Development of BMN 333, a long-acting version of vosoritide for FGFR3-related dwarfism and other skeletal dysplasias

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#P158

Introduction

Achondroplasia (ACH) is recognized as the most common form of disproportionate short stature worldwide, affecting roughly **1 in every 15,000–30,000 live births**. This condition is caused by a **gain-of-function mutation in the fibroblast growth factor receptor 3 (FGFR3) gene**, which results in an overactive FGFR3 protein. In ACH, this overactivity leads to reduced proliferation and abnormal maturation of growth plate chondrocytes, suppressing endochondral bone growth. Clinically, this manifests as disproportionate long bones (rhizomelia), short stature, mid-face hypoplasia, foramen and spinal stenosis, along with other skeletal complications, highlighting **FGFR3 as a negative regulator** of endochondral ossification.

CNP (C-type natriuretic peptide) **is a positive regulator** of endochondral bone growth. It plays a crucial role in the growth plate by **binding to natriuretic peptide receptor-B** (NPR-B, also known as NPR2) on chondrocytes. This interaction boosts intracellular cGMP, which in turn activates protein kinase G (PKG2), promoting chondrocyte proliferation and endochondral bone growth. Importantly, this process **inhibits the overactive FGFR3 downstream pathway (ERK/MAPK), central to the pathology of ACH**.

Therapeutically, **vosoritide became the first approved drug for ACH in 2021**. It is a longer-acting version of naturally occurring CNP22, rendered **resistant to neutral endopeptidase (NEP)**, and is administered via daily subcutaneous injection. Building on this, **BMN 333** is currently an investigational, **fully biodegradable treatment** aimed at extending vosoritide exposure.

The ultimate goal of our current research is to thoroughly investigate the effects of BMN 333 on growth velocity and other skeletal complications in children diagnosed with achondroplasia (ACH) and hypochondroplasia (HCH). By focusing on these objectives, we hope to provide meaningful improvements in treatment and quality of life for affected children.

CNP Pathway is a Master Regulator of Growth

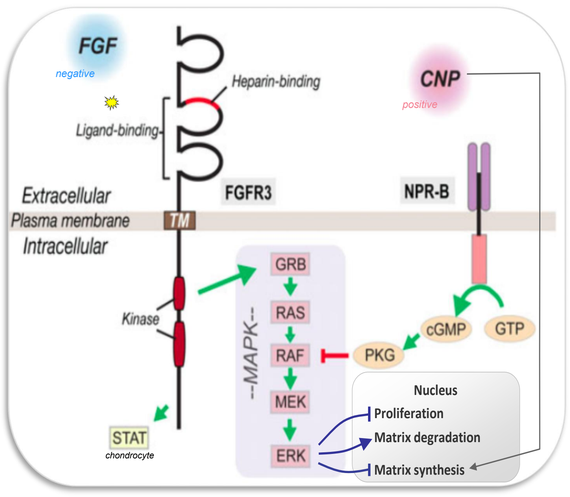

Figure 1. CNP signaling pathway
CNP inhibits signals that decrease endochondral bone growth (positive regulator)

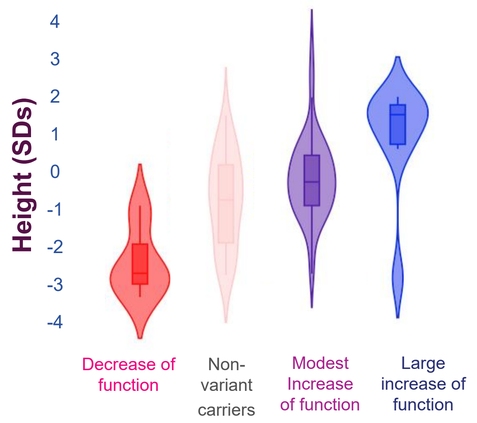

Figure 2. CNP receptor (NPR2) variants predict adult height
Violin plots of carriers of NPR2 variants tested in functional analyses

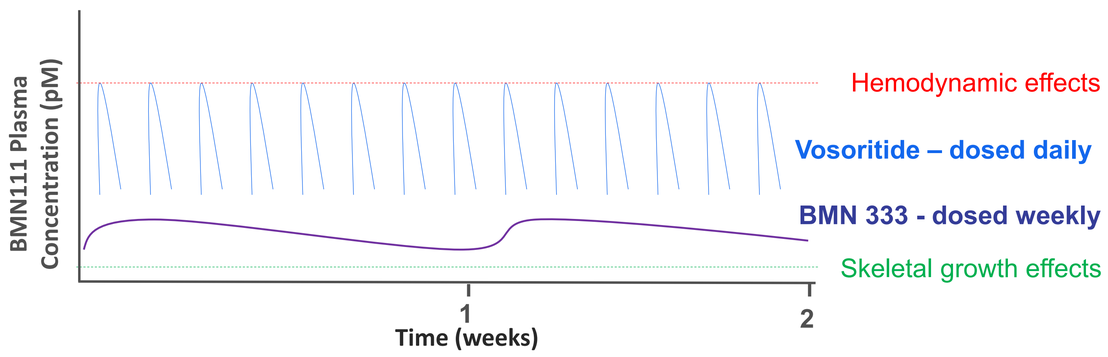

Figure 3: Theoretical BMN 333 exposure plot compared to vosoritide

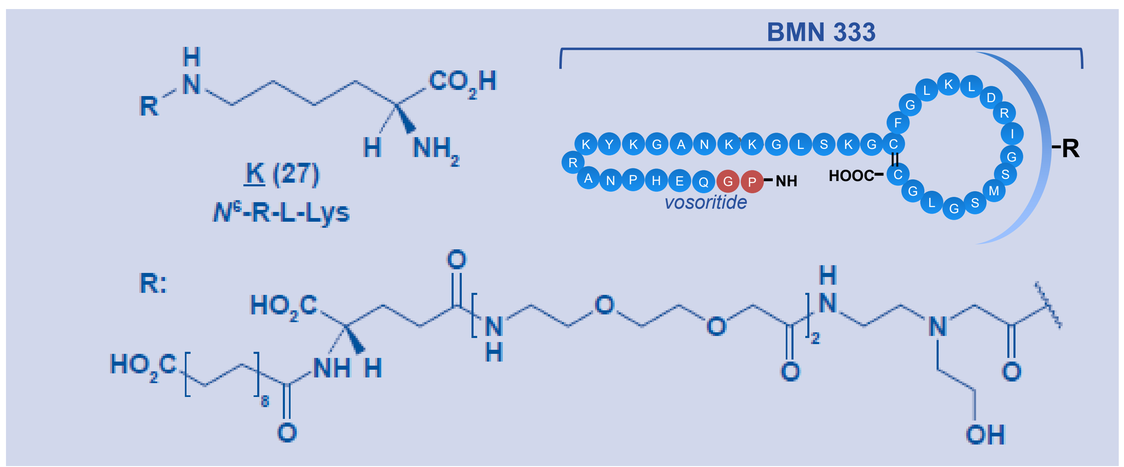

Figure 4. BMN 333 structure

Methods

In vivo PK analysis (mice): Adult male mice (n=48) received a single subcutaneous injection of BMN 333 at two dose levels (630 and 1900 µg/kg), quantified by LCMS/MS for pharmacokinetic (PK) assessment.

In vivo PD (growth) studies (mice): Male 3-week-old wild-type (wt) mice (n=40) received subcutaneous vehicle or BMN 333 at 80, 300, or 1000 µg/kg Q2D, or 500, or 1600 µg/kg QD for 5 weeks. Naso-anal and femoral lengths were measured via in vivo whole body microCT.

In vivo PK/PD studies (NHPs): Male and female 2-year-old cynomolgus monkeys (n=52) with telemetry implants received subcutaneous vehicle or BMN 333 at 75, 200, or 350 µg/kg once weekly (QW) for 26 weeks. Femoral lengths were measured radiographically at baseline and during treatment, and PK was assessed on Day 1 and Day 176 using LCMS/MS.

Results

BMN 333 PK analysis in wild-type mice shows sustained exposure

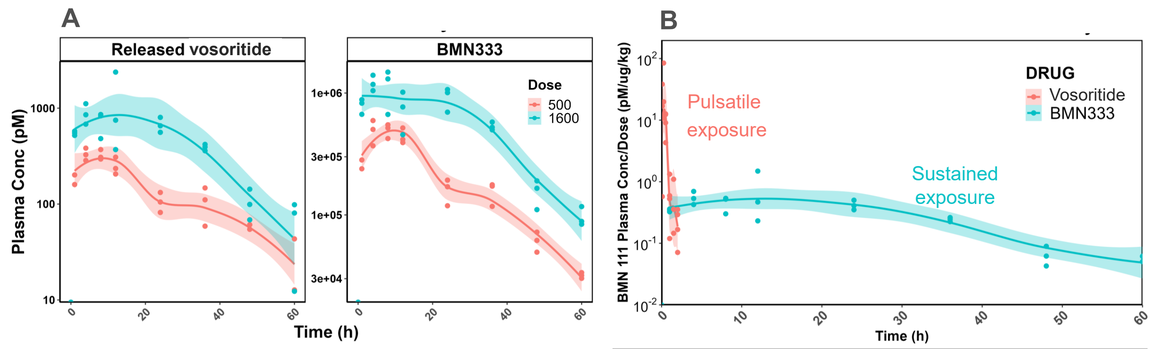

Figure 5. Plasma concentration vs. time profile of BMN 333/released vosoritide in mice
(A). Dose dependent increase in exposure of BMN 333 and released vosoritide
(B). Released vosoritide from BMN 333 shows sustained exposure compared to pulsatile administration of vosoritide (subcutaneous)

Dose (µg/kg)	Analyte	t1/2 (h)	Tmax (h)	Cmax (pM)	AUClast (h*pM)	AUCinf (h*pM)	%MR$_{Cmax}$	%MR$_{AUC}$
500	vosoritide	12.5	4	331	8220	8720	0.07	0.07
	BMN 333	10.5	8	496000	1.3E+07	1.3E+07		
1600	vosoritide	9.91	12	1170	30800	31700	0.10	0.08
	BMN 333	10.4	4	1210000	3.6E+07	3.8E+07		

Table 1. PK parameters after BMN 333 dosing
"Released" vosoritide had longer t1/2 compared to mice dosed with vosoritide (10h vs ~15min).

BMN 333 promotes significant skeletal growth in wild-type mice

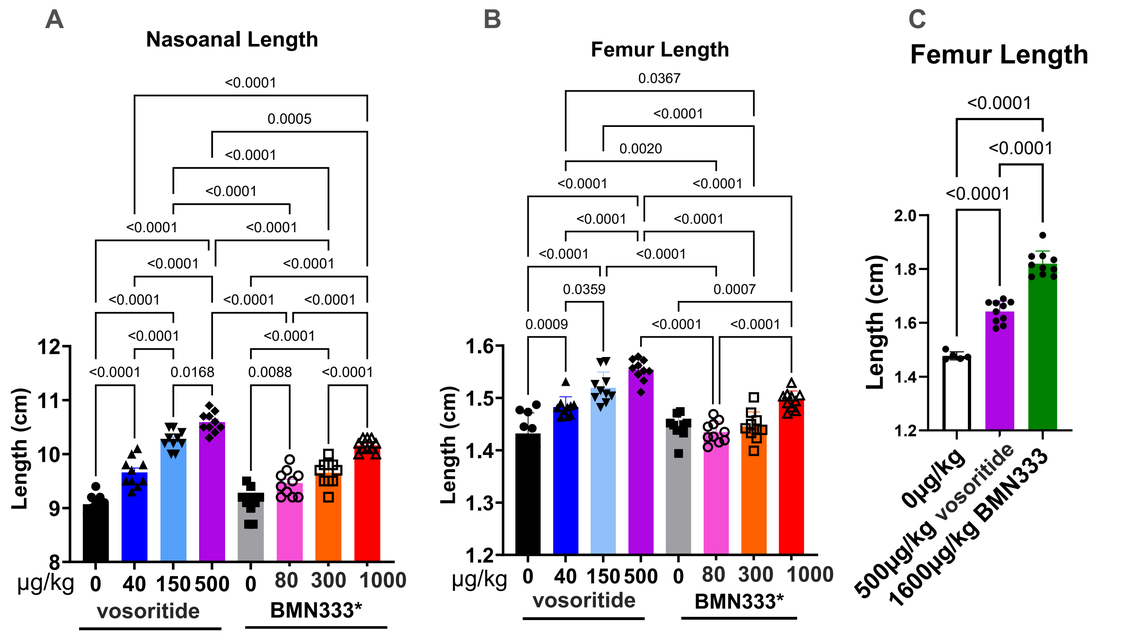

Figure 6. 3-wk old wild-type mice treated for 5-wks with either vosoritide or BMN 333
(A). Nasoanal and (B) femur lengths were measured at 8 wks of age. *BMN 333 was dosed every other day. (C) Significant femur length increase at higher daily dose of BMN 333. One-way ANOVA Tukey's multiple comparison test was performed.

BMN 333 PK/PD analysis in cynomolgus monkeys (NHPs)

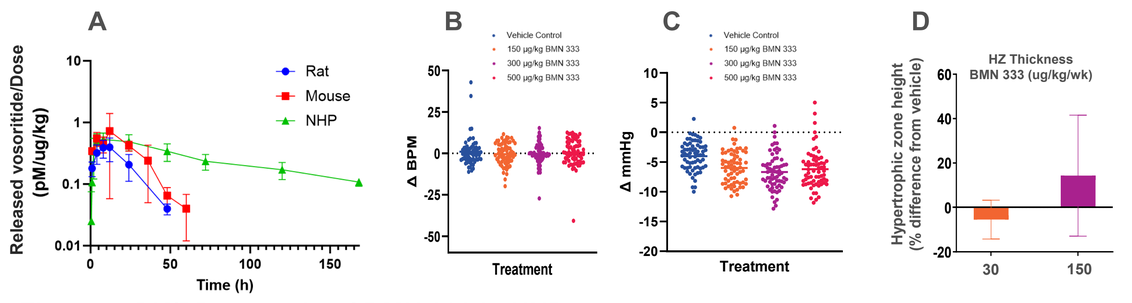

Figure 7. PK/PD analysis of BMN 333 in NHPs
(A). Comparative exposure profiles in various preclinical models; half-life of BMN 333 in NHPs was~60 hrs. (B and C) No changes in mean heart rate or mean arterial pressure from pre-dose over 72 hrs peak plasma levels in both male and female cynomolgus monkeys. (D) Dose and exposure related increases in the hypertrophic zone of the growth plate after 1 month treatment in male monkeys.

Conclusions

- BMN 333, a long-acting fully biodegradable version of vosoritide, provided extended systemic vosoritide exposure compared with directly administered vosoritide in both mice and NHPs
  - BMN 333 > 2-fold less Cmax than vosoritide; serum half-lives of ~11 hrs (mice) and ~60 hrs (NHPs) compared to ~ 0.5-1 hr for vosoritide
- Growth achieved with BMN 333 was comparable to or exceeded results of daily doses of vosoritide in wt mice without adverse hemodynamic effects (NHPs)
- See poster #79 for follow-on NHP studies; BMN 333 is currently in clinical trials.

Animal Welfare Statement

The Study Plan and procedures involving the care and use of animals in this study were reviewed and approved by an IACUC. During the study, the care and use of animals was conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care.

Disclosures

All authors are employees and shareholders of BioMarin Pharmaceutical Inc.

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