# YOUR OPPORTUNITY TO CHANGE CHILDREN'S LIVES WITH VOXZOGO

TO MEDICINRÅDET

BY aquîlo
GROWING HEALTHCARE

# DISCLOSURE OF INTEREST

This analysis was made on behalf of Danish parents of children suffering from achondroplasia (ACH).

The health economic outcome case was created by Aquilo Consulting, a healthcare consulting firm based in Copenhagen that specializes in real-world evidence and health economics for clients in pharmaceutics, medical devices, government reimbursement, and private health care around the world.

The work was completed pro bono, in good faith, and using internationally accepted healthcare economics methodologies.

The work was carried out for the betterment of Danish children currently experiencing discrimination.

One of Aquilo's team members is a parent of a child with bone dysplasia.

HEALTH ECONOMIC CASE FOR ACH CHILDREN

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HEALTH ECONOMIC CASE FOR ACH CHILDREN

# AQUILO'S ANALYSIS SUMMARY

# VOXZOGO CAN ALLEVIATE LIFE-THREATENING CONDITIONS – THE SEVERITY PRINCIPLE SHOULD APPLY

KEY TAKEAWAYS

1. Infants with Achondroplasia (ACH) have a 50 times higher risk of sudden death.[1] Thanks to its positive effects on foramen magnum diameter[2], Voxzogo is most likely to **reduce infant mortality to about average population rate.**

2. Voxzogo is most likely to increase the diameter of the spinal canal, improving spinal stenosis[3,4], thus **preventing ACH patients from being on disability pension** from the average age of 30 and allowing them to remain in the Danish workforce.

3. When taking societal costs into account, we calculate net savings of about **4,7 Million DKK per child** treated with Voxzogo.[5]

4. Taking an extremely conservative approach, **FINOSE does not consider key real-world evidence** from other countries that are currently reimbursing the drug nor existing evidence suggesting reductions in infant mortality.[6]

5. We believe that the Danish Medicine Council/Medicinrådet's own **severity principle should be applied to Voxzogo**, granting Danish children access to life-saving treatment.

# VOXZOGO HELPS DANISH CHILDREN WITH ACH AND UPHOLDS CLINICAL, ETHICAL AND ECONOMIC EXPECTATIONS

## INTRODUCTION

### WHY MEDICINRÅDET (DMC) IS ABOUT TO MAKE A MISTAKE

While international medical experts agree on Voxzogo's potential, its most likely long-term effects and its excellent safety profile, the DMC (Danish Medicines Council/Medicinrådet) is about to disregard this knowledge in its decision on whether or not to make Voxzogo available to Danish children suffering from achondroplasia (ACH).

The reason behind the DMC's "chosen blindness" is the FINOSE (a Nordic government-sponsored body) report on Voxzogo. FINOSE's report on Voxzogo, by design, disregards the view of FINOSE's own medical specialists and the view of leading international medical experts on the potential and the most likely long-term effects of the medication.[7]

Sweden has already rejected Voxzogo reimbursement to its ACH children based on the FINOSE report. Norway is believed to follow the Swedish decision, and in Denmark the DMC has confirmed the use of the FINOSE report in its evaluation.

Here at Aquilo we have conducted an in-depth analysis of the available scientific literature, case reports and international medical experts' views on Voxzogo. Through this analysis we have been obliged to study the FINOSE report, highlight its shortcomings and build a HEO (Health Economic Outcome) case that reflects the most likely long-term effect of the drug on children's health, and subsequent positive impact on healthcare and societal costs.

We believe that Voxzogo should qualify for reimbursement. Not only for its economic and clinical qualifications, but because it is in accordance with the severity principle.[8]

In fact, Voxzogo:

- Is given to children with ACH who are still growing
- Treats a chronic disease that causes severe limitations in life
- Treats a disease with several associated comorbidities, some of which cause death
- Is the only treatment for achondroplasia

Similar drugs have been recommended exclusively on the severity principle (eg. Nusinersen[9] and Burosumab[10]) and we believe Voxzogo deserves the same consideration.

**We conclude that with recent DMC decisions on similar drugs and the evidence at hand today, it makes medical, economical and ethical sense to fast-track a decision to make Voxzogo available to Danish children suffering from ACH.**

## THE CLINICAL CASE

### DWARFS WILL NOW BE SELF SUFFICIENT AND LIVE WITHOUT HANDICAPS

Voxzogo has proven to stimulate growth in children who are on the drug.[11,12,13] All data collected demonstrates sustained growth rates throughout the whole treatment, enabling patients to reach a height of 1,50m in adulthood. This growth allows people with achondroplasia to become self-sufficient and improves their physical and mental health.[14]

Voxzogo's safety profile is excellent, and only minor side effects have been observed in the many studies carried out on its safety.[15]

### VOXZOGO WILL ALLEVIATE SEVERE COMORBIDITIES

Voxzogo not only increases height, but international medical experts believe that it will improve several achondroplasia comorbidities, including spinal stenosis, foramen magnum stenosis and bowed legs.[16,17] This can prevent a life of suffering for children with ACH and allow them to work and participate in society as adults. These international medical experts do not base their opinions on hope or wishful thinking, but instead on:

1. Real-life evidence in children that have been part of Voxzogo clinical trials and trials in other countries that have already reimbursed the drug[18,19].
2. Their profound understanding of human anatomy and how increased skeletal length will decrease skeletal compression and erosion.
3. Confirmed results from laboratory experiments on animals[20], and reports on Voxzogo's positive effect on foramen magnum stenosis in humans.[21]

# VOXZOGO HELPS DANISH CHILDREN WITH ACH AND UPHOLDS CLINICAL, ETHICAL AND ECONOMIC EXPECTATIONS

## THE ECONOMIC CASE

### 4,7M DKK IN SOCIETAL PROFIT & 33 QALYS GAINED

We have built a Health Economic Outcome case based on:

1. The most likely outcome for children with ACH on Voxzogo.
2. The view shared by the world's leading medical experts of a comorbidity resolution and reduction in handicap adaptations of 70% and 100%, respectively.
3. The societal benefits of a reduction in handicap adaptations, expensive comorbidities, disability pension and mortality.

The case shows that solely from a HEO perspective it is profitable to make Voxzogo available to children with ACH at a lifetime societal profit of about DKK 4,7 million per child and a QALY gain of 33 QALYs.

## THE ETHICAL CASE

### LEAVE NO CHILD BEHIND

30+ countries across the world including many OECD & EU nations are reimbursing Voxzogo because of the evidence and potential of the drug, its economic benefits and for the ethical argument:

This is the first and only drug proven to help children currently living with and suffering from ACH. For the children yet to be born (3 per year in DK), Voxzogo will very likely alleviate the severe and painful complications associated with ACH – to a degree that these children will be as healthy as the general population. If treated early enough, they will grow up healthy and contribute positively to society.

Moreover, the drug's safety profile is excellent[22].

Is it then ethically defendable to prevent access to such a treatment?

Prevent access just in case the drug, against all likelihood, will only increase height but not alleviate any of the severe comorbidities?

Is it ethically defendable to turn a blind eye to the world's leading medical experts in this field?

Is it ethically defendable to turn a blind eye to the decision of many EU countries' health authorities like Germany, France, Italy, Spain etc. and more than 30 other countries, where the health authorities have chosen to listen to and act on what the world's leading medical experts say is the most likely scenario?

Is it ethically defendable to deprive the few Danish children that suffer from this terrible condition the potential of a life-changing treatment?

We will only have outcome certainty 30+ years from now. Danish ACH children are taking up space in special kindergartens, special schools, specialized hospitals, requiring special caretaking and looking into a future cocktail of suffering, surgical procedures, stigmatization, unemployability and an adult life on disability pension.

They cannot wait 30+ years.

The cost of the treatment for this rare disease is admittedly relatively high. Yet, compared with the fact that we, as a society, spend around DKK 270 billion every year on our healthcare system[23] and as much as DKK 7 billion on keeping terminally ill grandparents alive for a few extra months[24], it is impossible to comprehend that the cost of DKK 1,3 million (starting cost – this will come down over time) per child per year can at all be an issue in a country that can afford such lavish spending.

Danish ACH children and their families rely on you to make the right ethical decision and live up to the social contract the Danish healthcare system has with its citizens. Via our substantial taxes we mutually look out for each other – you may not use the healthcare system for years, but when you do need it or some of your loved ones need it – the system is there for you.

Thank you.

HEALTH ECONOMIC CASE FOR ACH CHILDREN

# VOXZOGO SAVES DKK 4,7M PER CHILD

# VOXZOGO SAVES DKK 4,7M PER CHILD BY IMPROVING THEIR FUTURE HEALTH AND WORKFORCE PARTICIPATION

1

## VOXZOGO IS EFFECTIVE AND SAFE

Voxzogo is the **first and only medication** proven to help children currently suffering from ACH

All available studies show significant **increased growth** and only minor reactions to the drug[25]

Medical experts agree on the treatment's potential **benefits on ACH complications**[26]

2

## VOXZOGO CREATES SOCIETAL SAVINGS

Patients will have **fewer surgeries**, less need for disability pension, and higher probability of joining the workforce as adults

Danish **health care budget is DKK ~270 Billion** per year, terminal cancer care costs DKK 7 Billion per year[27,28]

3 children born with achondroplasia each year, Voxzogo treatment costs DKK 1,3 Million per year/child

3

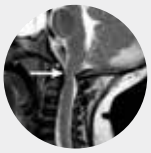
## DENMARK SHOULD LEAVE NO CHILD BEHIND

30+ countries, of which many are **OECD countries**, are **reimbursing Voxzogo today**

**Delaying the decision** will push today's children out of the age group for Voxzogo

The DMC has reimbursed similar drugs for rare diseases based only on the **severity principle**[29,30,31]

## ACHONDROPLASIA: A LIFE OF SUFFERING



### SPINAL & FORAMEN MAGNUM STENOSIS

**68%** develop spinal stenosis[32]
**20%** of infants undergo stenosis surgery[33]
**5%** sudden death rate until five y.o.[34]

### OBSTRUCTIVE SLEEP APNOEA

**57%** of children have sleep apnoea[35,36]
**57%** require a tonsillectomy[37]
**90%** need recurring surgery[38]

### OTHER COMPLICATIONS

**61%** have hearing loss[39]
**80%** live with major pain[40]
**10+** years shorter lifespan[41]

### NEUROSURGERY

**Almost 50%** require brain or spine surgery[42]
**19%** have hydrocephalus[43]
**13** lifetime operations after hydrocephalus diagnosis[44]

### PSYCHOLOGICAL DIFFICULTIES

**32%** suffer from depression[45]
**60%** are single[46]
Psychological distress affects the whole family[47]

### SOCIAL DIFFICULTIES

**50%** of adults forced to change their careers[48]
**30%** have difficulty performing basic needs[49]
Social stigmas make them feel like outcasts

## WHAT IS THE TREATMENT AND WHAT DOES IT DO?

**Voxzogo** is a novel drug that increases bone growth in children with achondroplasia.

It boosts children's bone growth[50]

It enables growth up to a height of 1,53m[51]

It prevents achondroplasia complications[52,53]

It allows children to enjoy life and participate in society

## HOW MUCH CAN VOXZOGO SAVE THE DANISH GOVENRMENT?

**DKK 20,7M**
Saved thanks to Voxzogo[54]
**PER PERSON**

**DKK 15,6M**
Lifetime cost of Voxzogo[54]
**PER PERSON**

**DKK 4,7M**
**Net savings** thanks to Voxzogo[54]
**PER PERSON**

&

**33 QALYs**
Restored thanks to Voxzogo[54]
**PER PERSON**

HEALTH ECONOMIC CASE FOR ACH CHILDREN

# STORIES OF DANES WITH ACH

# MILAN'S STORY: THE REALITIES OF ACHONDROPLASIA

Milan is 6 years old and has been in the hospital more than the average person will be in their lifetime.

## MILAN'S STRUGGLES SO FAR

| | | | | |
|---|---|---|---|---|
| 80 | specialist appointments | › | DKK 101K | cost of specialist appointments |
| 40 | surgeries & overnight stays | › | DKK 3,3M | cost of surgeries & overnight stays |
| 6 | years of requiring nonstop care from his mother & house/transport adaptations | › | DKK 4,8M | cost of his mother's productivity loss & house/transport adaptations |
| | | | DKK 8,2M | spent on Milan to this day[55] |
| 36 | more years on disability pension | › | DKK 24,1M | future productivity loss for his mother |
| 30 | average age of spinal stenosis onset, likely pushing Milan off the workforce | › | DKK 16,0M | future productivity loss for Milan |
| | | total | DKK 48,3M | will be spent on Milan[55] |

## MILAN'S SOCIAL STRUGGLES

People **laugh and take photos** in public

He **misses 1 month of school** after each surgery

His single mother had to **quit her job** to care for him

## HELP IMPROVE THE FUTURE OF CHILDREN LIKE MILAN

### VOXZOGO'S EFFECTS

No longer in and out of the hospital

Children will be able to join the workforce as adults

No need for disability pension

### THE NEW FUTURE OF CHILDREN LIKE MILAN

Less surgeries, less time in hospitals, less pain and more time with family and friends

Now able to work, can integrate into society and improve self image

Can now be self-sufficient, no need to rely on the government

**Voxzogo** can still change Milan and his family's lives

# LINE'S STORY: THE REALITIES OF ACHONDROPLASIA

Line was forced into disability pension due to achondroplasia at 31.

## LINE'S STRUGGLE SO FAR

| | | | | |
|---|---|---|---|---|
| 250+ | specialist appointments | › | DKK 827K | cost of appointments & physical therapy |
| 22 | surgeries & overnight stays | › | DKK 2,9M | cost of surgeries & overnight stays |
| 4 | years of disability pension & productivity loss | › | DKK 2,7M | cost of disability pension & productivity loss |
| | | | DKK 6,4M | already spent on Line to this day[55] |
| 1 | spinal stenosis surgery awaiting | › | DKK 380K | future cost of the next spinal stenosis surgery |
| 34 | more years of disability pension and productivity loss | › | DKK 22,9M | future cost of disability pension & productivity loss |
| | | total | DKK 29,7M | will be spent on Line[55] |

## LINE'S SOCIAL STRUGGLES

People **laugh and take photos** in public

Forced to take **mental disability tests** due to her appearance as a child

Had to **quit her job** because of chronic pain

## LINE'S LIFE WITHOUT VOXZOGO

**LEGS & HIPS**

**AT 3 & 6 YEARS OLD**
Two bilateral leg straightening surgeries

› **AT 31 & 33 YEARS OLD**
Bilateral total hip replacements

› **TODAY**
Uses crutches, prescribed morphine to manage pain

**SPINAL COLUMN**

**AT 11 YEARS OLD**
Diagnosed with spinal stenosis

› **AT 18 YEARS OLD**
1st surgery to correct spinal stenosis

› **TODAY**
Needs 2nd surgery to correct spinal stenosis

**JOINTS**

**AT 25 YEARS OLD**
Left ankle stiffened with metal screws, now limps

› **AT 31 YEARS OLD**
Forced on disability pension due to chronic pain

› **TODAY**
Arthritis in neck, back, shoulders, knee, ankles

"If Voxzogo gives others a chance that they'd endure less than I did, that is enough reason to approve the drug."

- Line

# TINA'S STORY: THE REALITIES OF ACHONDROPLASIA

Tina has been on disability pension for 21 years due to achondroplasia.


## TINA'S STRUGGLE SO FAR

| | | | | |
|---|---|---|---|---|
| 8 | surgeries | › | DKK 1,3M | cost of surgeries |
| 10 | one-month long hospital observations | › | DKK 690K | cost of month-long hospital observations |
| 21 | years of disability pension & productivity loss | › | DKK 15,4M | cost of disability pension & productivity loss |
| 63 | years of house/transport adaptations | › | DKK 1,8M | cost of house/transport adaptations |
| | | | DKK 19,2M | already spent on Tina to this day[55] |
| 6 | more years of disability pension and productivity loss | › | DKK 4,3M | future cost of disability pension & productivity loss |
| | | total | DKK 23,5M | will be spent on Tina[55] |

## TINA'S SOCIAL STRUGGLES

People **laugh and take photos** in public

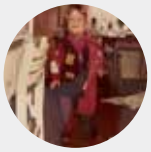
Took **10 years to find a job** as a kindergarten teacher

Had to **quit her job** because of chronic pain

## TINA'S LIFE WITHOUT VOXZOGO

### ENT COMPLICATIONS
- 6 ENT surgeries
- Constant ear pain
- Difficulty balancing while walking

› VOXZOGO COULD HAVE...
restored craniofacial anatomy, decreasing ENT complications



### SPINAL COMPLICATIONS
- Spinal stenosis surgery at 49
- Second spinal stenosis surgery at 51
- Excruciating pain for 1 year post-op

› VOXZOGO COULD HAVE...
increased the diameter of the spinal column, decreasing risk of stenosis

### CONSTANT PAIN
- Arthritis in neck, back and knees for 30 years
- Uses a wheelchair to travel
- Needs daily painkillers

› VOXZOGO COULD HAVE...
restored proportionality, decreasing arthritis and chronic pain

"I didn't want children because I didn't want them to go through the same pain as I do."

- Tina


HEALTH ECONOMIC CASE FOR ACH CHILDREN

# CASES FROM AROUND THE WORLD

# CHILDREN CURRENTLY ON VOXZOGO ARE SHOWING THE IMPROVEMENTS THAT MEDICAL EXPERTS BELIEVE THEY WOULD

## VOXZOGO IMPROVES LEG BOWING

**Meet Canon, he has been on Voxzogo for 4 years.**
His mother writes:

"We just had his 9 year-old check up – he grew 2,5 inches (around 6,5 cm) in a year. His paediatrician was so excited she was practically dancing!"

"He's grown 23cm total over the past 4 years and gotten more proportional along with dramatic improvement in knee bowing!"

## VOXZOGO INCREASES SIZE OF FORAMEN MAGNUM

**Meet Nate, he has been on Voxzogo for 15 months.**
His mother writes:

"Since he started taking Voxzogo 15 months ago, his foramen magnum has enlarged from 4mm to 6,6mm and his entire spine has less stenosis."

"You could see spinal fluid moving around the spinal cord where you couldn't before. She couldn't explain how these things happened. I reminded her of this medication he's taking, and she said that is the only explanation."

## VOXZOGO IMPROVES AGE-RELATED PHYSICAL MILESTONES

**Meet Alex, he has been on Voxzogo for 1 year.***
His mother writes:

"Today is 1 year since starting Voxzogo. In the two years prior, he grew around 5cm a year. He grew 9cm this past year."

"Height is awesome, of course, but the best improvement is he has been able to pull his pants down and up on his own!!"

* This patient's name and photo were changed to protect their privacy

"Voxzogo has a significant effect on health, not just height."

- Professor Ravi Savarirayan, world-leading expert in ACH

HEALTH ECONOMIC CASE FOR ACH CHILDREN

# NO CHILD SHOULD BE LEFT BEHIND

# FINOSE IS THE ONLY NEGATIVE OUTLIER AMONG FDA, EMA, JAPAN, AUSTRALIA AND EXPERT CONSENSUS ON VOXZOGO

## VOXZOGO IS REIMBURSED FOR CHILDREN IN MANY OECD NATIONS

Voxzogo is already reimbursed in 30+ countries, among which are:

Australia | France | United States | Japan | Germany | Italy | Spain | Portugal

The FDA and EMA, along with many other institutions, have approved the sale of Voxzogo

In the US, **Voxzogo has been approved via accelerated pathway**, as it addresses a serious condition with no other treatment options

Due to the importance of this treatment, many OECD countries have adopted the approach of **approving reimbursement while collecting more data** on Voxzogo

## AUSTRALIA IS LEADING REIMBURSEMENT

At the forefront of ACH research, Australia has been the first country to reimburse Voxzogo and administer the drug to children >2 months

### AUSTRALIA UNDERSTOOD VOXZOGO'S POTENTIAL

Driven by the promising data, Australia has granted access to Voxzogo to all children with ACH

### AUSTRALIA IS ALREADY SEEING VOXZOGO'S EFFECTS

Positive effects are already being seen, with children in the trials having less complications[56,57]

### AUSTRALIA IS PROVIDING AN EASIER LIFE TO ITS CITIZENS

Before reimbursement, some children had to fly to Japan to have access to Voxzogo

## FRANCE HAS GIVEN TEMPORARY AUTHORIZATION

France has granted Voxzogo temporary authorization, allowing the country some flexibility, while giving the children a chance

### FRANCE UNDERSTOOD VOXZOGO'S POTENTIAL

Due to its importance, France approved Voxzogo reimbursement

### FRANCE IS LEAVING NO CHILD BEHIND

France's authorization allows wider access and faster data collection

### FRANCE UNDERSTOOD VOXZOGO'S POTENTIAL

If collected data does not show Voxzogo's positive effects, France will revoke reimbursement

**Why** is Denmark not helping ACH children?

HEALTH ECONOMIC CASE FOR ACH CHILDREN

# EVIDENCE OVERVIEW

# FINOSE AGREES WITH INTERNATIONAL CONSENSUS ON VOXZOGO'S POTENTIAL, YET EXCLUDES IT FROM THEIR ESTIMATES

## VOXZOGO INCREASES GROWTH

| | |
|---|---|
| EMA: | "Voxzogo **stimulates growth of bones**, thereby improving the symptoms of the disease."[35] |
| PHASE 2 STUDY: | "Vosoritide (Voxzogo) was well-tolerated for up to 60 months with **growth velocity** and biomarker activity being **sustained**."[59] |
| PHASE 3 STUDY: | "Children who received Voxzogo grew about 1.57 cm more during the one year of treatment than those receiving placebo."[60] |
| FINOSE: | "It is agreed that the clinical study program has demonstrated that the Voxzogo treatment increases growth in children with ACH."[61] |

## VOXZOGO IS SAFE

| | |
|---|---|
| EMA: | "There have been **no important safety risks** identified associated with vosoritide (Voxzogo) at present."[62] |
| FINOSE: | "There have been no important safety risks identified associated with Voxzogo at present."[63] |

## VOXZOGO IMPROVES QUALITY OF LIFE

| | |
|---|---|
| FINOSE: | "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."[64] |
| EXPERTS IN ACH: | "**Over 80% of experts agree** that in individuals with achondroplasia, vosoritide (Voxzogo) likely **increases Health-Related Quality of Life** through their lifetime if long-term treatment is started before puberty."[65] |

## VOXZOGO IMPROVES COMPLICATIONS

| | |
|---|---|
| FINOSE: | "It is **plausible that Voxzogo treatment can have an impact on medical complications** due to its effect on bone growth."[66] |
| EXPERTS IN ACH: | "It seems **reasonable** to hypothesize, by extrapolation of the data showing the effects of vosoritide (Voxzogo) on long bone growth, that growth in the axial skeleton might be beneficially altered, resulting in a **direct effect on foramen magnum stenosis, spinal canal stenosis and kyphosis**."[67] |
| AUSTRALIAN NEWS: | "As a baby, recurring seizures due to ACH saw Oscar in and out of the hospital, but **after 5 years on Voxzogo his medical complications are mostly controlled**."[68] |
| AUSTRALIAN MOTHER: | "My son has been on Voxzogo for 4 years… he's grown 23cm and gotten more proportional and saw **dramatic improvements in knee bowing**. Pretty great results!"[69] |

## VOXZOGO IMPROVES SPINAL COMPLICATIONS IN MICE

| | |
|---|---|
| ANIMAL STUDY: | "CNP (C-type natriuretic peptide) **increased the width of the foramen magnum**, stimulated skull growth, and increased the length of the lumbar vertebrae and femurs in transgenic mice."[70] |
| EXPERTS IN ACH: | "Animal studies have shown an **effect** of **vosoritide (Voxzogo) on skull morphology** (mice) and on neural foraminal area of lumbar vertebrae."[71] |

## FINOSE ASSESSMENT WAS EXCESSIVELY CONSERVATIVE

| | |
|---|---|
| FINOSE: | "**FINOSE** excludes complications from the base case but **notes that this may be a conservative approach**."[72] |


HEALTH ECONOMIC CASE FOR ACH CHILDREN

# WHY FINOSE IS WRONG

# FINOSE IS LEAVING CHILDREN BEHIND

| TAKEAWAYS FROM FINOSE'S REPORT | AQUILO COMMENTS |
|---|---|
| **1. FINOSE HAS A PESSIMISTIC VIEW**<br>FINOSE does not believe there is enough economic gain for the reimbursement of Voxzogo | FINOSE has adopted a "glass-half-empty" perspective, stating that there is not enough evidence to support quality of life improvements, complication improvements and many more.<br>**All evidence collected so far points to additional benefits than the ones FINOSE accepted as valid.** |
| **2. FINOSE IGNORES POSITIVE LONG-TERM DATA**<br>"Efficacy of long-term impact of Voxzogo on height cannot be determined because there is no evidence" | FINOSE does not consider this:<br>• There is **data** coming from Phase 2 trials spanning **7,5 years**<br>• There is **data** coming from Phase 3 trials spanning **3,5 years**<br>• There are models estimating long-term growth<br>• All data collected proves growth rates are sustained<br>• Collecting long-term evidence will require another 7+ years. Meanwhile children will not have access to treatment |
| **3. FINOSE IGNORES CONSENSUS ON HEIGHT AFFECTING QUALITY OF LIFE**<br>FINOSE states: "the FINOSE medical experts believe that Voxzogo will provide clinically meaningful benefits …. (they) explain that even a small increase in height will be beneficial (and) agree that a gain in height will improve quality of life even in absence of any change in comorbidities. The FINOSE experts emphasised that no evidence is available on the final height achieved with Voxzogo" | **Quality of life improvements thanks to height increase are self-evident and unanimously agreed upon.**<br>Why is then so much evidence of Voxzogo achieving this growth discarded?<br>Why is no analysis presented where different efficacy scenarios are modelled to allow a more informed decision-making? |
| **4. FINOSE CHANGING TREATMENT STARTING AGE IS SHORT-SIGHTED**<br>FINOSE's model uses children aged 2 to 12 at the time of first treatment to estimate health outcomes on eligible children today | While it is true that today's patients will start treatment when aged 2 to 12, this is valid only for the first years of Voxzogo being reimbursed. After this first group of patients, **all children will start treatment at 2 years old**.<br>BioMarin's (the company) model has all children starting treatment at 2 years old. This is more accurate in describing Voxzogo's health effects in the long run, and should therefore be the preferred method to **support more meaningful and long-term decision making** |
| **5. FINOSE DOES NOT ANALYSE THE POSSIBILITY OF EARLIER TREATMENT**<br>FINOSE states that Voxzogo treatment begins at 2 years old and ends at 16 years old | While in line with the company submission, evidence suggests that starting treatment earlier will lead to greater results. Australia and Japan have revised the evidence and are now **reimbursing the medicine to infants from the age of 2 months**. |
| **6. FINOSE DOES NOT CONSIDER CONSENSUS ON SPINAL STENOSIS IMPROVEMENT**<br>To FINOSE, there is no definitive data provided linking increased height and decreased symptomatic spinal stenosis, so it is not included in the model | The short-term studies available do not portray the effects of height increase on spinal stenosis because spinal stenosis occurs around 30 years old. **We would need to wait decades** for this information to be published, but medical experts state that a small diameter increase of the spinal column with Voxzogo would produce massive improvements in spinal stenosis. |

# FINOSE IS LEAVING CHILDREN BEHIND

| TAKEAWAYS FROM FINOSE'S REPORT | AQUILO COMMENTS |
|---|---|
| **7. FINOSE DOES NOT CONSIDER CONSENSUS ON FORAMEN MAGNUM IMPROVEMENT**<br>To FINOSE, there is no data provided linking increased height and decreased foramen magnum stenosis | Foramen magnum stenosis occurs primarily in patients 0-2 years old. These children don't receive Voxzogo in Europe yet, so you will not see improvements. Medical experts agree that a **small increase** in **foramen magnum diameter would decrease the need for decompression surgery**. |
| **8. EXCLUDING CARETAKER COSTS IMPEDES GOOD DECISION-MAKING**<br>The decrease of the caretaker's quality of life is not considered in the report because FINOSE believes BioMarin did not submit enough data for height-complication dependence | Data on caretakers' quality of life was presented between parents of children with and without activity limitations. This was discarded.<br>**Caretaker quality of life** considerations cannot be excluded because their life **is negatively impacted** by their child's condition, and many are forced to leave their jobs. **This is a massive expense** for Danish society that any rational decision-maker should consider. |
| **9. EXCLUDING SOCIETAL COSTS UNDERESTIMATES THE ISSUE**<br>FINOSE excluded ACH productivity loss and does not assess BioMarin calculations in the matter | Excluding productivity loss costs leads to an underestimation of total costs savings and of Voxzogo's potential to alleviate comorbidities. 68% of adults with ACH also suffer from **spinal stenosis** and 80% suffer from chronic pain (among other things). This **forces them out of the workforce** and into the early/disability pensions schemes. This is a huge cost to Denmark that could be saved with Voxzogo. |
| **10. FINOSE IS NOT SUPPORTING INFORMED DECISION-MAKING**<br>The report excludes the cost of complications, mortality and productivity loss from the model because they do not consider available data as sufficient for the inclusion | Despite all evidence pointing towards the same direction, FINOSE disregards the possibility of Voxzogo improving ACH complications, while recognising that to be a "conservative approach."This "conservative approach" **leads to the presentation of the worst-case scenario for Voxzogo**, that looks only at definitive evidence available today, and **ignores all evidence of a greater potential**.<br>A better service to decision makers would have been to run various scenarios, where Voxzogo has a progressively greater impact, and then having doctors agree on the most plausible one. The whole analysis could have then been presented to decision makers for a truly informed decision. |
| **11. THERE IS NEED FOR A DIFFERENT APPROACH**<br>FINOSE takes a slow, academic approach, while a pragmatic approach must be taken for this treatment, respecting healthcare economic methodologies | FINOSE is ignoring the clear direction of Voxzogo's potential that available evidence points to.<br>At Aquilo we look at HEOs (Health Economic Outcomes) not from the perspective of who is the budget holder but from a 360 degrees, pragmatic, **most probable scenario perspective**, whilst respecting international healthcare economic methodologies. |
| **12. SOCIETAL PROFIT MUST BE PART OF DECISION-MAKING**<br>FINOSE is ignoring patients' ability to return as a net economic contributor in society | FINOSE chose not to include the societal impact of a healthier population in their evaluation of novel treatments.<br>At Aquilo, when we analyze a given treatment's economic impact, we **include future cost savings** for the **healthcare system and** the improvement in **societal productivity**, as a consequence of a treatment's impact on the patient's ability to return to work and be a net contributor to society. |

# FINOSE IS LEAVING CHILDREN BEHIND

| TAKEAWAYS FROM FINOSE'S REPORT | AQUILO COMMENTS |
|---|---|
| **13. DISCOUNTING HAS NO PLACE IN HEALTHCARE ECONOMICS**<br>FINOSE should remove the requirement of discounting future costs. This is only making future benefits of a treatment look less important. | The argument made by FINOSE for discounting future cost savings and societal profits only makes mathematical and economical sense if:<br>a) One operates a business (e.g. a private hospital), where a return on investment must be granted to shareholders. Here the discount rate would be equal to the risk premium required in a DCF model.<br>b) One would add the increased expected inflation to the future cost savings and productivity gain (GDP).<br>In public health, which by definition is non-profit, there is **no mathematical nor economical argument for operating with a risk premium** (discount rate).<br>As for the scenario b: It is a zero-impact exercise to add inflation to the expected future cost savings and productivity gain, only to deduct it through an inflation-based discount rate.<br>For these reasons, our models do not use discounting. |
| **14. FINOSE EXCLUDES COMORBIDITIES AND MORTALITY FROM QALYs**<br>FINOSE considers only height when estimating the quality of life of people with ACH. They criticise Biomarin (the company) for providing a low utility score of 0,2 and propose a new height-based utility score of 0,69 per year. | To reach a 0,69 utility score, FINOSE eliminates the impact that ACH has on comorbidities, mortality and caregivers. This utility score might be accurate when describing a patient with achondroplasia with no complications, but the majority of people living with ACH have at least one complication.[73] Therefore, the FINOSE utility score is overestimating their quality of life.<br>Moreover, this utility score does not allow decision makers to account for the lost QALYs due to higher mortality.<br>We at Aquilo recognise the lack of an established healthcare economics method that allows an easy estimate of utility score for patients with multiple concurrent comorbidities.<br>However, FINOSE should have provided additional comments to their 0,69 utility score and should have recognised the overestimation and the significant loss of QALYs to ACH, independent of Voxzogo's efficacy on reducing that loss. |
| **15. FINOSE'S EXCLUSION OF COMORBIDITIES AND MORTALITY UNDERESTIMATES VOXZOGO'S HEALTH BENEFITS BY 31 QALYs**<br>FINOSE models Voxzogo's health benefits only on their 0,69 height-based utility score, discarding all effects the treatment will have on complications and mortality. | Comorbidities and mortality should be included to understand how much ACH is detrimental to health and how Voxzogo could help restoring quality of life.<br>When considering:<br>• 10 years less of average lifespan for adults[74]<br>• 5% mortality rate of infants due to foramen magnum stenosis[75]<br>• ACH comorbidities, their prevalence, and their onset in early age and adulthood[76]<br>we estimate that ACH is responsible for 50 QALYs lost per person with ACH.<br>By addressing foramen magnum, spinal stenosis and other comorbidities **Voxzogo will be able to restore 33 QALYs lost to ACH**, effectively giving children a quality of life that is much closer to that of people without the condition. This result is significantly higher than the 2,62 QALYs restored by Voxzogo presented by FINOSE in its report, where only height increase is considered. |

HEALTH ECONOMIC CASE FOR ACH CHILDREN

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## CALCULATIONS:

[54] Aquilo estimate based on available literature and doctors interviews. Assumed cost per year of treatment of 1,3M DKK per child, for 12 years of treatment. The following were used to calculate the savings, the lifetime cost and the QALYs restored due to Voxzogo:

Savings Due to Voxzogo:
Less HC use, decreased foramen magnum-related infant death, less adaptions, less disability pension

Lifetime Cost of Voxzogo:
1,3M DKK per year * 12 years (average time of children that will receive the drug)

QALYs Restored:
Unlike FINOSE, complications and mortality are included in the QALYs restored

Detailed calculations available upon request

[55] Aquilo calculation based on interviews with the patient (or mother if under 18), Danish DRG codes and academic literature

The following factors were used to determine disability pension and future productivity loss:
Age when Louise (Milan's mother) started disability pension = 29
Age when Line started disability pension = 31
Age when Tina started disability pension = 42
Retirement Age = 69
Cost of disability pension per year = DKK 236.856 (single), DKK 201.336 (married)
Cost of productivity loss per year (human capital approach: GDP per capita) = DKK 473.420

ACH probability of spinal stenosis development = 68%
ACH probability of being out of the workforce due to spinal stenosis = 74%
ACH average onset age of spinal stenosis = 30
ACH average working years lost due to spinal stenosis = 39

ACH chance of obesity = 30% (prevalence of severe obesity in ACH population defined as BMI>40)
ACH lifetime cost of obesity = DKK 8.529.383
ACH total future cost of obesity = DKK 5.714.687

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## IMAGES:

All images on the individual patient stories have been provided by the patient themselves: Milan Kjær Knudsen's mother Luise Kjær Knudsen, Tina Quist Nerengård, and Line Hartmann Eriksen.

All patient images are used with their consent.


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