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

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INTRODUCTION

Achondroplasia (ACH) is the most common form of disproportionate short stature, affecting ~**1 in 15,000–30,000 live births**, caused by a **gain-of-function FGFR3 mutation**. Overactive FGFR3 suppresses growth plate chondrocyte proliferation and endochondral bone growth, causing severe disproportionate (rhizomelia) short stature and other skeletal issues, highlighting **FGFR3 as a negative regulator** of endochondral ossification.

CNP (C-type natriuretic peptide) **is a positive regulator** of endochondral bone growth. It binds to the guanylyl cyclase receptor-B (NPR-B/NPR2) on chondrocytes. This raises intracellular cGMP levels and initiates signaling that ultimately **inhibits the overactive FGFR3 downstream pathway (ERK/MAPK), central to the pathology of ACH**.

AIM

Vosoritide was the first approved drug for ACH (2021), a longer-acting CNP22 analog resistant to neutral endopeptidase (NEP), dosed by daily subcutaneous injection.

BMN 333 is an investigational, **fully biodegradable treatment** designed to extend vosoritide exposure (eg once/weekly injection). This poster highlights some of the key preclinical studies that were used during the development of BMN 333 that led to our successful IND submission (2024) as a treatment for children with ACH and hypochondroplasia (HCH).

METHOD

In vivo PK analysis (mice): Adult male mice (n=48) received a single SC injection of BMN 333 (630 and 1900 µg/kg), quantified by LCMS/MS.

In vivo PD (growth) studies (mice): Male 3-week-old wild-type (wt) mice (n=40) received SC injections of vehicle or BMN 333 (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 NHP PK/PD: 2.5-yr-old male cynomolgus monkeys (N=12) were treated with weekly SC injections of vehicle or BMN 333 at 30 or 150 µg/kg/week for a total of 5 doses over 1 month.

In vivo NHP Cardiovascular Effects: Animals (n=6) were implanted with telemetry devices and given ascending SC doses of BMN 333 at 150, 300, and 500 µg/kg every other week. Blood pressure and HR were monitored 72 hrs post-dose to capture the peak plasma period.

BACKGROUND

CNP Pathway is a Master Regulator of Growth

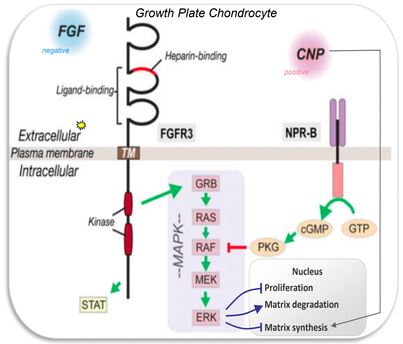


Figure 1. CNP signaling pathway
CNP inhibits signals that decrease endochondral bone growth (positive regulator)

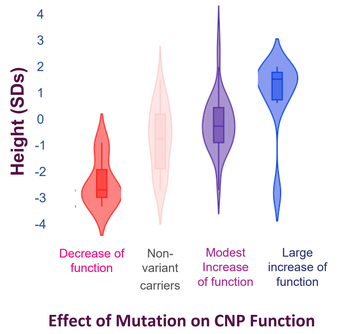


Figure 2. CNP receptor (NPR2) variants predict adult height
NPR2 variants tested in functional analyses

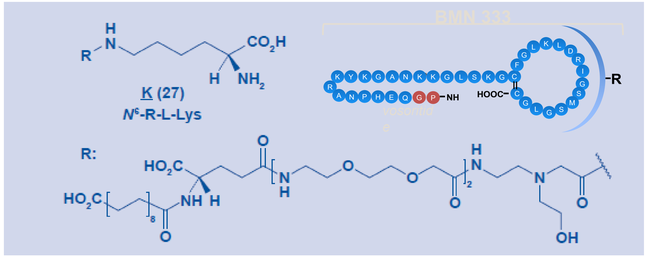


Figure 3. BMN 333 structure

RESULTS

BMN 333 PK/PD in wild-type mice shows sustained exposure & dose-dependent growth

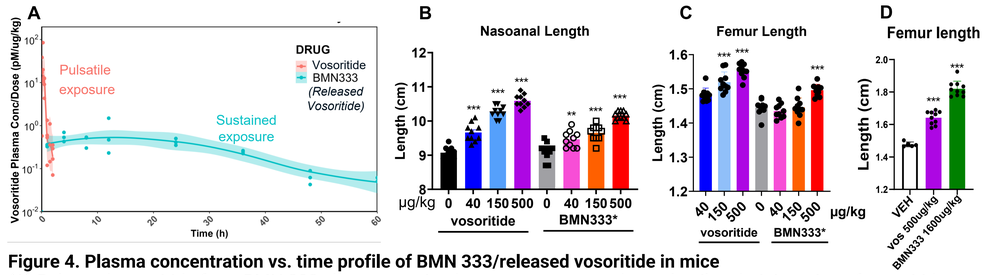


Figure 4. Plasma concentration vs. time profile of BMN 333/released vosoritide in mice
(A) Released vosoritide from BMN 333 shows sustained exposure compared to pulsatile administration of vosoritide (subcutaneous) (B-D) Dose/response skeletal growth effects of WT mice treated with vosoritide or BMN 333 on naso-anal and femur length. BMN 333 dosed every other day (B,C) or daily (D). One-way ANOVA Tukey's multiple comparison test was performed (* p=<0.05, ** p=<0.01, *** p=<0.001).

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

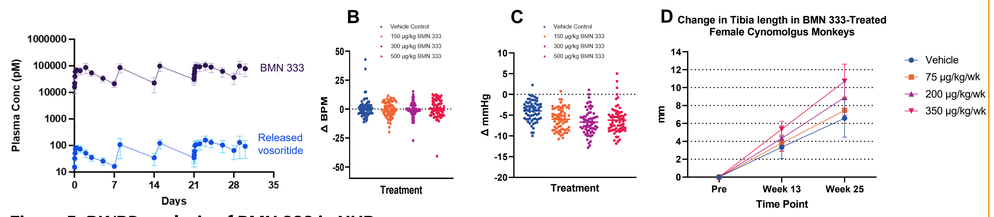


Figure 5. PK/PD analysis of BMN 333 in NHPs
(A) Exposure profile of BMN 333 and released vosoritide after weekly (150 ug/kg) SC injections; half-life of BMN 333 in NHPs was ~60 hrs. (B and C) No changes in mean heart rate or mean arterial pressure from pre-dose over 72 hrs peak plasma levels in both male and female cynomolgus monkeys. (D) Dose related increases in tibia growth after 6 months of weekly BMN 333 treatment in female monkeys.

CONCLUSIONS

- BMN 333 is a long-acting **fully biodegradable version of vosoritide that shows no evidence of metabolite accumulation** in tissues.
- Dose-dependent growth was achieved with BMN 333 in both mice and NHPs without adverse hemodynamic effects (NHPs)
- BMN 333 is being evaluated as a treatment for children with ACH/HCH in clinical trials.

See posters #SUN-092 and #SUN-115 for additional information on BMN 333.

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