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 (Voxzogo)

*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, Director Nordic Country Manager
Eventuell organisasjon/arbeidsplass	BioMarin Pharmaceutical Inc.
Kontaktinformasjon (e-post / telefon)	Mattias.janzen@bmrn.com / +46 703 777 970

3. Oppsummert innspill til metoden (besvares av alle)

Notification of a suspected mistake in NoMA's estimation of absolute shortfall in achondroplasia

When reviewing the absolute shortfall presented in NoMA's evaluation report for Voxzogo, BioMarin (the Company) found the presented absolute shortfall to be surprisingly modest, in the light of the substantial burden of disease and the severity of the condition described in the literature.

Looking at the details of NoMA's calculation, we have found indications that NoMA accidentally has estimated the absolute shortfall without accounting for the many medical complications and comorbidities that achondroplasia patients suffer from, complications

that are associated with a substantial negative impact on the quality of life for achondroplasia patients.

NoMA concluded (page 21, NoMA's evaluation report) that the absolute shortfall associated with achondroplasia was 11.6 QALYs when considering a baseline age of 7 years, and 12.0 QALYs when considering a baseline age of 2 years. In line with the protocol, the absolute shortfall was calculated as the difference in remaining lifetime QALYs between:

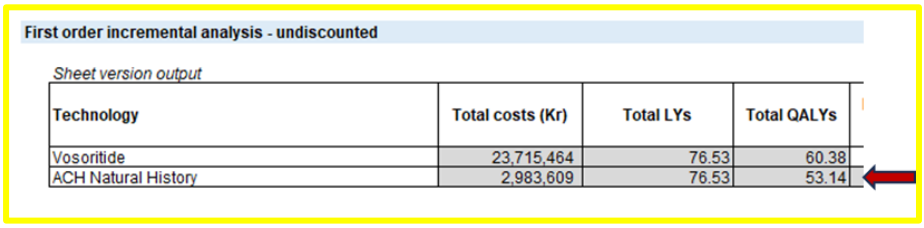
- a healthy individual of age x, and
- an untreated (i.e., current standard of care) individual of age x with achondroplasia,
- where x is the mean baseline age of the evaluated population.

In NoMA's calculation, the remaining lifetime QALYs were sourced as follows:

- a healthy individual: from NoMA's QALE table
- an untreated individual with achondroplasia: from the undiscounted QALY outcome for the comparator arm in the cost-effectiveness model

For an untreated ACH patient of 7 and 2 years, respectively, NoMA reported that the remaining lifetime QALYs are 53.0 and 57.2, respectively. These numbers match the total QALYs resulting from the comparator arm in the cost-effectiveness model, using the model settings according to the NoMA base case (Figure 1).

Figure 1. Undiscounted results of the cost-effectiveness model, using the NoMA base case settings (age at baseline 2-12 years = 7 years on average)



First order incremental analysis - undiscounted

Sheet version output

Technology	Total costs (Kr)	Total LYs	Total QALYs
Vosoritide	23,715,464	76.53	60.38
ACH Natural History	2,983,609	76.53	53.14

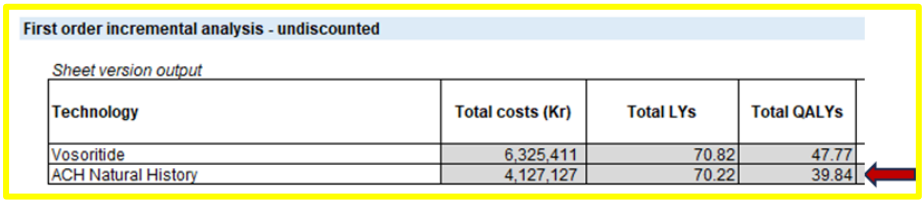
However - and here is where the misunderstanding may have occurred – since FINOSE did not include any treatment effect on reducing the incidence rates of achondroplasia-related complications, they excluded complications from the analysis in their base case. The way the cost-effectiveness model is programmed is that excluding complications causes an exclusion of <u>all</u> aspects of achondroplasia complications from the analysis. Unfortunately, this means that the cost-effectiveness model then does not account for the disutility associated with achondroplasia-related complications since it's not only the VOXZOGO effect on complications that is excluded, it's also the disutility from complications. From a cost-effectiveness perspective, this approach was considered unproblematic since any effects that are equal between the two model arms equals out and can be omitted. However, when the outcome of the cost-effectiveness model was used by NoMA to estimate the absolute shortfall of achondroplasia, it had the unfortunate effect that **the estimate therefore did not account for the impact of achondroplasia-related complications on the severity of disease.**

In the Company's view, this must be considered a mistake. All available evidence as well as testimonials from patients and clinical experts strongly support that the medical complications and comorbidities associated with achondroplasia have a profound impact

on the patients' quality-of-life and constitute a fundamental part of the burden of disease in achondroplasia.

In order to estimate the absolute shortfall of achondroplasia **including** the burden of complications, the Company has revisited the absolute shortfall calculations and run the cost-effectiveness model set to include complications. With all other settings identical to the NoMA base case, the resulting total lifetime QALYs in the comparator arm were 39.8 QALYs (Figure 2).

Figure 2. Undiscounted results of the cost-effectiveness model, using the NoMA base case settings (age at baseline 2-12 years = 7 years on average)



First order incremental analysis - undiscounted

Sheet version output

Technology	Total costs (Kr)	Total LYs	Total QALYs
Vosoritide	6,325,411	70.82	47.77
ACH Natural History	4,127,127	70.22	39.84

Similar analyses were undertaken for baseline populations of 2 and 0 years of age, respectively. The resulting remaining lifetime QALYs and associated absolute shortfall estimates are presented in Table 1.

Table 1. Absolute shortfall of achondroplasia including the impact of medical complications and comorbidities, at different baseline ages

Baseline Age	**Undiscounted Lifetime QALYs in CE model [1]**	**Healthy lifetime QALYs from baseline age [2]**	**Absolute Shortfall (Lifetime QALYs lost due to disease)**
2-12 (mean 7)	39.8	64.6	**24.8**
2	41.0	69.2	**28.2**
0	41.3	70.7	**29.4**

[1] *Source: Total resulting QALYs in the comparator arm of the VOXZOGO cost-effectiveness model analysed with NoMA base case settings and including complications in the analysis.*

[2] *Source: Metodevurdering av enkeltlegemiddel finansiert i spesialisthelsetjenesten Vosoritid (Voxzogo) ID2021_045, page 21 and 30.*

The Company therefore asks the involved Norwegian stakeholders to base the assessment of the severity of disease on the estimations presented here which importantly includes the impact of the achondroplasia-related complications, so that decisions made will be done with respect to the correctly assessed burden of disease suffered by achondroplasia patients.

The Company would also like to challenge NoMA's decision to use the starting age of 2-12 years old, rather than 2 years old as seen in the Company base case. While in the short-term (the first 1-2 years after vosoritide becomes available), it is expected that patients of different ages within the prevalent cohort will start treatment, from Y3 onwards, only new patients turning 2 years old are expected to start treatment each year since

achondroplasia is typically diagnosed at birth. Therefore, patients starting at 2-years old will be the primary population for vosoritide treatment over the long-term.

Considering this point, it is critical that the value of vosoritide treatment for the younger population is appropriately captured in the economic model. By focusing on the initial older, prevalent population for decision-making process, the Company believes NoMA are unfairly penalising the youngest patients (the primary population) who are expected to derive the highest benefit from vosoritide treatment over their lifetimes.

Furthermore, achondroplasia is a congenital disorder which impacts the life of the patients already from birth. As such, there is no debuting age that varies between patients. Therefore, in the assessment of the severity of disease/absolute shortfall, the Company believes that such an assessment needs to be done from birth in order to capture the full absolute shortfall associated with achondroplasia, or at the least from the age where vosoritide treatment may be initiated according to the approved indication. Therefore, **the Company strongly believes that the absolute shortfall starting from either 0 or 2 years of age is the relevant number for the assessment of the severity of the condition.**

Please note, the PBAC in Australia (currently the only HTA body to have completed and published a health economic report for vosoritide), agreed that the starting age in the cost-effectiveness model should be focused on the youngest age cohort. In fact, the PBAC allowed a starting age from zero for all patients in the economic model. Please see the extract from the 2022 Public Summary Document published by PBAC:

'… The PBAC recalled that it had considered an age agnostic listing appropriate (see paragraph 7.8) and noted that if the starting age was reduced to zero in the model then the ICER reduced to $155,000 to < $255,000 per QALY gained with a 3% discount rate.'

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: Fra hvilket tidspunkt har den vært i bruk: Hvor er eventuelt metoden i bruk:

5. Hvilken pasientgruppe i den norske spesialisthelsetjenesten er metoden aktuell for? (PICO)
Beskriv kortfattet:

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

7. Har du innspill til hva som vil være viktig for pasienter som er aktuelle for behandling med metoden? (PICO)
Hva kan oppfattes som en fordel for pasienter og brukere med denne metoden sammenlignet med aktuelle alternativer? Hvilke endepunkter/resultater av behandlingen er det aktuelt å måle? Beskriv kortfattet:

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:

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:

10. Andre kommentarer
This was sent in to NoMA via email 2023-12-13 but to do it official and to be published at Nye Metoders website we submit again via this innspillskjema as requested.

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