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,Director Nordic Country Manager
Eventuell organisasjon/arbeidsplass	BioMarin International Limited
Kontaktinformasjon (e-post / telefon)	mattias.janzen@bmrn.com / +46 703777970

3. Oppsummert innspill til metoden (besvares av alle)

Purpose of the document

Our objective for this document is to appeal the previous decision of Bestillerforums and explain why a cost utility analysis (CUA) is not an appropriate economic method for assessing vosoritide. We will provide a brief background of achondroplasia, the rarity, the significant burden and the unmet need of the disease, and an overview of the clinical evidence of vosoritide. We suggest the appropriate assessment for vosoritide should be based on the clinical evidence on efficacy and safety and budget impact of introducing vosoritide into Norway. 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

- 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

Disease description

Achondroplasia is a rare, progressive, autosomal dominant genetic disease which causes the inhibition of endochondral bone growth, resulting in extreme short stature, abnormal bone growth and an evolving range of serious and debilitating symptoms and complications over a lifetime reduced life expectancy, and life-long impairments to quality of life (QoL) and activities of daily living (ADL) [1-4]. Achondroplasia is most frequently diagnosed before or shortly after birth based on clinical characteristics and is typically confirmed and differentiated from other forms of dwarfism using genetic testing [1]

Epidemiology

Achondroplasia affects approximately 250,000 people worldwide with an estimated incidence at about 1/25,000 live births [5]. In Norway based on the information from the "Statistics Norway" website, the total number of live births in 2020 in Norway was 52,979 [6]. Applying the estimated birth prevalence to the live births of 2020, approximately 2 new achondroplasia patients are expected to be born every year.

Symptoms and burden of disease

Due to restricted growth, patients with achondroplasia experience extreme short stature (in general, 6 to 7 Standard Deviations (SDS) below the average of unaffected individuals) and disproportionality, which substantially reduces their mobility and reach [7]. In patients with achondroplasia, the final adult height is approximately 125.0 cm in females and 130.0 cm in males [1]. Furthermore, patients with achondroplasia experience a range of lifelong, serious, and debilitating symptoms and complications which progress and evolve over time; these frequently include orthopaedic; neurological; respiratory; ear, nose and throat; and dental problems [1]. A more comprehensive list of common complications by age can be seen in Figure 1 below.

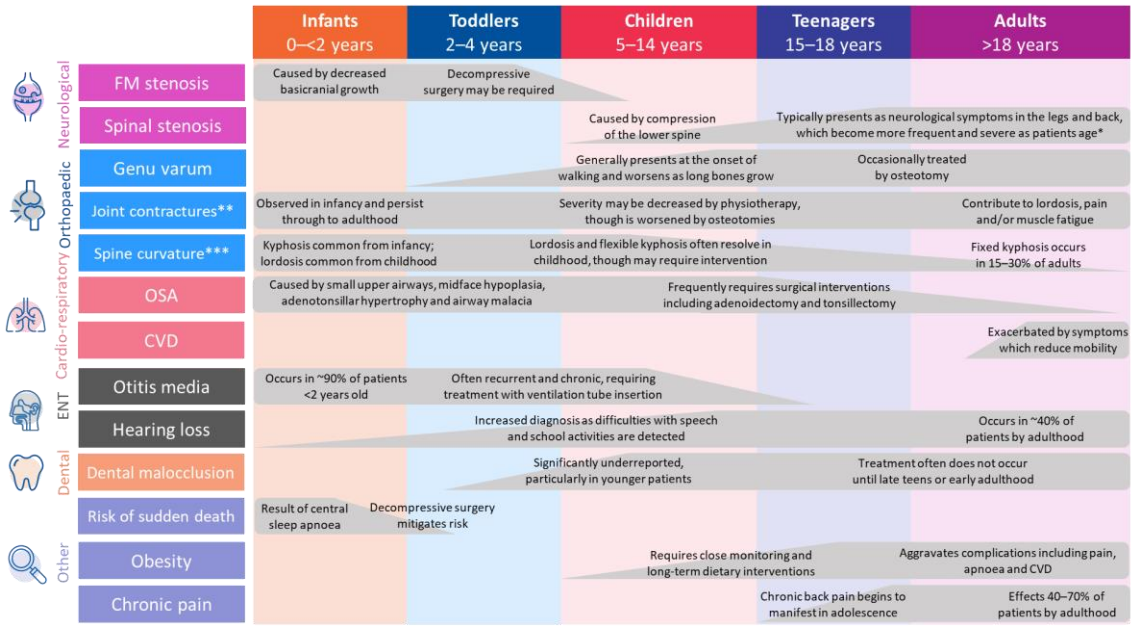
Patients with achondroplasia are often unable to independently conduct activities of daily living such as self-care and hygiene tasks, largely related to impaired mobility and reach [8]. Many patients also face chronic pain because of their symptoms, which further impairs functional independence and places a burden on everyday life .A population-based study on Norwegian community-dwelling adults with genetically confirmed achondroplasia showed that 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 [9].

Quality of life (QoL) among the achondroplasia population, including in paediatric and adult patients, is substantially reduced and compared with average stature individuals [10-13], patients with achondroplasia frequently experience impaired school functioning, restricted employment options, increased risk of unemployment, and impaired productivity [14, 15].

Furthermore, achondroplasia patients experience a substantially higher risk of death in their first year of life compared with the general population, primarily due to foramen magnum stenosis and cervicomedullary compression, and invasive surgery is often required to mitigate this risk

[16-18]. For achondroplasia patients who survive into adulthood, the average life expectancy is approximately 10 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 [16, 17].

Figure 1: Onset of common secondary complications of achondroplasia by age



Source: Pauli et al. 2019 [1]

Current management focuses on alleviating symptoms and complications. Patients rely on invasive surgical procedures, many of which are associated with a high risk of complications, and medications to manage the evolving range of symptoms and complications that they experience throughout their lives. Some patients opt to undergo limb lengthening surgical procedures, however they involve very long hospital stays, expose patients to numerous risks of post-operative complications, are tiring for patients and carers and are not solving the underlying cause of achondroplasia and don't address the complications related to it.

Vosoritide

Vosoritide is the first and only pharmacotherapeutic treatment that directly addresses the underlying cause of achondroplasia.

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 achondroplasia by initiating intracellular signals that ultimately inhibit the overactive FGFR3 pathway.

Vosoritide was granted orphan designation (EU/3/12/1094) in 2013 [19] and was licensed by the EMA on the 26th of August 2021 as a therapy for patients with achondroplasia, aged 2 years and older whose epiphyses are not yet closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing [20]. Vosoritide has been studied in an extensive and robust clinical development programme and has shown clinically and statistically significant efficacy data and a good safety and tolerability profile in paediatric patients.

Vosoritide clinical programme

Despite the rarity of achondroplasia and the limitations accompanied, the efficacy and safety of vosoritide has been investigated within an extensive and robust clinical development programme, which includes Phase II and Phase III placebo-controlled, randomised controlled trials (RCTs) and extension studies, as well as non-interventional natural history studies conducted in patients aged 0–18 years. Available results in patients aged 2–18 years show that vosoritide consistently achieved clinically meaningful sustained height outcomes.

Pivotal Phase III studies (111-301 and extension 111-302)

Design of studies

In the pivotal randomised, double-blind, placebo-controlled 52-week phase III study 111-301, patients were randomised to two groups, either vosoritide (n = 60) or placebo (n = 61) [21]. The vosoritide dose of 15 µg/kg was administered subcutaneously once daily. Prior to randomisation, all patients participated for at least 6 months in an observational study (Study 111-901) [22].

This recorded standing height at baseline and other growth assessments prior to treatment. Patients who had undergone limb-lengthening surgery in the 18 months prior or were planning limb-lengthening surgery during the study period were excluded. The study included a 52-week placebo-controlled treatment phase followed by an open-label extension study in which all patients received vosoritide (111-302) [23].

Results

The primary efficacy endpoint was the change from baseline in Annualised Growth Velocity (AGV) at week 52 compared to placebo. At 52 weeks, the mean incremental AGV was 1.57cm/year (95% CI: [1.22; 1.93], p <0.0001) in favour of vosoritide. The secondary outcome, Height Z-score (number of standard deviations from the mean), which is a relevant patient outcome, has also shown positive results at 52 weeks. The difference in the mean least squares variation between the two groups compared to inclusion was statistically significant and in favour of the vosoritide group: 0.28 SDS (95% CI: [0.17; 0.39], p <0, 0001) [21].

The result of 2 years of follow up in the phase III study (111-301) and its extension (111-302) was recently published by Savarirayan et al, 2021, confirming that the benefits of vosoritide has been sustained in the second year of treatment, without new safety concerns or deterioration in body proportions [23].

Long term phase II studies (111-202 and 111-205)

Design of studies

Patients with achondroplasia were treated with 15 µg/kg/day of vosoritide in an open-label dose escalation study (Study 111-202) [24] and in a long-term extension study (Study 111-205) [25]. Patient data from observational studies were collected to characterise the natural history of achondroplasia. Data on the height of untreated patients with achondroplasia-adjusted for age and sex were used as a historical control variable to assess the effect on height after up to 5 years of vosoritide treatment.

Results

The cumulative incremental growth for the patients who received vosoritide versus historical control was 9.08 cm [26]. In the extension study 111-205, improvement in AGV was reported in

all cohorts persisting up to 5 years, with mean (SD) variations in AGV at 48 months and at 60 months in all the cohorts compared to baseline being 1.65 (1.14) and 1.35 (1.07) cm / year, respectively, and statistically significant (p <0.0001). The maintenance of effect on AGV over 60 months with vosoritide is observed in the context of a natural downward trend in growth velocity of approximately 0.2 cm/year in children with achondroplasia of this age group [25].

Justification for not undertaking a CUA for vosoritide

In certain cases, a cost utility analysis cannot effectively evaluate the benefit of a treatment; this is especially the case with novel therapies in the space of rare diseases. Vosoritide is an innovative treatment which addresses the underlying cause of achondroplasia, a rare disease with few patients in Norway. As such, there is sufficient justification to seek an exemption from a CUA. The reasons are stated below:

- CUA is not an appropriate evaluation method due in part to the rarity of the disease and the nature of achondroplasia where there is uncertainty in long term outcomes which are not possible to address with clinical trial data. Specifically:
    - Treatment with vosoritide is approved to start from the age of 2 years and stops when epiphysis growth plates close for the patient. It is only possible to treat patients while they still have their epiphyses open. Consequently, the duration of treatment with vosoritide is connected to the period of a patient's life generally from 2 years up to a maximum of 18 years of age. However, achondroplasia is a lifelong disease with a range of complications occurring throughout the patient's life. Therefore, in a cost utility analysis there will be an upfront cost associated with drug acquisition that will be incurred in the early years until growth plates close but the benefits of treatment with vosoritide will accrue over the lifetime of the patient.
    - Complications are key outcomes that will impact QALYs but have not been measured in the trial program due to variation in time when they will occur in a patient's life (many occur later in life and beyond the time frame of the trials). Consequently, the trial used objective measures such as growth to measure efficacy, which must be indirectly mapped to QALYs and this creates uncertainty.
    - Achondroplasia is a rare disease, with potentially severe complications that start early in life and progress throughout patients' lives. These complications can vary to each achondroplasia patient increasing uncertainty for group assessment, they develop throughout the lifetime and require multiple treatments including surgeries of varying degrees of invasiveness. These ultimately affect the QoL and can even reduce the overall lifespan. A cost-utility analysis therefore cannot fully capture or represent the benefits of treatment when the patient is treated in their younger years as is the case with vosoritide. This would potentially lead to an underestimation of the potential benefit on cost savings and avoidance of surgeries in later age and possible complications, a number of clinical complications and effect on the QoL, as discussed in the clinical section.

- The clinical experience component for the patient population of achondroplasia cannot be fully captured in a cost utility analysis to the same extent as it can in more common diseases.

- Current standard of care is focused on managing the range of symptoms and complications that each patient presents with. A comparison therefore between vosoritide and a single treatment is not practical or possible in a cost-utility analysis.

- The calculation of QALYs would be based on the primary outcomes of the vosoritide clinical programme. As vosoritide is the first pharmacotherapeutic treatment to be licensed in achondroplasia in the European Union, the long-term evidence base is still being developed. This will mean the true QALYs will be under-represented within a cost utility analysis.

There is conflicting or lack of evidence regarding the impact achondroplasia has across different domains of QoL which can only be over the lifetime of achondroplasia patients, based on clinical opinion. As a result of the inherited nature of the disease, estimations of QALYs will be inherent with uncertainty due to clinical assumptions on complications / disutilities and the inherent disability paradox in capturing these utilities [27] .

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 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:
The treatment is fully reimbursed in Germany and is also available through early access programmes in France and Portugal. Furthermore, vosoritide is available through either individual funding on Name Patient Basis in several countries including Switzerland, Austria, Luxembourg and Israel.

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

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

The potential eligible population to be treated with vosoritide should be based on the EMA approved indication for the treatment of achondroplasia in patients 2 years of age and older

whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing [20].

According to the calculations based on information from the epidemiological data (1:25,000 live births, as described in Section 3), 2 new patients are expected to be born in Norway with achondroplasia every year and 30-40 patients would be eligible candidates for vosoritide treatment, aged 2 to the time epiphyses close, according to the EMA indication.

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

Beskriv kortfattet:

Current management focuses only on alleviating symptoms and complications. Patients rely on invasive surgical procedures, many of which are associated with a high risk of complications, and medications to manage the evolving range of symptoms and complications that they experience throughout their lives. Some patients opt to undergo limb lengthening surgical procedures, however, these procedures inolve a lot of risks without addressing the underlying cause of disease

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:

The assessment route should be focused on clinical effectiveness and budget impact of introducing vosoritide to Norway. 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 considered:

- 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 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:
Yes, granted on 26 August 2021

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, manufacturer and authorization holder for Voxzogo (vosoritide).

References

1. Pauli, R.M., *Achondroplasia: a comprehensive clinical review.* Orphanet Journal of Rare Diseases, 2019. **14**(1): p. 1.
2. Ireland, P.J., et al., *Optimal management of complications associated with achondroplasia.* The application of clinical genetics, 2014. **7**: p. 117-125.
3. Shirley, E.D. and M.C. Ain, *Achondroplasia: manifestations and treatment.* The Journal of the American Academy of Orthopaedic Surgeons, 2009. **17**(4): p. 231-241.
4. Merker, A., et al., *Growth in achondroplasia: Development of height, weight, head circumference, and body mass index in a European cohort.* Am J Med Genet A, 2018. **176**(8): p. 1723-1734.
5. *Orphanet. Achondroplasia. Available at: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=15. Last accessed: October 2020.*
6. Norway, S. *Live Births Norway*. [cited 2022.
7. Chilbule, S.K., V. Dutt, and V. Madhuri, *Limb lengthening in achondroplasia.* Indian journal of orthopaedics, 2016. **50**(4): p. 397-405.
8. Alade, Y., et al., *Cross-sectional assessment of pain and physical function in skeletal dysplasia patients.* Clin Genet, 2013. **84**(3): p. 237-43.
9. Fredwall, S.O., et al., *High prevalence of symptomatic spinal stenosis in Norwegian adults with achondroplasia: a population-based study.* Orphanet Journal of Rare Diseases, 2020. **15**(1): p. 123.
10. Gollust, S.E., et al., *Living with achondroplasia in an average-sized world: An assessment of quality of life.* American Journal of Medical Genetics Part A, 2003. **120A**(4): p. 447-458.
11. Lorne, H., C.J. Newman, and S. Unger, *Is height important for quality of life in children with skeletal dysplasias?* Eur J Med Genet, 2020. **63**(4): p. 103816.
12. Witt, S., et al., *Quality of life of children with achondroplasia and their parents - a German cross-sectional study.* Orphanet J Rare Dis, 2019. **14**(1): p. 194.
13. Witt, S., et al., *Understanding, Assessing and Improving Health-Related Quality of Life of Young People with Achondroplasia- A Collaboration between a Patient Organization and Academic Medicine.* Pediatr Endocrinol Rev, 2017. **15**(Suppl 1): p. 109-118.
14. Roizen, N., E. Ekwo, and C. Gosselink, *Comparison of education and occupation of adults with achondroplasia with same-sex sibs.* American Journal of Medical Genetics, 1990. **35**(2): p. 257-260.
15. *Pan W, Guillen-Navarro E, Queisser-Wahrendorf A, et al. 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. 2020.* San Antonia, TX, USA.
16. Hecht, J.T., et al., *Mortality in achondroplasia.* American journal of human genetics, 1987. **41**(3): p. 454-464.
17. Wynn, J., et al., *Mortality in achondroplasia study: a 42-year follow-up.* Am J Med Genet A, 2007. **143a**(21): p. 2502-11.
18. Matsushita, T., et al., *FGFR3 promotes synchondrosis closure and fusion of ossification centers through the MAPK pathway.* Hum Mol Genet, 2009. **18**(2): p. 227-40.
19. *Food and Drug Administration. Orphan drug designation for modified recombinant human C-type natriuretic peptide (CNP). Available at:*

https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=386012. Last accessed: November 2020.

20. Agency, E.M., *Summary of Product Characteristics, Voxzogo* 2021.
21. Savarirayan, R., 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**(10252): p. 684-692.
22. *NCT01603095, 111-901, Natural History Study*. Available from: https://clinicaltrials.gov/ct2/show/record/NCT01603095.
23. Savarirayan, R., et al., *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.* Sci Prog, 2021. **104**(1): p. 368504211003782.
24. Savarirayan, R., et al., *C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia.* N Engl J Med, 2019. **381**(1): p. 25-35.
25. Hoover-Fong, *Vosoritide for Children with Achondroplasia: A 60-month update from an ongoing Phase 2 clinical trial*, in *CMG Annual Clinical Genetics Meeting*. 2021.
26. EMA, *Voxzogo: EPAR- Public Assessment Report.* 2021.
27. O'Hara, J., et al., *Evidence of a disability paradox in patient-reported outcomes in haemophilia.* Haemophilia, 2021. **27**(2): p. 245-252.