Norsk Interesseforening for Kortvokste (NiK)
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Til: Bestillerforum, Nye Metoder

Statens Legemiddelverk

Oslo, 20. februar 2022

Fra: Norsk Interesseforening for Kortvokste (NiK)
Stallerudveien 89
0693 OSLO

Sak 067-21 (ID2021_045) – Voxzogo (Vosoritide) til behandling av akondroplasi - Henstilling om rask godkjennelse av medikament barn med akondroplasi i Norge.

Innledning
Det vises til sak 067-21 (ID2021_045), herunder den forestående kost-nyttevurderingen av medikament Voxzogo (tidligere Vosoritide) til behandling av barn med akondroplasi (kortvoksthet) i Norge.

På vegne av barn med akondroplasi henstiller vi sterkt til at nevnte medikament godkjennes så raskt som mulig for bruk i Norge. Medikamentet gir barna våre en historisk mulighet til å vokse tilnærmet normalt. En formidabel verdi for de svært få barna og familiene det gjelder, blant annet større funksjonalitet, mindre smerte og mer selvstendighet. Medikamentet er godkjent i EU og allerede tatt i bruk i mange andre land. Nå må vi la norske barn med akondroplasi få muligheten til å utvikle seg på samme måte.

Bakgrunn
Norsk Interesseforening for Kortvokste (NiK) er en landsomfattende organisasjon som arbeider for bedre levevilkår for mennesker med diagnoser som fører til veksthemning, herunder den sjeldne genetiske diagnosen akondroplasi. Akondroplasi er den vanligste årsaken til kortvoksthet med forandringer i skjelettet (skjelettdysplasi). Barn med akondroplasi har forsinket motorisk utvikling, men den intellektuelle utviklingen er normal. Typiske trekk for tilstanden er ekstremt hemmet og disproporsjonal vekst med korte armer og ben sammenlignet med resten av kroppen. Gjennomsnittlig slutthøyde er 125 cm og 133 cm for henholdsvis kvinner og menn. Akondroplasi innebærer i mange tilfeller mange andre alvorlige komplikasjoner som blant annet foramen magnum stenose, spinal stenose, søvnapnè, samt kroniske smertetilstander pga. feilstillinger i rygg og underekstremiteter.

https://www.nature.com/articles/s41574-021-00595-x#Sec30

For utdypende redegjørelse av tilstanden henvises til metodevarselet i sak 067-21 (ID2021_045), herunder redegjørelser fra BioMarins representant Mattias Janzen og Lege Svein Fredwall, Sak 067-21 (ID2021_045) Bestillerforum.

Som redegjort for i saksunderlaget til sak 067-21 har det hittil ikke vært noen tilgjengelig behandling for den underliggende årsaken (genmutasjonen) til tilstanden. Tiltak har derfor handlet om tilrettelegging og behandling av de mange komplikasjoner som følger sykdommen, samt smertefulle og inngripende forlengelsesoperasjoner som i mange tilfeller innebærer at barna/ungdommene passiveres og faller ut av sosiale sammenhenger i mange viktige år mens operasjonsprosessene

foregår. Det anslås at ca 50% av barn/ungdom med akondroplasi i Norge gjennomfører slike operasjoner.

Banebrytende medikament - Voxzogo

På denne bakgrunnen er det intet mindre enn banebrytende at det de siste årene er utviklet et medikament (Voxzogo) som langt på vei løser veksthemmingen som følger med diagniosen. Gjennom studier som er publisert i tre anerkjente tidsskrifter[1] er det dokumentert at medikamentet er trygt og at det fremmer vedvarende økt vekst på barn i vekstsonen: Barn uten akondroplasi vokser ca. 6-10 cm i året, mens barn med diagnosen vokser ca. 4 cm. Nevnte studier dokumenterer at medikamentet bidrar til å svekke effekten av genmutasjonen som hemmer veksten på en slik måte at barna vokser omtrent 1,5 cm ekstra årlig. Barna som får anledning til å ta en slik medisin vil nærme seg normal årlig vekst. Medikamentet har også en positiv effekt på proporsjonene (mellom for eksempel torso og bein/armer).

Med andre ord er dette et fantastisk gjennombrudd som vi unner norske barn å få ta del av så raskt som mulig.

Siden saken var oppe til vurdering hos Bestillerforum den 22. mars 2021 har den blitt godkjent i European Medicines Agency (EMA, 26.08.2021)[2] (**Vedlegg 1**), samt godkjent i USA av the U.S. Food and Drug Administration (FDA, 19.11.2021). Videre forelå det i etterkant resultatet av extended study Fase III, som dokumenterer vedvarende vekstøkning etter første året med behandling, jf. Genet Med 2021, Fase III (extended study) (**Vedlegg 2**).

Formidabel nyttverdi for barna det gjelder

På vegne av de svært få barna dette gjelder henstiller vi til at medisinen blir godkjent i Norge og at dette skjer raskt. Dette er en livsendrende behandling for en svært utsatt gruppe barn som hittil har vært henvist til et liv med et utall helsemessige, funksjonelle og psykososiale utfordringer. Nytteverdien for barna dette gjelder vil utvilsomt være formidabel. Vekstøkningen vil med all sannsynlighet føre med seg stor verdi psykososialt og funksjonelt, samt gjøre at barna/foreldrene slipper å ta stilling til om barna skal ta invaderende og smertefulle forlengelsesoperasjoner som typisk vil kunne sette dem på sidelinjen av ungdomslivet i flere år. Barna vil kunne være mer selvstendig i sine daglige aktiviteter som å kle på seg, vaske håret, åpne dører, benytte toaletter, alt dette forhold som kan være krevende for mennesker med akondroplasi pga. korte armer og bein. Barna vil også, etter all sannsynlighet, kunne gå eller løpe lenger med rettere bein og med mindre smerte.

Det er også viktig å understreke verdien av at medikamentet, i tillegg til å virke på vekst mht. makshøyde, også reduserer disproporsjonaliteten ved at armer og bein blir forholdsmessig lengre enn hvis ubehandlet. Det faktum at personer med akondroplasi ikke bare har korte bein og armer, men uforholdsmessig korte i forhold til resten av kroppen er en viktig del av det store bildet og fører i seg selv til en rekke problemer som det har formidabel verdi å slippe: Foruten funksjonsnedsettelser enten på grunn av disproporsjonalitet i seg selv eller i kombinasjon med total vekstmangel, fører dette i tillegg til andre plager også ofte til belastningsskader på grunn av feilbelastninger på bein og muskulatur som man ikke ville hatt dersom man hadde normale kroppsproporsjoner. Dette kan gi smerteplager og ytterligere nedsatt funksjonsevne av typer som friske ikke får, eller ikke opplever før de blir gamle. Disproporsjonaliteten kan også være problematisk mht. personlig hygiene, klær som ikke passer, og mye mer.

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[1] NEJM - Fase II, Lancet 2020 Fase III, Genet Med 2021, Fase III (extended study)
[2] Vosoritide: First Approval - PubMed (nih.gov)

Idet medikamentet virker på selve årsaken til diagnosen, er det dessuten sannsynlig at medikamentet vil ha positive effekter på de mange alvorlige komplikasjoner som følger med tilstanden også utover selve veksthemmingen. I **vedlegg 3** følger en artikkel om en studie (Savarirayan et al. 2021) som nettopp tar dette utgangspunktet. Fra artikkelen hitsettes:

> *Since most of the growth of the foramen magnum is achieved in the first 2 years of life, vosoritide might be of benefit in young children with achondroplasia, by increasing the growth of the foramen magnum, through its stimulatory effects on endochondral ossification. Vosoritide therapy may consequently reduce the risk of cervico-medullary compression, the morbidity and mortality associated with cervicomedullary compression, and the need for surgical decompression. Similarly, since the growth of the spinal canal is completed by 9 years of age, increased growth of the spinal canal during the first years of life, may also significantly reduce spinal morbidity later in life.*

Vurderingsmetode
Vi stiller spørsmål ved hvorfor Bestillerforum landet på å benytte Metode C (Kostnad-nytte) når representant for leverandør (BioMarin) anførte at denne metoden ikke er best egnet i dette tilfellet. I BioMarins v/Mattias Janzen innlegg fra mars 2021 pekes det på at mennesker med akondroplasi krever livslang oppfølging som i de fleste sammenhenger har økonomiske og sosiale kostnader som ikke direkte treffer helsesystemet og dermed er vanskelig å fange opp i en ren kostnadseffektivitetsanalyse, jf. Sakspapirer fra Nye Metoder mars 2021.

I nytt innlegg av mars 2022 har BioMarin v/ nevnte Janzen anket Bestillerforums beslutning om metodevalg, jf. Anke fra BioMarin mars 2022. I ankens punkt 3 redegjøres Grundig for hvorfor medikamentet ikke bør vurderes ved Kostnad-Nytte-metodikk (Cost Utility Analysis, CUA). Fra anken hitsettes:

> *"The key reasons a CUA would be an inappropriate assessment method are below: '*
>
> - *the nature of achondroplasia being a rare disease with only very few patients in Norway*
> - *limited clinical expertise in Norway with vosoritide treatment*
> - *the uncertainty associated with the lack of long-term evidence v. 1.0 – 21.02.2020 Side 2 av 10*
> - *the uncertainty due to the life-long nature of the disease where clinical evidence is captured for only a limited period of time*
> - *the challenges of capturing long term QoL benefits and long-term cost benefits; most of the benefit on disease burden will be experienced in the longer term and will be thus end up being discounted out and therefore not accurately represented or reflected in a CUA"*

Vi ber vurdert om slik Metode C, kost-nytte-vurdering, er best egnet i et tilfelle hvor det er tidskritisk å få pasienter i gang med behandlingen og det ikke fra før finnes noen adekvat behandling i dag på en sjelden og svært alvorlig diagnose. Det følger av myndighetenes vurdering av systemet for metodevurderinger, jf. 2021 Evaluering Nye Metoder kapittel 7.1.2 at Metode C «*er aktuell der en ny metode sammenliknes med en annen som allerede er i bruk*».

Selv om det ikke ennå er bevist at medikamentet virker på andre komplikasjoner enn veksthemmingen er det stor sannsynlighet for at den nettopp vil gjøre det. Det er ikke rimelig at barna som trenger å vokse nå skal vente – gå irreversibelt glipp av vekst – på at studiene har virket så lenge at også flere nytteverdier er bevist for de få barna dette rammer. Å kunne ta et medikament som sannsynligvis sikrer vekst på mellom 10-20 cm gir innebærer formidabel nytteverdi for en

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gruppe hvor ekstrem veksthemming i seg selv er årsaken til gruppens mange psykososiale og helsemessige utfordringer.

Som redegjort for av BioMarin i ovennevnte innlegg frykter vi at den reelle nytteverdien undervurderes i en sjablongmessig analyse av kostnadseffektivitet. Vi ber vurdert om det er mer rimelig og treffende å benytte en mer individuelt tilpasset og forenklet metode (metode D) for en slik sjelden, alvorlig diagnose hvor det nå foreligger et medikament som beviselig virker på selve årsaken til diagnosen.

At barn med akondroplasi (og foreldrene deres) opplever mange andre utfordringer enn de rent medisinske, og som er vanskelig å fange opp i kost-nyttevurderingen det legges opp til, underbygges av en helt ny og grundig artikkel om diagnosen, se **vedlegg 4**- Shediac et al «*Experiences of children and adolescents living with achondroplasia and their caregiver*». I artikkelen beskrives og dokumenteres store utfordringer knyttet til hygiene/toalettbesøk, kle på seg, ikke rekke opp til lysbrytere og dørhåndtak mv, problemer med å være med på utflukter og turer, men også ekstra tidsbruk for foreldrene, bekymringer om fremtiden, og at barna blir mer avhengig av sine foreldre og mindre selvstendige mv. Utfordringene med å være kortvokst gjelder hele livet. Mange har utfordringer i forhold til daglige gjøremål som handling, husarbeid, benytte offentlig kommunikasjon og offentlige toaletter, og delta i arbeidslivet. Mange utsettes også for mobbing, stigmatisering, vold og diskriminering, og beskriver ubehaget av alltid å bli stirret på og snakket om. Studier har også vist at mange kortvokste har dårlig selvbilde og sliter med sosial isolasjon og psykiske helseplager som angst og depresjon.

Det er essensielt at det nå velges en metode som på en egnet måte fanger opp den reelle verdien det vil ha for de få barna og familiene det gjelder når det nå foreligger et medikament som langt på vei løser selve kjernen til problemene, nemlig ekstremt hemmet og disproporsjonal vekst.

Tidskritisk behandling
Det er tidskritisk at behandlingen settes i gang i Norge for barn fra og med 2 årsalderen så raskt som mulig. Disse barna er i vekstsonen nå. For hver måned norske myndigheter venter med å godkjenne medikamentet i Norge fratas samtidig barna muligheten til å strekke seg opp mot samfunnets ulike dørhåndtak.

Medikamentet er foreløpig priset høyt, men vi peker på at denne kun er aktuell for svært få barn i Norge. Det fødes kun 2-3 barn hvert år med diagnosen, www.sunnaas.no/TRS, så den aktuelle pasientgruppen vil være mellom 30-45 barn mellom 2-18 år. Vi ber om at kostnadsbildet vurderes på bakgrunn av den formidable nytteverdien denne vil ha for et svært begrenset antall aktuelle pasienter.

Medikamentet er allerede godkjent og tatt i bruk i flere europeiske land. Norge er et fantastisk land som i utgangspunktet skal ta vare på de mest utsatte barna. Det kan ikke være slik at det skal være en ulempe for barn med akondroplasi å være født i Norge.

På denne bakgrunnen ber vi om å bli oppdatert på status i saken, samt henstiller til at medikamentet raskt godkjennes for bruk i Norge.

Med vennlig hilsen

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VEDLEGG 1

Review Drugs. 2021 Nov;81(17):2057-2062. doi: 10.1007/s40265-021-01623-w.

Vosoritide: First Approval

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Affiliations

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Abstract

Vosoritide (VOXZOGO®) is a modified recombinant human C-type natriuretic peptide (CNP) analogue, being developed by BioMarin Pharmaceutical for the treatment of achondroplasia. Achondroplasia is caused by a gain-of-function mutation in the fibroblast growth factor receptor 3 gene (FGFR3), which is a negative regulator of bone growth. Vosoritide acts to restore chondrogenesis through its binding to natriuretic peptide receptor B (NPR-B), resulting in the inhibition of downstream signalling pathways of the overactive FGFR3 gene. Vosoritide was approved in August 2021 in the EU for the treatment of achondroplasia in patients aged ≥ 2 years whose epiphyses are not closed; the diagnosis of achondroplasia should be confirmed by appropriate genetic testing. The drug is also under regulatory review in the USA for the treatment of achondroplasia and clinical development is underway in several countries. This article summarizes the milestones in the development of vosoritide leading to this first approval for achondroplasia in patients aged ≥ 2 years whose epiphyses are not closed.

Related information

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VEDLEGG 2

Clinical Trial Genet Med. 2021 Dec;23(12):2443-2447. doi: 10.1038/s41436-021-01287-7.

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Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study

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Free PMC article

Abstract

Purpose: Achondroplasia is caused by pathogenic variants in the fibroblast growth factor receptor 3 gene that lead to impaired endochondral ossification. Vosoritide, an analog of C-type natriuretic peptide, stimulates endochondral bone growth and is in development for the treatment of achondroplasia. This phase 3 extension study was conducted to document the efficacy and safety of continuous, daily vosoritide treatment in children with achondroplasia, and the two-year results are reported.

Methods: After completing at least six months of a baseline observational growth study, and 52 weeks in a double-blind, placebo-controlled study, participants were eligible to continue treatment in an open-label extension study, where all participants received vosoritide at a dose of 15.0 µg/kg/day.

Results: In children randomized to vosoritide, annualized growth velocity increased from 4.26 cm/year at baseline to 5.39 cm/year at 52 weeks and 5.52 cm/year at week 104. In children who crossed over from placebo to vosoritide in the extension study, annualized growth velocity increased from 3.81 cm/year at week 52 to 5.43 cm/year at week 104. No new adverse effects of vosoritide were detected.

Conclusion: Vosoritide treatment has safe and persistent growth-promoting effects in children with achondroplasia treated daily for two years.

Figures

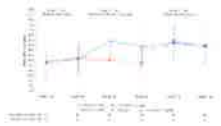

Fig. 1. Line plot of mean annualized...

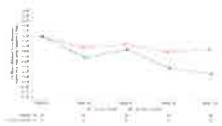

Fig. 2. Line plot showing analysis of...

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VED LEGG 3

Short Reports

SCIENCE PROGRESS

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Rationale, design, and methods of a randomized, controlled, open-label clinical trial with open-label extension to investigate the safety of vosoritide in infants, and young children with achondroplasia at risk of requiring cervicomedullary decompression surgery

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Abstract

Achondroplasia causes narrowing of the foramen magnum and the spinal canal leading to increased mortality due to cervicomedullary compression in infants and significant morbidity due to spinal stenosis later in adulthood. Vosoritide is a C-natriuretic peptide analogue that has been shown to improve endochondral ossification in children with achondroplasia. The objective of this trial is to evaluate the safety of vosoritide and whether vosoritide can improve the growth of the foramen magnum and spinal canal in children that may require decompression surgery. An Achondroplasia Foramen Magnum Score will be used to identify infants at risk of requiring decompression surgery. This is a 2-year open label randomized controlled trial of vosoritide in infants with achondroplasia ages 0 to $\leq$12 months. Approximately 20 infants will be randomized 1:1 to either open label once daily subcutaneous vosoritide combined with standard of care or standard of care alone. The primary and secondary aims of the study are to evaluate the safety and efficacy of vosoritide in children with cervicomedullary compression at risk of requiring decompression surgery. The trial will be carried out in specialized skeletal dysplasia treatment centers with well established multidisciplinary care pathways and standardized approaches to the neurosurgical management of cervicomedually compression. After 2 years, infants randomized to standard of care alone will be eligible to switch to vosoritide plus standard of care for an additional 3 years. This pioneering trial hopes to address the important question as to whether treatment with vosoritide at an early age in infants at risk of requiring cervicomedullary decompression surgery is safe, and can improve growth at the foramen magnum and spinal canal alleviating stenosis. This in turn may reduce compression of surrounding structures including the neuraxis and spinal cord, which could alleviate future morbidity and mortality.

Trial registrations: ClinicalTrials.gov, NCT04554940; EudraCT number, 2020-001055-40

Keywords

Clinical trials, skeletal dysplasia, precision therapy, genetics, achondroplasia

Background

Achondroplasia, the most common form of disproportionate short stature, is a rare condition, with a prevalence of between 1/15,000 (www.orpha.net) and 1/25,000.[1] The condition is caused by a gain-of-function pathogenic variant in the fibroblast growth factor receptor 3 gene (*FGFR3*) that constitutively activates the mitogen-activated protein kinase (MAPK) via the p38 and extracellular signal-regulated kinase (ERK) pathways in chondrocytes, which inhibits endochondral ossification.[2] Achondroplasia is *de novo* in the majority of cases (80%), and the most common variant is the p.(Gly380Arg) substitution in the region encoding the transmembrane domain of FGFR3.[3] FGFR3 is one of many physiological regulators of linear bone growth and normally functions as an inhibitor, acting negatively on both proliferation and terminal differentiation of chondrocytes, which are integral to endochondral bone formation, the principal means for long-bone growth.[4]

In infancy and early childhood, the most important medical challenge driving morbidity and mortality is narrowing of the foramen magnum, which has been implicated in an excess of sudden deaths in children with achondroplasia under age 4 years.[5,6] The foramen magnum is narrow in all individuals with achondroplasia but individuals with signs and symptoms of cervicomedullary compression at the

level of the foramen magnum tend to have critically stenosed foramen magnum dimensions.[7] The foramen magnum lies completely within the occipital bone and its margins form and grow by endochondral ossification and are uniformly affected in achondroplasia. Pathological foramen magnum stenosis, as seen in achondroplasia, is postulated to be secondary to hypertrophy of the occipital rim, overgrowth of the opisthion and abnormal position and premature closure of skull base synchondroses.[8] Stenosis of the foramen magnum has the potential to compromise the neural and vascular structures passing through this region and poses significant medical risks to all children born with this condition. Compression of vital brainstem structures including central respiratory centers, cranial nerve nuclei and cranial nerves can occur resulting in disordered breathing. Centrally mediated apnea, a recognized complication of foramen magnum stenosis, is a likely contributory factor to the increased risk of sudden unexpected death in infancy, which is reported to be as high as 7.5% in infants with achondroplasia.[6,9]

The base of the skull surrounding the foramen magnum has several synchondroses and these close at an earlier age in children with achondroplasia.[10] Unlike long bones, the foramen magnum attains 70%–80% of its final transverse and sagittal diameter by 1 year of age and, although it continues to grow into adulthood, the rate is much slower. In average-stature children, the entire extent of growth of the foramen magnum is around 1.5 cm in the transverse diameter and 2.4 cm in the sagittal diameter.[7] In infants with achondroplasia, the growth of the foramen magnum is significantly slower. The foramen magnum is small at birth and grows at a significantly slower rate during the first 2 years, particularly in the transverse diameter, as compared with average-statured children.[7,11–13] Increasing the growth rate of the foramen magnum in infancy could therefore be a crucial advance in the clinical management of children with achondroplasia, but the challenges of identifying those infants at greatest risk and initiating treatment as soon after birth as possible and at least before 2 years of age remain formidable.

Later in life, medical complications associated with the thoraco-lumbar spine tend to be more prominent than those associated with the cervical spine.[14] Short pedicles, ligamentous thickening and kyphotic deformity compromise the caliber of the spinal canal resulting in reduced space for the spinal cord and the cauda equina.[15] Exaggerated lumbar lordosis, anterior vertebral body wedging, and thickening of the pedicles and laminae are additional factors that mean that the spinal canal is one-third to one-half of the size of the canal in an individual of average stature. These features collectively contribute to a narrowed spinal canal as well as adjacent spinal foramina resulting in a clinical picture of myelopathy and radiculopathy.

Spinal growth is the product of more than 130 growth plates.[16] The neurocentral synchondroses in the spine are located at the junction of the pedicle and the vertebral body and are important in the growth of the vertebral body and the posterior arch. In average stature children, the neurocentral synchondroses fuse at approximately 9 years of age, and by 5 years of age the spinal canal has already grown to approximately 95% of its final size.[16] In children with achondroplasia the final size

of the spinal canal is achieved even earlier. Therefore, similarly to the foramen magnum, increasing the growth rate of the spine in infancy could be another crucial step forward in the clinical management of achondroplasia potentially benefitting these individuals throughout their adult lives as well.

Current standard of care

Achondroplasia typically presents in the last trimester or at birth, so recognition by neonatal and general pediatricians of early complications is important. Despite efforts to publish expert consensus driven clinical guidelines, there is a lack of alignment surrounding the need for and optimal timing and choice of screening modality for cervicomedullary compression in infants with achondroplasia.[8,15,17,18] The American Academy of Pediatrics recommends either CT or MRI to evaluate changes at the foramen magnum in all infants with achondroplasia.[15] However, more recently best practice guidance based on expert consensus recommended that MRI scans should be reserved for those infants with either an abnormal detailed clinical neurological history and examination (performed every 2 months for the first year of life), or polysomnography abnormalities suggestive of foramen magnum stenosis.[18] Abnormal neurological manifestations of foramen magnum stenosis include hypotonia, motor delay, feeding, and sleep disorders, and clinical features of myelopathy such as hyper-reflexia and ankle clonus, which when present strongly predict the need for decompression surgery in the infant population.[9,19] Neurological sequelae, however, are a late manifestation of high cervical spinal cord compression and considerable experience of what is "normal" in achondroplasia is required to determine what constitutes clinically significant findings. Studies examining the predictive value of polysomnography or cardiorespiratory sleep study parameters in the identification of foramen magnum stenosis in children with achondroplasia suggest low screening sensitivity.[20,21] Neurosurgical opinion regarding the need for surgery in the face of foramen magnum stenosis in achondroplasia remains inconsistent and practice varies significantly between different centers, with rates of cervicomedullary decompression ranging from 4.6% to 43%.[22,23] While the outcome of neurosurgical intervention is generally favorable, severe complications, such as cerebrospinal fluid leakage, vascular injury, and worsening neurological function, are well recognized.[24]

Having overcome the risks of surgery associated with foramen magnum stenosis and cervicomedullary compression, as children with achondroplasia reach adolescence and adulthood, they become at risk of symptomatic spinal canal stenosis (particularly in the lumbar spine), which can lead to significant morbidity throughout adult life.[4,14] By 20 years of age, approximately 20% have abnormal neurological signs. Back and leg pain occurs in up to 80% by the sixth decade of life.[14] Worsening stenosis of the canal and foramina results in sensory dysfunction, radicular pain, neurogenic claudication, bladder dysfunction, and, in severe cases, fecal incontinence. About one-third require specialist laminectomy surgery for symptomatic spinal canal stenosis.[4]

Table 1. Achondroplasia foramen magnum score (AFMS).

AFM risk score	MRI determined classification
AFMS 0	Normal cranio-cervical junction (CCJ)
AFMS 1	Narrowed cranio-cervical junction with cerebrospinal fluid (CSF) surrounding the cord
AFMS 2	Loss of CSF signal surrounding the cord at the CCJ without cord remodeling
AFMS 2a	Loss of CSF signal posterior to the cord
AFMS 2b	Loss of CSF signal posteriorly and anteriorly
AFMS 2c	Loss of CSF signal posteriorly, anteriorly and at the sides
AFMS 3	Remodeling of the cord at the CCJ
AFMS 3a	CSF signal remains visible at the CCJ
AFMS 3b	No CSF signal is visible at the CCJ
AFMS 4	High T2 signal in the cord at the CCJ
AFMS 4a	CSF signal remains visible at the CCJ
AFMS 4b	No CSF signal is visible at the CCJ

Recently, an Achondroplasia Foramen Magnum Score (AFMS) has been proposed based on magnetic resonance imaging (MRI) of the cervicomedullary junction.[25] The advantage of such a scoring system is that it relies on the progressive effect of the decreased foramen magnum size on the neuraxis as opposed to measurement of the dimensions of the foramen magnum. The advantage of such a scale is that it is easily determined via objective MRI findings, is age independent and does not require normalization. Further details of the scale are shown in Table 1. This trial takes advantage of this easily qualifiable scoring system in order to evaluate the progression of the score overtime and compare the intervention and control groups.

C-natriuretic peptide and vosoritide

The binding of C-type natriuretic peptide (CNP) to its receptor, natriuretic peptide receptor 2 (NPR2), inhibits FGFR3 downstream signaling at the level of Raf-1 and is a potent stimulator of endochondral ossification.[26] CNP overexpression in a transgenic mouse model is associated with skeletal overgrowth, including of the axial and appendicular skeleton, craniofacial bones, and foramen magnum.[27] Similarly, overexpression of CNP in the liver leading to increased serum CNP concentrations as well as continuous CNP infusions also rescue the craniofacial abnormalities, skeletal, and foramen magnum abnormalities of an achondroplasia mouse model.[28,29] Furthermore, pathogenic variants that result in overexpression of CNP in humans are also associated with enhanced skeletal growth, manifest by abnormally tall stature, supporting the hypothesis that systemic therapy with CNP should help ameliorate the skeletal phenotype of achondroplasia including at the foramen magnum.[30–32]

Vosoritide is a recombinant CNP analogue that has been engineered to resist degradation by neutral endopeptidase, allowing for a longer half-life and an impact on endochondral ossification. Like CNP, vosoritide activates NPR2 signaling with subsequent inhibition of FGFR3 downstream signaling, leading to the promotion of chondrocyte proliferation and differentiation, and subsequent increased endochondral bone formation.

Vosoritide administration restored impaired bone growth in a mouse model of achondroplasia and improved bone growth in wild-type monkeys.[33] These promising animal data led to an open-label, phase 2 study of vosoritide in children aged 5 to 14 years with achondroplasia.[34] This study showed that vosoritide was generally well tolerated at the doses tested and led to increases in annualized growth velocity (AGV) that were maintained for up to 42 months. This study was followed by a pivotal, phase 3, randomized, placebo-controlled, double-blinded study of vosoritide in 121 children aged 5 to 18 years with achondroplasia, where 60 participants were administered vosoritide and 61 a matching placebo for 52 weeks.[35] This study confirmed the effectiveness of vosoritide through increasing AGV in the treated group as compared to the placebo group, with similar side effect profiles observed in treated and placebo groups.

Since most of the growth of the foramen magnum is achieved in the first 2 years of life, vosoritide might be of benefit in young children with achondroplasia, by increasing the growth of the foramen magnum, through its stimulatory effects on endochondral ossification. Vosoritide therapy may consequently reduce the risk of cervico-medullary compression, the morbidity and mortality associated with cervicomedullary compression, and the need for surgical decompression. Similarly, since the growth of the spinal canal is completed by 9 years of age, increased growth of the spinal canal during the first years of life, may also significantly reduce spinal morbidity later in life. The primary aim of this study is to evaluate the safety of daily subcutaneous vosoritide injections in infants and young children with achondroplasia who are at increased risk of requiring surgical intervention for cervicomedullary compression. The study will also explore the efficacy of vosoritide in preventing the need for decompression surgery and contribute to the understanding of the natural history of moderate foramen magnum stenosis (AFMS grades 2 and 3).

Trial design and patient eligibility criteria

This is a stratified, randomized, controlled, open-label clinical study to investigate the safety of vosoritide treatment in infants and young children with achondroplasia who are at risk of requiring cervicomedullary decompression surgery. Patients aged 0 to $\leq$12 months who have achondroplasia confirmed by genetic testing and who meet the study eligibility criteria will be able to enroll directly into the study. While the management of children with achondroplasia may vary among clinical centers worldwide, this study will utilize an achondroplasia foramen magnum stenosis risk score using MRI criteria to identify eligible children.[25] Patient selection

Table 2. Inclusion criteria.

Inclusion criteria
1. Parent(s) or guardian(s) willing and able to provide signed informed consent after the nature of the study has been explained and prior to performance of any research related procedure. 2. Have ACH, documented by genetic testing. 3. Are willing and able to perform all study procedures as physically possible. 4. Age 0 to $\leq$12 months, at study entry (Day 1). 5. Parent(s) or caregiver(s) are willing to administer daily injections to the patient and complete the required training. 6. Have evidence of cervicomedullary compression that "may" require surgical intervention defined as: ○ Baseline MRI assessment from central blinded evaluation showing at least one of the following findings: • Narrowing of the foramen magnum with loss of cerebrospinal fluid space surrounding the cord. • Narrowing of the foramen magnum with flattening of the cervical cord without T2 signal change. ○ Supported by (but not required for eligibility) the following findings: • Baseline physical examination • Gross or fine motor developmental milestone delay compared to expected for ACH (e.g. lifting head when lying on stomach). • Abnormal reflex (e.g. brisk reflex/abnormal clonus for age). • Weakness (e.g. opisthotonus). • Baseline sleep study Sleep apnea with a primary central component (e.g. not secondary to obstructive sleep apnea).
Exclusion criteria
1. Have hypochondroplasia or short-stature condition other than achondroplasia (e.g. trisomy 21, pseudoachondroplasia, etc.). 2. Have cervicomedullary compression that either does not require surgical intervention (e.g. foramen magnum narrowing with preservation of the cerebrospinal fluid space) or does require immediate surgical intervention (e.g. narrowing of the foramen magnum with cervical cord signal change). 3. Have any of the following: ○ Untreated congenital hypothyroidism or maternal history of hyperthyroidism. ○ Insulin-requiring neonatal diabetes mellitus. ○ Autoimmune inflammatory disease. ○ Inflammatory bowel disease. ○ Autonomic neuropathy.

(continued)

Table 2. Continued

Inclusion criteria
4. Have a history of any of the following: ○ Renal insufficiency. ○ Chronic anemia. ○ Baseline systolic blood pressure below age and gender specified normal range or recurrent symptomatic hypotension (defined as episodes of low blood pressure generally accompanied by symptoms [e.g. pallor, cyanosis, irritability, poor feeding]). ○ Cardiac or vascular disease, including the following: • Cardiac dysfunction (abnormal echocardiogram determined to be clinically significant by investigator and medical monitor) at screening. • Hypertrophic cardiomyopathy. • Pulmonary hypertension. • Clinically significant structural heart disease or valvular insufficiency (associated with symptoms or requiring intervention). • Clinically significant cerebrovascular disease. • Aortic insufficiency or other clinically significant valvular dysfunction. • Clinically significant atrial or ventricular arrhythmias.
5. Have a clinically significant finding or arrhythmia that indicates abnormal cardiac function or conduction or QTc-Frederica $\geq$450 ms on screening ECG.
6. Current treatment with antihypertensive medications, ACE inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, calcium-channel blockers, cardiac glycosides, systemic anticholinergic agents, any medication that may impair or enhance compensatory tachycardia, drugs known to alter renal function that is expected to continue for the duration of the study.
7. Require any other investigational product prior to completion of the study period.
8. Have received another investigational product or investigational medical device within 30 days prior to Screening.
9. Have used any other investigational product or investigational medical device for the treatment of ACH or short stature at any time.
10. Require current chronic therapy with antihypertensive medication or any medication that, in the Investigator's judgment, may compromise the safety or ability of the patient to participate in this clinical study.
11. Have been treated with growth hormone, insulin-like growth factor 1, or anabolic steroids in the 6 months prior to screening, or long-term treatment (>3 months) at any time.
12. Have had regular long-term treatment (>1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma, or intranasal steroids, are acceptable) prior to screening.
13. Have ever had prior cervicomedullary decompression surgery.
14. Have had a fracture of the long bones or spine within 6 months prior to screening.
15. Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or total bilirubin >1.5× the upper limit of normal at Screening (except for patients with a known history of Gilbert's syndrome or transient indirect hyperbilirubinemia).
16. Have current malignancy, history of malignancy, or currently under work-up for suspected malignancy.
17. Have known hypersensitivity to vosoritide or its excipients.
18. Have a history of hip surgery or clinically significant hip abnormality in the 30 days prior to screening.

(continued)

Table 2. Continued

Inclusion criteria
19. Have a condition or circumstance that, in the view of the Investigator, places the patient at high risk for poor treatment compliance or for not completing the study.
20. Have any concurrent disease or condition that, in the view of the Investigator, would interfere with study participation or safety evaluations, for any reason.
While vitamin D deficiency (Vitamin D concentration <37.5 nmol/L or <15 ng/ml) is not an exclusion criterion, it should be immediately treated with oral supplementation with 2000 IU daily and the value repeated 4 weeks to confirm normalization of serum concentrations. Once achieved daily maintenance dose is recommended.
If there is evidence of severe cervicomedullary compression, that "does" in the opinion of the Investigator require surgical intervention then the child is not eligible to enroll. For example, the presence of abnormal MRI T2 signal intensity at and immediately above and below the cervicomedullary junction should be considered high risk for requiring surgery and the child would not be a candidate for this trial.

for entry into the study will be at specialized skeletal dysplasia units that routinely perform MRI in infants with achondroplasia as per standard of care. Confirmation of patient eligibility for the study will be performed through an independent blinded central read of the MRI confirming that the patient has an AFMS of AFMS2 defined as, "narrowing of the foramen magnum with loss of cerebrospinal fluid space surrounding the cord" or AFMS3 defined as, "narrowing of the foramen magnum with flattening of the cervical cord without T2 signal change,"[25] thereby including patients who are not in immediate need for foramen magnum decompression but nevertheless remain at risk of requiring it. A full list of all inclusion and exclusion eligibility criteria are shown in Table 2.

Approximately 20 patients will be enrolled into the trial, stratified based on age (0 to $\leq$ 6 months, $>$ 6 months to $\leq$ 12 months), and randomized 1:1 by a centralized IXRS randomization to either open label, once daily, subcutaneous vosoritide combined with standard of care (vosoritide + standard of care) or standard of care alone. After 24 months of randomized treatment, all patients may be eligible to complete an additional 36 months on-study receiving open-label vosoritide treatment + standard of care. Patients will be enrolled at up to four clinical centers worldwide. The overall study design is presented in Figure 1.

The primary objective is to assess the safety of daily subcutaneous vosoritide + standard of care versus standard of care alone when administered to infants and young children with achondroplasia and signs and symptoms of cervicomedullary compression. The secondary objective of the study is to evaluate the efficacy of vosoritide in children who are at risk of requiring cervicomedullary decompression surgery.

Patients randomized to receive vosoritide will be administered the dose determined to be appropriate for their current age as identified in the ongoing Phase 2 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety

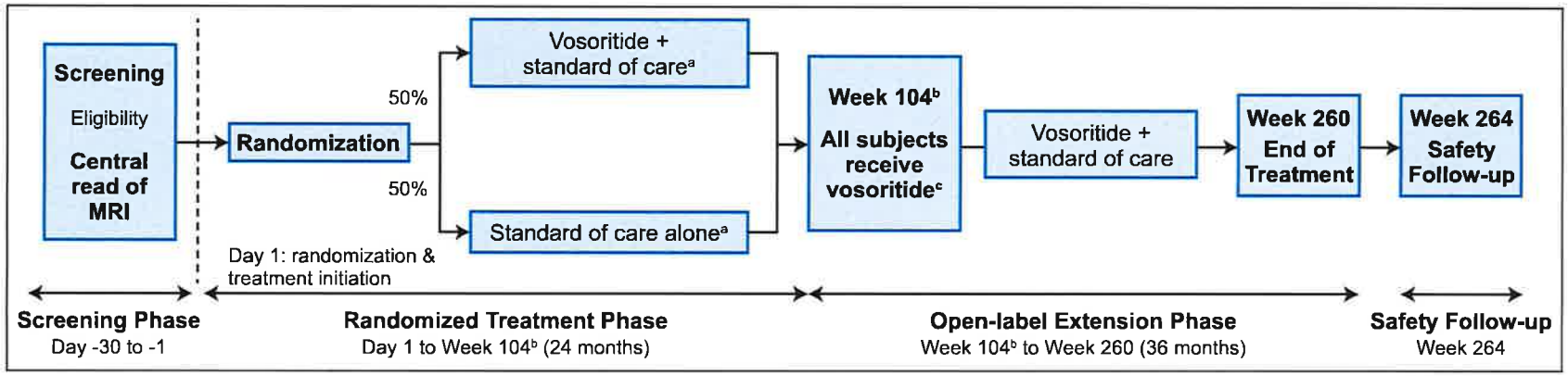

Figure 1. Study design.

This is a stratified, randomized, controlled, open-label clinical study to investigate the safety of vosoritide treatment in infants and young children with achondroplasia at risk of requiring cervicomedullary decompression surgery. Approximately 20 patients, aged 0 to ≤12 months who have documented achondroplasia confirmed by genetic testing and who meet the study eligibility criteria will be eligible to enroll. Enrolled patients will be stratified based on age (0 to ≤6 months, >6 months to ≤12 months) and will be randomized 1:1 to either open-label, once daily, subcutaneous vosoritide combined with standard of care (vosoritide + standard of care) or standard of care alone. After 104 weeks of randomized treatment, all patients will be eligible to complete an additional 156 weeks on-study receiving open-label vosoritide treatment + standard of care. All patients will complete a safety follow-up visit approximately 4 weeks after the end of treatment.

and efficacy of vosoritide in infants and young children with ACH, aged 0 to <60 months (111-206; NCT03583697). The 111–206 study determined the appropriate dose to achieve adequate exposure is age dependent with patients under 24 months of age requiring 30 μg/kg/day and those older than 24 months of age requiring 15 μg/kg/day. Therefore reaching 24 months of age is the criterion to de-escalate the dose. The de-escalation will occur on the visit immediately preceding a patient reaching 24 months of age.

Safety outcome assessments

Safety in this study will be determined from evaluation of Adverse Events, Serious Adverse Events, clinical laboratory assessments (chemistry, hematology), vital signs measurements (heart rate, blood pressure, respiratory rate, and temperature), physical examinations, ECGs, echocardiograms, and concomitant medications.

Any abnormal laboratory test results determined to be clinically significant by the Investigator will be repeated (at the Investigator's discretion) along with any necessary specialist consultation, until the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the Investigator determines that the abnormal value is no longer clinically significant.

For patients who have not previously had genetic testing confirming diagnosis of achondroplasia, molecular genetic diagnosis to identify the *FGFR3* pathogenic variant (p.(Gly390Arg), p.(Gly346Glu), p.(Gly375Cys), or "other") will be performed locally, within the screening period. If patients had previous genetic testing, patients must have a report from a certified laboratory with the study specific mutation documented.

Vital signs will include seated or supine systolic blood pressure and diastolic blood pressure measured in mmHg, heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius.

Complete physical examinations will include major body systems, including assessment of general appearance, cardiovascular function, dermatologic, head, eyes, ears, nose, and throat, lymphatic, respiratory, gastrointestinal, musculoskeletal, and neurological and genitourinary.

A standard 12-lead ECG will be performed and evaluated locally and will include assessment of heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities. If clinically significant abnormalities are noted, the Investigator or designee is required to report it as an Adverse Event and assess whether it is appropriate for the patient to continue in the study.

Cardiac anatomy and function will be evaluated by a standard two-dimensional Doppler echocardiogram by a local cardiologist. Echocardiograms will provide information regarding cardiac anatomy and function prior to enrollment and at the end of the study.

Data monitoring committee

In addition to safety monitoring by BioMarin personnel, an independent Data Monitoring Committee will act as an advisory body and will monitor the safety of patients in the study. If a study patient requires cervicomedullary decompression surgery, the committee will be informed and provided all available information for review. The Data Monitoring Committee will make recommendations for stopping or continuing the study on an individual patient level or on a study level according to the pre-specified criteria. The Data Monitoring Committee may also make endorsements for dose adjustments if needed.

Efficacy outcome assessments

Signs and symptoms of foramen magnum stenosis leading to cervicomedullary compression will be assessed and monitored during this study using a combination of data from MRI, neurological examinations, polysomnography, and condition specific developmental milestone acquisition.

Magnetic resonance imaging assessments

MRI assessments will be performed to evaluate the effect of vosoritide on the the skull and the brain (including volumes of the face, sinuses, calvarium, brain, and ventricles; and dimensions of the foramen magnum and relations to surrounding structures) as well as the whole spinal cord (including relations to the spinal canal). MRI will be carried out at screening, then biannually at weeks 26, 52, 78, and 104 and annually thereafter.

The MRI assessment procedures will be performed under general anesthesia, with the head in a neutral position and according to pre-defined parameters as shown in Table 3 (Brainstem and Skull) and Table 4 (Thoracolumbar Spine). Independent, blinded expert review of all MRI assessments will be performed to standardize eligibility assessment and interpretation of any changes observed during the study. Any decisions on whether surgery is required will remain the responsibility of the investigators and neurosurgeons at each participating site, who will be blinded to the AFMS assigned to their patients by the independent reviewer.

Neurological examination

To evaluate the effect of vosoritide on neurological signs and symptoms of cervicomedullary compression, complete neurological examinations will be performed at all visits, including assessment of lower cranial nerves, sensory and motor examinations, spinal reflexes, co-ordination, and gait.

Table 3. MRI parameters for the brainstem and skull.

Parameter	Description
Superior extent	Vertex of skull (one slice above skull)
Inferior extent	Cervical C4 (ensure the bottom of the chin is included in the image volume)
Sequences	Scout Sagittal 3D T1-weighted image (T1WI) Sagittal 3D T2-weighted image (T2WI) Axial and coronal reconstructions of the Sagittal T1 and T2
Plane	Sagittal (T2 and T1)
Reconstruction (MPR) plane	Axial and coronal
Slice thickness	1.2 mm or less for 3D Sagittal 1 mm for reconstruction scans
Interslice gap (Spacing)	0 mm
Matrix	256 × 256 highly recommended
FOV	20–25 cm required
NEX	1–2
Number of slices	Sagittal T1 and T2 should have the same number of slices. Follow up timepoint must be consistent with screening.

Age-specific developmental milestone acquisition

To assess the effect of vosoritide on age-specific developmental milestones, Bayley-III scores will be used according to age throughout the course of the study. The Bayley-III is a performance-based outcome assessment for use in children from 1 to 42 months. It is individually administered by the trained clinician to the patient/child. Scales include Cognitive subscale, Receptive and Expressive subscales, and Gross and Fine Motor subscales. The two language scales make up a composite Language Scale score and the Gross and Fine Motor subscales yield a composite Motor Scale score. The scales have clinical and research utility as a diagnostic assessment for young children with varied disorders and disabilities and reflect current professional standards for early childhood assessment.[36]

Sleep study

Polysomnography will be used to assess the presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation, pulse rate, and airflow during overnight monitoring. Assessment of episodes of sleep apnea will include the number of episodes of apnea and hypopnea per hour (Apnea/Hypopnea Index).

Table 4. MRI parameters for the thoracolumbar spine.

Parameter	Description
Superior extent	Vertex of T11 (one slice above T11). Bony detail should be visible from T-11
Inferior extent	Infracoccygeal (one slice below the tip of the coccyx)
Sequences	Scout Sagittal T1-weighted image (T1WI) Sagittal T2-weighted image (T2WI) Axial T1-weighted image (T1WI) Axial T2-weighted image (T2WI) Axial T2 gradient echo
Plane	Sagittal and axial
Slice thickness	3 mm
Interslice gap (spacing)	0 mm
Matrix	256 × 256 highly recommended
FOV	20–25 cm required
NEX	1–2
Number of slices	Follow up timepoint must be consistent with screening.

Anthropometric measurements

Anthropometric measurements will be taken during study visits with each measurement taken in triplicate and conducted using standardized techniques using the same equipment across all study sites.

Statistical analysis

Approximately 20 patients aged 0 months to ≤12 months at study entry will participate in this study. No formal sample size calculations were performed but the number of patients is considered appropriate to evaluate the safety and efficacy of vosoritide in this at-risk population.

The statistical analysis plan will provide additional details on the planned statistical analysis. Unless otherwise stated, all analyses will be performed using SAS v. 9.4. Because the completeness of the data affects the integrity and accuracy of the interim and final study analysis, every effort will be made to ensure complete, accurate, and timely data collection and, therefore, avoid missing data. Missing data will not be imputed in any of the summaries, with the exception of missing dates for medications or adverse events. Any patient who prematurely discontinues study drug will be encouraged to continue to participate in the study assessments for the remaining duration of the study, as long as in the judgment of the Investigator such continued participation would not detrimentally affect the health, safety, or welfare of the patient.

Efficacy and safety data will be summarized descriptively by study treatment allocation; no confirmatory statistical testing will be performed and differences

between treatment arms will be provided with 95% confidence intervals. Summaries of the continuous data will include the number of patients with assessments, mean, SD, median, 25th and 25th percentile, minimum and maximum, and 95% confidence limits. The frequency and incidence will be presented for categorical data.

Safety analyses

The safety analysis will be performed on the Safety Population. The MedDRA dictionary will be used to assign system organ class and preferred term classification to events and diseases, based on the original terms entered on the electronic case report form (eCRF).

The incidence of AEs will be summarized by system organ class, preferred term and study treatment allocation. All AEs, including SAEs and AEs that lead to permanent discontinuation from the study and from the study treatment, will be listed. Events of Interest such as hypersensitivity reactions, injection site reactions and symptomatic hypotension, and the percentage of patients who report these AEs will be presented.

Clinical laboratory data will be summarized by the type of laboratory test. For each clinical laboratory test, descriptive statistics will be provided on baseline as well as all subsequent visits. Shift tables from baseline to worst post-baseline value based on the Common Terminology Criteria Grading (Normal—Grade 5) will be generated.

All other safety measures including vital signs, physical examination, ECG, echocardiograms, and concomitant medication data will also be summarized descriptively. All safety results will be listed.

Efficacy analysis

The efficacy analysis will be performed on the Final Analysis Set (FAS) consisting of all randomized consented patients. Analyses to evaluate efficacy endpoints include:

- Frequency of surgical cervicomedullary decompression over the course of the study.
- Change in clinical signs and symptoms (including neurological assessment) every 6 months.
- Change in MRI measurement of area of foramen magnum and antero-posterior (AP) diameter, brain stem, and spinal cord volume and ratio of area of spinal cord to foramen magnum every 6 months.
- Change in MRI measurement of area of spinal canal, transverse and AP diameter, spinal cord volume and ratio of area of spinal cord to spinal canal every 6 months.
- Change in developmental skills (Bayley-III) every 6 months.

- Change in status of sleep apnea including central and obstructive components (sleep study) every 6 months.
- Change in anthropometric measurements every 6 months.

Descriptive summaries at each visit, including change from baseline (defined as date of randomization), will be provided by study treatment allocation and strata in which patients are enrolled.

Conclusion

Abnormal development and growth of the foramen magnum in infants and young children with achondroplasia, leading to compression of the brainstem and other vital structures passing through the cranio-cervical junction, is the most important factor leading to increased mortality and morbidity in these children in the first 5 years of life. Similarly, impaired growth of the spinal canal results in spinal canal stenosis and cord compression leading to significant morbidity later in adulthood. It follows that one of the key goals of any precision therapy aimed at improving the impaired endochondral ossification that lies at the source of this condition, is to improve and restore the growth rate of the foramen magnum and spinal canal.

The recent advent of vosoritide, combined with its safety profile, and promising effects on long bone growth in children with achondroplasia aged 5 to 18 years, allows us to hypothesize whether treatment of infants and young children with this therapy might be safe and have a positive effect on growth of the foramen magnum and spinal canal, decreasing consequent medical complications.

It is hoped that the underlying rationale, design and methods of this pioneering clinical trial will begin the journey to answering this key question, with potential life-saving or health-improving benefits for young children born with achondroplasia. It will also serve as a benchmark against which other potential therapies for achondroplasia (currently in early clinical development) can be assessed.[37]

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Received honoraria from BioMarin Pharma.

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Ethics approval

Ethical approval for this study was obtained from:

- United Kingdom—Yorkshire & The Humber—Sheffield Research Ethics Committee (20/YH/0182) and the Health Research Authority (282694).

- Australia: The Royal Children's Hospital Human Research Ethics Committee (HREC/64322/RCHM-2020).

Informed consent

Written informed consent was obtained from parents/caregivers of all subjects prior to enrolment into the study, including information that anonymized results arising from the study would be published in a peer-reviewed scientific journal.

Trial registration

ClinicalTrials.gov, NCT04554940; EudraCT number, 2020-001055-40

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References

1. Wynn J, King TM, Gambello MJ, et al. Mortality in achondroplasia study: a 42-year follow-up. *Am J Med Genet A* 2007; 143A(21): 2502–2511.
2. Foldynova-Trantirkova S, Wilcox WR and Krejci P. Sixteen years and counting: the current understanding of fibroblast growth factor receptor 3 (FGFR3) signaling in skeletal dysplasias. *Hum Mutat* 2012; 33(1): 29–41.
3. Bellus GA, Hefferon TW, Ortiz de Luna RI, et al. Achondroplasia is defined by recurrent G380R mutations of FGFR3. *Am J Hum Genet* 1995; 56(2): 368–373.
4. Horton WA, Hall JG and Hecht JT. Achondroplasia. *Lancet* 2007; 370(9582): 162–172.
5. Pauli RM, Scott CI, Wassman ER Jr, et al. Apnea and sudden unexpected death in infants with achondroplasia. *J Pediatr* 1984; 104(3): 342–348.
6. Hecht JT, Francomano CA, Horton WA, et al. Mortality in achondroplasia. *Am J Hum Genet* 1987; 41(3): 454–464.
7. Hecht JT, Nelson FW, Butler IJ, et al. Computerized tomography of the foramen magnum: achondroplastic values compared to normal standards. *Am J Med Genet* 1985; 20(2): 355–360.
8. Cheung MS, Alves I, Hagenäs L, et al. Meeting report from the achondroplasia foramen magnum workshop, Salzburg, Austria, 22 June 2019. *Bone* 2019; 127: 499–502.
9. Pauli RM. Achondroplasia: a comprehensive clinical review. *Orphanet J Rare Dis* 2019; 14(1): 1.
10. Matsushita T, Wilcox WR, Chan YY, et al. FGFR3 promotes synchondrosis closure and fusion of ossification centers through the MAPK pathway. *Hum Mol Genet* 2009; 18(2): 227–240.
11. Vital JM, Beguiristain JL, Algara C, et al. The neurocentral vertebral cartilage: anatomy, physiology and physiopathology. *Surg Radiol Anat* 1989; 11(4): 323–328.
12. Hecht JT, Horton WA, Redi CS, et al. Growth of the foramen magnum in achondroplasia. *Am J Med Genet* 1989; 32(4): 528–535.
13. Coin CG and Malkasian DR. Foramen magnum. In: Newton TH and Potts DG (eds.) *Radiology of the Skull and Brain. The Skull*, Vol. 1. St Louis, MO: Mosby, 1971, pp.275–286.
14. Wright MJ and Irving MD. Clinical management of achondroplasia. *Arch Dis Child* 2012; 97(2): 129–134.

15. Trotter TL and Hall JG; American Academy of Pediatrics Committee on Genetics. Health supervision for children with achondroplasia. *Pediatrics* 2005; 116(3): 771–783.
16. Canavese F and Dimeglio A. Normal and abnormal spine and thoracic cage development. *World J Orthop* 2013; 4(4): 167–174.
17. Kubota T, Adachi M, Kitaoka T, et al. Clinical practice guidelines for achondroplasia. *Clin Pediatr Endocrinol* 2020; 29(1): 25–42.
18. White KK, Bompadre V, Goldberg MJ, et al. Best practices in the evaluation and treatment of foramen magnum stenosis in achondroplasia during infancy. *Am J Med Genet A* 2016; 170A(1): 42–51.
19. Ruiz-Garcia M, Tovar-Baudin A, Del Castillo-Ruiz V, et al. Early detection of neurological manifestations in achondroplasia. *Childs Nerv Syst* 1997; 13(4): 208–213.
20. Mogayzel PJ Jr, Carroll JL, Loughlin GM, et al. Sleep-disordered breathing in children with achondroplasia. *J Pediatr* 1998; 132(4): 667–671.
21. White KK, Parnell SE, Kifle Y, et al. Is there a correlation between sleep disordered breathing and foramen magnum stenosis in children with achondroplasia? *Am J Med Genet A* 2016; 170A(1): 32–41.
22. Nadel JL, Wilkinson DA, Garton HJL, et al. Screening and surgery for foramen magnum stenosis in children with achondroplasia: a large, national database analysis. *J Neurosurg Pediatr* 2018; 23(3): 374–380.
23. Sanders VR, Sheldon SH and Charrow J. Cervical spinal cord compression in infants with achondroplasia: should neuroimaging be routine? *Genet Med* 2019; 21(2): 459–463.
24. Ho NC, Guarnieri M, Brant LJ, et al. Living with achondroplasia: quality of life evaluation following cervico-medullary decompression. *Am J Med Genet A* 2004; 131(2): 163–167.
25. Cheung MS, Irving M, Cocca A, et al. Achondroplasia foramen magnum score: screening infants for stenosis. *Arch Dis Child* 2021; 106(2): 180–184.
26. Yasoda A and Nakao K. Translational research of C-type natriuretic peptide (CNP) into skeletal dysplasias. *Endocr J* 2010; 57(8): 659–666.
27. Kake T, Kitamura H, Adachi Y, et al. Chronically elevated plasma C-type natriuretic peptide level stimulates skeletal growth in transgenic mice. *Am J Physiol Endocrinol Metab* 2009; 297(6): E1339–E1348.
28. Yamanaka S, Nakao K, Koyama N, et al. Circulatory CNP rescues craniofacial hypoplasia in achondroplasia. *J Dent Res* 2017; 96(13): 1526–1534.
29. Yasoda A, Kitamura H, Fujii T, et al. Systemic administration of C-type natriuretic peptide as a novel therapeutic strategy for skeletal dysplasias. *Endocrinology* 2009; 150(7): 3138–3144.
30. Bocciardi R, Giorda R, Buttgereit J, et al. Overexpression of the C-type natriuretic peptide (CNP) is associated with overgrowth and bone anomalies in an individual with balanced t(2;7) translocation. *Hum Mutat* 2007; 28(7): 724–731.
31. Bocciardi R and Ravazzolo R. C-type natriuretic peptide and overgrowth. *Endocr Dev* 2009; 14: 61–66.
32. Moncla A, Missirian C, Cacciagli P, et al. A cluster of translocation breakpoints in 2q37 is associated with overexpression of NPPC in patients with a similar overgrowth phenotype. *Hum Mutat* 2007; 28(12): 1183–1188.
33. Lorget F, Kaci N, Peng J, et al. Evaluation of the therapeutic potential of a CNP analog in a Fgfr3 mouse model recapitulating achondroplasia. *Am J Hum Genet* 2012; 91(6): 1108–1114.
34. Savarirayan R, Irving M, Bacino CA, et al. C-type natriuretic peptide analogue therapy in children with achondroplasia. *N Engl J Med* 2019; 381(1): 25–35.

35. Savarirayan R, Tofts L, Irving M, et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomized, double-blind, phase 3, placebo-controlled, multicentre trial. *Lancet* 2020; 396: 684–692.
36. Bayley N. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt.
37. Legeai-Mallet L and Savarirayan R. Novel therapeutic approaches for the treatment of achondroplasia. *Bone* 2020; 141: 115579.

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ORIGINAL ARTICLE

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Experiences of children and adolescents living with achondroplasia and their caregivers

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Abstract

Background: Achondroplasia, caused by a pathogenic variant in the fibroblast growth factor receptor 3 gene (*FGFR3*), leads to significant multisystem complications across the lifespan that may affect the health-related quality of life (HRQoL) of individuals and families living with the condition.

Methods: The objective of this qualitative study was to describe the HRQoL of children and adolescents with achondroplasia and their caregivers. Thirty-four caregivers and 12 adolescents from the United States and Spain participated in one of eight focus groups or completed an individual interview, which was audio-recorded and transcribed. Thematic analysis of qualitative data was performed to identify commonly occurring themes pertaining to HRQoL.

Results: Caregivers and adolescents described challenges with physical functioning and medical complications due to achondroplasia. Key challenges included difficulties performing activities of daily living, issues of accessibility, bullying, or unwanted attention in public, and negative effects on self-esteem. Caregivers were concerned about accessing appropriate medical care for their child, and also reported experiencing financial, relational, and emotional challenges in their families. Achondroplasia also affected individuals and their families in positive ways, including increasing empathy, receiving positive attention, and feeling supported by the achondroplasia community.

Conclusions: These findings underscore the importance of regular assessments of HRQoL and the provision of psychosocial support to affected children and families.

KEYWORDS
achondroplasia, quality of life, skeletal dysplasia

1 | INTRODUCTION

Achondroplasia (OMIM 100800), the most common skeletal dysplasia, occurs in approximately 1/25,000 live births (Foreman et al., 2020) and is estimated to affect over 250,000 people worldwide (Horton et al., 2007; Pauli, 2019). Achondroplasia is caused by a gain-of-function mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene, leading to impaired endochondral bone growth (Horton et al., 2007). Clinical features include disproportionate short stature with narrow chest, short fingers and limbs, midface hypoplasia, macrocephaly with frontal bossing, abnormal spinal curvature, hypermobility in the knees and hips, hypotonia, and tibial bowing (Fredwall et al., 2020; Hoover-Fong et al., 2021; Horton et al., 2007; Pauli, 2019). Individuals with achondroplasia face a range of medical issues over the lifespan, including foramen magnum stenosis and cervicomedullary compression, developmental motor milestone delays, ear infections, hearing loss, genu varum, spinal stenosis, chronic pain, and respiratory dysfunction (Fredwall et al., 2020; Hoover-Fong et al., 2021; Horton et al., 2007; Pauli, 2019; Pfeiffer et al., 2021a, 2021b).

In addition to medical complications, achondroplasia can impact multiple domains of health-related quality of life (HRQoL) in affected children (Alade et al., 2013; Ireland et al., 2011; Pfeiffer et al., 2021b; Witt et al., 2017; Witt et al., 2019), adolescents (Alade et al., 2013; Matsushita et al., 2019; Witt et al., 2017), and adults (Alade et al., 2013; Dhiman et al., 2017; Gollust et al., 2003; Mahomed et al., 1998; Matsushita et al., 2019; Witt et al., 2017; Yonko et al., 2021). Compared to individuals of average stature, individuals with achondroplasia consistently demonstrate lower HRQoL scores in physical domains (Alade et al., 2013; Dhiman et al., 2017; Gollust et al., 2003; Ireland et al., 2011; Mahomed et al., 1998; Matsushita et al., 2019; Pfeiffer et al., 2021b; Witt et al., 2017; Yonko et al., 2021). Some studies have also reported that individuals with achondroplasia score lower in social, emotional, and school-related domains (Dhiman et al., 2017; Gollust et al., 2003; Pfeiffer et al., 2021b; Witt et al., 2017; Witt et al., 2019) compared to average stature individuals. Additionally, in one quantitative study, parents of children with achondroplasia reported significantly lower mental health scores compared to a reference population (Witt et al., 2019). A qualitative study of parents of children with achondroplasia aged 2–12 years found that the majority experienced worry or concern for their child, and that many felt stressed or overwhelmed, and described impacts on caregiver employment, family relationships, family activities, and social well-being (Pfeiffer et al., 2021a). However, interventional programs provided by patient advocacy groups that are tailored specifically to the needs of individuals with achondroplasia and their families have been shown to improve HRQoL of participants compared to no change in HRQoL of non-participants (Witt et al., 2017).

It is important for clinicians and other stakeholders to understand current experiences within achondroplasia communities in order to improve the quality of care of affected individuals and to inform clinical practice guidelines (Savarirayan et al., 2021). Qualitative studies can provide more detailed insights into people's experiences compared to purely quantitative studies; moreover, utilizing focus groups enables participation from individuals who may be reluctant to partake in individual interviews, and the group interaction facilitates exploration on how and why people think the way they do (Kitzinger, 1995). The objective of this qualitative study was to better characterize how achondroplasia affects HRQoL for children and adolescents and their caregivers using concept elicitation focus groups and interviews. While previous studies have reported HRQoL in adolescents using quantitative measures, to our knowledge, no qualitative studies have described the experiences of adolescents from their own perspective. Additionally, we recruited participants from the United States (US) and Spain, two countries with divergent approaches to certain aspects of achondroplasia management (surgical limb lengthening is commonly practiced in Spain but rarely performed in the US), to examine country- and cultural-specific similarities and differences in experiences with achondroplasia.

2 | METHODS

2.1 | Study design

This study consisted of four focus group discussions in both the US and Spain: adolescents (ages 13–17 years) with achondroplasia, and the caregivers of children/adolescents with achondroplasia aged 0–4, 5–12, and 13–17 years. As the type and severity of complications associated with achondroplasia differ across life stages (Hoover-Fong et al., 2021), focus groups were segmented by age. Additionally, three one-on-one telephone interviews with US adolescents were conducted due to low attendance in the US adolescent focus group. While focus groups can be conducted with young children (Adler et al., 2019), it was not deemed appropriate for children under age 13 years to participate in this study given the complexity of the topics of interest and the planned duration of the sessions (outlined below); we, therefore, relied on caregiver reports to gain insight into the experiences of younger children. Focus groups and interviews were conducted by experienced qualitative researchers with study-specific training.

Focus groups were conducted in three 90-minute sessions organized around the following topics: (a) understand the impact of achondroplasia on affected individuals' and caregivers' lives; (b) obtain perceptions of the risk, benefits, and important aspects of treatments; and (c) understand the clinically meaningful change in height, proportionality, independence with activities of daily living, and meaningful change in scores of three HRQoL instruments (Pediatric Quality of Life Inventory (PedsQL™) (Varni et al., 2001), Quality of Life in Short Stature Youth (QoLISSY) (Bullinger et al., 2013) and Functional Independence Measure for Children (WeeFIM) (Slomine, 2011). The objective of this manuscript is to report the experiences of living with achondroplasia, which was primarily discussed in the first session. Data gathered in the second and third sessions were of interest for use in potential future studies; however, data from all sessions were included in this analysis.

2.2 | Eligibility and recruitment

Participants resided in the US or Spain and were able to communicate fluently in the local language. Participants were ineligible if they (or their child with achondroplasia) had another unrelated condition or chronic illness which impacted HRQoL. Caregivers were defined as a primary caregiver to the individual with achondroplasia, and potentially included adoptive parents or grandparents. Only one caregiver with achondroplasia was permitted to participate in each of the caregiver focus groups, so that representation would be similar to the achondroplasia population with 20% of parents affected (Horton et al., 2007).

Recruitment was conducted through Global Perspectives. In Spain, participants were identified through the support organization Fundación ALPE Acondroplasia. In the US, participants were identified through a variety of sources, including Global Perspectives databases, a recruiter with close personal links to the community, and patient support groups willing to share the study announcement on social media.

2.3 | Study procedures

A semi-structured focus group discussion guide was developed based on consultation with five international clinical experts representing a range of specialties (clinical genetics, pediatrics, orthopedics) whose clinical experience with achondroplasia spanned 22–40 years. The discussion guide began with broad questions to elicit responses spontaneously, followed by specific questions based on impacts identified by the clinical experts. Examples of discussion guide topics and questions are provided in Table 1. The adolescent focus group discussion guide was also used for the individual Interviews.

2.4 | Analysis

Focus groups and interviews were audio recorded and transcribed verbatim. Spanish sessions were transcribed directly into English with review for accuracy by the bilingual moderators.

Thematic analysis, as described by Joffe and Yardley (2004) and based broadly on grounded theory (Glaser & Strauss, 1967), was the selected analytic approach to meet the research objectives. Initial codes were based on pre-defined concepts and themes; analysts added data-driven codes that emerged during the focus groups and interviews.

MAXQDA qualitative analysis software was used to help organize the data and code the transcripts (Software, 2020). The lead analyst reviewed several transcripts to develop a preliminary codebook. Two transcripts (one per country and representative of different age cohorts) were double coded independently by two analysts and compared. Discrepancies were discussed and addressed by modifying the organization of the codebook or clarifying code definitions. After the second inter-coder exercise showed high agreement, one analyst coded the remaining transcripts. Before the codebook was finalized, a second analyst familiar with the dataset reviewed the results.

3 | RESULTS

3.1 | Sample description

Focus groups and interviews were conducted between August and October 2018. Participants included 34 caregivers (US $n = 16$, Spain $n = 18$) and 12 adolescents (US $n = 6$, Spain $n = 6$). Sample characteristics are provided in Tables 2 and 3. Children of caregivers were distributed across the age groups. In the US, all caregivers were female; in Spain, most caregivers were female ($n = 14/18$, 78%). All caregivers were biological or adoptive parents.

Themes related to individuals' and caregivers' experiences, respectively, are illustrated in Figure 1 and Figure 2.

3.2 | Experiences of children and adolescents with achondroplasia, as reported by themselves and their caregivers

In describing results, we use the terms "children," "adolescents," or "individuals" to refer to, respectively, children, adolescents, or both children and adolescents

TABLE 1 Examples of discussion guide questions

Topic	Caregiver discussion guides	Adolescent discussion guide
Physical impacts	In terms of any physical impacts, please can you describe how achondroplasia impacts physical functioning and say a little about how these impact your child's daily life?	In terms of any physical impacts, please can you describe how achondroplasia affects your physical functioning and say a little about how these impact your daily life?
Activities of daily living	Ages 0–4 years: Does achondroplasia affect your child's ability to do activities appropriate for their age? Ages 5–17 years: Is your child able to manage their self-care in relation to going to the toilet, washing, and dressing? (If no, do you think this will change?)	Are you able to manage your own self-care? (going to the toilet, washing, and dressing)
Social impacts	Have there been any social impacts for your child due to achondroplasia? (How is school life for your child? How do any challenges impact your child?)	Are you affected socially because you have achondroplasia? (How is school life for you? How do any challenges affect you?)
Medical care	Tell me about your experiences with medical care for your child (Does your child have any routine follow-up appointments related to achondroplasia? If so, how often?) (Do you have a medical provider who understands how to treat children with achondroplasia?)	Tell me about your experiences with medical care (Do you have any routine follow-up appointments related to achondroplasia? If so, how often?) (Do you have a medical provider who understands how to treat individuals with this condition?)
Impacts on family	Do you think there are specific impacts in having a child with achondroplasia on the family overall?	*Not asked*
Treatments	Before we discuss specific types of treatments, it would be useful to know in general what you think about medical treatment for this condition (Have your thoughts on this changed over time at all? If so, why? What led to this change?)	

Note: Examples of probes, or potential follow-up questions after spontaneous responses to the first question, are shown in parentheses. Due to the semi-structured nature of guide, not all probes were asked directly and moderators could also ask other follow up questions according to the flow of the discussion. Note that this table provides several examples by topic only and does not show all possible probes included in the full discussion guide.

with achondroplasia. The term "participants" applies to anyone who took part in focus groups or interviews directly, including the caregivers and adolescents with achondroplasia.

3.2.1 | Physical functioning and related complications

All caregivers reported a delay in early physical developmental milestones, such as holding up the head, walking, crawling, and sitting up, and caregivers of all age groups discussed mobility limitations and challenges (e.g., balance issues that affect walking ability). Although all caregivers expected developmental delays, some expressed anxiety about delayed milestones. One caregiver shared, "...the doctors at [specialist center] kept saying 'He's going to get there...' I am looking at my...13-month-old who is not even sitting up, [thinking] 'They're out of their mind. He's never going to do anything'....Then, all of a sudden, they do it." Several caregivers noted how their children adapted movements to increase mobility, such as scooting with legs while not lifting up their head.

Participants reported physical complications of achondroplasia, such as stenosis/spinal compression, breathing and sleeping difficulties, pain, weight management, and otolaryngological issues. Spinal and neurological issues, such as kyphosis, foramen magnum compression, and stenosis, were noted for their severity and complexity, involving frequent medical appointments and surgical procedures, and were of particular concern to caregivers in their child's earlier years. Breathing and respiratory challenges of varying severity, including sleep apnea, hypopnea, and poor sleep quality, were frequently mentioned by caregivers, especially those of affected children aged 0–4 years.

Participants frequently reported pain that limited physical functioning and stamina. Pain was also associated with sitting without back support and being unable to bend the knees when sitting in a chair due to leg shortness. Pain, with the back the most common site, was most often discussed in the adolescent focus groups, with one adolescent describing backaches that "happen every day... [and] last for like 20 minutes."

Management of weight and maintaining physical activity were described as challenges, with parental awareness of the issue starting at their child's young age and continuing throughout adolescence. Adolescents with achondroplasia also acknowledged challenges with weight control and the consequences of weight gain (e.g., additional pressure on the back and legs, and having a more difficult time losing weight compared to people of average stature).

TABLE 2 Sample characteristics: US

	Caregivers of ages 0–4 years ($n = 6$)	Caregivers of ages 5–12 years ($n = 6$)	Caregivers of ages 13–17 years ($n = 4$)	Adolescents ages 13–17 years ($n = 6$)[a]
Sex of caregiver				
Male	0	0	0	—
Female	6	6	4	—
Caregivers with achondroplasia	1	1	0	—
Ethnicity (child)				
Caucasian	5	6	4	4
Asian[b]	0	0	2	2
Unknown	1	0	0	0
Education (caregiver)				
High school	1	0	0	—
Some college	2	1	1	—
Bachelor's degree	2	4	2	—
Master's degree	1	1	1	—
Employment (caregiver)				
Full time	1	2	0	—
Part time	4	0	2	—
Self employed	0	1	2	—
Stay at home	0	3	0	—
Student	1	0	0	—
Unemployed	0	0	0	
Marital status (caregiver)				
Married	4	6	3	—
Divorced/separated	1	0	1	—
Single	1	0	0	—
Sex of child				
Male	4	5	3	4
Female	2	1	1	2

[a]Includes two adolescents who completed telephone interviews and whose parents did not participate in the caregiver focus groups. Additionally, one adolescent whose mother participated in the focus groups completed a telephone interview.

bTwo adolescents were adopted from China by two US families.

Caregivers and adolescents described some otologic issues, and placement of ear tubes was a common medical intervention. Caregivers tended to view this as less concerning than other medical issues, but two caregivers reported moderate deafness and hearing loss.

3.2.2 | Challenges and difficulties in acquiring Independence in activities of daily living

Caregivers discussed the challenges and the need for more assistance with activities of daily living than their other children or peers. Caregivers and adolescents most frequently mentioned needing assistance with toileting, such as undressing and wiping. Several caregivers felt it was important to encourage independence early in life to help children learn to adapt. For example, a caregiver in Spain explained, "She likes to feel that we are helping her, and I think that's a bad thing." Another caregiver in Spain shared their reaction when requested for assistance: "With 'Can you help me with [wiping] my bottom?'...I say, 'Son, please. I'm still going to be doing this after you are married at this rate.'" Difficulties with performing tasks related to personal hygiene, such as not easily being able to reach sinks or shower heads to wash, were noted as a challenge; however, participants also noted improvements with age. Participants also discussed the challenge of independently dressing, especially pulling up pants.

TABLE 3 Sample characteristics: Spain

	Caregivers of ages 0–4 years ($n = 6$)	Caregivers of ages 5–12 years ($n = 6$)	Caregivers of ages 13–17 years ($n = 6$)[a]	Adolescent ages 13–17 years ($n = 6$)[a]
Sex of caregiver				
Male	1	1	2	—
Female	5	5	4	
Caregivers with achondroplasia	0	1	1	—
Ethnicity (child)				
Caucasian	5	6	6	6
Caribbean	1	0	0	0
Education (caregiver)				
High school	1	1	3	—
Technical/vocational	1	1	3	—
University diploma	3	3	0	—
Postgraduate degree	1	1	0	—
Employment (caregiver)				
Full time	4	5	5	—
Part time	1	1	1	—
Self employed	0	0	0	—
Stay at home	0	0	0	—
Student	0	0	0	—
Unemployed	1	0	0	
Marital status (caregiver)				
Married	5	5	5	—
Divorced/separated	0	0	1	—
Single	1	1	0	—
Sex of child				
Male	3	4	2	4
Female	3	2	4	2

[a]Sample comprises four parents and adolescents from the same family, two additional adolescents, and two additional parents.

3.2.3 | Accessibility challenges and adaptations

All participants spoke of modifications and adaptations made at home to increase accessibility, although the cost and level of modification varied. For example, one family had completely renovated a bathroom to accommodate their young child with achondroplasia, while other families simply acquired footstools and strategically arranged things, like storing dishes in lower kitchen cabinets.

Caregivers discussed the frustration related to lack of accessibility experienced by the younger children: "...she cannot reach the light switch or the doorbell, so she starts crying." By adolescence, as individuals become more independent and home adaptations are in place, most challenges of accessibility are outside of the home (e.g., public bathrooms, hotels, restaurants, and grocery stores) and involve issues such as reaching sinks, doorbells, and elevator buttons. One adolescent described specific challenges at school: "Sometimes our lockers are pretty high [and] they are actually a little bit out of my reach...and also the school sinks are very high, too, so it's a little difficult to wash my hands." Furthermore, adolescents frequently mentioned impacts on their social activities in public domains, such as being excluded from theme parks rides due to height requirements or difficulty seeing over the crowd at concerts.

3.2.4 | Social impacts of achondroplasia

A range of social experiences was described, from negative ones such as receiving rude comments and being bullied, to positive ones such as being popular at school due to their unique size.

Caregivers of children across all age groups discussed challenges in keeping up with peers athletically and how

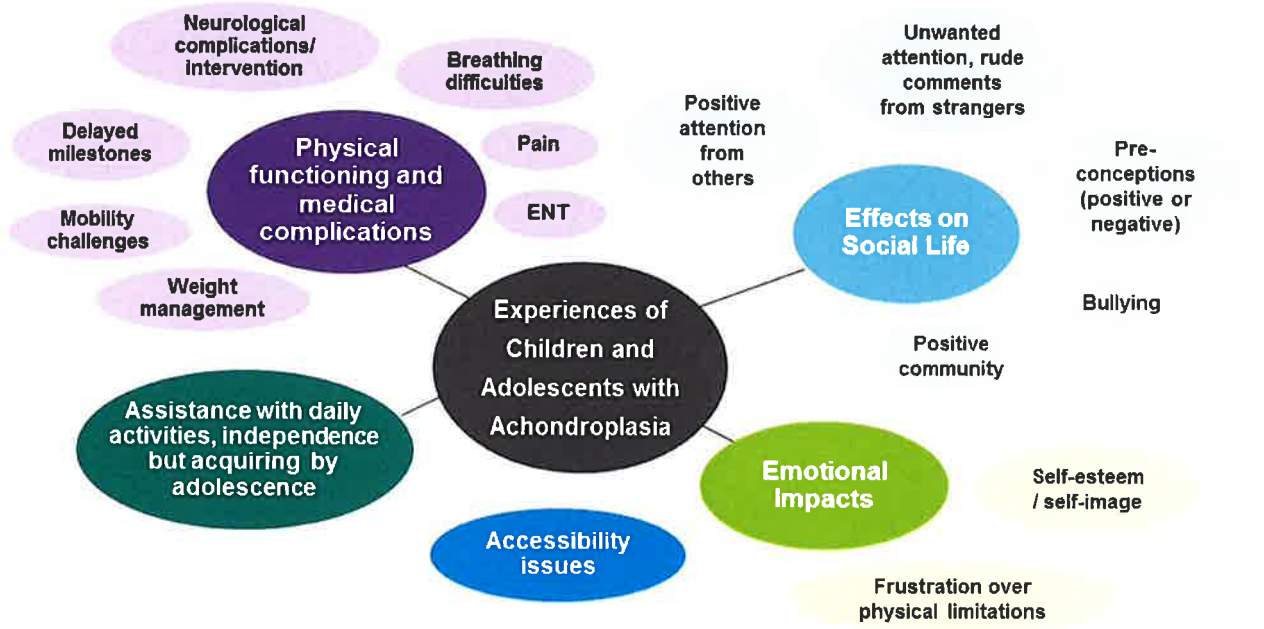

FIGURE 1 Themes and sub-themes of experiences of children and adolescents with achondroplasia (ages 0–17 years). Bubble sizes are not reflective of frequency of mention

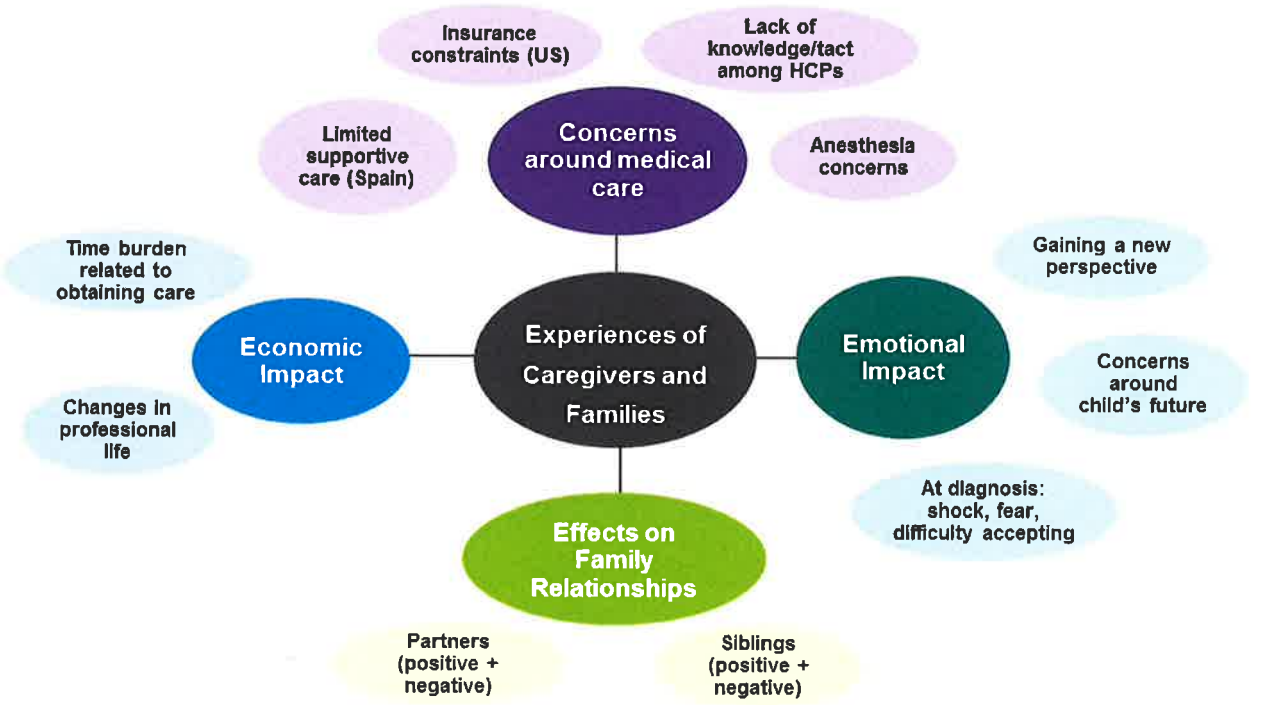

FIGURE 2 Themes and sub-themes of caregivers' and families' experiences. Bubble sizes are not reflective of frequency of mention. HCPs, health care provider

their children's physical limitations could cause exclusion from activities. One parent explained, "He's the only one that's a little person ...For his size, he does great, but he's always the last person, always behind ...It's hard at this age." Other social impacts were not being invited to participate in activities.

Social impacts in school appeared to be minimal for some, while others reported incidents of bullying. A

caregiver shared their child's struggle with the transition to high school and how they were treated: "I'm having to face something new that is happening to me. They think I'm deaf. I'm short, but not deaf. They whisper and point their finger at me." Two children were reported to have enrolled in a different school due to bullying. One adolescent described the impact of bullying: "It started in elementary school and died down a bit. It follows me here. It still hurts." Nearly all participants spoke of an increase in attention when starting school, especially from younger students. One parent shared how a teacher helped their child with achondroplasia by addressing and discussing differences with other students.

Many caregivers discussed their child receiving unwanted or special attention in public: "Walking down the street, and nobody said anything mean, nobody was nasty, but that constant attention on him. You can't walk past a person without them noticing." Caregivers reported their child receiving special or unwanted attention from strangers, having to cope with stares, comments, and even, in extreme cases, asking for photographs. One adolescent shared how this increased attention affects them: "You've had a bad day, for example, and you go somewhere and have to put up with people staring.... It annoys me." Caregivers spoke of building up the children's self-esteem and working on developing skills to handle these situations.

Some participants experienced special attention as positive or an advantage. One adolescent stated, "It makes me stand out a little more, people remember me." A caregiver reported that, while their child does not mind the attention, they did not like patronizing comments. They explained, "I think it's different for a girl for some reason. .... Everybody thinks she's so cute and everybody stops her in the halls, 'you're so cute, you're like a doll.' She hates that part, but she doesn't mind the attention at all."

Participants noted that individuals with achondroplasia are often subjected to preconceived perceptions. While these included positive preconceived notions, negative perceptions were also prevalent, as described by one adolescent: ".... first impressions for us with people are different....Sometimes people automatically have a prejudice against us and don't like us before they know our names.... Or, people make fun of us before they ever meet us, while other people are just people in their minds."

Due to their height, individuals with achondroplasia were perceived to be younger than their true age or less capable than average stature individuals. The height difference was especially confusing for average stature young children in primary school. A parent of an adolescent girl shared that "... people naturally tend to think of her as being younger or less capable...In some instances, they want to help more, which can be good or bad....I think it's harder for her peers or for adults to see her as the same age as her peers because of her height."

Despite some challenges in their local communities, all participants mentioned having support systems, including family, friends, and community members. Nearly all participants spoke of the importance of the support, guidance, and information provided by local achondroplasia organizations. Caregivers of older children voiced positive feelings about support organizations and events organized by these foundations. One parent shared how their child felt about ALPE: "It's such a normal thing. It's like he has another large family; he says, 'I've got my family and then I've got my ALPE family.'"

3.2.5 | Emotional effects of living with achondroplasia

The negative emotional impacts of living with achondroplasia included hurt feelings, loss of self-esteem, and frustration or anger. One caregiver described how their adolescent child struggles with achondroplasia: "She says 'I know some children have cancer and other diseases, but I have the only condition that is funny, laughable, and people point out and make fun at you'....It's hard to live your daily life with a burden on you from the day you are born." Adolescents discussed self-esteem and the psychological impacts of having to deal with stares and unwanted attention from strangers in public: "...When people stare or make comments or call me a mean name or things, it makes me feel bad."

For the youngest age group, 0–4 years, feelings of frustration appear to stem from physical limitations and the beginning of comparing their abilities to their peers. In Spain, caregivers reported that their children felt frustrated and angry when they were unable to reach items, such as door handles, light switches, and the intercom.

3.3 | Decision-making and perceptions of limb lengthening treatment

Among the Spanish adolescents, two had already undergone limb lengthening surgery, two were currently considering surgery, and two had decided not to have surgery. The two adolescents who had undergone limb-lengthening surgery acknowledged the pain and challenges of recovery including the frequency of heparin injections, difficulty of wound dressings, and long period of limited mobility while recovering, including spending a year in a wheelchair and missing school. One adolescent spoke positively about the results of surgery, especially the gain in stature, and explained "I

thought about it and said 'Let's do it.' But I have always known that I would have surgery since I was young." A parent shared their child's rationale for the surgery: "My daughter's motto is that she prefers to spend three or four bad years of her life because of the lengthening, but then she enjoys it for the rest of her life." The two adolescents who had completed the surgery reported greater independence in daily activities, such as the ability to reach items or maintain personal hygiene.

In the US groups, none of the participants or their children had undergone or considered undergoing limb lengthening surgery, which was generally perceived as intrusive, extremely painful, requiring a long recovery, and unnecessarily risky.

3.4 | Experiences of caregivers and families

3.4.1 | Concerns around access to appropriate medical care

Challenges and concerns regarding their child's medical care were the most discussed parental impact theme. Caregivers frequently mentioned a lack of confidence in providers, the challenge of accessing specialist care, and the economic burden of medical care.

In both countries, participants voiced concern about medical providers' lack of knowledge. Caregivers also reported a wide range of providers' efforts to gain or ensure they had appropriate knowledge and understanding of achondroplasia. Several caregivers voiced frustration with their pediatrician's lack of effort in learning more, for example: "He's almost 3 and I can't believe how they still don't know anything. [I'm thinking] 'Can anyone Google this? I mean, I figured it out." In Spain, two mothers shared experiences of medical providers suggesting termination in a tactless manner upon learning of the achondroplasia diagnosis in utero.

Participants reported concerns regarding the associated risks of anesthesia and the lack of knowledge and experience of anesthesiologists working with individuals with achondroplasia. A few caregivers voiced the need to question the anesthesiologist before the surgery to ensure they were aware of the potential complications of administering anesthesia to children with achondroplasia.

Many participants reported that access to care was a challenge. In Spain, caregivers reported having access to supportive care up to a certain age, though some reported struggling to get referrals to appropriate specialists. In the US, participants reported lack of access due to insurance constraints (not being covered) and location, with some reporting traveling hours away to see specialists.

3.4.2 | Economic impact

Caregivers discussed the indirect costs due to the amount of time needed to ensure their affected child received the necessary medical care, including time spent on the phone with insurance companies, getting second and third opinions from different providers, and attending frequent medical appointments.

Some caregivers reported modifying their work schedule or the need for flexibility to accommodate the numerous medical appointments required in the early years of achondroplasia. A few caregivers in the US discussed the challenge of finding competent care for their children so they can return to work, with two mothers choosing to stay home to care for their child. A caregiver in the US noted that, despite a desire to stay home, she returned to her work when her child with achondroplasia was born to ensure health insurance coverage.

3.4.3 | Effects of achondroplasia on family relationships

Caregivers reported that having a child with achondroplasia could strain their marriage or partnership. Some caregivers discussed the challenges that arose specifically during the child's early years, with disagreements regarding treatment and supportive services or groups, while others noted stress arising from having a child who is in pain.

Caregivers discussed the negative and positive impacts of having a child with achondroplasia on the family. Some caregivers reported that siblings felt jealous and struggled with the amount of attention the child with achondroplasia received. Other participants remarked about the bond between siblings, reporting that their average stature children are protective of their sibling with achondroplasia. Caregivers also reported that having a child with achondroplasia strengthened the family bond.

3.4.4 | Emotional effects on caregivers

Upon learning their child's diagnosis, caregivers most often reported feelings of denial and fear but also reported feeling guilt, shock, worry, isolation, grief, and anger. One caregiver described her initial denial: "I denied it until the labor. I was saying, 'It doesn't matter if [the doctors] are eminences because they are wrong.'" Another explained

their initial fear and how they adapted: "...from what the doctors told me at first, I was very terrified, honestly, and I was afraid that all these things were going to go wrong. I suppose part of it is getting used to the rhythm of raising a kid with achondroplasia. But now...we have medical issues sometimes, but they're not things that we can't handle."

Caregivers discussed future concerns that they had for their children, most frequently mentioning medical issues and complications. A few caregivers voiced concerns about having to decide whether to pursue potential new drug treatments at a young age, with one explaining, "... What if she turns to me and tells me 'Why didn't you try, mom?' or the opposite, '[Why didn't you] embrace [my short stature]?'" Other future concerns were related to social impacts, romantic relationships, employment, and general worries about quality of life.

Caregivers also described positive emotional impacts of having a child with achondroplasia and shared how they learned to appreciate life in a different way, for example, "My life has changed. I am convinced that it's been for the better."

4 | DISCUSSION

This first qualitative study involving both children and adolescents with achondroplasia and their caregivers provides a rich narrative of the challenges of living with achondroplasia in the US and Spain. Although the physical impacts of achondroplasia noted by study participants, including delayed milestones, limitations in mobility and physical functioning, accessibility barriers and the need for assistance, adaptations, and accommodations, and medical complications, have been described previously in the literature (Alade et al., 2013; Hoover-Fong et al., 2021; Ireland et al., 2011; Pfeiffer et al., 2021a; Thompson et al., 1999; Wigg et al., 2016), this study uniquely captured the frustration, anxiety, and unmet needs of patients and caregivers in addressing these physical challenges. While the negative social and emotional experiences of affected children and the burden on caregivers highlighted in previous studies were mirrored and expanded upon in our study findings, it was new to hear participants describe examples of positive attention received by children and adolescents with achondroplasia in social/school settings, and the ways in which having a child with achondroplasia can enhance familial bonds and the lives of caregivers. In concert, these study findings—voiced directly by individuals affected by achondroplasia and their caregivers—provide important context for understanding the complex and varied impacts of achondroplasia.

This study adds to the sparse literature on the quality of life of caregivers of children and adolescents with achondroplasia. Similar to findings reported by Pfeiffer et al. (2021b), caregivers in the present study reported experiencing concern for their child's emotional and social well-being, their child's ability to function independently, the health and safety of their child, and future implications. In addition, they reported challenges in navigating the medical system and seeking appropriate care, advocating for their child, and monitoring their child's health. This study demonstrates evidence of bureaucratic and physical barriers to accessing care for children with achondroplasia. Reasons for the challenges related to health care access differed between the two countries, reflecting the difficulties of two different healthcare systems. Caregivers in Spain reported difficulty accessing specialists after their child reached a certain age, while those in the US reported insurance and location constraints for accessing providers far from home. Moreover, this study provides a narrative description of caregivers' experiences with pediatricians and other specialists, highlighting lack of knowledge and experience with achondroplasia.

Our results demonstrate differences in preferences and practices across countries. In particular, the opposition to limb lengthening expressed by US caregivers, which was in contrast to broader acceptance in Spain, has not been described in previous research on this topic (Balci et al., 2015; Kim, Agashe, et al., 2012; Kim, Balce, et al., 2012; Leiva-Gea et al., 2020). As new and less invasive treatment modalities become available (Legeai-Mallet & Savarirayan, 2020; Savarirayan et al., 2019; Savarirayan et al., 2020), it will be important to understand how these treatments are perceived by caregivers in different countries and whether these treatments positively affect the quality of life, in terms of both physical and socioemotional functioning.

Our findings underscore the importance of routine psychosocial assessments and the provision of psychosocial support for those directly and indirectly impacted by achondroplasia. A number of instruments have been used to assess outcomes in individuals with achondroplasia (Hoover-Fong et al., 2021); to date, the Quality of Life in Short Stature Youth (QoLISSY) and the Pediatric Quality of Life Inventory (PedsQL™) are the only outcome tools for children that have been demonstrated to be reliable and valid in a cross-cultural context (Bloemeke et al., 2019). Participation in patient organizations has a positive impact on HRQoL, a finding that is consistent with those from other studies. (Pfeiffer et al., 2021a; Witt et al., 2017).

The main limitation of this study was a relatively small sample size located in two countries, which limits the generalizability of findings. However, our sample is diverse in terms of age and sex of individuals with achondroplasia

and geographic regions within the United States. As we conducted only one focus group per age group in each country, it was not possible to assess data saturation; however, the themes and perspectives reported by the same age groups in different countries were similar and verified by the caregivers. The structure of focus groups made it difficult to accurately quantify the frequency of impacts; instead, we provided an indication of prevalence of experiences but focused primarily on qualitative descriptions of important concepts.

5 | CONCLUSION

Study results provide a rich description of the multifaceted impacts of achondroplasia on the quality of life of affected children of varying ages and their families. Despite describing significant physical and socio-emotional challenges of living with achondroplasia, individuals, and caregivers also discussed positive aspects of achondroplasia and highlighted the importance of an accepting and supportive community. Insights and themes from this study could be further explored in larger qualitative and quantitative studies.

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CONFLICT OF INTERESTS

R. Shediac, J. Quinn, and D. Kelly are employees and shareholders of BioMarin Pharmaceutical Inc. J. Hoover-Fong has received consulting fees from BioMarin, Therachon, and Ascendis, and grants from BioMarin. K. Mohnike has received honoraria from Biomarin, Kyowa Kirin, and Novo Nordisk and is a consultant for QED and investigator for Biomarin and Pfizer. R. Savarirayan has received consulting fees and grants from BioMarin, and consulting fees from Ascendis, QED, and Pfizer.

AUTHOR CONTRIBUTIONS

R. Shediac, D. Kelly, J. Quinn, O. Moshkovich, and R. Ballinger were involved in the conception and design of the study. O. Moshkovich, R. Ballinger, H. Gerould, A. Williams, and M. A. Bellenger were involved in the acquisition and analysis of the data. R. Shediac, D. Kelly, J. Quinn, O. Moshkovich, R. Ballinger, J. Hoover-Fong, K. Mohnike, and R. Savarirayan were involved in the interpretation of the data. All authors were involved in drafting and revising the manuscript.

ETHICS

The study was approved by a central institutional review board, Salus IRB (Austin, TX, USA). Informed consent was obtained for each participant prior to the focus groups; adolescent participants, who were consented to by their caregivers, also provided assent.

DATA AVAILBILITY STATEMENT

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for non-commercial, academic purposes. Additional supporting documents may be available upon request. Investigators will be able to request access to these data and supporting documents via a data-sharing portal beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed methods of data analysis. Research proposals will be evaluated relative to publicly available criteria available at www.BioMarin.com/patients/publication-data-request/ to determine if access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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REFERENCES

Adler, K., Salanterä, S., & Zumstein-Shaha, M. (2019). Focus group interviews in child, youth, and parent research: An integrative literature review. *International Journal of Qualitative Methods, 18*, 160940691988727. https://doi.org/10.1177/1609406919887274

Alade, Y., Tunkel, D., Schulze, K., McGready, J., Jallo, G., Ain, M., Yost, T., & Hoover-Fong, J. (2013). Cross-sectional assessment of pain and physical function in skeletal dysplasia patients. *Clinical Genetics, 84*(3), 237–243. https://doi.org/10.1111/cge.12045

Balci, H. I., Kocaoglu, M., Sen, C., Eralp, L., Batibay, S. G., & Bilsel, K. (2015). Bilateral humeral lengthening in achondroplasia with unilateral external fixators: Is it safe and does it improve daily life? *The Bone & Joint Journal, 97-b*(11), 1577–1581. https://doi.org/10.1302/0301-620x.97b11.36037

Bloemeke, J., Sommer, R., Witt, S., Bullinger, M., Nordon, C., Badia, F. J., González, F. L., Leiva-Gea, A., Delgado Rufino, F. B., Mayoral-Cleries, F., Romero-Sanchiz, P., Clamagirand Saiz, V., Nogueira-Arjona, R., Mohnike, K., & Quitmann, J. (2019). Cross-cultural selection and validation of instruments to assess patient-reported outcomes in children and adolescents with achondroplasia. *Quality of Life Research, 28*(9), 2553–2563. https://doi.org/10.1007/s11136-019-02210-z

Bullinger, M., Quitmann, J., Power, M., Herdman, M., Mimoun, E., DeBusk, K., Feigerlova, E., Lunde, C., Dellenmark-Blom, M., Sanz, D., Rohenkohl, A., Pleil, A., Wollmann, H., & Chaplin, J. E. (2013). Assessing the quality of life of health-referred children and adolescents with short stature: Development

and psychometric testing of the QoLISSY instrument. *Health and Quality of Life Outcomes*, *11*, 76. https://doi.org/10.1186/1477-7525-11-76

Dhiman, N., Albaghdadi, A., Zogg, C. K., Sharma, M., Hoover-Fong, J. E., Ain, M. C., & Haider, A. H. (2017). Factors associated with health-related quality of life (HRQOL) in adults with short stature skeletal dysplasias. *Quality of Life Research*, *26*(5), 1337–1348. https://doi.org/10.1007/s11136-016-1455-7

Foreman, P. K., van Kessel, F., van Hoorn, R., van den Bosch, J., Shediac, R., & Landis, S. (2020). Birth prevalence of achondroplasia: A systematic literature review and meta-analysis. *American Journal of Medical Genetics. Part A*, *182*(10), 2297–2316. https://doi.org/10.1002/ajmg.a.61787

Fredwall, S. O., Maanum, G., Johansen, H., Snekkevik, H., Savarirayan, R., & Lidal, I. B. (2020). Current knowledge of medical complications in adults with achondroplasia: A scoping review. *Clinical Genetics*, *97*(1), 179–197. https://doi.org/10.1111/cge.13542

Glaser, B. G., & Strauss, A. L. (1967). *The discovery of grounded theory: Strategies for qualitative research*. Aldine.

Gollust, S. E., Thompson, R. E., Gooding, H. C., & Biesecker, B. B. (2003). Living with achondroplasia in an average-sized world: An assessment of quality of life. *American Journal of Medical Genetics. Part A*, *120A*(4), 447–458. https://doi.org/10.1002/ajmg.a.20127

Hoover-Fong, J., Cheung, M. S., Fano, V., Hagenas, L., Hecht, J. T., Ireland, P., Irving, M., Mohnike, K., Offiah, A. C., Okenfuss, E., Ozono, K., Raggio, C., Tofts, L., Kelly, D., Shediac, R., Pan, W., & Savarirayan, R. (2021). Lifetime impact of achondroplasia: Current evidence and perspectives on the natural history. *Bone*, *146*, 115872. https://doi.org/10.1016/j.bone.2021.115872

Horton, W. A., Hall, J. G., & Hecht, J. T. (2007). Achondroplasia. *The Lancet*, *370*(9582), 162–172. https://doi.org/10.1016/s0140-6736(07)61090-3

Ireland, P. J., McGill, J., Zankl, A., Ware, R. S., Pacey, V., Ault, J., Savarirayan, R., Sillence, D., Thompson, E. M., Townshend, S., & Johnston, L. M. (2011). Functional performance in young Australian children with achondroplasia. *Developmental Medicine and Child Neurology*, *53*(10), 944–950. https://doi.org/10.1111/j.1469-8749.2011.04050.x

Joffe, H., & Yardley, L. (2004). *Content and thematic analysis, in research methods for clinical and health psychology*. SAGE.

Kim, S. J., Agashe, M. V., Song, S. H., Choi, H. J., Lee, H., & Song, H. R. (2012). Comparison between upper and lower limb lengthening in patients with achondroplasia: A retrospective study. *Journal of Bone and Joint Surgery. British Volume (London)*, *94*(1), 128–133. https://doi.org/10.1302/0301-620x.94b1.27567

Kim, S. J., Balce, G. C., Agashe, M. V., Song, S. H., & Song, H. R. (2012). Is bilateral lower limb lengthening appropriate for achondroplasia?: Midterm analysis of the complications and quality of life. *Clinical Orthopaedics and Related Research*, *470*(2), 616–621. https://doi.org/10.1007/s11999-011-1983-y

Kitzinger, J. (1995). Qualitative Research. Introducing Focus Groups. *BMJ*, *311*(7000), 299–302. https://doi.org/10.1136/bmj.311.7000.299

Legeai-Mallet, L., & Savarirayan, R. (2020). Novel therapeutic approaches for the treatment of achondroplasia. *Bone*, *141*, 115579. https://doi.org/10.1016/j.bone.2020.115579

Leiva-Gea, A., Delgado-Rufino, F. B., Queipo-de-Llano, A., Mariscal-Lara, J., Lombardo-Torre, M., & Luna-Gonzalez, F. (2020). Staged upper and lower limb lengthening performing bilateral simultaneous surgery of the femur and tibia in achondroplastic patients. *Archives of Orthopaedic and Trauma Surgery*, *140*(11), 1665–1676. https://doi.org/10.1007/s00402-020-03360-3

Mahomed, N. N., Spellmann, M., & Goldberg, M. J. (1998). Functional health status of adults with achondroplasia. *American Journal of Medical Genetics*, *78*(1), 30–35. https://doi.org/10.1002/(sici)1096-8628(19980616)78:1<30::aid-ajmg7>3.0.co;2-p

Matsushita, M., Kitoh, H., Mishima, K., Yamashita, S., Haga, N., Fujiwara, S., Ozono, K., Kubota, T., Kitaoka, T., & Ishiguro, N. (2019). Physical, mental, and social problems of adolescent and adult patients with achondroplasia. *Calcified Tissue International*, *104*(4), 364–372. https://doi.org/10.1007/s00223-019-00518-z

Pauli, R. M. (2019). Achondroplasia: A comprehensive clinical review. *Orphanet Journal of Rare Diseases*, *14*(1), 1. https://doi.org/10.1186/s13023-018-0972-6

Pfeiffer, K. M., Brod, M., Smith, A., Gianettoni, J., Viuff, D., Ota, S., & Charlton, R. W. (2021a). Assessing physical symptoms, daily functioning, and well-being in children with achondroplasia. *American Journal of Medical Genetics. Part A*, *185*(1), 33–45. https://doi.org/10.1002/ajmg.a.61903

Pfeiffer, K. M., Brod, M., Smith, A., Gianettoni, J., Viuff, D., Ota, S., & Charlton, R. W. (2021b). Assessing the impacts of having a child with achondroplasia on parent well-being. *Quality of Life Research*, *30*(1), 203–215. https://doi.org/10.1007/s11136-020-02594-3

Savarirayan, R., Irving, M., Bacino, C. A., Bostwick, B., Charrow, J., Cormier-Daire, V., le Quan Sang, K. H., Dickson, P., Harmatz, P., Phillips, J., Owen, N., Cherukuri, A., Jayaram, K., Jeha, G. S., Larimore, K., Chan, M. L., Huntsman Labed, A., Day, J., & Hoover-Fong, J. (2019). C-type natriuretic peptide analogue therapy in children with achondroplasia. *The New England Journal of Medicine*, *381*(1), 25–35. https://doi.org/10.1056/NEJMoa1813446

Savarirayan, R., Tofts, L., Irving, M., Wilcox, W., Bacino, C. A., Hoover-Fong, J., Ullot Font, R., Harmatz, P., Rutsch, F., Bober, M. B., Polgreen, L. E., Ginebreda, I., Mohnike, K., Charrow, J., Hoernschemeyer, D., Ozono, K., Alanay, Y., Arundel, P., Kagami, S., ... Day, J. (2020). Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: A randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *Lancet*, *396*(10252), 684–692. https://doi.org/10.1016/s0140-6736(20)31541-5

Savarirayan, R., Ireland, P., Irving, M., Thompson, D., Alves, I., Baratela, W. A. R., Betts, J., Bober, M. B., Boero, S., Briddell, J., Campbell, J., Campeau, P. M., Carl-Innig, P., Cheung, M. S., Cobourne, M., Cormier-Daire, V., Deladure-Molla, M., Pino, M., Elphick, H., ... Fredwall, S. O. (2021). International consensus statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia. *Nature Reviews Endocrinology*, 1–17. https://doi.org/10.1038/s41574-021-00595-x. Online ahead of print.

Slomine, B. (2011). Functional Independence measure for children. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of*

clinical neuropsychology. Springer. https://doi.org/10.1007/978-0-387-79948-3_1607

Software, V. (2020). *MAXQDA*. VERBI GmbH.

Thompson, N. M., Hecht, J. T., Bohan, T. P., Kramer, L. A., Davidson, K., Brandt, M. E., & Fletcher, J. M. (1999). Neuroanatomic and neuropsychological outcome in school-age children with achondroplasia. *American Journal of Medical Genetics*, *88*(2), 145–153. https://doi.org/10.1002/(sici)1096-8628(19990416)88:2<145::aid-ajmg10>3.0.co;2-b

Varni, J. W., Seid, M., & Kurtin, P. S. (2001). PedsQL™4.0: Reliability and validity of the pediatric quality of life inventory™ version 4.0 generic core scales in healthy and patient populations. *Medical Care*, *39*, 800–812. https://doi.org/10.1097/00005650-200108000-00006

Wigg, K., Tofts, L., Benson, S., & Porter, M. (2016). The neuropsychological function of children with achondroplasia. *American Journal of Medical Genetics. Part A*, *170*(11), 2882–2888. https://doi.org/10.1002/ajmg.a.37779

Witt, S., Kolb, B., Bloemeke, J., Mohnike, K., Bullinger, M., & Quitmann, J. (2019). Quality of life of children with achondroplasia and their parents—A German cross-sectional study. *Orphanet Journal of Rare Diseases*, *14*(1), 194. https://doi.org/10.1186/s13023-019-1171-9

Witt, S., Rohenkohl, A., Bullinger, M., Sommer, R., Kahrs, S., Klingebiel, K. H., Klingebiel, R., & Quitmann, J. (2017). Understanding, assessing and improving health-related quality of life of young people with achondroplasia—A collaboration between a patient organization and academic medicine. *Pediatric Endocrinology Reviews*, *15*(Suppl 1), 109–118. https://doi.org/10.17458/per.vol15.2017.wrm.improvinghealthrelatedquality

Yonko, E. A., Emanuel, J. S., Carter, E. M., & Raggio, C. L. (2021). Quality of life in adults with achondroplasia in the United States. *American Journal of Medical Genetics Part A*, *185*(3), 695–701. https://doi.org/10.1002/ajmg.a.62018

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