Consistent and sustained treatment effect with mean height Z-score gain > 1SDS after 4 years

AchNH reference derived from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis. 2021*).

Treated children aged ≥2 years consistently demonstrated greater height gain over 4 years compared to controls

Age group ≥2 years: Forest plot of differences in mean change from baseline in **height**

Timepoint Studies	Comparator	Number of subjects Vosoritide	 Comparator	Treatment difference
1 year				
Study 111-206 (FAS randomized)	111-206 placebo	15	16	0.96
Study 111-206 (FAS)	111-206 placebo	19	16	0.87
Study 111-206 (FAS randomized)	AchNH longitudinal	15	124	1.85
Study 111-206/111-208	AchNH longitudinal	34	198	1.76
Study 111-206/111-208	AchNH cross-sectional	34	761/701	1.66
Study 111-206/111-208	Obs/Pbo longitudinal	34	72	1.37
Study 111-206/111-208	Obs/Pbo cross-sectional	34	77/134	0.92
2 year				
Study 111-206/111-208	AchNH longitudinal	30	146	2.79
Study 111-206/111-208	AchNH cross-sectional	30	725/614	2.89
Study 111-206/111-208	Obs/Pbo longitudinal	30	55	2.21
Study 111-206/111-208	Obs/Pbo cross-sectional	30	80/163	1.86
3 year				
Study 111-206/111-208	AchNH longitudinal	22	107	4.10
Study 111-206/111-208	AchNH cross-sectional	22	672/484	4.12
Study 111-206/111-208	Obs/Pbo longitudinal	22	21	3.26
Study 111-206/111-208	Obs/Pbo cross-sectional	22	80/167	3.06
4 year				
Study 111-206/111-208	AchNH longitudinal	8	30	6.41
Study 111-206/111-208	AchNH cross-sectional	9	444/254	7.77
Study 111-206/111-208	Obs/Pbo cross-sectional	9	79/109	6.27



Consistent and sustained treatment effect with height gain > 6 cm over 4 years

AchNH reference derived from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis. 2021*).

Height restoration in treated children aged ≥2 years vs controls

Age group ≥2 years

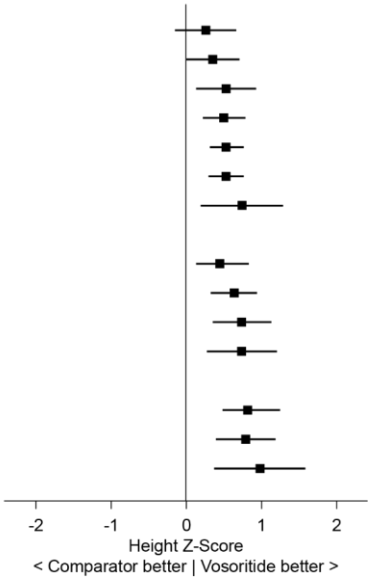
	Height Gain (cm) After x-Year Follow-up					
	After 4 Years		After 3 Years		After 2 Years	
	Vosoritide	AchNH	Vosoritide	AchNH	Vosoritide	AchNH
	(N=9)	(N=30)	(N=22)	(N=107)	(N=30)	(N=146)
Average Stature	26.21	26.36	20.43	20.47	13.89	13.94
ACH	23.71	17.31	17.59	13.49	11.99	9.21
% Height gain ACH vs Average Stature	**90.45**	**65.66**	**86.10**	**65.90**	**86.29**	**66.08**

AchNH reference derived from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis. 2021*).
Average stature estimated from CDC chart

In treated children aged <2 years, height Z-score consistently increased over 3 years compared to controls

Age group <2 years: Forest plot of differences in mean change from baseline in **height Z score**

Timepoint Studies	Comparator	Number of subjects Vosoritide	Number of subjects Comparator	Treatment difference
1 year				
Study 111-206 (FAS randomized)	111-206 placebo	17	16	0.26
Study 111-206 (FAS)	111-206 placebo	24	16	0.35
Study 111-206 (FAS randomized)	AchNH longitudinal	16	216	0.53
Study 111-206/111-208	AchNH longitudinal	32	287	0.50
Study 111-206/111-208	AchNH cross-sectional	32	788/716	0.53
Study 111-206/111-208	Obs/Pbo longitudinal	32	31	0.53
Study 111-206/111-208	Obs/Pbo cross-sectional	28	49/56	0.74
2 year				
Study 111-206/111-208	AchNH longitudinal	25	223	0.48
Study 111-206/111-208	AchNH cross-sectional	25	767/638	0.63
Study 111-206/111-208	Obs/Pbo longitudinal	25	20	0.74
Study 111-206/111-208	Obs/Pbo cross-sectional	25	55/64	0.74
3 year				
Study 111-206/111-208	AchNH longitudinal	14	150	0.86
Study 111-206/111-208	AchNH cross-sectional	14	715/509	0.79
Study 111-206/111-208	Obs/Pbo cross-sectional	14	61/85	0.98



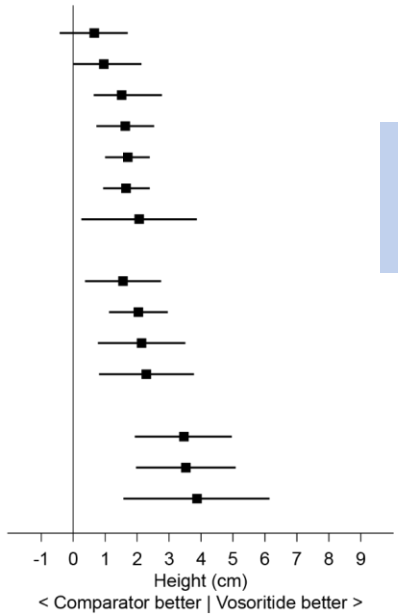
Consistent and sustained treatment effect with mean height Z-score gain > 0.79 SDS over 3 years

AchNH reference derived from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis. 2021*).

In treated children aged <2 years, height consistently increased over 3 years compared to controls

Age group <2 years: Forest plot of differences in mean change from baseline in **height**

Timepoint Studies	Comparator	Number of subjects Vosoritide	Number of subjects Comparator	Treatment difference
1 year				
Study 111-206 (FAS randomized)	111-206 placebo	17	16	0.65
Study 111-206 (FAS)	111-206 placebo	24	16	0.96
Study 111-206 (FAS randomized)	AchNH longitudinal	16	216	1.51
Study 111-206/111-208	AchNH longitudinal	32	287	1.63
Study 111-206/111-208	AchNH cross-sectional	32	788/716	1.70
Study 111-206/111-208	Obs/Pbo longitudinal	32	31	1.66
Study 111-206/111-208	Obs/Pbo cross-sectional	28	49/56	2.07
2 year				
Study 111-206/111-208	AchNH longitudinal	25	223	1.57
Study 111-206/111-208	AchNH cross-sectional	25	767/638	2.04
Study 111-206/111-208	Obs/Pbo longitudinal	25	20	2.14
Study 111-206/111-208	Obs/Pbo cross-sectional	25	55/64	2.29
3 year				
Study 111-206/111-208	AchNH longitudinal	14	150	3.45
Study 111-206/111-208	AchNH cross-sectional	14	715/509	3.52
Study 111-206/111-208	Obs/Pbo cross-sectional	14	61/85	3.87



Consistent and sustained treatment effect with height gain > 3 cm over 3 years

AchNH reference derived from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis. 2021*).

Height restoration in treated children aged <2 years vs controls

Age group <2 years

	Height Gain (cm) After x-Year Follow-up					
	After 3 Years		After 2 Years		After 1 Year	
	Vosoritide	AchNH	Vosoritide	AchNH	Vosoritide	AchNH
	(N=14)	(N=150)	(N=25)	(N=223)	(N=32)	(N=287)
Average Stature	26.37	26.46	20.77	20.81	11.78	11.70
ACH	21.10	17.66	15.30	13.74	9.45	7.81
% Height gain ACH vs Average Stature	**80.02**	**66.74**	**73.68**	**66.02**	**80.21**	**66.73**

AchNH reference derived from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis. 2021*)
Average stature estimated from CDC chart

Upper:lower body segment ratio

- No worsening in upper:lower body segment ratio was observed over time

- Cross-sectional analyses show consistent improvement in upper:lower body segment ratio over time in treated children aged ≥2 years
  - Improvement with vosoritide vs observational/placebo control after 4 years of treatment
    - Mean (95% CI) decrease from baseline = -0.10 (-0.19, -0.00)

- No consistent trend observed in treated children aged <2 years
  - May reflect challenges of obtaining accurate anthropometric measurements in very young children

Conclusions

- Daily injections of vosoritide were well tolerated with no treatment limiting adverse events, and no new safety issues were observed in these young children receiving vosoritide for up to 4 years
- Most common adverse events observed were mild and self-limiting injection site reactions
- Consistent and durable treatment effect of vosoritide on growth in young children who started treatment before age 5 years, demonstrating benefit of early treatment initiation
- No worsening in body proportions over time

Acknowledgments

- Study participants
- Investigators and study teams
- Study sponsor: BioMarin Pharmaceutical Inc.
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  - Hiroshi Mochizuki, M.D., Saitama Children's Hospital, Saitama, Japan
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  - Howard M. Saal, M.D, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA
  - Lynn Han, Ph.D, BioMarin Pharmaceutical Inc., Novato, CA, USA
  - Elena Fisheleva, M.D., Ian Sabir, M.B., B.Chir., Alice Huntsman-Labed, Ph.D., and Jonathan Day, M.B., B.S., BioMarin (U.K.) Limited, London, UK