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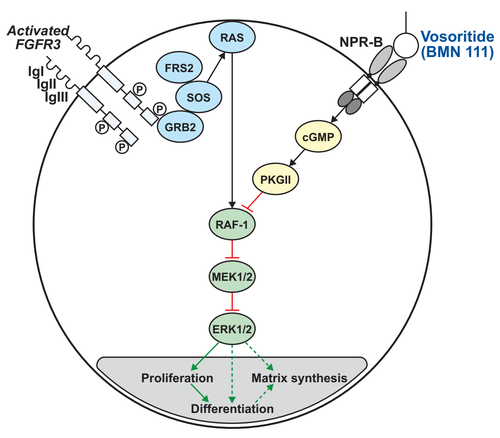
Impact of vosoritide on polysomnography parameters among children aged 3–59 months

Paul Gringras[1], Moira Cheung[2], Paul Harmatz[3], Lynda E. Polgreen[4], Louise Tofts[5], Takuo Kubota[6], Paul Arundel[7], Carlos A. Bacino[8], Donald Basel[9], Ricki S. Carroll[10], Carlos Prada[11], Asako Tajima[12], Andrea Low[13], Elena Fisheleva[14], Melita Irving[1], Keiichi Ozono[15], William R. Wilcox[16], Ravi Savarirayan[17]

[1]Guy's and St. Thomas' NHS Foundation Trust, Evelina Children's Hospital, London, UK; [2]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [3]UCSF Benioff Children's Hospital Oakland, CA, USA; [4]Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA, USA; [5]The Children's Hospital at Westmead, Westmead, New South Wales, AUS; [6]Osaka University, Osaka, Japan; [7]Sheffield Children's NHS Foundation, Sheffield, UK; [8]Baylor College of Medicine, Houston, TX, USA; [9]Medical College of Wisconsin, Milwaukee, WI, USA; [10]Nemours Children's Hospital, Wilmington, DE, USA; [11]Lurie Children's Hospital of Chicago, Chicago, IL, USA; [12]Saitama Children's Hospital, Saitama, Japan; [13]BioMarin Pharmaceutical Inc. Novato, CA, USA; [14]BioMarin (U.K.) Limited, London, UK; [15]Iseikai International General Hospital, Osaka, Japan; [16]Emory University, Atlanta, GA, USA; [17]Murdoch Children's Research Institute, Royal Children's Hospital, and University of Melbourne, Parkville, Victoria, AUS

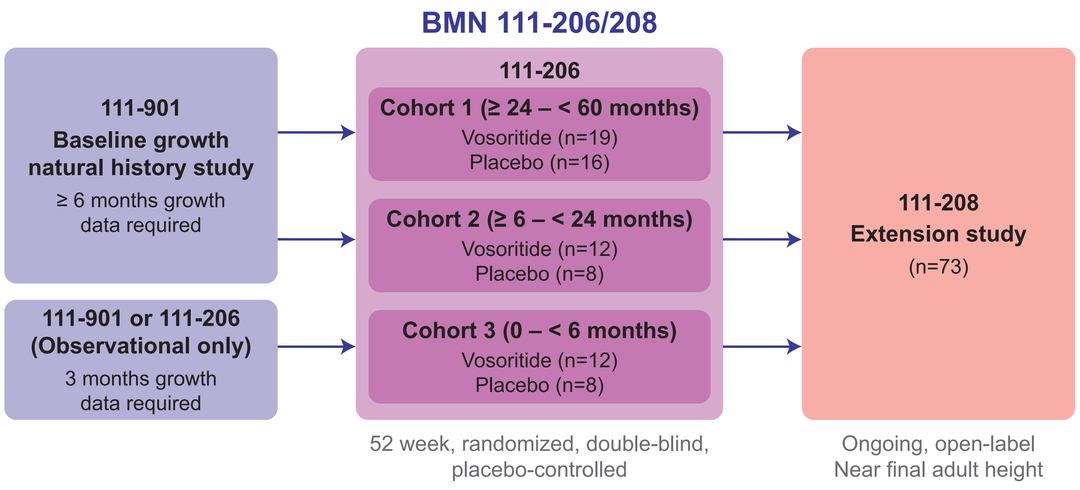
Introduction

- 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]
- An open-label, two year 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 (BMN 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
- Sleep disordered breathing (SDB) is a common disorder in children with achondroplasia, including obstructive sleep apnea (OSA) and central apnea which can be associated with sudden unanticipated death in infancy, due to skull and upper airway anatomy

Materials and Methods



- BMN 111-206: An open-label 52-week placebo-controlled trial (111-206) studied the impact of vosoritide on linear growth in children with achondroplasia who initiated treatment before the age of 5 years. Polysomnography was conducted at baseline and week 52. Children were eligible to enroll in an open label extension of vosoritide (111-208) after completion of the 52-week trial
- Children were not eligible to participate in 111-206 if they had severe sleep apnea at screening
- Key clinically meaningful parameters were selected for analysis for change from baseline. These additional parameters are presented as shift analyses to better capture changes in SDB in the vosoritide treatment group versus placebo, incorporating baseline values. Shift analyses in the Apnea/Hypopnea in the Apnea/Hypopnea index (AHI), the Central Apnea Index (CAI), and the oxygen desaturation index (ODI) >3% were evaluated at week 52 for the vosoritide group (all cohorts combined) and placebo

Results

Table 1. Baseline Demographic Characteristics and Height Z-score by Study Arm (111-206)

Characteristic	Vosoritide (N=43)	Placebo (N=32)
Age on day 1, months		
Median (IQR)	21.82 (5.91-36.86)	26.43 (7.67-40.39)
Male sex, no. (%)	25 (58.1)	13 (40.6)
Race, no. (%)		
White	29 (67.4)	25 (78.1)
Asian	11 (25.6)	6 (18.8)
Multiple	3 (7.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (3.1)
Hispanic or Latino ethnicity, no. (%)	3 (7.0)	3 (9.4)
Height Z-score		
Median (IQR)	−3.90 (−4.41, −3.17)	−4.12 (−5.44, −3.20)

- The distribution of sleep-related disorders at study baseline was roughly equivalent across study arm, with approximately half reporting a history of sleep apnoea. More children in the vosoritide arm had a history of adenoidal or tonsillar hypertrophy, whereas fewer reported adenoid or tonsillectomies **(Table 2)**

Table 2. Medical History of Sleep-related Disorders by Study Group at Baseline

Preferred term	Vosoritide N=43 n (%)	Placebo N=32 n (%)
Sleep apnoea syndrome	22 (51.2%)	16 (50%)
Adenoidal hypertrophy	6 (14.0%)	2 (6.3%)
Tonsillar hypertrophy	3 (7.0%)	0
Obstructive airways disorder	0	1 (3.1%)
Cervical cord compression	3 (7.0%)	1 (3.1%)
Procedures		
Adenoidectomy	7 (16.3%)	7 (21.9%)
Tonsillectomy	4 (9.3%)	5 (15.6%)
Adenotonsillectomy	1 (2.3%)	2 (6.3%)
Posterior fossa decompression	3 (7.0%)	3 (9.4%)

- Of the 75 enrolled participants, 84% (n=36/43) of children in the vosoritide arm and 81% (n=26/32) in the placebo arm had sleep study data at week 52
- After 1 year of vosoritide, improvements in AHI were observed in 10 participants, a normal to mild AHI shift was observed in 4 (9.3%) participants, and a moderate to severe shift was observed in 1 (2.3%) participant
- In the placebo group, improvement in the AHI index was observed in 9 participants, a normal to mild shift was observed in 3 (9.4%) participants, normal to moderate shift was observed in 1 (3.1%) participant, and mild to severe shift was observed in 2 (6.3%) participants
- During this period, 6 children had a tonsillectomy or adenoidectomy in the vosoritide arm, and one had an adenoidectomy in the placebo arm

Table 3. Shift Table of Apnea Hypopnea Index (Number per Hour) from Baseline to Week 52 in All Vosoritide Group

Baseline	Week 52					
	Missing	<1/hour (normal)	1-5/hour (mild)	>5-10/hour (moderate)	>10/hour (severe)	Overall
Missing	1 (2.3%)	1 (2.3%)	0	0	0	2 (4.7%)
<1/hour (normal)	0	3 (7.0%)	4 (9.3%)	0	0	7 (16.3%)
1-5/hour (mild)	4 (9.3%)	4 (9.3%)	17 (39.5%)	0	0	25 (58.1%)
>5-10/hour (moderate)	1 (2.3%)	4 (9.3%)	1 (2.3%)	0	1 (2.3%)	7 (16.3%)
>10/hour (severe)	1 (2.3%)	0	1 (2.3%)	0	0	2 (4.7%)
Overall	7 (16.3%)	12 (27.9%)	23 (53.5%)	0	1 (2.3%)	43 (100%)

Table 4. Shift Table of Apnea Hypopnea Index (Number per Hour) from Baseline to Week 52 in Placebo Group

Baseline	Week 52					
	Missing	<1/hour (normal)	1-5/hour (mild)	>5-10/hour (moderate)	>10/hour (severe)	Overall
Missing	0	0	0	0	0	0
<1/hour (normal)	1 (3.1%)	4 (12.5%)	3 (9.4%)	1 (3.1%)	0	9 (28.1%)
1-5/hour (mild)	2 (6.3%)	6 (18.8%)	5 (15.6%)	1 (3.1%)	2 (6.3%)	16 (50.0%)
>5-10/hour (moderate)	2 (6.3%)	0	3 (9.4%)	0	0	5 (15.6%)
>10/hour (severe)	1 (3.1%)	0	0	0	1 (3.1%)	2 (6.3%)
Overall	6 (18.8%)	10 (31.3%)	11 (34.4%)	2 (6.3%)	3 (9.4%)	32 (100%)

- There were no worsening shifts in the CAI in either arm

Table 5. Shift Table of Central Apnea Index (Number per Hour) from Baseline to Week 52 in All Vosoritide Group

Baseline	Week 52			
	Missing	<5/hour (normal)	≥5/hour	Overall
Missing	1 (2.3%)	1 (2.3%)	0	2 (4.7%)
<5/hour (normal)	6 (14.0%)	33 (76.7%)	0	39 (90.7%)
≥5/hour	0	2 (4.7%)	0	2 (4.7%)
Overall	7 (16.3%)	36 (83.7%)	0	43 (100%)

Table 6. Shift Table of Central Apnea Index (Number per Hour) from Baseline to Week 52 in Placebo Group

Baseline	Week 52			
	Missing	<5/hour (normal)	≥5/hour	Overall
Missing	0	0	0	0
<5/hour (normal)	5 (15.6%)	24 (75.0%)	0	29 (90.6%)
≥5/hour (raised)	1 (3.1%)	1 (3.1%)	1 (3.1%)	3 (9.4%)
Overall	6 (18.8%)	25 (78.1%)	1 (3.1%)	32 (100%)

- For the ODI using a threshold of <7/hour versus ≥7/hour, there were no shifts from normal to raised ODIs in the vosoritide arm, whereas this shift was observed in 2 (6.3%) participants in the placebo group

Table 7. Shift Table of Desaturation per Hour ≥3% (Number per Hour) from Baseline to Week 52 in the All Vosoritide Group (<7/hour or ≥7/hour)

Baseline	Week 52			
	Missing	<7/hour (normal)	≥7/hour (raised)	Overall
Missing	1 (2.3%)	1 (2.3%)	0	2 (4.7%)
<7/hour (normal)	4 (9.3%)	31 (72.1%)	0	35 (81.4%)
≥7/hour (raised)	2 (4.7%)	3 (7.0%)	1 (2.3%)	6 (14.0%)
Overall	7 (16.3%)	35 (81.4%)	1 (2.3%)	43 (100%)

Table 8. Shift Table of Desaturation per Hour ≥3% (Number per Hour) from Baseline to Week 52 in Placebo Group (<7/hour or ≥7/hour)

Baseline	Week 52			
	Missing	<7/hour (normal)	≥7/hour (raised)	Overall
Missing	0	0	0	0
<7/hour (normal)	5 (15.6%)	23 (71.9%)	2 (6.3%)	30 (93.8%)
≥7/hour (raised)	1 (3.1%)	0	1 (3.1%)	2 (6.3%)
Overall	6 (18.8%)	23 (71.9%)	3 (9.4%)	32 (100%)

Conclusions

- These data demonstrate that vosoritide is not associated with detrimental effects on sleep-related breathing parameters in young children with ACH after treatment for 1 year
- Longer term data from the open label extension study is needed to ascertain the effect of continued treatment on these parameters

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