FINOSE Joint HTA
Fimea NoMA TLV

FINOSE joint assessment report

Voxzogo (vosoritide)

Subcutaneous injection

Assessed indication
Voxzogo is indicated 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.

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FINOSE

The Nordic collaboration FINOSE offers effective and transparent evaluations of pharmaceutical products with a view to reimbursement or procurement in the three countries Finland, Norway and Sweden. The collaborating agencies are the Finnish Medicines Agency (Fimea), the Norwegian Medicines Agency (NoMA) and Sweden's Dental and Pharmaceutical Benefits Agency (TLV).

Joint assessments of pharmaceutical products include both relative effectiveness and health economics. The evaluation reports are designed to support the decision processes in the three countries, according to the legal standards and procedures of each country. The three agencies take turns at the different tasks of the evaluation; this leads to high quality reports and time efficient procedures. In the present FINOSE report, NoMA and TLV acted as authors and Fimea performed a reviewer role.

Joint assessments lead to less divergence in HTA methodologies and evidence requirements between the Nordic agencies. A joint view may also facilitate potential future joint negotiations. However, price negotiation and procurement is not within the FINOSE team's remit.

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Summary

- FINOSE has made a joint health economic assessment of Voxzogo (vosoritide) for the treatment of achondroplasia.
- Achondroplasia is a bone growth disorder that results in disproportionate short stature. The condition is caused by a mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene. The final average adult height is approximately 132 cm in males and 124 cm in females. Achondroplasia causes an increased risk of medical complications.
- Voxzogo is a medicine for treating achondroplasia in patients aged 2 years and older whose bones are still growing.
- The active substance in Voxzogo, vosoritide, works by reducing the activity of FGFR3 and thereby stimulate growth of bones.
- The clinical study program demonstrates that Voxzogo treatment increase growth in children with achondroplasia. Children aged 5 - 17 years who received Voxzogo grew about 1.57 cm more during one year of treatment than those receiving placebo. Results from the ongoing extension studies suggest that an improvement in growth is maintained. No data is available on the final adult height that can be achieved with Voxzogo treatment.
- There is no evidence currently available on the potential impact of Voxzogo treatment on medical complications, activities of daily living and quality of life.
- Voxzogo treatment is generally well tolerated. The most common side effects are injection site reactions (such as swelling, redness, itching or pain), vomiting and decreased blood pressure.
- FINOSE agrees with the company that best supportive care is the most relevant comparator as there are currently no disease modifying treatments available.
- The company estimates the annual cost of treatment with Voxzogo to be 1 993 000 SEK.
- The company presents a cost-effectiveness model for Voxzogo compared to best supportive care.
- Uncertainties in the analyses are considered to be very high, especially due to lack of proof of a clear correlation between height and health related quality of life and complications.
- In the FINOSE base case the cost per QALY is 5 651 000 SEK, and the QALYs gained are 2,62. The results are based on the prices submitted by the company for the FINOSE assessment. The modelled final height is 143 cm for the Voxzogo arm and 130 cm for the BSC arm. The modeling of utility by height, height gained from treatment, treatment starting and stopping age, and discount rates have the greatest impact on the ICER.

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1 Scope

This report is a FINOSE joint assessment of Voxzogo (vosoritide) for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed.

The assessment is primarily based on the documentation presented by BioMarin.

The aim of this FINOSE report is to inform national policy decision regarding the use of Voxzogo in the FINOSE countries. The primary focus of this report is to assess the relative effectiveness, the safety and the cost effectiveness of Voxzogo. The FINOSE reports may be complemented with national versions of the report with additional or local information and conclusions.

P (population)	Patients with achondroplasia from 2 years of age and older whose epiphyses are not closed
I (intervention)	Voxzogo
C (comparison, comparators)	Best supportive care (BSC)
O (outcomes)	• Growth as measured by annualized growth velocity (AGV), height Z-score, and upper to lower body segment ratio. • Medical complications of achondroplasia • Adverse events • Health-related quality of life • Costs • Incremental cost-effectiveness ratio (ICER)

2 Medical background

2.1 Achondroplasia

Achondroplasia (ACH) is a bone growth disorder that results in disproportionate short stature. The condition is caused by a mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene. This mutation leads to impaired bone formation. The final average adult height is approximately 132 cm in males and 124 cm in females [1]. This corresponds to a total average height deficit compared to the general population of 45 cm for males and 40 cm for females. Clinical features include a relatively long trunk and shortened arms and legs [2]. This is most noticeable in the upper parts of the arms and legs (called rhizomelic shortening). Other common features may include a larger head with a prominent forehead, a flattened bridge of the nose, and shortened hands and fingers.

ACH causes delayed motor development and an increased risk of medical complications [3]:

- **Growth and motor development** - Gross motor development is delayed in children with ACH. Most children start walking between 18 months and 2 years of age. ACH-specific growth charts and screening tools for developmental milestones are used for monitoring.

- **Foramen magnum stenosis** - The foramen magnum is the opening at the base of the skull where the brain stem and spinal cord pass through. Foramen magnum stenosis happens when the opening narrows, causing pressure on the brain or spinal cord. This is a well-recognized complication in infants with ACH, especially during the first two years of

life. Foramen magnum stenosis were documented in 28% of patients in a multinational observational study [4]. Severe foramen magnum stenosis can lead to serious neurological complications, respiratory arrest (central sleep apnoea) and sudden infant death.

- **Sleep apnoea** - Obstructive sleep apnoea occurs in up to 50-70% of children with ACH and around 60% of adults and is due to narrowing of the upper airways [5-7]. The most common symptoms include breathing stopping and starting, loud snoring, waking up a lot, excessive daytime sleepiness and irritability.

- **Otitis media and hearing impairments** - Recurrent upper respiratory infections and otitis media are common in children with ACH. In chronic otitis media, hearing and language development can be affected.

- **Kyphosis and lordosis** – Kyphosis, excessive curvature in the middle section of the spine, is very common in infants with ACH. It usually spontaneously resolves when the child begins to walk (around 2-3 years of age) and is replaced by an excessive spine curvature in the lower back (lordosis).

- **Bowed legs (Genu Varum)** – Bow-leggedness is first noticed at standing age in approximately 40% of all toddlers with ACH. This complication can cause pain when walking.

- **Spinal stenosis** – Individuals with ACH have a congenital narrow spinal canal, which increases the risk of developing symptomatic spinal stenosis later in life. Symptoms can appear as early as 10-12 years of age, and the incidence increases with increasing age. A population-based study in one of the FINOSE countries (Norway) found a prevalence of 68% of symptomatic spinal stenosis in adults with genetically confirmed ACH [8]. Spinal stenosis is associated with pain, tingling, and weakness in the legs that can cause difficulty with walking. In severe cases the bladder or bowel control can be affected.

- **Obesity** – Obesity is common in this population. Obesity (BMI ≥ 30 kg/m^2) was found in 67% of Norwegian adults with ACH in a population-based study, and 18% of the participants had severe obesity (BMI ≥ 40 kg/m^2)[9]. Increased weight will have an adverse effect on joints and subsequent mobility and independence.

- **Dental malocclusion** - Changed anatomical conditions in the jaw due to ACH can cause crowded or misaligned teeth.

The clinical features of ACH can in turn lead to problems with ambulation (walk long distances, climb the stairs), impaired self-care or ability to perform activities of daily living (bathing, dressing, toileting), reduced health-related quality of life (HRQoL), and reduced work participation.

Most people with ACH have a normal or near normal life expectancy [2]. However, there is an increased risk for premature death related not only to sudden unexpected deaths in infancy but also, it appears, to cardiovascular complications in mid-adult life.

ACH is most frequently diagnosed before or shortly after birth based on clinical characteristics and is confirmed using genetic testing. Only 20% of individuals with ACH inherit the condition from a parent; the majority have a de novo spontaneous mutation and are born to parents without ACH [10].

International epidemiology estimates suggest that ACH occurs in 1 per 20,000 – 30,000 live-births [10], which gives an estimated annual incidence of about 5 new patients per year in Sweden, and 2-3 new patients per year in Finland and Norway. The estimated prevalence of ACH is approximately 300-400 persons in Sweden, 120-130 in Norway and 150-200 in Finland. According to the approved therapeutic indication for Voxzogo, patients with ACH are eligible for treatment from 2 years of age until epiphyseal closure. The company has estimated that [--] patients in Finland, [--] patients in Norway and [--] patients in Sweden would currently be eligible for treatment with Voxzogo and represents the anticipated patient population.

2.2 Voxzogo

2.2.1 Therapeutic indication

Voxzogo is indicated for the treatment of ACH in patients 2 years of age and older whose epiphyses are not closed (i.e., whose bones are still growing). The diagnosis of ACH should be confirmed by appropriate genetic testing [11].

2.2.2 Mechanism of action

In patients with ACH, the *FGFR3* gene, which regulates growth, is permanently 'switched on'. This prevents normal growth of bones, leading to bones that are shorter than normal. The active substance in Voxzogo, vosoritide, is a modified recombinant human type C natriuretic peptide (CNP). Vosoritide works by binding to the natriuretic peptide receptor type B (NPR-B), which reduces the activity of *FGFR3*. This stimulates growth of bones, thereby improving the symptoms of the disease [11].

2.2.3 Posology and method of administration

Voxzogo is given as a subcutaneous injection once a day. The usual dose is 15 µg/kg body weight [11].

It is important to initiate treatment in children as young as possible. Treatment should be stopped upon confirmation of no further growth potential, indicated by a growth velocity of < 1.5 cm/year and closure of epiphyses [11].

Voxzogo injections can be given by the patients' caregiver after proper training from a healthcare professional.

2.3 Current treatment options

2.3.1 Treatment guidelines in Finland, Norway and Sweden

Swedish, Norwegian and Finish clinics follow the international treatment recommendations by Pauli 2019[2], the international consensus statement published in 2021 by Savarirayan et al.[12] and European guidelines for ACH [13]. In Norway, these guidelines are summarized by Sunnaas hospital [3]. Clinics in Sweden also use guidelines by Lars Hagenäs, Karolinska University Hospital [14].

The management of ACH require lifelong involvement by an experienced multidisciplinary team to anticipate and manage complications, support independence, and improve quality of life. According to consulted clinical experts, the clinical management is similar across the FINOSE countries.

ACH patients typically require several symptomatic treatments, including both surgical and pharmacological interventions. Common types of surgeries are middle ear procedures, tonsillectomies/adenoidectomies, and brainstem decompression surgeries [4]. Limb lengthening surgery is sometimes performed with the aim of increasing height and reach. Utilisation of limb lengthening surgery differs between the Nordic countries according to estimates from the company. It is very rarely performed in Finland (0-5%), and only in the later teens; while in Sweden, the estimated occurrence is relatively higher (25%), and the procedure is mostly done in the late teen ages and mainly as part of corrective surgery. In Norway, it is estimated that 30-35% of ACH patients aged 8-10 years undergo limb lengthening surgery, and again mainly as part of corrective surgery. Limb lengthening is associated with pain, and risk of complications.

Common medications include antibiotics, pain management, and drugs for obstetric airway diseases. Growth hormone therapy has limited evidence to suggest clinical effectiveness and is not relevant in ACH treatment.

In addition to surgery and prescribed medications, patients and their families are often recommended to make environmental and behavioral changes to adapt to the needs of the ACH patient. For example, use of furniture adaptations and reach extenders.

2.3.2 Comparator

The company uses best supportive care (BSC) as comparator to Voxzogo, because there are currently no licensed treatments available addressing the underlying cause of ACH. Supportive therapies focus on mitigating symptoms and comorbidities of ACH, behavioural/environmental interventions, as well as close supervision. Utilization of limb lengthening surgery differs between the Nordic countries (0-5% in Finland, 25% in Sweden, 30-35% in Norway).

FINOSE conclusion: FINOSE agrees with the company that best supportive care is the relevant comparator as there are currently no disease modifying treatments available.

3 Clinical efficacy and safety

The assessment of clinical efficacy and safety is mainly based on the evidence included in the submission dossier prepared by the company. The authoring team has checked the information retrieval included in the company's submission dossier for completeness against
- a search in ClinicalTrials.gov and PubMed
- the studies included in the European public assessment report (EPAR)

3.1 Clinical trials

3.1.1 Methods of the clinical trials

The clinical development programme for Voxzogo in treatment of ACH includes Phase 2 and Phase 3 placebo-controlled, randomized controlled trials (RCTs) and extension studies, as well as non-interventional natural history studies, conducted in patients aged 0–18 years (Table 1).

Data on the effectiveness of Voxzogo is taken from the **Study 111-301**. The trial with longest follow-up time is study 111-205 with up to 7.5 years of Voxzogo treatment.

Table 1. Summary of relevant trials

Study	Study	Study	Intervention	Key endpoints

	design	population		
111-301 [15, 16] NCT03197766 Completed	- phase 3 - randomised - double-blind - placebo-controlled - multicentre	121 ACH patients 5 to <18 years old	vosoritide 15 µg/kg daily, 52 weeks (n=60) placebo, 52 weeks (n=61)	Primary: AGV, change from baseline at Week 52 Key secondary: - Height Z-score - Upper to lower segment body ratio
111-302 [16-18] NCT03424018 Extension study to 111-301 Ongoing DCO: 25 Feb 2022	- phase 3 - open-label - multicentre	119 ACH patients who completed 1 year of vosoritide or placebo treatment in 111-301	vosoritide 15 µg/kg daily	Primary: AGV, change from baseline every year Secondary: - Height Z-score - Upper to lower segment body ratio
111-206 [16, 19] NCT03583697 Completed	- phase 2 - randomised - double-blind - placebo-controlled - multicentre	75 ACH patients 0 to <5 years old	Intervention: Cohort 1 (≥ 24 to <60 months): vosoritide 15 µg/kg daily Cohort 2 (≥ 6 to <24 months): vosoritide 30 µg/kg daily, adjusted to 15 µg/kg daily when patients reach 2 years of age Cohort 3 (0 to <6 months): vosoritide 30 µg/kg daily Control: placebo	Primary: Z-score for height/length, change from baseline at Week 52 Secondary: - Safety - AGV - Upper to lower segment body ratio
111-208 NCT03989947 Extension study to 111-206 Ongoing, no results	- phase 2 - open-label	70 patients who completed 1 year of vosoritide or placebo treatment in 111-206	Vosoritide 15 or 30 µg/kg daily	Primary: - Long-term safety and tolerability - Height/length Z-score Secondary: - AGV - Upper to lower body segment ratio
111-202 [16, 20] NCT02055157 Completed	- phase 2 - open-label - dose-escalation	35 ACH patients 5 to 14 years old	Cohort 1: vosoritide 2.5 µg/kg daily Cohort 2: vosoritide 7.5 µg/kg daily Cohort 3: vosoritide 15 µg/kg daily Cohort 4: vosoritide 30 µg/kg daily After a 6-month dose-finding phase patients either received an escalated dose or continued to receive their initial dose the following 18-month period	Primary: Safety and side-effect profile Secondary: Change from baseline at 6 months in AGV, height Z-score, and upper to lower segment body ratio
111-205 [16, 21] NCT02724228 Extension study to 111-202 Ongoing DCO: 25 Feb 2022	- phase 2 - open-label	30 ACH patients who completed 24 months of vosoritide treatment in 111-202	Cohort 1: vosoritide up to 15 µg/kg daily Cohort 2: vosoritide up to 15 µg/kg daily Cohort 3: vosoritide 15 µg/kg daily Cohort 4:	Primary: Safety and side-effect profile Secondary: - AGV - height Z-score - upper to lower segment body ratio

			vosoritide 30 µg/kg daily	
111-901 [16, 22] NCT01603095 Natural History Study	- observational - prospective - multicentre	363 ACH patients 0 to <18 years old considered for subsequent enrolment in future BioMarin sponsored clinical trials	No study drug was administered	Growth measurements at baseline and then subsequently at 3-month intervals, e.g.: - AGV - Height Z-Score - Standing or sitting height, - Upper to lower body segment ratio
111-501 (LIAISE) [4] NCT03449368 Natural History Study	- observational - retrospective - cross-sectional	195 ACH patients ≥5 years	No study drug was administered	Standing height, PedsQoL, QoLISSY, WeeFIM, healthcare resource use

AGV: annualized growth velocity (cm/year). DCO: Data cut off used for this assessment. PedsQoL: Pediatric Quality of Life Inventory 4.0. QoLISSY: Quality of Life in Short Stature Youth. WeeFIM: Pediatric Functional Independence Measure.

3.1.2 Efficacy outcome measures

Annualized growth velocity (AGV)
AGV is the average yearly rate of standing height growth (cm/year).

AGV is a key indicator of skeletal growth, well-documented over the paediatric age range, highly sensitive to factors that impact growth negatively or positively, and easily and objectively measurable in an accurate non-invasive manner [16].

AGV for a given interval was calculated as follows:

$$\text{AGV} = \frac{Standing\ Height\ at\ Date\ 2 - Standing\ Height\ at\ Date\ 1}{Interval\ Length\ (Days)} \text{ x } 365.25$$

In average stature children, infancy and puberty are periods of rapid linear growth. In infants, mean AGV is highest shortly after birth (44 cm/year) and thereafter decreases up to age 5 before remaining relatively steady up until puberty (at 5.5 to 7 cm/year). At puberty, average stature children experience a growth spurt with AGV of 8.3 to 9.3 cm/year [22].

Median (inter-quartile range, IQR) AGV in subjects with ACH enrolled in the natural history study 111-901 was 11.65 (10.22, 12.92) cm/year for girls and 14.55 (14.19, 14.90) cm/year for boys for those aged < 1 year [22]. By 1 year of age, median (IQR) AGV decreased to 7.45 (5.09, 8.24) cm/year in girls and 7.28 (5.48, 8.82) cm/year in boys. By age 11 years, AGV was approximately 4 cm/year for girls and boys. The number of subjects aged >12 years was small.

Published data have shown that the growth pattern of ACH subjects is similar to that of children of average stature until puberty; however, the magnitude of growth is lower in all age groups. Height velocity among children with ACH is particularly compromised during what would typically be the periods of most rapid growth— infancy and puberty. In contrast to children of average stature, pubertal linear growth spurt is absent in children with ACH [23].

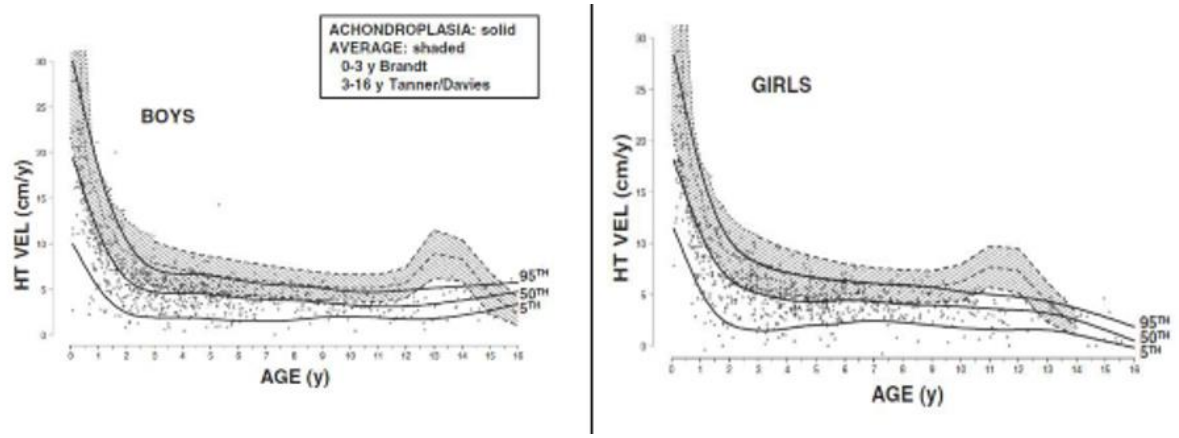

Figure 1. Height velocity (HT VEL) curves (5th, 50th, and 95th percentiles) from 0 to 16 y of age in boys and girls with ACH (solid lines) compared with data for children of average stature (dotted and shaded section) from Brandt (22; 0–3 y; 10th, 50th, and 90th percentiles) and Tanner/Davies (23; 3–16 y; 3rd, 50th, and 97th perc*entiles)* [23].

Height Z-score

Height Z-scores were derived from standing height measurements using age-sex specific CDC[1] or WHO reference data for average stature children. Data are presented as standard deviation score (SDS) above or below the age-specific reference (which is equivalent to 0). Short stature is defined as a height of ≥ 2.0 SDS below the population-specific mean height for age and gender. Patients with ACH experience extreme short stature of 5.0 – 7.0 SDS below average stature in adulthood [1].

For subjects with ACH enrolled in study 111-901, the mean (SD) length deficit for those aged < 1 year was −2.51 (1.04) SDS for girls and -3.18 (1.21) SDS for boys compared with average stature children of a similar age [22]. Mean height deficit increased during the following years. By 5 years of age, the mean (SD) Z-scores was -5.30 (1.08) SDS for girls and -4.64 (0.78) SDS for boys. The height deficit remained high in all age groups throughout study 111-901.

Upper to lower body segment ratio

Upper to lower body segment ratio provides an assessment of whether the treatment effect is occurring proportionally in both the spine and the lower limbs.

The upper to lower body segment ratio changes from birth to adulthood in a similar fashion for both the general population as well as children with ACH with a decline between 0 and approximately 7 years of age reaching its final value around 10 years of age [22]. The difference between the general population and children with ACH is that the ratio itself differs. Average stature children have an upper to lower body segment ratio at birth of 1.7 which decreases to about 1.1 by 5 to 6 years of age and reaches a final value of 1 by 10 years of age. In contrast, disproportionate growth in the lower limbs of ACH patients causes the upper body to represent a greater proportion of total height than the lower body. Published data show a mean value at birth of about 2.6, reaching about 2 at 5 to 6 years of age and plateauing around 1.8 at 10 years [23, 24].

Data from subjects with ACH enrolled in the natural history study 111-901 show disproportionality in upper to lower body ratio and are consistent with the published data in children with ACH. A steep decline from 0 to 3 years was observed followed by a slow decline up to the age of 10 and 12 years for girls and boys, respectively. Mean (SD) upper to lower body segment

[1] Centers for Disease Control and Prevention

ratio in both girls and boys was highest for those aged <1 year (respectively 2.94 [0.60] and 2.80 [0.37]) and decreased gradually to approximately 2 for both girls and boys at 4 years of age.

3.1.3 Study 111-301

The pivotal study 111-301 is a completed multicenter, randomised, double-blind, placebo-controlled Phase 3 trial which evaluated the efficacy and safety of 52 weeks of treatment with Voxzogo compared with placebo in children aged 5 to < 18 years with a clinical diagnosis of ACH confirmed by genetic testing. Eligible children had at least a 6-month period of pre-treatment growth assessment, including standing height, in study 111-901.

A total of 121 subjects were enrolled into the study and randomized 1:1 to receive either Voxzogo 15.0 µg/kg (n=60) or placebo (n=61) administered by daily subcutaneous injections in their homes by trained caregivers. Children with radiographic evidence of closed growth plates, planned bone surgery, severe untreated sleep apnea, and other medical conditions or treatments known to impact growth were excluded.

A summary of baseline characteristics for the full analysis set (FAS) is presented in Table 2. The patients were slightly younger in the Voxzogo group (more patients aged 5–8 years old).

Table 2. Patient characteristics in study 111-301

	Placebo (n=61)	Voxzogo (n=60)	Overall (n=121)
Age at Day 1 (years)			
Mean (SD)	9.06 (2.47)	8.35 (2.43)	8.71 (2.47)
Median (min, max)	9.31 (5.1, 14.9)	7.78 (5.1, 13.1)	8.99 (5.1, 14.9)
Age at Day 1, n (%)			
≥ 5 to < 8 years	24 (39.3)	31 (51.7)	55 (45.5)
≥ 8 to < 11 years	24 (39.3)	17 (28.3)	41 (33.9)
≥ 11 to < 15 years	13 (21.3)	12 (20.0)	25 (20.7)
Sex, n (%)			
Male	33 (54.1)	31 (51.7)	64 (52.9)
Female	28 (45.9)	29 (48.3)	57 (47.1)
Race, n (%)			
White	41 (67.2)	45 (75.0)	86 (71.1)
Asian	13 (21.3)	10 (16.7)	23 (19.0)
Tanner stage			
I	48 (78.7)	48 (80.0)	96 (79.3)
>I	13 (21.3)	12 (20.0)	25 (20.7)
Weight (kg)			
Mean (SD)	24.62 (9.07)	22.88 (7.96)	23.76 (8.55)
Median (min, max)	23.00 (11.6, 68.9)	21.33 (13.6, 53.0)	21.50 (11.6, 68.9)
Weight Z-score			
Mean (SD)	−1.62 (1.44)	−1.49 (1.19)	−1.56 (1.32)
Median (min, max)	−1.52 (−5.1, 2.6)	−1.27 (−4.8, 1.6)	−1.45 (−5.1, 2.6)
BMI (kg/m2)			
Mean (SD)	22.64 (5.43)	22.22 (3.44)	22.43 (4.54)
Median	21.88	21.56	21.78

BMI, body mass index; Max, maximum; Min, minimum; SD, standard deviation.
Tanner Stage (I, > I) is determined using the genitalia and breast Tanner Stage for males and females respectively.
Z-Scores were derived using age-sex specific reference data (means and SDS) for average stature children per the Centers for Disease Control and Prevention

Two patients in the Voxzogo group discontinued during the study (1 subject discontinued study due to an AE [anxiety about injections] and 1 subject discontinued study due to subject request [subject was experiencing pain during injections]. All 61 subjects in the placebo group completed the study.

The primary endpoint in study 111-301 was change from baseline in **annualised growth velocity (AGV)** at Week 52. At baseline, the mean AGV was similar between the two treatment

groups, placebo 4.06 cm/year and Voxzogo 4.26 cm/year. By Week 52, AGV was significantly improved with Voxzogo compared with placebo, with a mean change from baseline of 1.35 cm/year in the Voxzogo group compared with −0.12 cm/year in the placebo group. The difference in Least Squares (LS) mean change from baseline between the groups was 1.57 cm/year (95%CI: 1.22, 1.93), two-sided p-value <0.0001.

Change from baseline in **height Z-score** at week 52 was a key secondary endpoint. Data are presented as standard deviation score (SDS) above or below the age-specific reference (equivalent to 0) for average stature children calculated using CDC or WHO. The difference in LS mean change from baseline was statistically significant in favour of Voxzogo at 0.28 SDS (95% CI: 0.17, 0.39; p<0.0001).

The **upper to lower body segment ratio** was another key secondary efficacy variable in study 111-301. This is an indicator of changes to body proportionality, whereby ratio falls to 1 by approximately 10 years of age in average stature children and never reaches 1 in untreated children with ACH. LS mean changes from baseline to Week 52 in upper to lower segment body corresponded to a difference of −0.01 (95% CI: −0.05, 0.02; P<0.5060), indicating that there was no difference between treatment groups.

Efficacy results from study 111-301 are shown in Table 3.

Table 3 Efficacy results from study 111-301

	Placebo			Voxzogo			Voxzogo vs. placebo
	Baseline	Week 52	Change	Baseline	Week 52	Change	LS mean difference in changes (95 % CI)
AGV (cm/year)							
Mean ± SD	4.06 ± 1.20	3.94 ± 1.07	-0.12 ± 1.74	4.26 ± 1.53	5.61 ± 1.05	1.35 ± 1.71	**1.57** (1.22, 1.93) (p =<0.0001)
Height Z-score							
Mean ± SD	-5.14 ± 1.07	-5.14 ± 1.09	0.00 ± 0.28	-5.13 ± 1.11	-4.89 ± 1.09	0.24 ± 0.32	**0.28** (0.17, 0.39) (p =<0.0001)
Upper to lower body segment ratio							
Mean ± SD	2.01 ± 0.21	1.98 ± 0.18	−0.03 ± 0.09	1.98 ± 0.20	1.95 ± 0.20	−0.03 ± 0.11	**−0.01** (−0.05, 0.02) (p = 0.5060)
Standing height							
Mean ± SD	102.94 ± 10.98	106.87 ± 10.84	3.93 ± 1.08	100.20 ± 11.90	105.80 ± 12.03	5.59 ± 1.06	**1.57** (1.21, 1.93) (p =<0.0001*)

AGV: annualized growth velocity. CI: confidence interval. LS: least squares. SD: standard deviation.
*descriptive analysis only- the endpoint was not controlled for Type I error

HRQoL as measured by the Quality of Life in Short Stature Youth (QoLISSY) and Pediatric Quality of Life Inventory (PedsQL) questionnaires were secondary endpoints in study 111-301. At Week 52, no difference was observed in change from baseline between the Voxzogo and placebo groups in any of the PedsQL domains (caregiver- and self-reported scores) or in any of the caregiver reported QoLISSY domains.

Functional independence was measured by the Functional Independence Measure for Children (WeeFIM). WeeFIM is an assessment tool that measures functional performance across three domains (self-care, mobility and cognition) assessed by the clinician, and with input from the parent/caregiver. At Week 52, no difference was observed in change from baseline between the Voxzogo and placebo groups in any of the domains.

3.1.4 Extension study 111-302

After completion of study 111-301, 119 patients (n = 58 from the Voxzogo arm [vos/vos] and n = 61 from the placebo arm [plc/vos]) were enrolled into the ongoing long-term extension study 111-302, where all participants received Voxzogo at a dose of 15.0 µg/kg/day. Baseline is defined as the last assessment prior to the first dose of Voxzogo.

By the cut-off date February 25, 2022, 52 patients in the vos/vos treatment arm had received 15 µg/kg Voxzogo for 156 weeks (3 years) in total. In the plc/vos treatment arm 59 patients had received 15 µg/kg Voxzogo for 130 weeks (2,5 years) in total. A total of 8 participants overall discontinued from treatment (4 of whom also discontinued the study). Two participants discontinued treatment as they had reached near final adult height (NFAH).

The analyses of data from 111-302 showed the effect on growth, observed in the first year of treatment with Voxzogo (mean AGV [---] cm/year, mean change from baseline [---] cm/year), is maintained at 3 years of treatment (mean **cumulative AGV** [---] cm/year, mean change from baseline [---] cm/year) and 3.5 years of treatment (mean cumulative AGV [---] cm/year, mean change from baseline [---] cm/year). The maintenance of positive effect on cumulative AGV resulted in continuous improvement in **height Z-score**, with change from baseline of [---] SDS after 3 years of treatment and [---] SDS after 3.5 years of treatment. Participants with 2.5 years on-treatment data after switching from placebo to Voxzogo treatment in 111-302, showed similar improvement in growth compared to those originally randomized to Voxzogo and treated for 2.5 years in 111-301/302. No worsening in **upper to lower body segment ratio** over time was observed in the treatment groups. Imaging results show normal skeletal maturity over time.

Table 4 Efficacy results from study 111-302

	Baseline	Year 1	Year 2	Year 3	Year 4
AGV (cm/year), 12-month interval*					
n	119	111	98	50	8
Mean ± SD	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]
Change from baseline	--	[---] [---]	[---] [---]	[---] [---]	[---] [---]
AGV (cm/year), cumulative**					
n	119	111	106	57	9
Mean ± SD	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]
Change from baseline	--	[---] [---]	[---] [---]	[---] [---]	[---] [---]
Height Z-score					
n	119	111	106	57	9
Mean ± SD	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]
Change from baseline	--	[---] [---]	[---] [---]	[---] [---]	[---] [---]
Upper to lower body segment ratio					
n	119	104	99	37	8
Mean ± SD	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]
Change from baseline	--	[---] [---]	[---] [---]	[---] [---]	[---] [---]

AGV: annualized growth velocity. SD: standard deviation.
*12-month interval AGV for Year X was calculated as follows: (Standing Height at Year X) – (Standing Height at Year X – 1 Year)
**Cumulative AGV for Year X was calculated as follows: [(Standing Height at Year X – Standing Height at Baseline) / Interval Length; Days] x 365.25
***Results from Week 182 (3.5 years). According to BioMarin the Week 156 (3 years) upper to lower body segment ratio was erroneously noted as 21.85 due to an incorrect sitting height assessment for one patient.

3.1.5 Study 111-206

Study 111-206 was a 52-week multicenter, Phase 2, randomized, double-blind, placebo-controlled clinical trial. The main objectives of the study were to evaluate the safety of Voxzogo and its impact on growth in infants and younger children recruited from birth to less than 60 months (5 years) of age with genetically confirmed diagnosis of ACH. A total of 75 participants were enrolled, of which 64 participants were randomized to receive Voxzogo or placebo, and 11 participants were enrolled to receive Voxzogo (sentinel participants).

Subjects were enrolled into three age Cohorts based on age at study screening:

- Cohort 1: children aged ≥ 24 to < 60 months (n=31 randomized)
- Cohort 2: children aged ≥ 6 to < 24 months (n=16 randomized)
- Cohort 3: children aged 0 to < 6 months (n=17 randomized)

Eligible children had baseline growth data collected in study 111-901; at least 6 months for Cohorts 1 and 2; and at least 3 months for Cohort 3.

Patients received Voxzogo in one of the following daily dosing regimens: Cohort 1: 15 µg/kg, Cohort 2: 30 µg/kg adjusted to 15 µg/kg when patients reach 2 years of age. Cohort 3: 30 µg/kg.

Cohort 1 included children aged 2 to < 5 years of age and is relevant for this assessment. Treatment of patients within cohort 2 and 3 (< 2 years of age) are outside the currently licensed indication and thus outside the scope of this assessment.

In Cohort 1, an improvement in height Z-score ([---]SDS), standing height ([---]cm) and AGV ([---]cm/year) was observed in Voxzogo participants compared with placebo at week 52. Due to the small sample size, there was an imbalance in the treatment groups with greater height deficit at baseline in the placebo group in Cohort 1.

Table 5 Efficacy results from Cohort 1 (2 to < 5 years of age) in study 111-206, FAS (randomized)

	Placebo (n=16)		Voxzogo (n=15)		Voxzogo vs. placebo
	Baseline	Change from baseline, LSM (95 % CI)	Baseline	Change from baseline, LSM (95 % CI)	Difference in LSM (95 % CI)
Height Z-score					
Mean ± SD	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---] [---]
Standing height (cm)					
Mean ± SD	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---] [---]
AGV (cm/year)					
Mean ± SD	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]

AGV: annualized growth velocity. LSM: Least squares Mean. SD: standard deviation

Following completion of study 111-206, subjects in all treatment groups are eligible to receive Voxzogo in the open-label extension study 111-208, to assess safety and efficacy of longer-term treatment with Voxzogo. No results are currently available.

3.1.6 Study 111-202 and extension study 111-205

Study 111-202 was a Phase 2, open-label dose-escalation study to assess the safety and tolerability of daily subcutaneous injections of Voxzogo administered for 6 months up to 24 months. Eligible children were 5 to 14 years of age at screening, had ACH confirmed by genetic testing, and had completed at least 6 months of pretreatment growth assessment in study 111-901. A total of 35 patients were enrolled (19 girls and 16 boys) with a mean (±SD) age of 7.6±1.7 years

(range, 5 to 11). During the first 6 months of the study, patients received Voxzogo in one of the following daily dosing regimens: Cohort 1: 2.5 µg/kg (n=8), Cohort 2: 7.5 µg/kg (n=8), Cohort 3: 15.0 µg/kg (n=10), Cohort 4: 30.0 µg/kg (n=9).

By Month 6, a positive, dose-dependent change in mean (SD) AGV from baseline was observed among patients receiving Voxzogo up to 15 µg/kg daily. The reported AGV mean change from baseline was 2.014 cm/year (95% CI: 0.58; 3.44, p = 0.0111) with the 15 µg/kg dose (Cohort 3). There was no additional benefit in effect on AGV seen with 30 µg/kg daily dose compared with 15 µg/kg.

After 6 months of dosing in 111-202, patients in Cohorts 1 and 2 were titrated to receive 15 µg/kg, while patients in Cohort 3 and 4 continued to receive 15 µg/kg and 30 µg/kg, respectively. During the 18-month extension period, one patient discontinued from each of Cohorts 1 and 2, bringing the total number of patients who completed the two-year study to 30.

Patients who completed 2 years of Voxzogo treatment in 111-202 were enrolled in the 111-205 extension study to continue receiving the same stable dose of Voxzogo received upon completion of 111-202 (15 or 30 µg/kg daily). As of 25 February 2022, of the 30 participants who entered 111-205, 16 participants were continuing treatment and 20 participants were continuing in the study.

The efficacy results demonstrated improvements in cumulative **AGV**, which were maintained for up to 7.5 years in study 111-205. The 12-month interval AGV demonstrated a small decline in change over time relative to baseline. According to the company this is expected. Mean age at treatment start was 7.6 years, and a natural downward trend in growth velocity is observed in children with ACH at this age [23]. Increase in AGV resulted in improvements in **height Z-score** relative to average stature children. There was no worsening of body proportion and a trend for **upper to lower body segment ratio** to improve over time. X-Ray results over time did not show any abnormal acceleration of skeletal maturity.

Table 6 Efficacy results from extension study 111-205, pooled cohorts

	Baseline	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
AGV, 12-month interval*							
n	30	29	28	29	25	17	8
Mean ± SD	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]
Change from baseline	--	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]
AGV, cumulative**							
n	30	29	29	29	NA	18	9
Mean ± SD	[---] [---]	[---] [---]	[---] [---]	[---] [---]	NA		
Change from baseline	--	[---] [---]	[---] [---]	[---] [---]	NA	[---] [---]	[---] [---]
Height Z-score							
n	30	29	29	29	25	18	9
Mean ± SD	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]
Change from baseline	--	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]
Upper to lower body segment ratio							
n	30	29	29	29	23	16	9
Mean ± SD	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]
Change from baseline	--	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]	[---] [---]

AGV: annualized growth velocity. SD: standard deviation.
*12-month interval AGV for Year X was calculated as follows: (Standing Height at Year X) – (Standing Height at Year X – 1 Year)
**Cumulative AGV for Year X was calculated as follows: [(Standing Height at Year X – Standing Height at Baseline) / Interval Length; Days] x 365.25

In the relevant Cohort 3, who had received the 15 µg/kg dose from start, the reported mean (SD) 12-month interval AGV was [----------
----

----------].

A total of five participants (4 girls and 1 boy) reached near final adult height, defined as evidence of decreased growth velocity (AGV < 1.5 cm/year) as assessed over a period of at least 6 months and growth plate fusion as assessed by radiographic imaging of distal femur and proximal tibia.

3.2 Results of clinical efficacy and quality of life

In this section the results of clinical efficacy and quality of life from the Voxzogo clinical trials are summarized per outcome. The relevant Voxzogo clinical trials are described in the previous sections and include the pivotal 111-301/111-302 studies in children aged > 5 years, the 111-206 study in children aged 2 to < 5 years (Cohort 1), and the 111-202/111-205 studies with the longest follow-up data for children > 5 years.

AGV:

- In children aged > 5 years (n=121), the adjusted mean difference in AGV between patients in the Voxzogo group and placebo group was 1.57 cm/year in favour of Voxzogo (95% CI 1.22–1.93; two-sided p<0.0001) after 52 weeks of treatment (study 111-301).
- The effect on growth observed in the first year of treatment with Voxzogo (mean AGV [-----] cm/year, mean change from baseline [----] cm/year), was maintained at 3 years of treatment (mean cumulative AGV [----] cm/year, mean change from baseline [----] cm/year) in the extension study (study 111-302).
- The longest follow-up data for children > 5 years treated with Voxzogo demonstrated a small decline in change over time relative to baseline in the 12-month interval AGV (study 111-205). The reported mean 12-month interval AGV was 3.75 cm/year at baseline (n=30), 5.59 cm/year at Year 2 (n=29), 5.29 cm/year at Year 3 (n=28), 5.19 cm/year at Year 4 (n=29), 4.29 cm/year at Year 5 (n=25), 3.98 cm/year at Year 6 (n=17), and 3.86 cm/year at Year 7 (n=8).
- In children aged 2 to < 5 years (n=31), the adjusted mean difference in AGV between patients in the Voxzogo group and placebo group was [----] cm/year in favour of Voxzogo (95% CI [----------]; two-sided p?) after 52 weeks of treatment (study 111-206, Cohort 1).

Height Z-score:

- In children aged > 5 years (n=121), the adjusted mean difference in height Z-score between patients in the Voxzogo group and placebo group was 0.28 SDS in favour of Voxzogo (95% CI 0.17–0.39; two-sided p<0.0001) after 52 weeks of treatment (study 111-301).
- The height Z-score continued to improve over time in the extension study, with change from baseline of [-----] SDS after 2 years of treatment (n=106), [------] SDS after 3 years of treatment (n=57), and [------] SDS after 4 years of treatment (n=9) (study 111-302).
- The longest follow-up data for children > 5 years treated with Voxzogo demonstrated an improvement in the height Z-score in the first four years of treatment, which then appears to level off the following years. Change from baseline in height Z-score was +0.66 SDS at Year 2 (n=29), +0.90 SDS at Year 3 (n=29), +1.04 SDS at Year 4

(n=29), +0.88 SDS at Year 5 (n=25), +0.98 SDS at Year 6 (n=18), and +0.88 SDS at Year 7 (n=9).
- In children aged 2 to < 5 years (n=31), the adjusted mean difference in height Z-score between patients in the Voxzogo group and placebo group was [-----] SDS in favour of Voxzogo (95% CI [---------]; two-sided p=0.0570) after 52 weeks of treatment (study 111-206, Cohort 1).

Upper to lower body segment ratio:
- In children aged > 5 years (n=121), the adjusted mean difference in upper to lower segment body ratio between patients in the Voxzogo group and placebo group was −0.01 (95% CI: −0.05, 0.02; P<0.5060) after 52 weeks of treatment, indicating that there was no difference between treatment groups (study 111-301).
- There was no worsening of body proportion and a trend for upper to lower body segment ratio to improve over time with continued Voxzogo treatment in the extension studies (study 111-301 and 111-205).

Quality of life:
- Quality of life endpoints are being studied in the 301/302 studies and 206/208 studies. So far, results only from study 111-301 have been reported. No clinically meaningful differences were observed in change from baseline between the placebo and Voxzogo groups in health-related quality of life (assessed by PedsQL and QoLISSY), or functional independence (assessed by WeeFIM), after completion of the 52-week study period in study 111-301.

Complications:
- There are no data currently available on the potential impact of treatment with Voxzogo on medical complications. We will have to wait for long-term data to assess these outcomes. BioMarin is committed to studying the impact of Voxzogo on ACH-related complications through ongoing clinical trials, extension trials and post-hoc studies.

3.3 Results of safety

Daily injections of Voxzogo were generally well tolerated in the Phase 2 and 3 studies. There have been no important safety risks identified associated with Voxzogo at present. The majority of adverse events were Grade 1 (mild) and no unexpected safety findings were observed. No life-threatening or fatal adverse events were reported.

The most common adverse reactions to Voxzogo were injection site reactions (85%), vomiting (27%), and decreased blood pressure (13%) [11].

Injection site reactions, such as swelling, redness, itching or pain, were reported in 85% patients treated with Voxzogo compared to 82% patients on placebo.

Voxzogo is an analogue of the C-type natriuretic peptide (CNP). Due to the biological effects of CNP on vascular function, transient decreases in diastolic blood pressure could be expected, and were described under the most common adverse events. To reduce the risk of a potential decrease in blood pressure and associated symptoms (dizziness, fatigue and/or nausea), pa-

tients should be well hydrated at the time of injection. Patients with significant cardiac or vascular disease and patients on anti-hypertensive medicinal products were excluded from participation in premarketing clinical trials.

Since Voxzogo is a peptide, immunogenicity and potential hypersensitivity adverse events are of special interest with respect to safety. The immunogenicity results currently available did not indicate a risk from immunogenicity-caused complications, but anti-drug antibodies were detected with an incidence of 38%. Neutralising antibodies (NAb) were detected in 2% of the same population, probably transient, and had no negative impact on growth [16].

At present, there is no signal that the improvement in growth is associated with any detectable premature bone maturation, disproportionate skeletal growth or abnormal bone morphology.

It should be considered that the safety database is numerically limited, especially for the younger ACH children (< 5 years of age). Furthermore, potential long-term risks, particularly regarding bone and joint malformation that could lead to osteonecrosis and cartilage dysfunction after longer treatment durations is not fully evaluable at present. According to EMA, this seems to be the most important uncertainty regarding safety assessment. Long term safety will be further characterized in the post-marketing setting from the ongoing long-term studies (111-205, 111-208, and 111-302) and the planned post-authorization safety study.

3.4 FINOSE discussion

Efficacy

The clinical study program demonstrates that Voxzogo treatment increase growth in children with ACH. A strength of the clinical study program is the availability of placebo-controlled data; from study 111-301 in patients aged 5 to <18 years and from study 111-206 in patients aged 0 to <5 years. This data allows a comparison to placebo during the first 52 weeks of treatment, and to quantify the relative effect of Voxzogo versus no treatment on growth parameters in this short-term period. In children aged > 5 years in study 111-301, the adjusted mean difference in AGV between patients in the Voxzogo group and placebo group was 1.57 cm/year in favour of Voxzogo (95% CI 1.22–1.93; two-sided p<0.0001) after 52 weeks of treatment. The FINOSE clinical experts stated that an increase in growth of 1.57 cm/year in ACH children could be considered clinically relevant. The result was supported by the key secondary endpoint height Z-Score. The adjusted mean difference in height Z-score between patients in the Voxzogo group and placebo group was 0.28 SDS in favour of Voxzogo (95% CI 0.17–0.39; two-sided p<0.0001). In children aged 2 to < 5 years in study 111-206 (Cohort 1), the adjusted mean difference in height Z-score between patients in the Voxzogo group and placebo group was [----] SDS in favour of Voxzogo (95% CI [--------]; two-sided p=0.0570) after 52 weeks of treatment.

Data on long-term efficacy on growth is limited. At present, no children have received treatment with Voxzogo from 2 years of age and until the epiphyses close. Data on the final adult height that can be achieved after a full course of treatment with Voxzogo is therefore lacking. Results from the ongoing extension studies suggest that an improvement in growth is maintained. However, it is not known to which extent growth is increased with Voxzogo treatment compared to no treatment over long-term due to lack of control groups in the extension studies. The 12-month interval AGV demonstrated a small decline in change over time relative to baseline in the extension studies 111-302 (4 years follow-up) and 111-205 (7.5 years follow-up). At the same time, the results in study 111-302 show continuous improvement in height Z-score during the 4 years follow-up period, and this supports that an improvement in growth persists. In study 111-205, however, there seems to be no further improvement in height Z-score after 4 years of treatment. The mean age at treatment start was 7.6 years in this study, and the patients

will thus be around 11 - 12 years on average after 4 years of treatment. A natural downward trend in growth velocity is observed in children with ACH at this age, and this may explain the results [23]. Of note, the results are based on a small number of patients and must be interpreted with caution.

The FINOSE clinical experts explained that based on the mechanism of action of Voxzogo, there is reason to believe that the effect on growth will persist with continued treatment. However, the possibility that Voxzogo could lose effect when used in long term (i.e., tachyphylaxis) cannot be fully excluded. Whether undesired consequences of counteracting FGFR3 function will arise or whether tissue resistance to CNP could complicate this therapy are still unknown [2].

Voxzogo is indicated in patients from 2 years of age, and earlier treatment initiation will likely result in a greater final height than later treatment. The pivotal study 111-301 enrolled children aged 5 to < 18 years, and mean age at baseline was about 9 years. Efficacy data in the younger population from 2 to 5 years is currently available only for 15 children treated with Voxzogo for one year in study 111-206 (Cohort 1). More data are needed to confirm the persistence of the effects of Voxzogo on growth for an extended period and the impact of age at treatment initiation on final height.

There is currently no available evidence for a direct effect of Voxzogo on medical complications of ACH.

The documentation is also limited in the ability to determine whether improvements in growth will translate into benefits of functionality, activities of daily living and quality of life. The FINOSE clinical experts believe that Voxzogo will provide clinically meaningful benefits compared with current care. Voxzogo is the first medicine to treat the underlying cause of ACH. If the treatment effect on growth persists, 10 - 15 years of treatment with Voxzogo can result in an increased adult height of about 15 - 20 cm, which corresponds to a final average adult height of approximately 147 - 152 cm in males and 139 - 144 cm in females (estimated based on adult height in ACH as reported by Merker 2018). The FINOSE clinical experts explain that even a smaller increase in height would be beneficial for the patients. The FINOSE clinical experts agree that a gain in height would improve quality of life for the average patients even in the absence of any change in comorbidities. The FINOSE experts emphasized, however, that at present no evidence is available on what the final adult height that can be achieved with the Voxzogo treatment can be.

Safety

Voxzogo treatment is generally well tolerated. The most common side effects are injection site reactions (such as swelling, redness, itching or pain), vomiting and decreased blood pressure. Since Voxzogo needs to be subcutaneous injected once daily this may be a tolerability issue.

Voxzogo is an analogue of the C-type natriuretic peptide (CNP). CNP is a natural peptide with known hemodynamic effects, and the same is seen with Voxzogo. To reduce the signs and symptoms of potential decreases in blood pressure (dizziness, fatigue and/or nausea), patients should be well hydrated at the time of injection. It is recommended patients eat a light snack and drink a glass of fluid about 30 minutes before injecting.

There have been no important safety risks identified associated with Voxzogo at present. The long-term experience is however still limited.

FINOSE conclusion: It is agreed that the clinical study program has demonstrated that the Voxzogo treatment increases growth in children with ACH. Children aged > 5 years who received Voxzogo in study 111-301 grew about 1.57 cm more during the one year of treatment than those receiving placebo. Results from the ongoing extension studies suggest that an improvement in growth is maintained. However, it is not known to which extent growth is increased with Voxzogo treatment compared to no treatment over long-term due to lack of control groups in the extension studies.

FINOSE notes that there are important knowledge gaps. Data on long-term efficacy on growth is limited and data on the final adult height that can be achieved after a full course of treatment with Voxzogo is lacking. In addition, there are no data currently available on the direct impact of Voxzogo treatment on complications, functionality, activities of daily living and quality of life.

4 Cost-effectiveness methods

The following chapter is based on the dossier sent in by the company. All assumptions described are based on the application if not otherwise stated. The conclusions boxes after each section gives a short assessment of the choices related to key parameter inputs, used methods, simplifications and scientific judgements made by the company. The results of the FINOSE scenario analyses are presented in section 5.2.

4.1 Company model description

The company has submitted a cost-effectiveness evaluation using an individual simulation model, in which patients who have been treated with Voxzogo are compared with patients who have received best supportive care, which focuses on mitigating complications associated with untreated ACH. The model has a lifetime horizon (100 years) and uses a time cycle of one year. In each cycle, the model calculates the impact of any one-time events (e.g. surgery) and the impact of complications (See Model Schematic below, Figure 2). The model considers the incidence of complications above the rate expected in the general population.

In the base case, the modelled population reflects patients with ACH aged 2 years and older, confirmed by genetic testing, with open growth plates. The company assumes that the age of growth plate closure occurs at 15 years for the average patient. The impact of treatment on bone growth is assumed to be maintained for the full duration of treatment. In total 1 000 patients are simulated in the model.

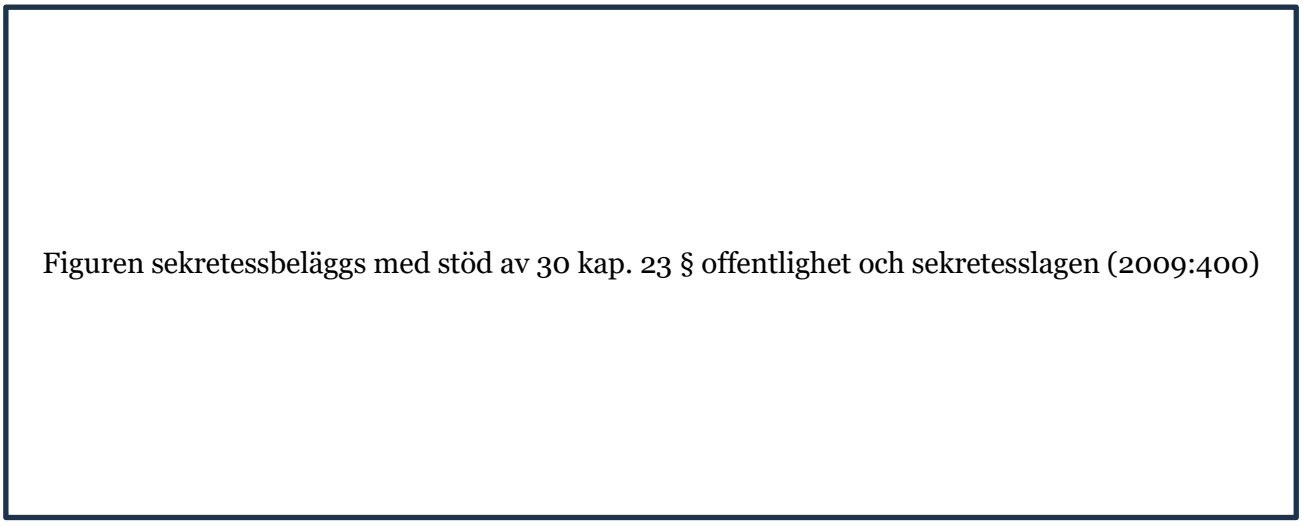

Figure 2 The company's model schematic

FINOSE discussion
FINOSE find the lifetime perspective of the model to be reasonable for this chronic condition in order to capture the costs and effects. The company's choice of simulation 1 000 patients is deemed enough to produce stability in the results. FINOSE's clinical expert supports the representativeness of the model population. The company has submitted a patient level Markov model which is better at capturing the heterogeneity of the patient population than a cohort Markov model, but the output given by the model complicates validation of some outcomes.

FINOSE conclusion: FINOSE concludes that the model structure is suitable to evaluate the decision problem, but the model outputs make the validation of the model more difficult.

4.2 Effectiveness outcomes

4.2.1 Clinical effectiveness

Treatment effect in the model: PRAGV
The company models growth on a yearly basis according to the height of the simulated patient at entry into the model. For each year of childhood, the mean AGV and SD are used to determine the AGV for each simulated children according to the centile of their height at entry into the model (patients with a greater height for their age at model entry will experience higher AGV in the model). The company uses data on the distribution of baseline height in children with ACH by age from Merker (2018) who reported growth references from a European cohort of children with ACH.

For each simulated patient in the model, the corresponding baseline height and growth curve in the absence of ACH (i.e average stature) is also modelled based on the Swedish WHO standardised growth charts for height and weight [25]. Growth trajectory in the absence of ACH was simulated according to the growth curve for the average stature population on the same centile value for their height according to the population distribution.

The treatment effect of VOS is modelled as percentage recovery of expected AGV (PRAGV). In the base case, the company uses a PRAGV of 77.28%. Treatment with Voxzogo was thus assumed to restore 77.28% of the shortfall in AGV for a patient with ACH compared to an average stature person (AGVas) of the same age, sex, and birth height percentile, in the given year of treatment. While AGV is age dependent, it is assumed in the model that the PRAGV is independent of age.

The PRAGV was based on 52 weeks efficacy data from Study 111-301 (Table 7). To estimate the PRAGV, a weighted mean of the percentage of AGVas was first calculated for the Voxzogo and placebo arms [----------]. The PRAGV was then calculated as the ratio of the difference between the percentage recovery of AGVas in the Voxzogo and placebo arms [----------], and 1 minus the percentage recovery of AGVas in the placebo arm [----------]. This generated a PRAGV of 77.3%.

Figuren sekretessbeläggs med stöd av 30 kap. 23 § offentlighets- och sekretesslagen (2009:400)

Table 7. Data on height gain at 52 weeks in Study 111-301 (FAS population) as used in the calculation of PRAGV.

Complications
In addition to the treatment effect on growth, the company assumes that increase in bone growth reduces the risk of complications arising from ACH. The risk reduction is estimated as the reduction in height difference compared to average stature individuals at the same age, relative to ACH patients without treatment calculated as $(Height_{VOS} - Height_{ACH}) \div (Height_{AverageStature} - Height_{ACH})$. For instance, if an ACH patient is 20 cm shorter than an average stature

person for a given age, and Voxzogo restores 10 cm, then the assumed risk reduction for complications for this patient is 50%. Assumptions regarding complications are in the base case based on the Lifetime Impact of Achondroplasia Study in Europe (LIAISE), supplemented with studies from the published literature where data for relevant complication was not available in the LIAISE. The LIAISE-study was commissioned by BioMarin and enrolled 195 patients from six European countries (Austria, Denmark, Italy, Germany, Spain and Sweden). The study assessed amongst other things the impact of ACH on QoL as well as clinical burden (including functional impact, comorbidities, complications, medical and surgical care). The company has modelled the complications stated below.

- Foramen magnum stenosis requiring decompression surgery
- Hydrocephalus requiring shunt surgery
- Sleep apnoea
- Spinal stenosis requiring surgery (laminectomy)
- Kyphosis and lordosis requiring surgery (spinal fusion)
- Genu varum (leg bowing)
- Cardiovascular disease (infarction/stroke)
- Depression
- Chronic pain
- Otitis media
- Hearing loss
- Dental malocclusionm

Reduced life expectancy associated with ACH is assumed to arise from raised mortality risks associated with complications arising from the condition. The company assumes that foramen magnum stenosis, sleep apnoea, spinal stenosis, CVD, major depression, and chronic pain increase mortality. Mortality is not assumed to be affected by height itself, and the difference in mortality between the arms is due to differences in complications alone. In Figure 3 the mortality of the VOS arm, the BSC arm, and the general population is shown.

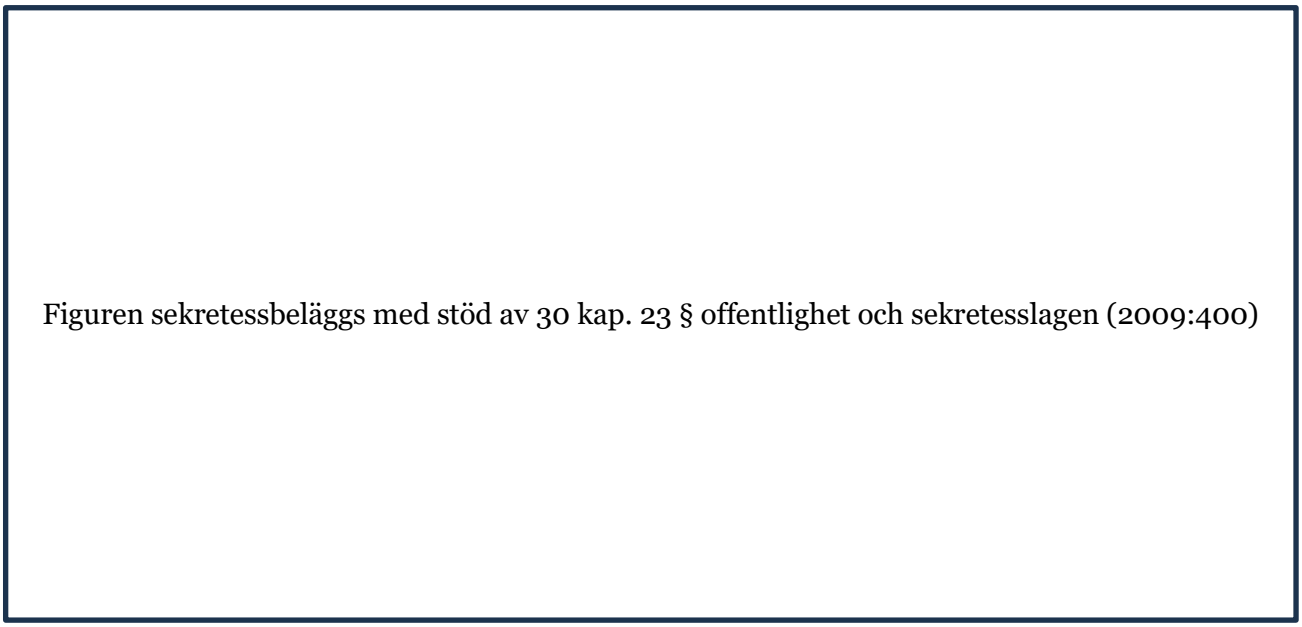

Figure 3. Output from the economic model (Company's base case): Overall Survival

Limb lengthening

Based on clinical expert opinions, the company assumes that utilization of limb lengthening surgery differs between the Nordic countries ([----] in Finland, [----] in Sweden, [-------] in

Norway). In the base case, the company applies a [---] probability of limb lengthening at an age of 20 in the BSC arm based on input from the Swedish clinical expert to the company. In the Voxzogo arm, the probability of limb lengthening was reduced in proportion to the height gain using the same approach as complication risk reduction. The company assumes a total improvement in height of 6 cm [26].

FINOSE discussion

Treatment starting and stopping age
Treatment starting and stopping age, and thus Voxzogo treatment duration, has a large effect on the model results.

In the company base case all patients are assumed to start treatment at the age of 2 years. FINOSE believes this starting age will be representative for a future patient population, but not the current population in the FINOSE countries. ACH is diagnosed before or shortly after birth and patients diagnosed from now on are expected to start treatment with Voxzogo from the age of 2 years according to the SmPC label. However, in today's clinical practice patients in the wider age range from 2 years to near the end of puberty, when the epiphysis close, will be eligible for treatment. In the model, earlier treatment initiation results in a greater final height than later treatment initiation. When all patients start treatment at the age of 2 years in the company base case, this overestimates the treatment benefit of Voxzogo for the current populations in the FINOSE countries.

Study 111-301 enrolled children aged 5 to < 18 years, and mean age at baseline was about 9 years. The youngest study participant was 5.1 years at the start of treatment, and the oldest 14.9 years. Most patients were in the youngest age group. The distribution in age groups at baseline was 45.5% of the patients from 5 to < 8 years, 33.9% from 8 to < 11 years, and 20.7% from 11 to < 15 years. The FINOSE clinical experts assume that the study population is representative of the target population, although the population in clinical practice will be somewhat younger, as children aged 2 to 5 years will also be eligible for treatment but were not included in the 111-301 study. At present, no children have received a full treatment course with Voxzogo from 2 years of age and until the epiphyses close as modelled in the company's base case.

To achieve a clinically relevant increase in height with Voxzogo treatment, the treatment duration must be long enough. It is therefore important to initiate treatment with Voxzogo in children as young as possible. At a certain age, it may be considered too late to initiate treatment because there is too little time left before the growth plates close. The FINOSE clinical experts suggest starting before puberty or that the patients should have at least 4 remaining years of growth at treatment start. This corresponds to the age of approximately 11 years for girls and 13 years for boys. However, the clinical experts highlight that more documentation is needed to be able to determine an age limit. For example, data on whether Voxzogo treatment can stimulate a growth spurt during puberty, and whether spinal stenosis can be improved.

In the FINOSE base case the treatment starting age is adjusted from 2 years for all patients to an age range from 2 to 12 years to better reflect eligible patients in today's clinical practice and available study data. Results of a sensitivity analysis with starting age of 2 are presented in chapter 5.2.2.

According to the SmPC treatment should be discontinued upon confirmation of no further growth potential, indicated by a growth velocity of < 1.5 cm/year and closure of epiphyses. The FINOSE clinical experts explain that in clinical practice further growth potential is assessed based on growth velocity and not based on closure of epiphyses. They find it challenging to estimate at what age the treatment with Voxzogo would be stopped. The clinical experts refer

to experience with growth hormone treatment in patients without ACH. Growth hormone treatment is usually stopped when the growth velocity is reduced to approximately 2 cm/year. In children with ACH the magnitude of growth is lower in all age groups, and treatment discontinuation for Voxzogo at growth velocity < 1.5 cm/year seems reasonable according to the FINOSE clinical experts. They consider it plausible that this slowdown in growth velocity will happen at about the same age in children with ACH as in normal stature children, i.e., 14 – 16 years for girls and 15 – 17 years for boys. In the 111-205 trial a total of five participants (4 girls and 1 boy) had reached near final adult height at the data cutoff 25 Feb 2022 (up to 7.5 years follow-up). Age at near final adult height was from 14.5 – 15.9 years for the girls and at 16.3 years for the boy. In the model, the company uses data from Merker (2018) to model growth in children with ACH in the BSC arm [1]. The study was based on a mix of cross-sectional and longitudinal data of 466 European children of European origin. In the study the height gain is < 1.5 cm/year when the patients on average reach 16 years of age among girls and 18 years among boys. Based on the inputs from the FINOSE clinical experts, and the growth references for ACH, FINOSE believe that the treatment stopping age of 15 years in the company's base case is low. In the FINOSE base case the treatment stopping age is adjusted to 16 years. Results of a sensitivity analysis with stopping age of 15 and 17 are presented in chapter 5.2.2.

Treatment effect:
The final height in the company base case is 152 cm for the Voxzogo arm and 130 cm for the BSC arm. The height in the BSC arm is aligned with the Merker 2018 publication on which the modelling of height is based on. In this study adult height was 132 cm in boys and 124 cm in girls. As previously described no patients has received Voxzogo covering the entirety of the model ages which hinders validation of the treatment effect.

The treatment effect of Voxzogo is one of the most influential input parameters in the economic model. The treatment effect is applied as a percentage recovery of expected annualized growth velocity, PRAGV. The method of PRAGV calculation appears correct. The potential issue is the application of the fixed Voxzogo treatment effect to the average stature height and not to the ACH height. In the model Voxzogo treatment restores normal growth relative to average stature, rather than adds growth relative to ACH natural history. This is problematic as there is no growth spurt during puberty in ACH, hence the Voxzogo effect during puberty is likely overestimated. In addition, the PRAGV is derived from study 111-301 where the effect of Voxzogo was compared head-to-head to placebo. Meanwhile, the CUA models the effect of Voxzogo relative to external average stature data, introducing additional uncertainty in the results.

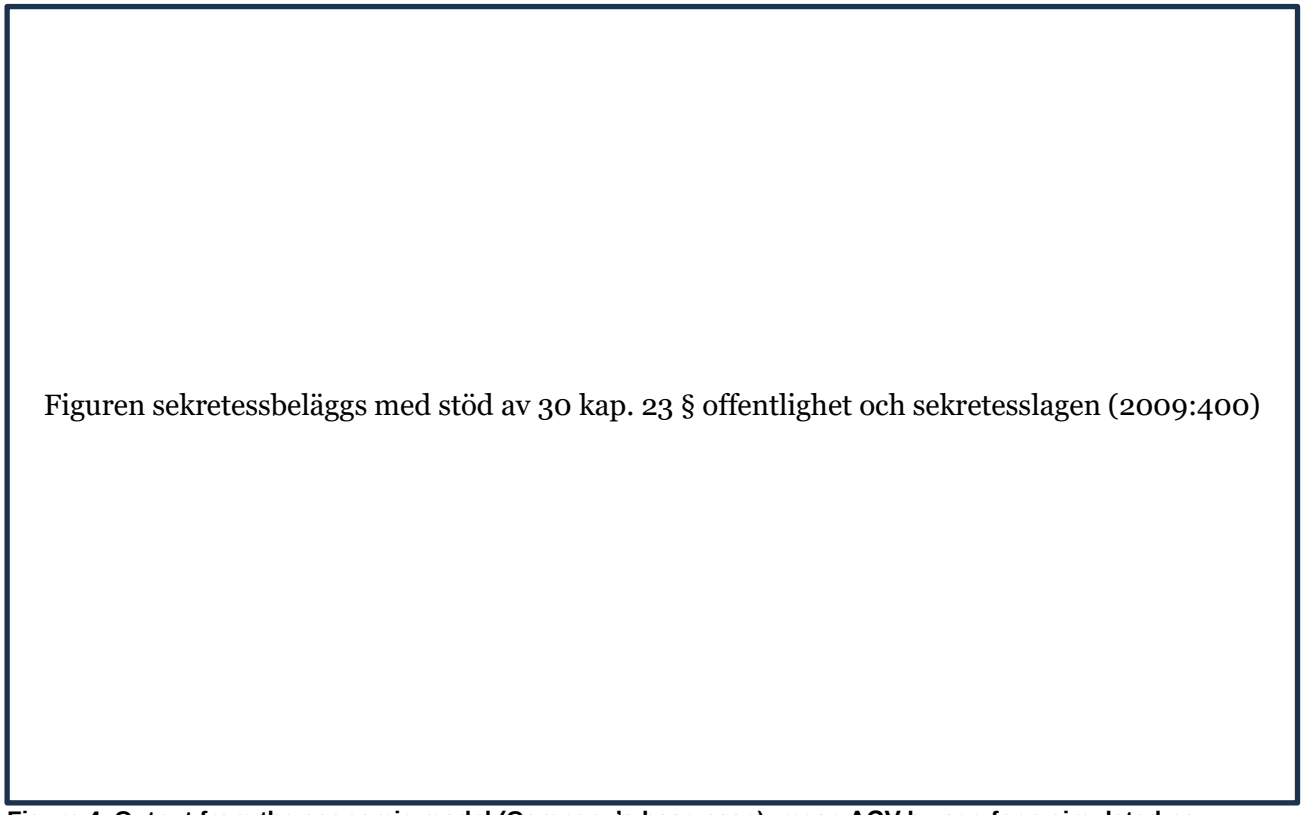

Figure 4. Output from the economic model (Company's base case): mean AGV by age for a simulated patient

FINOSE explored an alternative approach where a height difference of 1,59 cm (calculated as weighed average difference between placebo and Voxzogo in study 111-301, based on the same age categories as used for PRAGV calculation) was applied cumulatively directly to the ACH height starting from year 2, hence avoiding dependence on the average stature height and the implausible growth spurt in puberty. The resulting gender weighted average AGV for years 2-15 was 5.6cm, which was very similar to the company's base case model outputs of 5.9cm.

The constancy of treatment effect is another assumption with great uncertainty in the economic model. Data from an open-label single arm extension study 111-302 show that the AGV of 5.61 (SD 1.05) as obtained in the Voxzogo arm in study 111-301 is maintained over 48 months. When indirectly compared to external data, the AGV seems to be aligned with the average stature population adjusted for age and gender, and the treatment effect appears constant when compared to the ACH natural history data (AchNH) [18]. Similarly, results from a small single arm multi-cohort Study 111-202 and extension study 111-205 (with mean starting age of 7.6 years) showed that the AGV of around 5 was maintained for 3 years, after which it started declining and reached AGV of 4 at year 7. The company claims that such decline is expected in ACH patients at that age. Indeed, height data from Merker 2018 show that the decline in AGV can be observed among boys from age 15 and among girls from age 11.

The economic model produces an average height difference between Voxzogo and placebo of 22.2cm in final adult height. Given that the treatment starting age in the company's base case is 2 years, and the stopping age is 15, the extrapolation of the height increment of 1.57 cm from study 111-301 would give a similar result if the benefit would continue. The height increment of 22.2cm is therefore considered optimistic as it implies that the treatment effect of Voxzogo

does not decline over the years. To support these results, the company has conducted comparative analyses between Cohort 3 (subjects who received 15 µg/kg) from Studies 111-202/205 (N=10) and Achondroplasia Natural History (AchNH) study (N=360) over 5 years. After adjusting for differences at baseline, the treatment with Voxzogo resulted in a difference vs external placebo of [----------] cm at year 5. These results were consistent when using a sex and age matched external control group from the pooled other natural history sources [----------]. This was more than would be observed in Study 111-301 [----------]. FINOSE has not evaluated the quality of these comparative analyses but notes that the sample size of ten is extremely small.

An option of using age dependent PRAGV as opposed to fixed PRAGV is available in the economic model but the source of PRAGV is not provided. For this option a PRAGV of 75% is applied for ages 3-10, 70% for ages 11-13, 60% for ages 14-15 and 50% for ages 16-17. Given the limitations discussed in the paragraphs above, the declining PRAGV could be reasonable. However, these PRAGV values are not supported by the study 111-301 results. The use of age dependent PRAGV produces a height difference of 21,1 cm in final adult height.

Complications:
As described in section 2.1 of the report, ACH causes delayed motor development and an increased risk of medical complications. The company assumes that increased height reduces the risk of complications proportional to the height gain, as described in section 4.2.1.

The FINOSE clinical experts explain that there is currently no evidence to support an effect of Voxzogo on medical complications of ACH and emphasize that long-term data are needed to assess these outcomes. In theory, however, it is plausible that Voxzogo treatment can have an impact on medical complications due to its effect on bone growth. However, some complications such as foramen magnum stenosis may be difficult to impact due to changes that occur prenatally and in the neonatal period [27]. A positive effect of treatment on this complication can only be expected if treatment is started very early in life. On the other hand, symptomatic spinal stenosis and kyphosis, and related back pain, are most prevalent in adults with ACH and may be altered if treatment is started at a later age, when spinal growth can still be improved. Symptomatic spinal stenosis is prevalent in adults with ACH, and is associated with reduced walking distance, activity limitations, and more pain [8]. It would therefore be of great benefit for the patients if spinal stenosis could be improved with Voxzogo treatment.

FINOSE concludes that the company provides support for an increased risk of complications between the affected patient population and the general population, however, the company fails to provide evidence of the effect of treatment and height gain on the risk decrease of complications. Consequently, FINOSE excludes complications from the base case but notes that this may be a conservative approach. Additionally, with the removal of complications there is no longer any risk difference in mortality between Voxzogo and BSC. Lastly, a scenario analysis with complications included resulted in very low average utility values in the BSC arm which is not supported by the literature (see FINOSE discussion under chapter 4.2.2.).

Other:
Patients receiving Voxzogo will not receive limb lengthening surgery. The company states that the proportion of patients that undergo limb lengthening surgery differs between Norway, Sweden and Finland and FINOSE deems these values to be reasonable. Sensitivity analyses exploring different proportions are presented in chapter 5.2.2.

FINOSE conclusion: Treatment starting and stopping age, and thus Voxzogo treatment duration, has a large effect on the model results. FINOSE adjusts the treatment starting age from 2 years for all patients to an age range from 2 to 12 years to better reflect eligible patients in

today's clinical practice and available study data. Treatment should be discontinued at growth velocity < 1.5 cm/year and FINOSE adjusts stopping age from 15 to 16 years based on inputs from clinical experts and growth references for ACH.

The modelling of treatment effect through PRAGV can be accepted. FINOSE had concerns about the application of the treatment effect to the average stature height instead of the comparator arm in the model, however, this does not seem to affect the model results. The constancy of treatment effect over the time horizon was another strong assumption as long-term data is limited. The modelled incremental height of 22 cm between the arms in the company's base case indicates that the growth increment observed in study 111-301 continues, and limited data exist to validate these results. FINOSE accepts the modeling of the treatment effect due to the lack of a better estimate, but notes that this is a large source of uncertainty. Alternative PRAGV values have been explored in sensitivity analyses.

FINOSE concludes that the company fails to provide evidence of the effect of treatment and height gain on the risk decrease of complications and therefore, complications are excluded from the FINOSE base case.

4.2.2 Health related quality of life

The company has not included health related quality of life (HRQoL) values from the clinical study but instead calculated a health state utility value (HSUV) as a function of patient age, height, and comorbidities based on literature. The number of years the simulated patient lives is summed up after weighting each year with the HSUV and discounting, to calculate lifetime QALYs.

The company estimates the HSUV for a patient as a function of the patient's z-score using a regression model being initially estimated from data in the Health Survey for England (HSE). An age adjustment multiplier is applied based on the patient's age at the given cycle, based on Swedish population values. A multiplier is then applied to the HSUV for each existing comorbidity with values estimated from the literature. After application of all relevant multipliers, an additive disutility is added to the HSUV for relevant complications in the year in which they occur, see Table 8 below for multipliers and disutilities associated with complications. A utility increment is assumed for patients that reach heights above a disability threshold of 150 cm. Finally, a disutility is estimated for caregiver burden as a function of patient height. No disutility associated with adverse events was included in the model.

Table 8. Multipliers and disutilities for modelled complications

Complication	Multiplier	Disutility	Duration	Source
Sleep apnoea	0.920		Lifetime	Schmidlin 2010 [28]
Spinal stenosis	0.810		Lifetime	Nayak 2019 [29]
		-0,263		
Kyphosis/lordosis	0.916		2 years	Abodor 2010 [30]
		[------]	[----------]	[----------]
Leg bowing	[-----]		[-------]	[----------]
		[------]	[----------]	[----------]
CVD	0.798		Lifetime	Pockett 2018 [31]
		-0,150	One time disutility the year of the event	Matza 2015 [32]
Depression	0.798		Lifetime	Wu 2015 [33]

Chronic pain	0.725		Lifetime	Wu 2015 [33]
Hearing loss	0.896		Lifetime	Baek 2016 [34]
Orthodontic surgery	0.940		1 year	Sullivan 2011 [35]
Tympanostomy	[-----]		[-------]	[----------]
Obesity	0.950		Lifetime	Sach 2007 [36]
Decompression surgery		-0,244	One time disutility the year of the event	Nayak 2019 [29]
Shunt insertion		-0,070	One time disutility the year of the event	Matza 2014 [37]
Limb lengthening		-0,521	One time disutility the year of the event	Hafez 2022 [38]

Adjustment of HSUV as a function of height

The company has conducted a literature review search for HRQoL and HSUV in ACH but did not identify sufficient data to estimate the improvement in QoL associated with an increase in height. Instead, the company used the results of the Christensen et al paper where the relationship between EQ-5D-3L and height based on 14,416 Health Survey for England respondents was reported (Figure 5) [39].

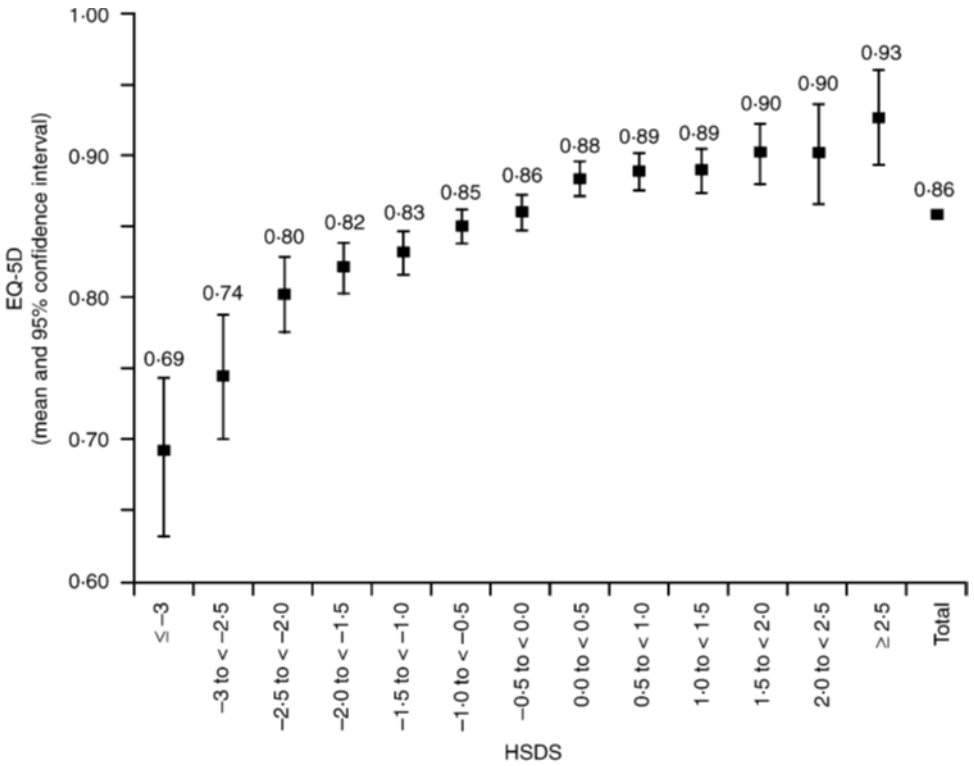

Figure 5. Relationship between height standard deviation score and EQ-5D score (mean and 95% confidence interval) from Christensen 2007[39].

The company digitalized the pooled published results, excluded the extremes (HSDS ≥ 2.5 and HSDS ≤ -3), and fitted a regression line based on 11 HSDS/EQ-5D points. The quadratic model was chosen over a linear model due to a better visual and mathematic fit (R^2 and AIC). The resulting quadratic polynomial function was:

Utility=〖-0.0064×HSDS〗^2+0.0298×HSDS+0.8748

Age adjustment of HSUV by patient age

In the model, age-dependent HSUV multipliers are estimated based on quality-of-life data measured with EuroQol 5-Dimension (EQ-5D) in the Swedish general population as reported by Burström et al 2001 [40]. The study did not report utility values for age spans 0-19 and ≥89 years. For these age spans, respectively, it was assumed in the current model that the HSUV was the same as in the adjacent age span. The multiplier at a given age represents the percentage decrement comparing the HSUV at that age relative to the general population HSUV at baseline.

Adjustment of HSUVs for comorbidities

The combined impact of all relevant complications at a given cycle was used to generate a decremental complication disutility by multiplying the product of all factors with the age-dependent HSUV for the general population. The difference between the resulting value and the age-dependent HSUV represented the decremental utility associated with complications at the given cycle:

[Utility decrement] = [General population HSUV by age] – [General population HSUV by age] × [Multiplier, complication 1] × [- - -] × [Multiplier, complication n].

The multiplier values were based on various research papers and assumptions. How the source articles were selected was not described. The assumptions on duration were mainly based on the outcome of the company's advisory board and feedback from clinicians contacted by the company.

Caregiver disutility

A carer disutility is included in the model whilst patients remain children, based on the data from Kuhlthau and co-workers [41]. The study compared EQ-5D-3L tariff scores for 15,972 parents of children with and without activity limitations. Multivariate analysis, controlling for differences in child and parent characteristics, estimated a reduction in parental EQ-5D-3L tariff score of 0.070 (95% CI: 0.03, 0.10) associated with child activity limitations. The model assumes a reduction in carer disutility proportional to the reduction in the gap between AGV for the simulated patient with ACH and an average stature child of the same age, sex and percentile height. This reduction is 77.3% in the base case analysis. Consequently, the model assumes a reduction in carer disutility to 0.0159 associated with Voxzogo treatment. This is implemented as a gain of 0.0541 QALYs for each year a patient is on Voxzogo treatment.

Utility increment from exceeding height threshold

In the economic model, once a patient exceeds 150cm in height, an incremental utility of 0.1 was arbitrary added for that patient. This adjustment was justified with the opinion from clinical experts contacted by the company who stated that over certain height thresholds, the QoL improves substantially. According to the clinical experts, the regression model based on the Christensen data alone more probably underestimates the QoL gain from height improvement.

FINOSE discussion

In Study 111-301, no difference was observed in change from baseline to week 52 between the Voxzogo and placebo groups in any of the used QoL measures; The Pediatric Quality of Life Inventory score (PedsQLTM 4.0), The Quality of Life in Short Stature Youth (QoLISSY®), The Pediatric Functional Independence Measure II (WeeFIM®-II). FINOSE acknowledges that the study duration of 52 weeks was likely too short to capture that effect of height on QoL. The FINOSE clinical experts uniformly agree that a gain in height would improve QoL for the average patients even in the absence of any change in comorbidities. However, the literature reporting the association between height and HRQoL is limited [42]. A cross-sectional study based on 184 Japanese ACH patients showed that physical, but not social or mental components of a HRQoL measure, SF-36 questionnaire, are affected by height [43]. The company's observational study LIAISE based on 186 European ACH patients showed that compared to general population values, patients reported impaired QoL particularly for physical functioning domains. In addition, patients reported difficulty carrying out daily activities independently and pain starting in childhood. However, the correlation analysis between height/z-score and patient-reported outcomes showed negligible to low correlation.

Utility in the economic model were ultimately modelled as a function of HSDS, i.e. increasing height translated in improvements in QoL. Age and comorbidity-related utility adjustment was added outside of the regression model. The regression coefficients for HSDS were estimated from 11 data points from a published paper [39], where the relationship between HRQoL as measured using the EQ-5D and a number of exploratory variables (HSDS, gender, age, limiting long-standing illness, social class and weight) in adult general UK population was assessed. This study showed that short adult stature is significantly correlated with HRQoL. The representativeness of those results to the ACH population is questioned. Firstly, the relationship between height and utilities based on adult population might not be translatable to children. Secondly, life quality data from general population are not transferable to ACH patients with the same height as ACH patients have in addition shorter arms and disproportionality that negatively affects their QoL. Thirdly, the Christensen results were based on general population with the mean height of 175 cm and 161cm in male and female, respectively. Subsequently, the least frequent HSDS of <=-3 (which is also the most relevant for the ACH population) was pooled into one data point, and mostly irrelevant HSDS of -3 to >=2.5 were split into 11 categories in the paper. The resulting regression coefficients in the utility equation are therefore based on irrelevant HSDS for the ACH population. Furthermore, as the regression is based on pooled published results, as opposed to patient level data, the variance of the estimates is likely underestimated. The mathematical fit of data to the regression model is high (R^2=0.96) and the variance of HRQoL appears to be almost exclusively explained by the single height variable, which is not believed to be the case in real life. In fact, the multivariate regression in the Christensen publication shows that apart from HSDS, other variables such as gender, limiting illness, and weight are significant predictors. Even with 6 exploratory variables, the goodness-of-fit is low (i.e R^2 of about 0.3) in the Christensen publication. Overall, modelling utilities as a function of gender- and age-dependent HSDS, where age adjustment and complication disutilities are added outside the regression model is considered a simplistic approach.

To compensate for the potential underestimation of the QoL gain from height improvement, the economic model adds a utility increment of 0.1 once a patient reaches 150cm. The clinical experts contacted by FINOSE suggested the height of 140 cm –150 cm to be sufficient to ensure that daily activities are possible without considerable adjustments. A paper by Matsushita et al (2019) based on ACH patients (10–67 years old) confirms that physical functioning improves with this height threshold and that a treatment strategy would be planned to gain a final height of 140 cm or taller during childhood [43]. However, the analyses in this paper did not adjust for age nor age-related musculoskeletal complaints/pain which could be important drivers of the results. Overall, FINOSE agrees that adding a utility increment of 0.1 might be reasonable

from a clinical perspective. However, it must be stressed that this utility increment is added outside the regression model described above risking double counting the effect of growth on QoL gain.

The company argues that there is a significant burden on the caregivers of ACH patients. This is very probable given the well-being, help and adaptions needed for the patients. The company provided the results from a survey study comparing EQ-5D-3L tariffs between parents to children with and without activity limitations and applied a disutility proportional to the reduction in height difference between the patient and an average stature child. There is however no evidence of the impact on QoL for caregivers of ACH patients, or the impact of reduction of disability on the caregivers QoL presented. In alignment with the different guidelines within Norway, Finland and Sweden, caregivers QoL are not included in the FINOSE base case. Results of a sensitivity analysis with inclusion of caregivers QoL are presented in chapter 5.2.2.

When the disutilities for complications are included in the economic model, the model produces 14.71 QALYs over 74.50 life years in the comparator group (undiscounted results), which implies that an average patient has 0.2 utility value per year over lifetime. This is extremely implausible given the mean EQ-5D-5L index value of 0.7 in the LIAISE study. When complications are excluded from the model, total QALYs for the comparator arm increases to 28.51, which gives average utility of 0.38 (Company's base case, but with complications excluded). The company argues that the utility value of 0.7 reported in LIAISE is based on the EQ-5D which is considered insensitive to measuring QoL in ACH due to issues such as the 'disability paradox' whereby patients with ACH experience adaptation effects and consider themselves to be in better health than if members of the general population rated their health state. Furthermore, the EQ-5D in LIAISE was administered to adult patients who are particularly prone to adaptation effects (i.e., having learnt to cope with their condition). FINOSE acknowledges these arguments but notes that the burden of evidence lies with the company and that disease-specific QoL evidence has not been submitted. In fact, the correlation analysis between height (or HSDS) and Quality of Life in Short Stature Youth (QoLISSY) shows low correlation even with the physical score. FINOSE also believes that an average utility of 0.38 for ACH patients receiving current standard of care lacks face validity. Utilities at this low level are otherwise reported for patients with severe disabilities at late stages of progressive and fatal diseases, such as amyotrophic lateral sclerosis (ALS)[44] and multiple sclerosis (MS)[45].

Given the above limitations and concerns, FINOSE run their own regression on the QoL-height results from the Christensen publication where all the points were included in the analysis. The fit of the company's linear model (based on -3, -2.5 and -2 HSDS points from the Christensen publication), the company's base case polynomial model (including all the points), and FINOSE's linear model is shown in Figure 6.

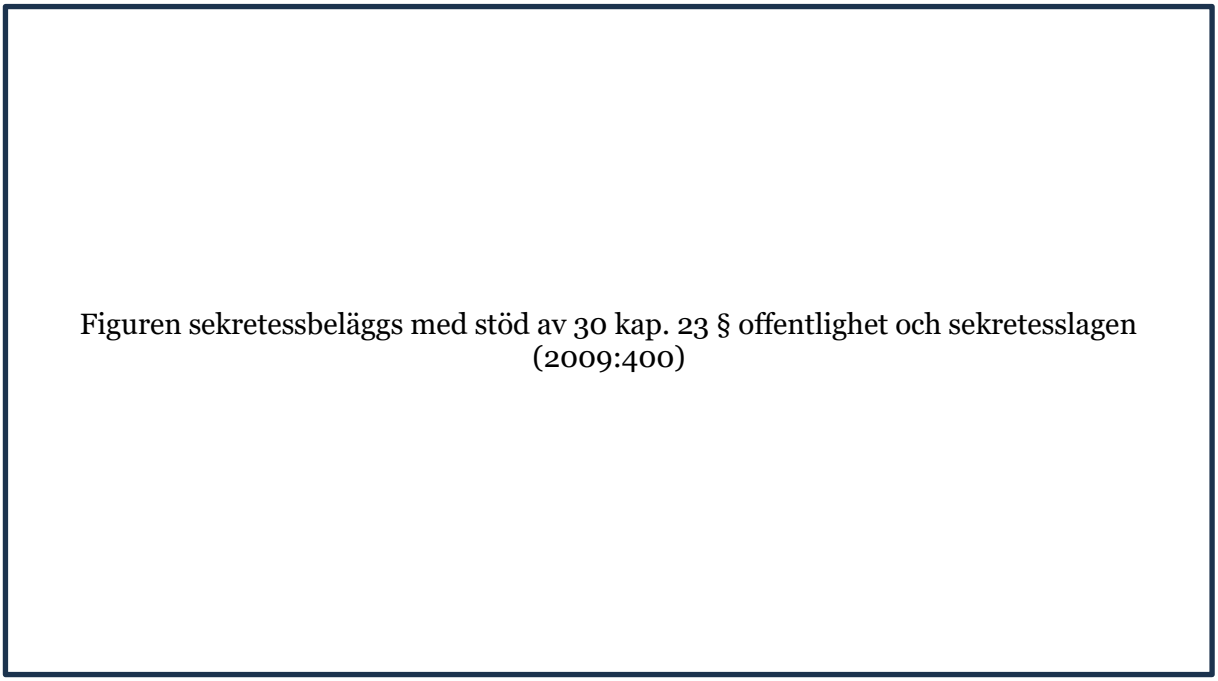

Figure 6. Fitting regression models for mean EQ-5D score vs. HSDS. Data points were digitalised from the Christensen publication, Fig.1 [39].

Regression coefficients for all the models are shown in Table 9. The FINOSE's linear model resulted in a less steep slope meaning that lower Z-scores translated in higher utility values than in the company's analyses. Consequently, the CUA model produced an average utility value in the comparator arm of 0.69 (with complications removed, undiscounted) which is more aligned with the LIAISE results than the average utility of 0.38 produced with the company's polynomial model (Table 10). In the pivotal study 111-301, the median baseline PedsQL score was 72 (Voxzogo) and 74 (placebo, caregiver-reported) or 74 (across both arms, self-reported in subjects ≥ 8 years old). This score is lower than would be expected in a healthy pediatric population [46]. According to the survey based on 20 031 families with children ages 2–16 years throughout the State of California (and 51% response rate), healthy children have a mean PedsQL score of 84 and those with chronic conditions have a mean score of 74 (self-reported). A chronic health condition was identified by their parents as having 1 of the following conditions: asthma, diabetes, attention deficit hyperactivity disorder (ADHD), depression, or "other"[47]. The cut-off scores for at risk status for impaired HRQoL data was 70 (self-reported) and 65 (caregiver-reported). Given the baseline PedsQL score in Study 111-301, FINOSE has compared the utility output from the economic model with the utilities observed in diabetes or asthma. A review of utility values for economic modeling in Type 2 Diabetes based on 19 articles showed that index value estimates for T2DM without complication ranged from 0.711 to 0.940. Utility decrement associated with complications ranged from 0.014 (minor hypoglycemia) to 0.28 (amputation)[48]. For asthma, a systematic review based on 52 eligible studies showed that the pooled utility value of EQ-5D-3L was 0.72 for uncontrolled to 0.87 for well-controlled asthma [49]. Overall, these studies support the modelling of the comparator's utilities with the FINOSE's linear model.

Table 9. Regression coefficients for mean EQ-5D score vs. HSDS. Data points were digitalised from the Christensen publication, Fig.1 [39].

	Company's linear model (points -3, -2.5, -2)	Company's polynomial model (all data points)	FINOSE's linear model (all data points)
Constant	[-----]	[-----]	0.853
HSDS	[-----]	[-----]	0.033
$HSDS^2$	[-]	[-----]	-

As shown in Table 10, with the FINOSE's linear model the average utility increment between the arms is 0.09 as compared to 0.22 with the company's base case polynomial model. In the LIAISE study, adult patients who underwent limb lengthening, what could be considered as a proxy for a treatment effect on height of Voxzogo, reported an average utility of 0.8 compared to the utility of 0.7 in ACH patients without limb lengthening. The modelled increment of 0.1 would therefore be justifiable. Overall, the internal and external evidence is limited, and the modelling of utilities is uncertain.

Table 10 Impact of different modelling of EQ-5D vs HSDS relationship on the average utility in the CUA model over the time horizon. With complications and caregiver QoLs removed, undiscounted results.

	Average utility in the BSC arm	Average utility in the Voxzogo arm	**Average utility increment**
Company's linear model [----------]	0.44	0.61	**0.17**
Company's base case polynomial model [----------]	0.34	0.55	**0.22**
FINOSE's linear model (all data points)	0.69	0.79	**0.09**

FINOSE conclusion: The company's modelled average utility value of 0.38 (with complications removed, undiscounted) in the comparator arm does not find support in the literature. FINOSE agrees to model utilities as a function of HSDS based on the Christensen publication. But modelling of utilities is oversimplified as it implies that HSDS is the only predictor of HRQoL. Furthermore, FINOSE chooses to estimate utilities based on the FINOSE's linear regression model instead of the company's polynomial model as it aligns closer with observed data in the patient population, but these estimates are still associated with high uncertainty. The utility increment of 0.1 for exceeding 150 cm in the CUA model is accepted due to clinical plausibility.

As stated previously FINOSE concludes that the company did not provide sufficient evidence for the effect of Voxzogo on the reduction of complications. Therefore, FINOSE does not include any utility from complications. Additionally, the caregiver utility is excluded from the FINOSE base case.

4.3 Costs and resource utilisation

The company includes four main cost components: drug treatment costs, health care resource use, one-off costs of interventions for complications, and ongoing costs for management of complications. In most cases the company uses healthcare unit costs from "Södra sjukvårdsregionens prislista" 2023 and costs for surgical interventions were sourced using DRG costs from 2023. Some costs are based on literature. The company includes costs for adverse events and routine drug treatments, however these costs have a minor impact on the result of the analysis and are hence not discussed in detail in the report.

4.3.1 Dosage/Administration

Voxzogo is administered daily by a subcutaneous injection at a dose of 15µg/kg. The drug is supplied in a prefilled syringe at three doses: 400 µg, 560 µg, and 1,2 mg.

The company states that the doses are sufficient to treat a child of 26,7 kg, 37,3 kg, and 80 kg, respectively. The price of each of the three doses is the same, and hence the cost of treatment is the same for all children weighing less than 80 kg. The company assumes that a 1.2 mg vial will be sufficient to treat all children and that there is no vial sharing.

Data from Study 111-301 indicates a mean participant weight of 23,8 kg and a maximum of 68,9 kg. The company assumes an average of 4,4 missed doses per year, generating an estimate of 360,85 doses per year. The company estimates the annual cost of treatment with Voxzogo to be 1 993 000 SEK. See Table 11 below for details regarding cost, packaging and dosing of Voxzogo.

Table 11. ***Costs and details of packaging of Voxzogo (vosoritide)***

Drug	Drug form	Drug unit	Vial size	Pack size	Cost per pack (SEK)	Weight based dosing (kg)	
						From	To
Voxzogo	Vial	µg	400	10	55 231	0,00	26,67
			560			26,67	37,33
			1 200			37,33	80,00

The model includes a cost of one initial health care visit to provide training to administer Voxzogo, applied in the first cycle of the model (4 549 SEK).

4.3.2 Costs for health care and use of resources and other directs costs

Complication costs

The company splits complication costs into costs associated with the immediate management of the complication in the year of occurrence ("cost per event") and subsequent ongoing management costs ("cost per year"). The costs for obesity, CVD and depression are taken from literature.

Table 12 Complication costs

Complications and surgeries	Cost per event (SEK)	Source	Cost per year (SEK)	Source
Chronic pain	29 953	BTMLBÅ "Team med läkare, barnsmärtenheten"	10 911	BTMLBÅ "Team med läkare, barnsmärtenh återbesök"
Decompression surgery	102 191	DRG H24C "Andra rygg- och halsoperation K"		
Depression	29 793	Lundberg et al [50]	29 793	Lundberg et al [50]
Hearing loss/deafness	34 618	DRG C49N "Andra sjd öra näs mun hals"	3 397	DRG C49O "Läk andra sjd ÖNH"
Laminectomy (spinal stenosis)	182 051	DRG A25N "Op ryggmärg & närligg vävnad"		
Limb lengthening	168 608	DRG H17C "Stor op höft/lår ej prot>17K"		
Myocardinal infarction (CVE)	66 704	Hallberg et al [51]	12 660	Hallberg et al [51]
Obesity	4 678	Andersson et al [52]	4 678	Andersson et al [52]
Orthodontic surgrey	58 612	DRG C56N "Tandkirurgi"		
Osteotomy (leg bowing)	111 803	DRG H37C Op fotled underben öarm <18K"		

Shunt insertion	625 722	DRG A09A “Intrakraniell shuntkirurgi M”		
Sleep apnoea	60 997	DRG C17 N “Op för sömnapnésyndrom”	13 876	DRG C17O ”Op för sömnapnésyndrom O”
Spinal fusion	363 812	DRG H20C “Spinal korrekt el komb fusion K”		
Tympanostomy	96 915	DRG C13N “Op hörselben “andra ben i öra”		

The company models contact rates with different types of health care professional by age subgroup. The data were extracted from medical records of participants in the LIAISE study. Costs were sourced from Södra Regionvårdsnämndens 2023 price list.

4.3.3 Indirect costs

In the company’s base case the analysis adapts a societal perspective which includes costs for productivity loss, out-of-pocket expenses and travel costs.

The company estimates lost productivity from excess unemployment in the ACH population (6,6%), yearly salary (607 342 SEK) and estimated sick days due to ACH (22) and are applied in the age span of 18-65 years. Out-of-pocket expenses [----------] are based on house and car adaptations and [----------]. Travel costs are calculated using the average distance from hospital, number of visits per year (10 visits) and the cost of hospital parking (50 SEK). Transportation costs per hospital visit is assumed to be 340 SEK.

FINOSE discussion

The modelled one vial daily use is assumed to be reasonable and representative of real-world practice. Additionally, the company assumes 4 missed doses per year based on observed results in the Voxzogo clinical trial 111-301. FINOSE finds this reasonable and possibly conservative considering the compliance observed in study 301 and 302 (99,1% and 97,8% respectively), and the impact of the assumption will be tested in sensitivity analyses.

With the removal of complications, see discussion in section 4.2.1, the costs of complications are also removed. FINOSE has therefore not further assessed the validity of the complication costs.

Direct medical costs are modelled as event rates and unit costs. The difference between Voxzogo and BSC for these costs is due to survival. Difference in survival in the model is due to complications, and with the removal of complications (see section 4.2.1), the difference in direct medical costs is consequently removed. Therefore, FINOSE has not further assessed the validity of event rates and unit costs for direct medical costs. The company includes indirect medical costs in the form of transportation costs and OOP. Indirect costs (productivity losses) are excluded in the FINOSE base case in alignment with the guidelines in Norway, Finland, and Sweden. The calculations of the company for these costs have therefore not been assessed further.

FINOSE conclusion: FINOSE concludes that the company’s modeling of drug costs is relevant and reasonable. The company included missed doses per year based on observed data from the clinical trials, FINOSE finds this inclusion relevant but will also conduct sensitivity analysis without missed doses. Due to the exclusion of complications, costs for complications and by extension costs for health care visits are excluded.

5 Results of the cost-effectiveness analysis

In the base case analysis Voxzogo is compared with BSC. The best estimation of cost per QALY gained is 5 651 000 SEK for the entire patient population according to the FINOSE assessment, presented in detail in section 5.2. The estimate is presented without considering potential payment models. The company's base case is presented in section 5.1.

5.1 The company's base case

The company assumes Voxzogo treatment improves both survival and health-related quality of life and their result in the model is 1 900 000 SEK per QALY gained. The company estimates an incremental QALY gain of 10,8, and an incremental cost increase of 20 100 000 SEK. Of the 10,8 QALYs gained, 8,3 is due to height difference between Voxzogo and BSC.

5.1.1 Key assumptions in the company base case scenario

Key assumptions in the company's base case scenario are:

- HRQoL in the model are assumed to be separate processes derived from height itself and complications.
- HRQoL by height is estimated from the general population and extrapolated for the patient population height.
- Complication risk reduction is proportional to the patient's height gained.
- Inclusion of a QoL weight for caregivers.
- A constant effect of treatment over time.
- All patients start treatment at age two.
- A stopping age of 15
- Inclusion of productivity losses.

5.1.2 Results in the company base case scenario

In the company's base case scenario, shown in Table 13, the cost per QALY amounts to 1 859 SEK.

Table 13: Company base case results (no payment model), SEK

	Voxzogo	BSC	Difference
Treatment costs	20 782 950	-	20 782 950
Administration costs	4 549	-	4 549
Adverse event costs	2 796	-	2 796
Disease management costs			
Decompression surgery costs	10 834	14 084	- 3 250
Hydrocephalus - Shunt insertion costs	153 261	218 081	- 64 820
Sleep apnoea costs	76 941	91 419	- 14 478
Spinal stenosis costs	10 626	14 756	- 4 129
Kyphosis/Lordosis costs	42 394	70 446	- 28 052
Leg bowing costs	17 616	23 507	- 5 892
Obesity costs	-	-	-
Cardiovascular disease costs	81 700	106 885	- 25 186
Depression costs	57 085	73 269	- 16 184
Chronic pain costs	44 227	56 002	- 11 775

Otitis media costs	14 092	17 978	- 3 886
Hearing loss/Deafness costs	24 609	33 161	- 8 552
Dental malocclusion - Orthodontic surgery costs	14 386	15 405	- 1 019
General ACH management costs	13 830	13 770	60
Medication costs	556	554	2
Alternative height enhancement procedures			
Limb lengthening costs costs	12 182	24 661	- 12 479
Societal costs	515 462	982 787	- 467 325
Total costs	21 880 096	1 756 766	20 123 331
Life years	75,70	74,50	1,20
QALYs	18,86	8,03	10,82
Cost per LY gained			16 741 540
Cost per QALY gained			1 859 410

5.1.3 Company's sensitivity analyses

The company has performed sensitivity analyses of their base case scenario. In Table 14 the ten most influential parameters are listed. The most influential parameter is the bone growth velocity, when the model is run with the lower bound value the ICER increases to 2 million SEK and decreases to 1,7 million SEK with the upper bound value. The following nine most influential parameters concern the utility calculations, whereas the first three are related to the patient's height. In all of these sensitivity analyses the ICER remains within 100 000 SEK of the base case ICER.

Table 14: Sensitivity analyses of the company base case, SEK

Parameter		+/- Δ Costs	+/- Δ LYs	+/- Δ QALYs	Cost/ QALY
Bone growth velocity - all ages (% normal)	0,69552	20 196 135	1,11	9,88	2 044 503
	0,85008	20 043 792	1,31	11,69	1 714 814
Utility coefficient - quadratic	-0,00576	20 123 331	1,20	10,26	1 961 981
	-0,00704	20 123 331	1,20	11,39	1 767 032
Utility coefficient - linear	0,02682	20 123 331	1,20	10,57	1 904 700
	0,03278	20 123 331	1,20	11,08	1 816 224
Utility benefit from exceeding disabilitating height	0,09	20 123 331	1,20	10,71	1 878 360
	0,11	20 123 331	1,20	10,93	1 840 839
Utility weight: Hearing Impairment	0,8064	20 123 331	1,20	10,92	1 842 403
	0,9856	20 123 331	1,20	10,72	1 876 734
Caregiver utility from vosoritide treatment	0,04869	20 123 331	1,20	10,77	1 869 154
	0,05951	20 123 331	1,20	10,88	1 849 768
Utility weight: Myocardial infarction	0,7182	20 123 331	1,20	10,88	1 849 937
	0,8778	20 123 331	1,20	10,77	1 868 982
Utility weight: Sleep apnoea	0,828	20 123 331	1,20	10,87	1 850 689
	1	20 123 331	1,20	10,78	1 867 062
Utility weight: Pain	0,6525	20 123 331	1,20	10,87	1 851 386
	0,7975	20 123 331	1,20	10,78	1 867 505
Utility weight: Depression	0,7182	20 123 331	1,20	10,85	1 855 031
	0,8778	20 123 331	1,20	10,80	1 863 810

5.2 FINOSE base case

The best estimation of cost per QALY gained is 5 651 000 SEK for the entire patient population according to the FINOSE assessment.

5.2.1 Key assumptions in the FINOSE base case scenario

In the FINOSE base case the following assumptions differ from the company base case. Key assumptions are:

- HRQoL by height is estimated using FINOSE linear model estimated on the company provided data points for QoL by height
- Exclusion of complications in the model
- Treatment starting age range of 2 to 12
- Treatment stopping age of 16
- Exclusion of caregivers quality of life
- Exclusion of productivity losses

Table 15 FINOSE base case results (no payment model), SEK

	Voxzogo	BSC	Difference
Treatment costs	15 049 687	-	15 049 687
Administration costs	4 549	-	4 549
Adverse event costs	2 025	-	2 025
General ACH management costs	11 832	11 832	0
Medication costs	558	558	0
Alternative height enhancement procedures			
Limb lengthening costs costs	22 015	29 376	- 7 361
Direct non-medical costs	784 449	1 059 292	- 274 844
Total costs	15 875 115	1 101 059	14 774 056
Life years	76,5	76,5	0
QALYs	24,4	21,8	2,62
Cost per LY gained			NA
Cost per QALY gained			5 650 566

5.2.2 FINOSE sensitivity analyses

FINOSE has conducted several sensitivity analyses to explore the impact of uncertainties identified. This includes sensitivity analyses on the treatment start and stopping age, complications, modeling of utility by height, and limb lengthening surgery.

The greatest effect on the ICER has choices regarding the modeling of utility by height, PRAGV, discount rates and, treatment starting age.

Table 16: FINOSE sensitivity analyses based on FINOSE base case (no payment model), SEK

Sensitivity analyses		+/- Δ Costs	+/- Δ LYs	+/- Δ QALYs	Cost/ QALY
FINOSE base case		14 774 056	0	2,62	5 650 566
kFINOSE scenario 1 – treatment start at age 2		21 513 128	0	4,67	4 607 734
FINOSE scenario 2 – complications included		15 437 866	0,608	2,89	5 092 630
FINOSE scenario 3 & 4– Utility models	Company linear, no complications	14 774 056	0	4,67	3 166 823
	Company linear, complications	14 713 632	0,61	4,87	3 020 429
FINOSE scenario 5 & 6 – stopping ages	15	13 284 846	0	2,54	5 238 443
	17	16 197 376	0	2,61	6 194 554
FINOSE scenario 7 & 8 – probability of limb lengthening surgery	35% (Norway)	14 766 171	0	2,62	5 631 465
	0% (Finland)	14 763 333	0	2,58	5 731 401
FINOSE scenario 9 – effect of limb lengthening surgery	15 cm	14 765 221	0	2,6	5 670 871
FINOSE scenario 10 & 11 – added utility if certain height reached	140 cm	16 262 113	0	9,27	1 753 712
	Excluded	14 763 333	0	2,58	5 731 401
FINOSE scenario 12 – no missed doses		14 957 563	0	2,61	5 720 751
FINOSE scenario 13 – inclusion of caregivers QoL		14 774 056	0	3,02	4 887 004
FINOSE scenario 14 – inclusion of productivity losses		14 756 936	0	2,61	5 644 019
FINOSE scenario 15 – 4 % discount rate (costs and effects)		14 265 942	0	2,02	7 068 819
FINOSE scenario 16 & 17 - PRAGV	70%	14 797 942	0	2,33	6 359 337
	60%	14 836 015	0	1,94	7 657 263

5.2.3 Cost per QALY gained at different price levels

In Figure 7, the cost per QALY is shown under different discount rates in 10% increments. For every 10% step the cost per QALY is reduced with 576 000 SEK.

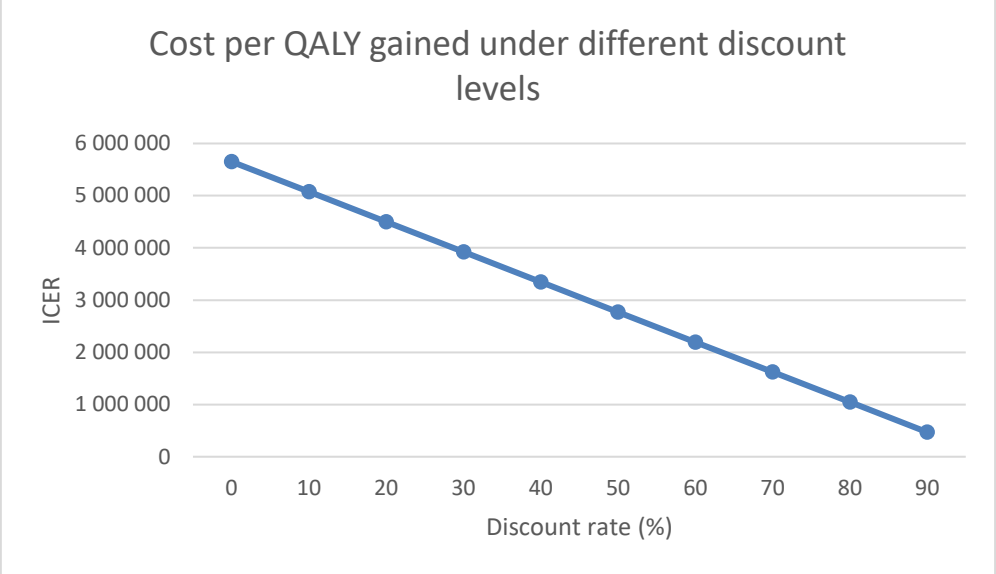

Figure 7: Sensitivity analyses on discount rate on acquisition cost of Voxzogo based on FINOSE base case, SEK

5.3 Overall summary and conclusion

This is a joint FINOSE health economic assessment of Voxzogo for ACH. FINOSE agrees with the company that the most relevant comparator is BSC.

In the FINOSE base case scenario the cost per QALY gained is 5 651 000 SEK. This result is associated with great uncertainty, especially regarding the modeling of height gain, and HRQoL by height which has a large impact on the cost-effectiveness result. Different assumptions have a large impact on the outcomes in the model, and while the exclusion of disease complications does not have a great impact on the ICER it is associated with uncertainty of the disease importance.

6 Assessments in other countries

The National Institute for Health and Care Excellence (NICE) in the UK was asked to conduct an appraisal of Voxzogo for treating ACH in children and young people under 18 years on 24 November 2020. The project is awaiting development and the scoping is planned to take place at a later date in 2023 [53].

According to the Federal Joint Committee (G-BA) of Germany there is a hint for a non-quantifiable additional benefit of Voxzogo in the treatment of ACH patients 2 years of age and older whose epiphyses are not closed. G-BA concludes that the scientific data does not allow quantification of the benefit [54, 55].

There is currently no information about ongoing or planned assessments of Voxzogo at the Canadian Agency for Drugs and Technologies in Health (CADTH), Scottish Medicines Consortium (SMC) or Institute for Clinical and Economic Review (ICER) in the US.

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