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Persistence of growth promoting effects in infants and toddlers with achondroplasia: Results from a phase II extension study with vosoritide

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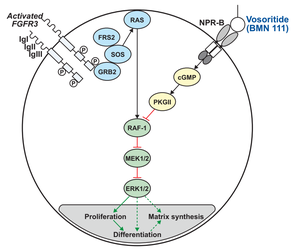
Background

Vosoritide: Targeted therapy for achondroplasia

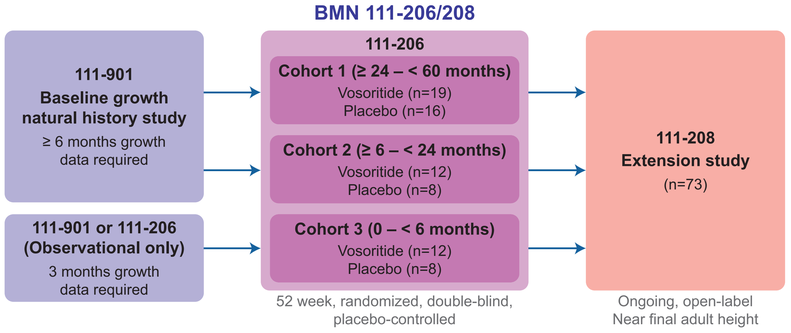
- Achondroplasia (ACH) is the most common form of disproportionate short stature (approx. 1:25,000 live births)[1,2]
- ACH is caused by a pathogenic variant in *FGFR3* that constitutively activates the downstream inhibitory signaling pathway in chondrocytes, leading to impaired endochondral bone growth 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]



Increase in growth was 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[6,7]
- 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[8]; AGV improvement sustained after 3 years of vosoritide treatment in extension study BMN 111-302[9,10]
- 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)[11]
- Vosoritide is approved for use in children with ACH and open epiphyses from birth in the USA, Japan and Australia, and aged ≥ 4 months in EU and ≥ 6 months in Brazil

Design and Methods



- 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

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[12]
- **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)

Results

Subject disposition

Age at start of vosoritide	Total	Number of participants: 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

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

- **Age group ≥ 2 years:** Participants aged 2 – < 5 years at start of vosoritide (in either study 111-206 or 111-208). Participants ≥ 5 years at the start of vosoritide were not included.
- **Age group < 2 years:** participants aged 3 months to <2 years at start of vosoritide (in either study 111-206 or 111-208)

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 (as of Feb 25th 2023)

Children ≥ 2 years at start of treatment

	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)

Children < 2 years at start of treatment

	Age at start of vosoritide < 2 years (N=33; Total exposure: 86.52)
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

Height Z-score consistently increased over time in treated children vs controls

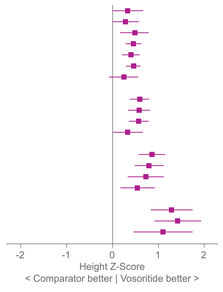
Children ≥ 2 years at start of treatment

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

AchNH reference derived from CLARITY[12]

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

Treatment difference (95% CI) Vosoritide minus comparator



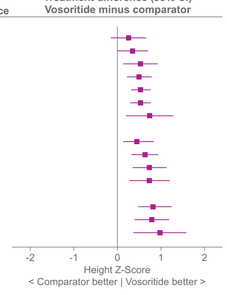
Children < 2 years at start of treatment

Timepoint / Studies	Comparator	Number of subjects: Vosoritide	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

AchNH reference derived from CLARITY[12]

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

Treatment difference (95% CI) Vosoritide minus comparator



Height increased over time in treated children vs controls

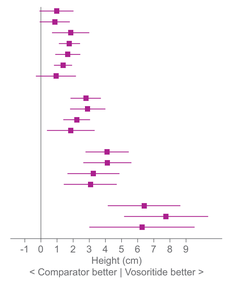
Children ≥ 2 years at start of treatment

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

AchNH reference derived from CLARITY[12]

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

Treatment difference (95% CI) Vosoritide minus comparator



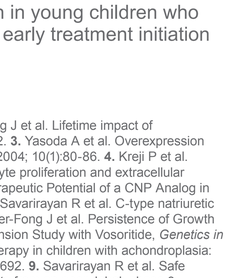
Children < 2 years at start of treatment

Timepoint / Studies	Comparator	Number of subjects: Vosoritide	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

AchNH reference derived from CLARITY[12]

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

Treatment difference (95% CI) Vosoritide minus comparator



Height restoration in treated children vs controls

Children ≥ 2 years at start of treatment

	Height gain (cm) after x-year follow-up: After 4 years Vosoritide (N=9)	After 4 years AchNH (N=30)	After 3 years Vosoritide (N=22)	After 3 years AchNH (N=107)	After 2 years Vosoritide (N=30)	After 2 years AchNH (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[12]. Average stature estimated from CDC chart.

Children < 2 years at start of treatment

	Height gain (cm) after x-year follow-up: After 3 years Vosoritide (N=14)	After 3 years AchNH (N=150)	After 2 years Vosoritide (N=25)	After 2 years AchNH (N=223)	After 1 year Vosoritide (N=32)	After 1 year AchNH (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**

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

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Disclosures

All authors are investigators in this clinical trial with the exception of LH, AL, EF, and JD, who are employees of BioMarin. RS and LT have received consulting fees and grants from BioMarin. MI and WRW have received consulting fees from BioMarin. JC and DB have received grants from BioMarin. LEP, PA and RC have received honoraria from BioMarin. CB and PH have received consulting fees, honoraria, and grants from BioMarin. Other authors declare no competing interests.

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