Nye metoder: Innspill til metoder (forslag/metodevarsler/oppdrag)

Alle har anledning til å komme med tilleggsopplysninger til en metode som er foreslått for nasjonal metodevurdering. Det er ønskelig at innspill kommer inn så tidlig som mulig i prosessen, fortrinnsvis før behandling i Bestillerforum RHF.

Bruk dette skjemaet for å gi innspill til forslag, metodevarsler og oppdrag. På nyemetoder.no vil nye forslag/metodevarsler ha statusen «Forslag mottatt/åpent for innspill» før behandling i Bestillerforum RHF. Utfylt skjema sendes nyemetoder@helse-sorost.no.

NB: **Punkt 1-3 og 11 fylles ut av alle.** Punkt 4-9 fylles ut avhengig av rolle og kjennskap til metoden.

Jeg er klar over at skjemaet vil bli publisert i sin helhet på nyemetoder.no (kryss av): ☒
Har du informasjon du mener ikke kan offentliggjøres, ta kontakt med sekretariatet før innsending.

Jeg har fylt ut punkt 11 nedenfor «Interesser og eventuelle interessekonflikter» (kryss av): ☒

1.Hvilken metode gjelder innspillet?	
Metodens ID nummer*:	ID2021_045
Metodens tittel:	Vosoritide til behandling av akondroplasi

*ID-nummer finner du på metodesiden på nyemetoder.no og har formen ID2020_XXX

2. Opplysninger om den som gir innspill	
Navn	BioMarin via Mattias Janzén, Nordic Country Manager
Eventuell organisasjon/arbeidsplass	BioMarin Pharmaceutical Inc.
Kontaktinformasjon (e-post / telefon)	mattias.janzen@bmrn.com / +46 703777970

3. Oppsummert innspill til metoden (besvares av alle)
Achondroplasia (ACH) is a rare genetic disorder that affects approximately 1:25 000 people in Norway, in which a mutation in the FGFR3 gene causes impaired endochondral bone formation in the long bones, ribs and vertebrae. Due to this altered bone formation patients experience disproportionate growth, extreme short stature, and life-long impairments in quality of life (QoL) and activities of daily living (ADL).[1] Patients with achondroplasia experience a substantially higher risk of death in their first year of life, primarily due to foramen magnum stenosis and cervicomedullary compression, and invasive surgery is often required to mitigate this risk[2]. For achondroplasia patients who survive

[1] Pauli RM. Achondroplasia: a comprehensive clinical review. Orphanet Journal of Rare Diseases 2019;14:1.
[2] Wynn J, King TM, Gambello MJ, et al. Mortality in achondroplasia study: a 42-year follow-up. Am J Med Genet A 2007;143a:2502-11. Hecht JT, Francomano CA, Horton WA, et al. Mortality in achondroplasia. American journal of human genetics 1987;41:454-464.

into adulthood, the average life expectancy is approximately 10 to 15 years shorter than the general population, and mortality associated with heart disease is estimated to be more than 10 times greater amongst young adults with achondroplasia compared with average stature individuals[2]. Throughout their lives, patients with achondroplasia experience serious and debilitating symptoms and comorbidities which progress and evolve over time; these frequently include orthopaedic, neurological, respiratory, ears, nose and throat (ENT), and dental problems.[3] These physical challenges often cause chronic pain and impaired mobility which impact ADL, and as a result, patients with achondroplasia frequently experience impaired school functioning, restricted employment options, increased risk of unemployment, and impaired productivity compared with unaffected individuals[4].

The cross-sectional study from cohort of Norwegian adults with ACH had overall low physical fitness levels, with achievements within a wide range, compared to Norwegian population reference values. There were no gender differences within the ACH study sample, except for VO2 peak, where men performed better. There was a high correlation between cardiorespiratory fitness (VO2 peak) and the – minute walking test (6MWT)[5].

Another population-based study on Norwegian community-dwelling adults with genetically confirmed achondroplasia shows symptomatic spinal stenosis (SSS) was highly prevalent in Norwegian adults with achondroplasia, with symptom onset at young age, and multiple spinal levels affected. The presence of SSS was associated with reduced walking distance, activity limitations, and more pain[6].

Vosoritide is an analogue of CNP, which down-regulates aberrant FGFR3 signalling in chondrocytes and helps to restore normal physiology of bone growth. Vosoritide is a stabilised version of naturally occurring CNP engineered to retain the activity and specificity of the naturally occurring peptide on bone growth but resist degradation and have a longer half-life. It was developed to counteract the effects caused by the activating FGFR3 gene mutation in ACH by initiating intracellular signals that ultimately inhibit the overactive FGFR3 pathway. Vosoritide has a robust global clinical development programme. It consists of an observational baseline growth study (190-901), four phase II studies, (the 111-202 study and its extension study 190-205, the study 190-206 and its extension 190-208 study) and the pivotal Phase III study 190-301 and its extension 190-302. In Phase II (111-202) and Phase III (111-301) trials, achondroplasia patients aged 2–18 years treated with vosoritide showed significant improvements in height outcomes as compared with untreated natural history populations (111-202) and placebo-treated patients (111-301). Vosoritide has shown a favourable tolerability and safety profile across all trials, with low incidences of treatment-related serious adverse events (SAEs), and no trial discontinuations due to adverse events (AEs) reported[7].

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;18:227-40.

[3] Pauli RM. Achondroplasia: a comprehensive clinical review. Orphanet Journal of Rare Diseases 2019;14:1.
Hunter AG, Bankier A, Rogers JG, et al. Medical complications of achondroplasia: a multicentre patient review. J Med Genet 1998;35:705-12.

[4] BioMarin. 111-501 Observational Study Report. 2020(O).
Roizen N, Ekwo E, Gosselink C. Comparison of education and occupation of adults with achondroplasia with same-sex sibs. American Journal of Medical Genetics 1990;35:257-260.
Pan W G-NE, Lifetime impact of achondroplasia on health-related quality of life (HR-QoL) and healthcare resource use: Interim results from a multinational study. ACMG Annual Clinical Genetics Meeting. San Antonia, TX, USA, 2020.

[5] de Vries OM, Johansen H, Fredwall SO. Physical fitness and activity level in Norwegian adults with achondroplasia. Am J Med Genet Part A. 2020; 1–10.

[6] Fredwall et al. Orphanet Journal of Rare Diseases (2020) 15:123 https://doi.org/10.1186/s13023-020-01397-6

[7] Savarirayan R, Irving M, Bacino CA, et al. C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia. N Engl J Med 2019;381:25-35.
BioMarin. Interim Clinical Study Report: 111-206 and 111-208. 2020(L).
BioMarin. 111-302 Clinical Study Report. 2020(P).

There are no licensed treatments currently available for the achondroplasia for underling cause of the disease. Limb lengthening surgery is quite widely used procedure in Norway in approximately 50% of children. Achondroplasia patients are frequently monitored, especially during the first years of their life and receive symptomatic treatment in order to manage their complications, rather than treatment of the underlying disease.

Since achondroplasia is a very rare disease in Norway with limited patient population due to epidemiology and because treatment duration is limited to when epiphyses close, assessment route should be focused on relative effectiveness and budget impact. As a genetic disease which is easily identified and diagnosed at birth, budget impact can be calculated with relative precision.

The below outcomes should be taken into account:

- Clinical efficacy relative to comparator (standard of care) measuring Annualized Growth Velocity (AGV) and height Z-score, which were primary and key secondary endpoints respectively in the vosoritide clinical trials. These endpoints are possible to measure in the follow up time of the clinical trials and they directly link to the underlying disease manifestation (disproportionate short stature. Improvements in these endpoints have been correlated with improvements in health-related quality of life of patients and expert opinion has confirmed that they impact on the daily living activities and social functioning of the patients.
- Safety profile
- Budget impact
- Severity of disease (lifelong disease, no other disease modifying treatment)
- Other (social and education consequences of impact of achondroplasia on ADL)

In summary the lifelong consequences of achondroplasia require long-term follow up and therefore there is a high degree of uncertainty in projecting the impact of treatment on the lifelong disease. Furthermore, the disease has significant economic and social impacts which fall outside of the healthcare system including on education, employment and caregivers. These impacts are not easily accounted for in cost-utility analysis.

Patients with achondroplasia have to make significant changes in their mindset to cope with living with their condition as such HRQoL/health utilities could be challenging to capture due to the 'disability paradox', where patients coping mechanism predominate responses.

Savarirayan R, Tofts L, Irving M, et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. The Lancet 2020;396:684-692.
National Library of Medicine. A Study to Evaluate Long-Term Safety, Tolerability, & Efficacy of BMN 111 in Children With Achondroplasia. Available at: https://clinicaltrials.gov/ct2/show/NCT02724228. Last accessed: December 2020.

Nærmere informasjon om metoden og innspill til PICO*

*PICO er et verktøy for å formulere presise problemstillinger i metodevurderingsarbeid. PICO er en forkortelse for Population/Problem – Intervention – Comparison – Outcome. PICO brukes til å presisere hvilken populasjon/problem som skal studeres, hvilke(t) tiltak (metode/behandling) som skal vurderes, hvilket tiltak det er naturlig å sammenligne med, og hvilke utfall/endepunkter det å er relevant å måle/vurdere. PICO er viktig for planlegging og gjennomføring av en metodevurdering.

4. Kjenner du til om metoden er i bruk i Norge i dag?
Er metoden i bruk utenom kliniske studier i dag: no, only in clinical trials Fra hvilket tidspunkt har den vært i bruk: not applicable Hvor er eventuelt metoden i bruk: no use outside clinical trials

5. Hvilken pasientgruppe i den norske spesialisthelsetjenesten er metoden aktuell for? (PICO)
Achondroplasia (ACH) is a rare genetic disease and the most common form of human dwarfism. ACH is characterized by failure of normal conversion of cartilage into bone, which results in disproportionate short stature. This condition is caused by a mutation in the Fibroblast Growth Factor Receptor 3 (FGFR3), a negative regulator of bone growth. Disproportionate growth between endochondral bone and underlying organs leads to a number of orthopaedic, neurological, respiratory, ear, nose, and throat (ENT) issues and increased mortality. Adults reach an average height of 131±5.6 cm (men) and 124±5.9 cm (women). The condition is autosomal dominant; however, most cases are not inherited. More than 80% of children with achondroplasia have parents of average stature and have the condition as the result of a spontaneous gene mutation.[8] Patients who have inherited the defective gene from both parents are the most severely affected and normally die around birth or a few months afterwards. In patients with only one defective FGFR3 gene, achondroplasia causes long-term disability and may result in a shorter life span due to cardiopulmonary complications. Beyond disproportionate short stature, people with achondroplasia can experience serious health complications, including respiratory problems, cardiovascular disease, chronic pain, foramen magnum compression, sleep apnea, bowed legs, mid-face hypoplasia, permanent sway of the lower back, spinal stenosis, recurrent ear infections and obesity. Some of these complications can result in invasive surgeries such as spinal cord decompression and straightening of bowed legs.

[8] Biomarin. Vosoritide (BMN 111) for Achondroplasia. 2020. Available from: https://www.biomarin.com/products/pipeline/bmn-111/, accessed on the 21/12/2020
Orphanet. Achondroplasia. 2019. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=15, accessed on the 21/12/2020

Indication (label): Anticipated indication is the treatment of achondroplasia for children. A more precise indication should be expected closer to the EMA approval.

The potential eligible population to be treated with vosoritide in Norway.

The potential eligible population to be treated with vosoritide should be clearly estimated. Based on information from the "Statistics Norway" website,[9] the total number of live births in 2019 in Norway was 54,495. Applying the estimated frequency (assumed prevalence of 1:25000), would suggest that there could be approximately 2-3 people born in Norway with achondroplasia per year. Multiplying this number of cases by 13 years (from the age of 5 till the age of 18, point where patients' growth plates close), the maximum number of eligible patients for vosoritide in Norway could be around 26-39.

6. Er du kjent med behandlingsalternativer til denne metoden og hvordan disse fungerer for pasientgruppen i dag? (PICO)

There are no licensed treatments currently available for the achondroplasia for underling cause of the disease. Limb lengthening surgery is quite widely used procedure in Norway in approximately 50% of children. Achondroplasia patients are frequently monitored, especially during the first years of their life and receive symptomatic treatment in order to manage their complications, rather than treatment of the underlying disease.

7. Har du innspill til hva som vil være viktig for pasienter som er aktuelle for behandling med metoden? (PICO)

Achondroplasia is a rare and severe disease and has a limited patient population in Norway due to epidemiology and because treatment duration is limited to when epiphyses close. No alternative licensed pharmacological therapies are available to treat this disease. As such, assessment route should be focused on relative effectiveness and budget impact versus standard of care. As a genetic disease which is easily identified and diagnosed at birth, budget impact can be calculated with relative precision.

The below outcomes should be taken into account:

- Clinical efficacy relative to comparator (standard of care) measuring Annualized Growth Velocity (AGV) and height Z-score, which were primary and key secondary endpoints respectively in the vosoritide clinical trials. These endpoints are possible to measure in the follow up time of the clinical trials and they directly link to the

[9] Live Births Norway, 2019, Statbank, https://www.ssb.no/en/statbank/table/04231/tableViewLayout1/, accessed on the 22/12/2020

underlying disease manifestation (disproportionate short stature. Improvements in these endpoints have been correlated with improvements in health-related quality of life of patients and expert opinion has confirmed that they impact on the daily living activities and social functioning of the patients.

- Safety profile
- Budget impact
- Severity of disease (lifelong disease, no other disease modifying treatment)
- Other (social and education consequences of impact of achondroplasia on Activities of Daily Life)

The lifelong consequences of achondroplasia require long-term follow up and therefore there is a high degree of uncertainty in projecting the impact of treatment on the lifelong disease. Furthermore, the disease has significant economic and social impacts which fall outside of the healthcare system including on education, employment and caregivers. These impacts are not easily accounted for in cost-utility analysis.

8. Spesielt for medisinsk utstyr (besvares av leverandør): CE-merking

Foreligger det CE-merking for bruksområdet som beskrives i metoden? I så fall angi type og tidspunkt: Not applicable

9. Spesielt for legemidler (besvares av leverandør): Markedsføringstillatelse (MT)

Har legemiddelet MT for indikasjonen som omfattes av metoden? Angi i så fall tidspunkt eller ventet tidspunkt for MT: EMA estimated approval date is August 2021 (subject to change)

10. Andre kommentarer

11. Interesser og eventuelle interessekonflikter

Beskriv dine relasjoner eller aktiviteter som kan påvirke, påvirkes av eller oppfattes av andre å ha betydning for den videre håndteringen av metoden som det gis innspill på (for eksempel: økonomiske interesser i saken, oppdrag eller andre bindinger).

Beskriv kortfattet: Mattias Janzen is an employee of BioMarin Pharmaceutical Inc., manufacturer and authorization holder for Voxzogo (vosoritide).