BMN 333 clinical development program in achondroplasia: Phase 1 results and phase 2/3 study design overview

Poster P84

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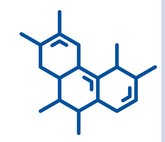
Introduction

- Achondroplasia is a rare skeletal dysplasia caused by excess fibroblast growth factor 3 (FGFR3) signaling that impairs endochondral bone growth, thereby hindering growth[1–2]
- Vosoritide, the first approved targeted treatment for achondroplasia, is a recombinant C-type natriuretic peptide (CNP) analog that counteracts excess FGFR3 signaling and promotes endochondral bone growth[2,3]
  - Over a decade of clinical trial and growing real-world data demonstrate that vosoritide is well tolerated and improves long-term growth[4–6]
  - Vosoritide is the only approved therapy for achondroplasia with long-term clinical and real-world data
- Most children with achondroplasia who receive treatment do not reach average stature, suggesting that achieving greater vosoritide exposure may further optimize growth
- BMN 333 is an investigational drug in early clinical development that is fully biodegradable and designed to release vosoritide, its active moiety, in a time-dependent manner to extend exposure (**Figure 1**)

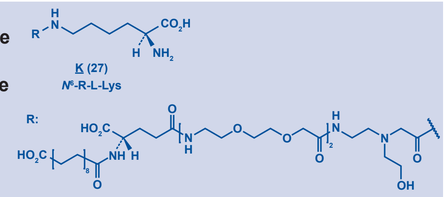
Objective

To describe phase 1 study results of BMN 333 in healthy volunteers and outline the study design of ASPEN (NCT07441876), the first active-controlled phase 2/3 study in untreated children with achondroplasia to compare the safety and efficacy of BMN 333 and evaluate its superiority vs vosoritide

Figure 1. BMN 333 structure and preclinical results



Fully biodegradable components and extends the half-life of vosoritide, its active moiety, with time-dependent release



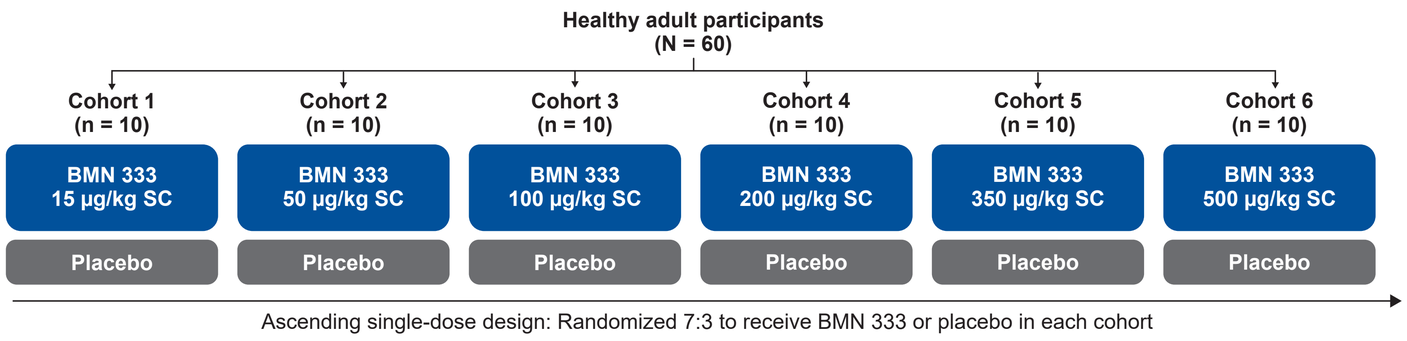
In NHPs, BMN 333 has

- **Demonstrated a gradual and sustained vosoritide release**
- **Reduced hemodynamic effects while enabling dose-dependent long-bone growth, with no observed adverse events**

NHP, non-human primates.

Phase 1: Completed phase 1 results support phase 2/3 studies of BMN 333 in children with achondroplasia

Figure 2. Phase 1 study design



Summary of results

Safety

- BMN 333 was well tolerated, dose escalation was completed up to 500 µg/kg, and no clinically significant abnormalities were observed

PK/PD

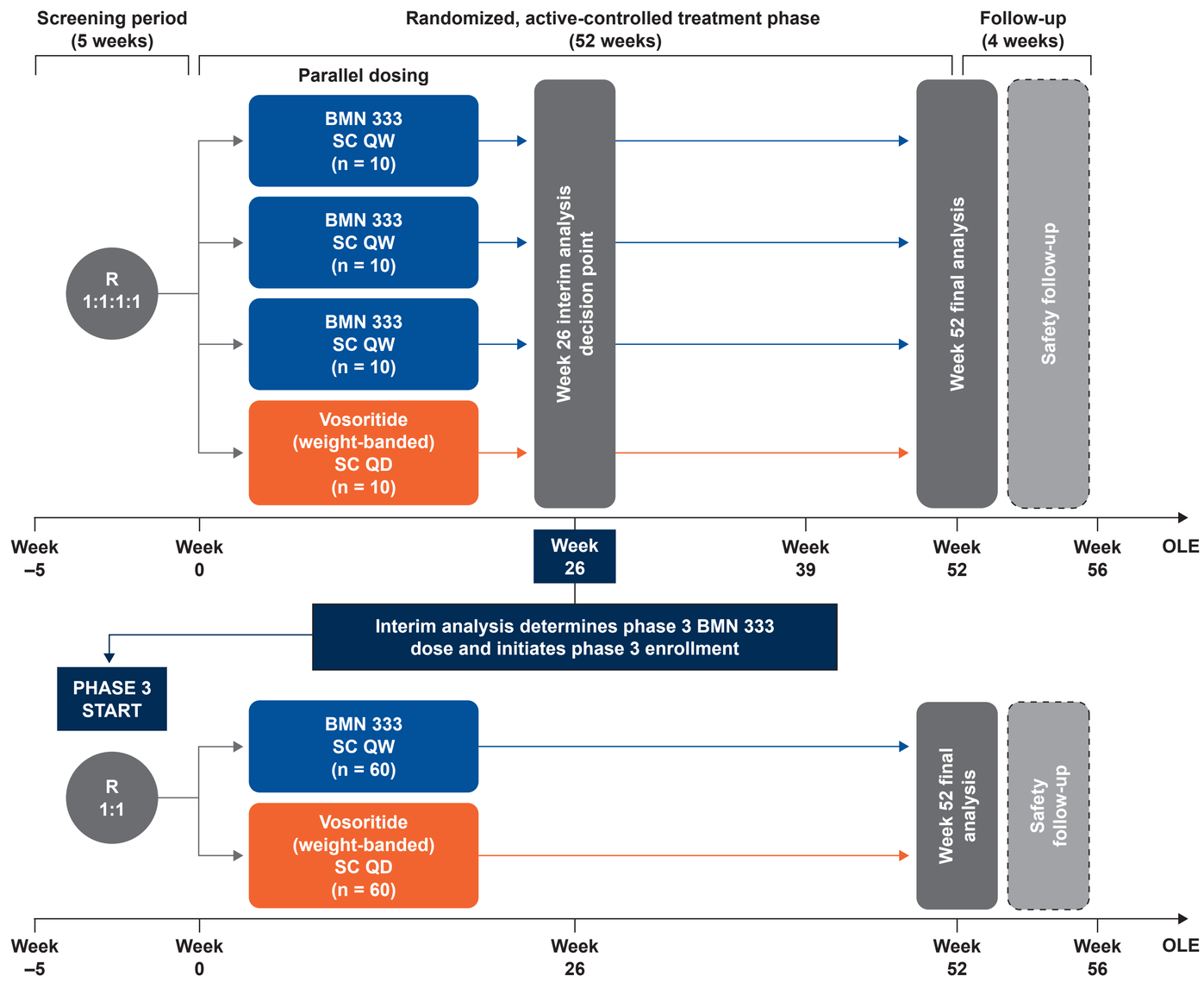
- BMN 333 exhibited slow absorption and elimination
- Elimination half-life for released vosoritide ranged between 3 to 4 days across all examined doses of BMN 333
- Low C_{max}, extended T_{max}, and more sustained plasma vosoritide levels
- Dose-dependent increases in plasma cGMP and urinary cGMP normalized to creatinine were observed, indicative of on-target vosoritide activity through NPR-B
- The maximum examined dose of BMN 333 (500 µg/kg) increased exposure to free CNP by up to >13x compared with another long-acting CNP agent[7]

ACH, achondroplasia; cGMP, cyclic guanosine monophosphate; C_{max}, maximum observed plasma concentration; CNP, C-type natriuretic peptide; NPR-B, natriuretic peptide receptor B; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous; T_{max}, time to maximum plasma concentration.

ASPEN: The first head-to-head, active-controlled, operationally seamless phase 2/3 study in achondroplasia

- Enrollment into the phase 2 part began in the first half of 2026

Figure 3. Phase 2/3 study design and overview



[a]AGV at week 52 is predicted based on AGV at weeks 26, 39, and 52 (available cumulative data).

Key design features

- No observational period
- Parallel dosing in phase 2
- Historical placebo data used as modeled comparator
- Augmentation of phase 2 vosoritide treatment arm with historical data for an interim analysis at week 26
- The phase 3 study will examine the superiority of once-weekly BMN 333 compared with once-daily vosoritide (randomized 1:1) over 52 weeks in children with achondroplasia aged 2 to <18 years
- Option to receive BMN 333 in an OLE study after phase 2 and phase 3

Population

Inclusion criteria

- Aged 2 to <11 years (phase 2) or 2 to <18 years (phase 3)
- Tanner Stage I (phase 2) or any Tanner Stage (phase 3)
- ACH confirmed by genetic testing
- Open epiphyses assessed using X-rays

Exclusion criteria

- Other short-stature conditions
- Any condition (hormonal, metabolic, autoimmune) that could interfere with growth, recurrent hypotension, or cardiovascular disease
- GH treatment in prior 6 months or previous use of a growth-promoting agent

Study endpoints

Primary endpoint

- Predicted AGV at week 52[a] (phase 2) or AGV at week 52 (phase 3)

Selected secondary endpoints

- AGV at weeks 26 and 52 (phase 2)
- Change from baseline in standing height, height Z-score, and upper-to-lower body ratio at weeks 26 and 52 (phase 2) or week 52 (phase 3)
- Safety and tolerability of BMN 333 (phase 2 and 3)
- PK of BMN 333 and released vosoritide (phase 2 and 3)

Selected HRQOL endpoints

- Change from baseline in QoLISSY physical domain and total scores at weeks 26 and 52 (phase 2 and 3)
- Change from baseline in PedsQL physical domain and total scores at weeks 26 and 52 (phase 2 and 3)

Predicted change in AGV for BMN 333

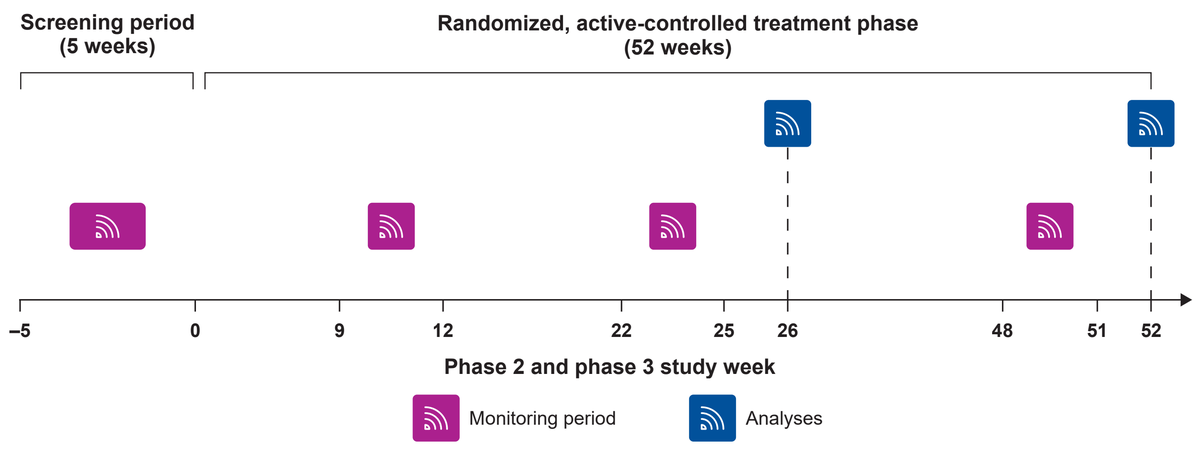
BMN 333 dosage, µg/kg/QW	Predicted % change in AGV compared with 15 µg/kg/QD vosoritide, cm/year	
	Log-linear model	E_{max} model
150	−2%	9%
250	22%	40%
350	31%	52%

ACH, achondroplasia; AGV, annualized growth velocity; E_{max}, maximum efficacy; GH, growth hormone; HRQOL, health-related quality of life; OLE, open-label extension; PedsQL, Pediatric Quality of Life Inventory; PK, pharmacokinetic; QD, once daily; QoLISSY, Quality of Life in Short Stature Youth; QW, once weekly; R, randomized; SC, subcutaneous.

ASPEN: Digital health technology (DHT)

- DHT will be used to evaluate the effect of BMN 333 vs vosoritide on physical functioning. Changes from baseline DHT measures will be compared with clinical outcome assessment scores for observable signs and symptoms, health-related quality of life, and physical functioning (**Figure 4**)
- All participants will wear an activity monitor on their dominant wrist and ankle during monitoring periods only to track upper and lower limb movements and functional activity
- To our knowledge, this is the first achondroplasia study design that uses novel, data-rich DHT-based endpoints for a more sensitive and participant motivation-independent assessment of real-world physical functioning

Figure 4. DHT assessments



DHT, digital health technology.

Conclusions

- BMN 333 is designed to safely extend systemic vosoritide exposure and provide superior efficacy with once-weekly treatment
- ASPEN, the first active-controlled, head-to-head study for achondroplasia, will compare the safety and efficacy of BMN 333 and examine its superiority vs vosoritide using an operationally seamless transition from phase 2 to phase 3
- ASPEN is the first study to employ the use of DHT to compare physical functioning between participants who receive BMN 333 vs vosoritide and to evaluate the utility of DHT measures for assessing real-world functioning in future achondroplasia studies
- Enrollment for the phase 2 part of ASPEN began in the first half of 2026

References

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