EXPERT OPINIONS REGARDING IMPACT OF ACHONDROPLASIA ON HEALTH-RELATED QUALITY OF LIFE AND LONG-TERM EFFECTS OF VOSORITIDE: A MODIFIED DELPHI STUDY

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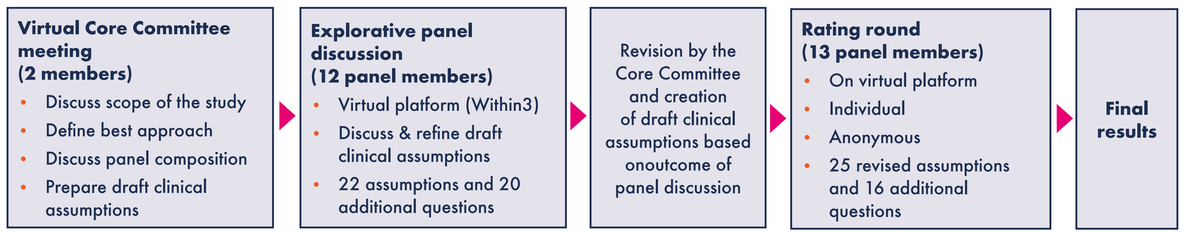
INTRODUCTION AND OBJECTIVES

- Achondroplasia is a rare genetic disorder, characterized by impaired endochondral bone formation, which results in disproportionately restricted growth and short stature [1]
- Medical complications that can occur across the lifespan of individuals with achondroplasia include foramen magnum stenosis in infants, thoracolumbar kyphosis, symptomatic spinal stenosis, sleep apnea, tibial bowing, recurrent otitis and conductive hearing loss [2]
- Vosoritide (Voxzogo®) is the first medicine to treat the underlying cause of achondroplasia. It was recently approved in the EU [3] and the US [4]
- Follow-up data from the vosoritide phase 2 and phase 3 extension studies up to 60 months and 2 years, respectively, showed persistent growth velocity increases and improvements in upper-to-lower body segment ratio in treated subjects [5,6]

METHODS

- Aim of the study: to explore the impact of achondroplasia and the anticipated modifying effect of vosoritide on medical complications, physical function, and health-related quality of life (HRQoL) beyond the currently available follow-up time of the clinical trials using extrapolation of existing data and expert opinion
- Expert opinion was obtained by a modified Delphi study among 14 clinicians from different medical specialties (clinical genetics, pediatrics, pediatric endocrinology, pediatric neurosurgery, and pediatric orthopedics), wide geographical spread and with relevant expertise in managing achondroplasia, including 7 principal investigators in the vosoritide clinical trials
- The study was performed between May-July 2021 and consisted of a structured explorative phase, followed by an anonymous and individual rating round on refined assumptions rated on a 5-point Likert scale (strongly disagree – disagree – neutral – agree – strongly agree) (Figure 1)
- Panelists answered questions based on published data and their own clinical experience or opinion and provided reasons underlying their answers

Figure 1. Study design



RESULTS

- Expert panel agreement of ≥75% was obtained for 19 assumptions, ≥80% agreement for 16 assumptions
- Overall, the panelists anticipate (% agreement 75-100%) that:
  - In individuals starting long-term treatment with vosoritide before puberty, growth velocity increases will be maintained until final height is reached and will likely/very likely result in clinically meaningful improvements in upper-to-lower body segment ratio; favorable results in terms of final height and proportionality are more likely with earlier treatment (Figure 2)
  - Increased frequency of surgeries in achondroplasia has a substantial negative short-term impact on HRQoL; complications such as symptomatic spinal stenosis, kyphosis and foramen magnum stenosis can still have considerable impact on aspects of HRQoL and/or healthcare resources if no surgery is required
  - Although current data are limited, the panelists believe that the earlier long-term treatment is started, the larger the probability of a positive impact on the lifetime incidence of symptomatic spinal stenosis, kyphosis, obstructive sleep apnea, and foramen magnum stenosis (Figure 3). These are among the most clinically important complications because of their impact on comorbidity, HRQoL, and/or mortality, as confirmed by literature [1,7-9] and feedback of the panel on questions
  - Vosoritide will likely improve HRQoL if long-term treatment is started before puberty. A positive impact is more likely in individuals starting long-term treatment at an earlier age than in those starting treatment later (Figure 4)

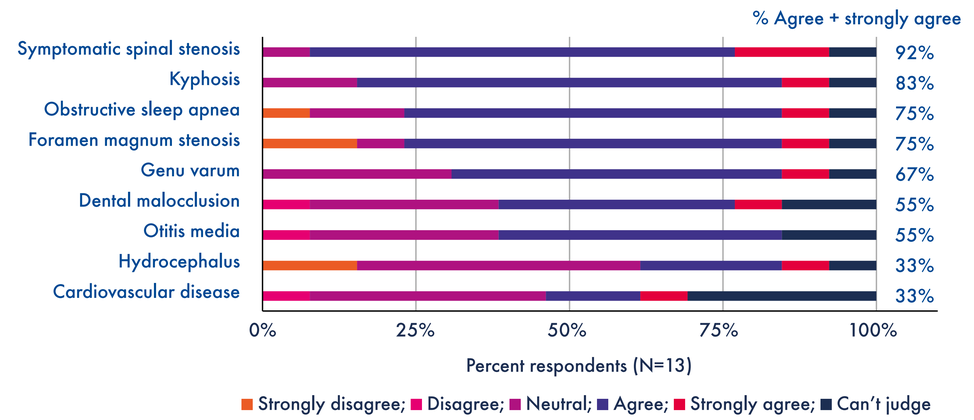
Figure 2. Assumptions and questions related to impact of vosoritide on growth velocity, height, and body proportions reaching ≥75% panel agreement

Assumption	% Panelists[a]						% Agreement[b]
It is likely that long-term treatment with vosoritide increases growth velocity until final height is reached in individuals with achondroplasia starting treatment between 2 years of age and puberty (Tanner stage >1)	0%	0%	8%	54%	31%	8%	92%
It is likely that long-term treatment with vosoritide results in a greater final height in those starting at an earlier age than in those starting later	0%	0%	0%	54%	38%	8%	100%
A clinically meaningful positive impact of vosoritide on abnormal upper-to-lower body segment ratio is more likely in individuals with achondroplasia starting long-term treatment at an earlier age than in those starting treatment later	0%	0%	8%	54%	31%	8%	92%
Question	% Panelists[c]						% Likely + Very likely[d]
How likely do you consider long-term treatment with vosoritide to result in a clinically meaningful improvement in upper-to-lower body segment ratio in individuals with ACH starting between 2 years of age and puberty (Tanner stage >1)?	0%	0%	15%	62%	23%	0%	85%

[a]% of panelists (N=13) voting ■ Strongly disagree; ■ Disagree; ■ Neutral; ■ Agree; ■ Strongly agree; ■ Can't judge
[b]% of panelists agreeing or strongly agreeing with the assumption, excluding "can't judge" votes
[c]% of panelists (N=13) voting ■ Very unlikely; ■ Unlikely; ■ Neutral; ■ Likely; ■ Very likely; ■ Can't judge
[d]% of panelists voting "likely" or "very likely", excluding "Can't judge" votes

Figure 3. Panel rating results regarding the potential impact of vosoritide on medical complications of achondroplasia and % panel agreement[a]

Assumption: Although current data are limited, it is conceivable that the earlier long-term treatment is started, the larger the probability of a positive impact of vosoritide on the lifetime incidence of the following medical comorbidities of achondroplasia:



[a]% of panelists (N=13) agreeing or strongly agreeing with the assumption, excluding "can't judge" votes

Figure 4. Assumptions related to HRQoL and % panel agreement

Assumption	% Panelists[a]						% Agreement[b]
Apart from the impact of comorbidities, short stature (final height <140 cm) likely has an independent negative impact in individuals with achondroplasia on:							
• Physical health-related quality of life	8%	0%	17%	50%	17%	8%	73%
• Mental health-related quality of life	0%	17%	17%	42%	17%	8%	64%
In individuals with achondroplasia, vosoritide likely increases HRQoL through lifetime if long-term treatment is started before puberty (Tanner stage >1)	0%	0%	17%	58%	17%	8%	82%
A positive impact of vosoritide on HRQoL is more likely in individuals with achondroplasia starting long-term treatment at an earlier age than in those starting treatment later	0%	0%	0%	67%	33%	0%	100%
Increased frequency of surgeries relative to the general population has a substantial negative short-term impact on HRQoL in individuals with achondroplasia	0%	0%	0%	67%	33%	0%	100%
A positive impact of vosoritide on the incidence of surgeries is more likely in individuals with achondroplasia starting long-term treatment at an earlier age than in those starting later	0%	8%	0%	58%	17%	17%	90%
A positive impact of vosoritide on chronic pain through lifetime is more likely in individuals with achondroplasia starting long-term treatment at an earlier age than in those starting later	0%	0%	8%	50%	8%	33%	88%
A positive impact of vosoritide on work participation through lifetime is more likely in individuals with achondroplasia starting long-term treatment at an earlier age than in those starting later	0%	0%	17%	50%	8%	25%	78%
A positive impact of vosoritide on activities of daily living through lifetime is more likely in individuals with achondroplasia starting long-term treatment at an earlier age than in those starting later	0%	0%	25%	58%	8%	8%	73%

[a]% of panelists (N=12) voting ■ Strongly disagree; ■ Disagree; ■ Neutral; ■ Agree; ■ Strongly agree; ■ Can't judge
[b]% of panelists agreeing or strongly agreeing with the assumption, excluding "can't judge" votes

CONCLUSIONS

- The results of this explorative study, based on international expert opinion, provides further insight into the medical and functional impacts of achondroplasia and how these might be modified through long-term use of vosoritide
- The responses of the panel are based on many years of experience in managing individuals with achondroplasia and might be used to guide the direction and design of future research to validate the assumptions that are based on extrapolation of current data
- The results may also be used in discussing potential outcomes of treatment with vosoritide with families and health care providers as its use becomes more prevalent
- Careful and critical prospective data collection will be required before these expert assumptions can be substantiated

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FUNDING

The design, conduct, and interpretation of data of the modified Delphi study as well as the development of this poster were supported by BioMarin Pharmaceutical, Inc. BioMarin was not involved in the voting process or analysis of the results