Plain Language Summary of Publication

Journal of Comparative Effectiveness Research

Selumetinib for children with neurofibromatosis type 1 and plexiform neurofibromas that can't be removed by surgery, and impact on how the condition affects caregivers: a plain language summary

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Summary

What is this summary about?

Neurofibromatosis type 1 (also called NF1) is a rare genetic condition. It causes a range of symptoms that develop from childhood onwards and worsen over time. Some children with NF1 develop non-cancerous nerve tumors called plexiform neurofibromas. Plexiform neurofibromas can grow large and compress nearby tissues. This can cause severe pain, reduced movement, vision and hearing loss, and other medical problems. Some children can have plexiform neurofibromas removed surgically. Most children have tumors that cannot be removed by surgery (known as inoperable tumors). Children with inoperable plexiform neurofibromas can receive a medicine called selumetinib. This plain language summary includes important findings from two selumetinib studies in children with NF1 and inoperable plexiform neurofibromas:

The SPRINT selumetinib studies are part of a clinical study program that looked at how well selumetinib works in treating children with symptomatic, inoperable plexiform neurofibromas. The SPRINT studies program included the first studies of this medicine done in children, called phase 1 and phase 2 studies. For the phase 2 study, some children had severe symptoms and some children did not. The group of children with severe symptoms is called group 1, and their results are included in this summary. The researchers monitored the participating children for up to 5 years in a long-term study to better understand how the treatment works over time.

The NF1 caregivers experience study is a related study where caregivers shared their experiences of caring for children with NF1and plexiform neurofibromas.

What were the results?

A total of 74 children took part in the SPRINT phase 1 and phase 2 (group 1) study. Their ages ranged from 3 to 18.5 years, and their average age was 10.3 years. After more than 4 years of treatment, around 70% of the children (52 out of 74) had smaller tumors. For most children, the responses lasted beyond 1 year. There was a significant and lasting reduction in the intensity of the children's tumor pain, noticeable as early as 2 months after starting the treatment. After 12 months, children reported their pain dropped from an average score of 2.2 to 0.6 and stayed low at 0.58 over 4 years. There was also an improvement in how much their pain affected the children's ability to do daily tasks. Some children had side effects related to selumetinib, although these were generally manageable.

Results from the NF1 caregivers experience study showed caregivers of children with plexiform neurofibromas face significant impacts in physical, psychological, economic, and social aspects. These effects often result in a loss of productivity and difficulties with daily activity.

What do the results of the study mean?

Children with NF1 who have symptomatic, inoperable plexiform neurofibromas can benefit from selumetinib treatment. Selumetinib is generally well-tolerated, but it is important to monitor side effects during treatment. Caring for a child with NF1and symptomatic, inoperable plexiform neurofibromas has a significant impact on family members and others providing daily care. This highlights the importance of improving treatment and quality of life for both children with the condition and their caregivers.

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How to say (double click on the sound icon to play the sound)

Neurofibromatosis: nyuor-row-fai-brow-muh-TOW-suhs
Plexiform neurofibroma: PLEK-sih-form NOOR-oh-fy-BROH-muh
Selumetinib: SEL-yoo-MEH-tih-nib
Kinase inhibitor: KAI-nays in-HIH-bih-ter
Cutaneous neurofibroma: kyoo-TAY-nee-uhs NOOR-oh-fy-BROH-muh
Diarrhea: die-uh-REE-uh

Where can I find the original articles on which this summary is based?

You can read the original articles for free in the following sources:

- The article reporting the SPRINT phase 1 study is called "Activity of Selumetinib in Neurofibromatosis Type 1-Related Plexiform Neurofibromas" and is available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1605943
- The article reporting the SPRINT phase 2 study is called "Selumetinib in Children with Inoperable Plexiform Neurofibromas" and is available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1912735
- The article reporting the SPRINT long-term study is called "Long-term safety and efficacy of selumetinib in children with neurofibromatosis type 1 on a phase 1/2 trial for inoperable plexiform neurofibromas" and is available at: https://academic.oup.com/neuro-oncology/article/25/10/1883/7146403
- The NF1 caregivers experience study is called "Burden Among Caregivers of Pediatric Patients with Neurofibromatosis Type 1 (NF1) and Plexiform Neurofibroma (PN) in the United States: A Cross-Sectional Study" and is available at: https://link.springer.com/article/10.1007/s40120-022-00365-5

Who is this article for?

This article may be helpful for:

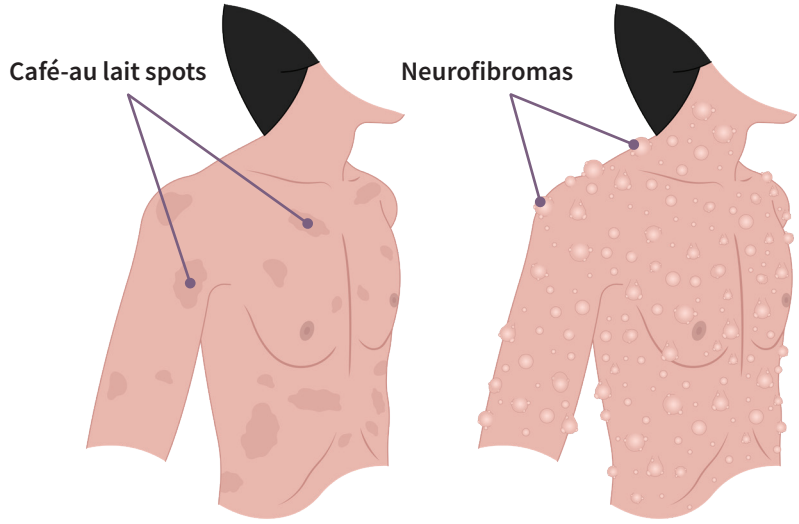
- People with NF1 and plexiform neurofibromas and their caregivers.
- Patient groups or other organizations helping children with NF1 and plexiform neurofibromas and their caregivers.
- Doctors, nurses and wider healthcare teams who treat children with NF1 and plexiform neurofibromas.
- Healthcare providers or policymakers who draft management recommendations for NF1and plexiform neurofibromas.

What is neurofibromatosis type 1?

NF1 is a rare condition that people are born with and affects around 1 in 3000 people. The symptoms can develop gradually over many years. The severity of the condition can vary from person to person.

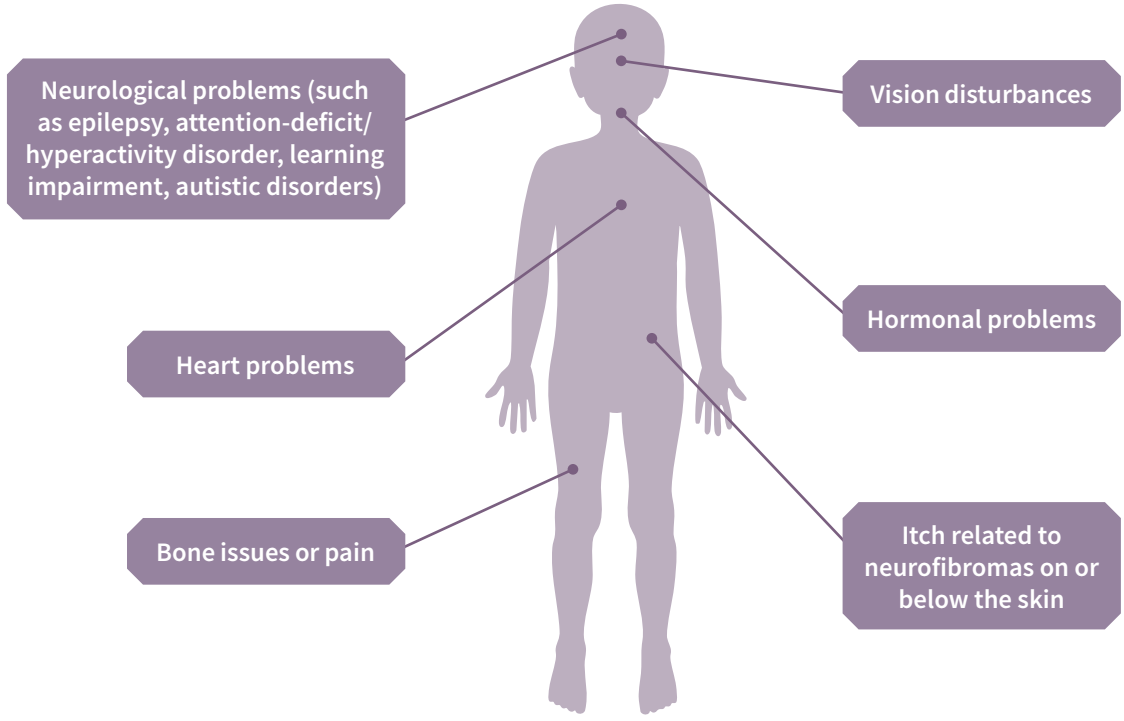
NF1 usually affects the skin, causing signals and symptoms such as:

- Light or dark brown patches called "café-au-lait spots". These can appear anywhere on the body and look like birthmarks.
- Clusters of freckles in places that don't usually get exposed to sunlight, such as the armpits, groin and under the breast.
- Benign tumors called neurofibromas that may grow on or under the skin.



Signals and symptoms can appear at different stages of life. Certain signals such as café-au-lait spots and freckling often show up early in childhood. Other signals and symptoms such as neurofibromas, develop more prominently during puberty and beyond.

Complications of NF1 can include:



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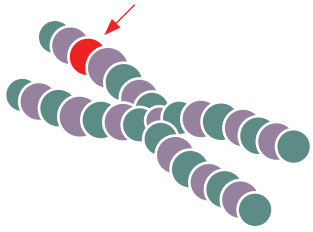
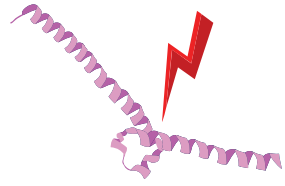
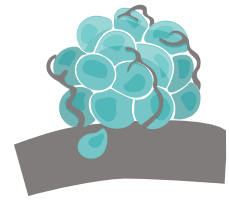
What causes neurofibromatosis type 1?

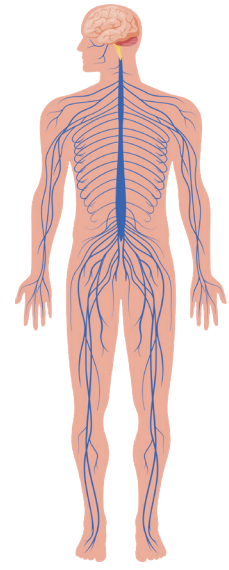
- NF1 is a genetic disorder caused by changes in a gene called *NF1*.
- *NF1* gene changes can be:
  - Inherited from parents. About half of people with NF1have inherited gene changes from a parent who also has to some extent the condition.
  - New gene changes. Around half the time, people with NF1 have gene changes that are not inherited from their parents.
- The *NF1* gene produces neurofibromin, a protein that controls cell growth and division. Changes in the *NF1* gene mean that the neurofibromin protein doesn't work properly, leading to uncontrolled cell growth.

How changes in the *NF1* gene lead to tumor growth

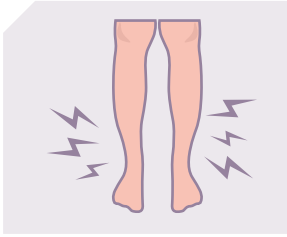
Changes in a gene (called *NF1*)	Protein alteration	Uncontrolled growth
		
• Genes are parts of chromosomes that act like instruction books for cells. • Changes in genes can lead to proteins that don't work correctly, causing problems in the body.	• Changes in the *NF1* gene cause issues in neurofibromin, a protein that normally acts as a brake on cell growth.	• Cells grow and divide too much because the systems that regulate their growth stop working.

What are plexiform neurofibromas?

Plexiform neurofibromas are non-cancerous tumors, meaning they don't spread to other body parts. They develop in the tissue covering the nerves in the body outside the brain and spinal cord (called peripheral nerves – these connect the brain and spinal cord to the rest of the body to control movement and feeling).



Plexiform neurofibromas may grow on the face, neck, arms, legs, back, chest, abdomen, and internal organs. Large tumors can compress nerves, which in turn can damage nearby bone, skin, and muscle. This can cause symptoms such as:

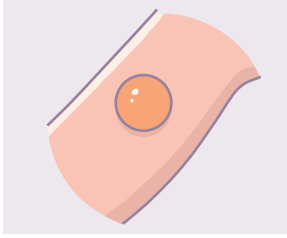


Pain

- Tumors can cause intermittent or constant pain, especially if they press on nearby nerves.

Nerve problems

- Symptoms may include weakness or paralysis, numbness, tingling, and difficulty using the affected nerve properly.



Changes to appearance

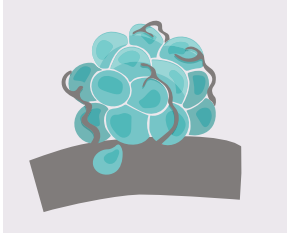
- Tumors, especially those on the face or limbs, can lead to changes in appearance, swelling, or lumps.

Pressure on organs

- Large tumors can press on nearby organs, leading to breathing problems, stomach issues, or problems with bladder or bowel control.

Growth problems in children

- Tumors in children can interfere with normal growth, causing bone deformities or overgrowth of the affected body part.



Cancer risk

- Though rare, tumors can sometimes become cancerous, leading to rapid increase in size, intense pain, and new problems with the nerves.

Some plexiform neurofibromas can be removed surgically; however, not all are operable due to factors such as size, location, potential within surgery and post-surgery risks, and the patient's overall health. Decisions about surgery are made on a case-by-case basis, typically involving a team of specialists.

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What is selumetinib?

Selumetinib is the only approved medication in the European Union, the USA, and many other countries to treat symptomatic, inoperable plexiform neurofibromas in children with NF1.

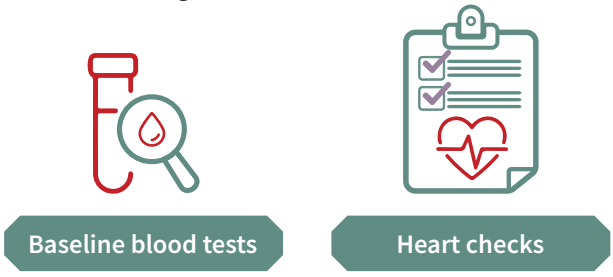
Selumetinib belongs to a group of medicines called kinase inhibitors. It works by blocking the action of a protein that signals tumors to grow. This can help slow down or even stop tumor growth.

Selumetinib is taken as a capsule by mouth twice a day, with or without food.

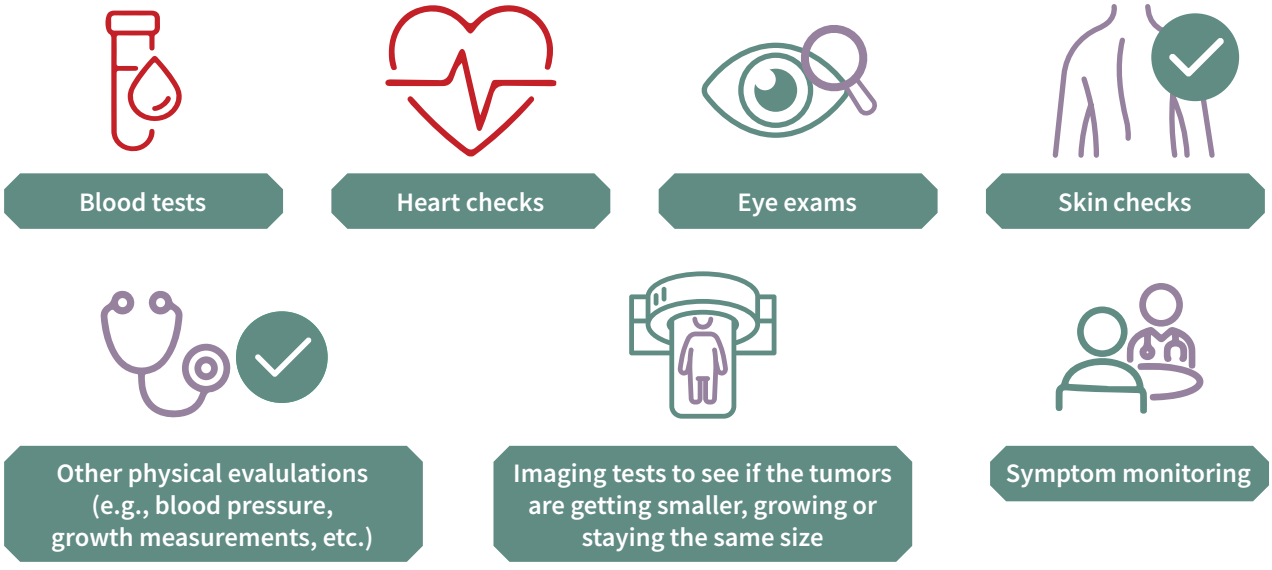
How are people taking selumetinib treatment monitored?

People taking selumetinib for plexiform neurofibromas must be carefully monitored to check for side effects and whether the treatment is working.

- Tests before starting treatment:



- Regular tests during treatment:



Heart checks include ultrasound scans of the heart, called echocardiograms, and heart rhythm tests, called electrocardiograms .

People who are starting the medicine and their caregivers should be asked to take it exactly as prescribed. They should also report any new or worsening signals or symptoms, whether related to the condition or potential side effects of the treatment.

What is the SPRINT study and why was it done?

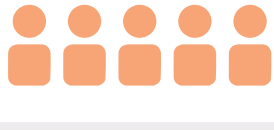
Paths from phase 1 and 2 (group 1) studies to the ongoing selumetinib study

In the phase 1 study, the researchers looked at the safety and the appropriate dose of selumetinib in a small group of participants with NF1 and inoperable plexiform neurofibromas. Phase 1 demonstrated that selumetinib could be effective.

What is a phase 1 clinical study?

- Tests a new treatment for safety, side effects, and the best dose and method of administration.
- Involves a small number of participants, often those who haven't responded to other treatments or healthy volunteers.

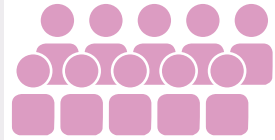
Phase 1 study



24 children
(enrolled from Sep 2011 to Feb 2014)

Treated for around 28 months

Phase 2 study (group 1)



50 children
(enrolled from Aug 2015 to Aug 2016)

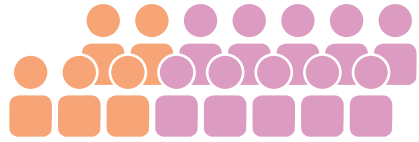
Treated for around 33 months

Initial efficacy and safety results

Treated for around 42 additional months

Treated for around 18 additional months

Long-term follow-up study



74 children
Long-term efficacy and safety results (Feb 2021)

In the phase 2 study, the researchers looked at whether selumetinib was safe and effective in a larger group of children. In this study, there were two groups of children. Group 1 included children with NF1 and inoperable plexiform neurofibromas causing serious health problems. The results for the children in this group are reported here.

- Group 2 included children without plexiform neurofibroma-related complications. The results of group 2 are not included in the selumetinib label and are not mentioned here.

What is a phase 2 clinical study?

- Evaluate a drug's effectiveness and safety for a specific condition.
- Can estabilish a does for further studies.
- **Key point:** in rare cases, when no effective treatments are available, a drug can be approved based solely on phase 2 results, as with selumetinib.

Long-term follow-up study. The researchers also collected data about the safety and effectiveness of selumetinib for up to 5 additional years after the phase 1 and 2 studies ended. These long-term results are reported here, while safety monitoring remains ongoing to gather further insights.

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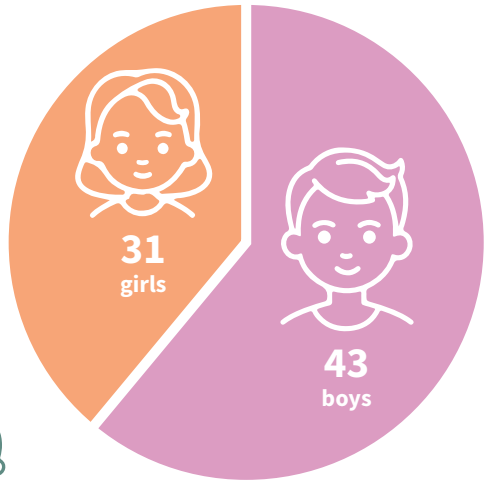
Who took part in the SPRINT study?

74
children took part in the study



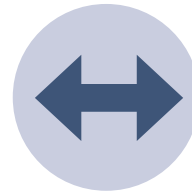
Youngest
3 years

Average age: around 10 years

Oldest
18.5 years

Condition of the most significant plexiform neurofibroma (based on its size, location, or symptoms) when children joined the study

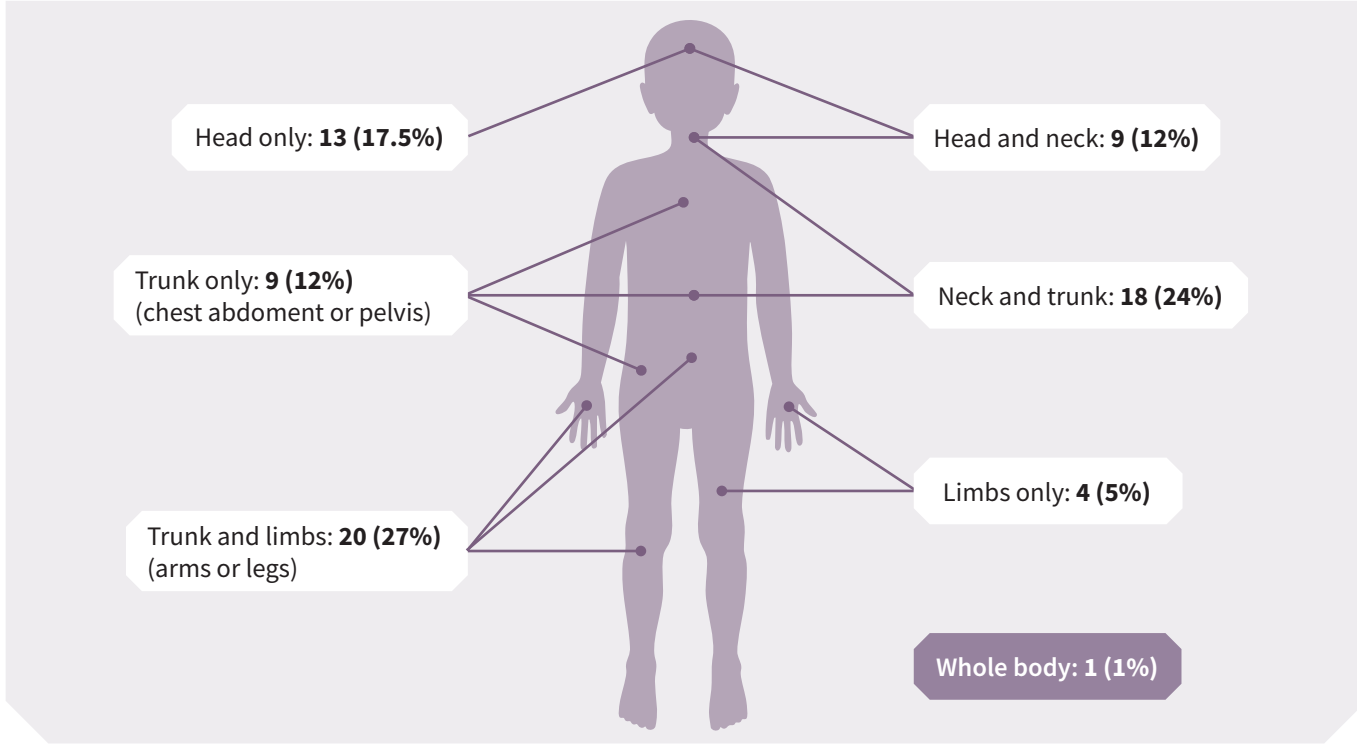
Growing in 30 children (41%)



Staying the same size in 23 children (31%)

Growth unknown in 21 children (28%)

Location of the main plexiform neurofibromas



What did researchers find out in the phase 1 study?

In the phase 1 study, 24 children received selumetinib for around 28 months.

- The researchers found the appropriate dose of selumetinib for children.
- They also found that selumetinib was generally safe overall. The most common side effects of selumetinib included:
  - An acne-like skin rash (red bumps on the skin).
  - Gastrointestinal issues (such as nausea, abdominal pain, vomiting, diarrhea, etc.).
  - Increased levels of creatine phosphokinase (CPK for short) in the blood. CPK is an enzyme found mainly in muscles, and high levels usually indicate muscle damage. However, in this study no children had symptoms related to high CPK levels.

What did researchers find out in the phase 2 study (group 1)?

In the phase 2 (group 1) study, 50 children received selumetinib for around 33 months.

The researchers used magnetic resonance imaging scans (known commonly as MRI scans) to see whether the size of the most significant tumor was changing during selumetinib treatment.

- 34 children (68%) had a 20% or greater reduction in tumor size, lasting for at least 3 months.
  - For 28 of these children (56%), this reduction in tumor size lasted for at least 1 year.
- After 1 year of treatment, children and their caregivers both reported significant improvements in pain intensity, daily functioning, and quality of life. They noticed a decrease in pain intensity as early as 2 months after starting the treatment.
- 5 children stopped taking selumetinib because it caused serious side effects.
- 6 children stopped treatment because their most significant plexiform neurofibroma was growing.
- Common side effects included gastrointestinal issues (similar to those seen in phase 1), increased CPK levels (without any symptoms), acne-like skin rash, and paronychia (infection around a fingernail).

How many children received treatment in the long-term study?

- The long-term part of the study provides up to 5 years of additional safety and effectiveness data from the phase 1 and 2 studies.
- At the time that this long-term data was published, 9 out of 24 children (38%) in the phase 1 study and 23 out of 50 (46%) in the phase 2 study were still receiving treatment.

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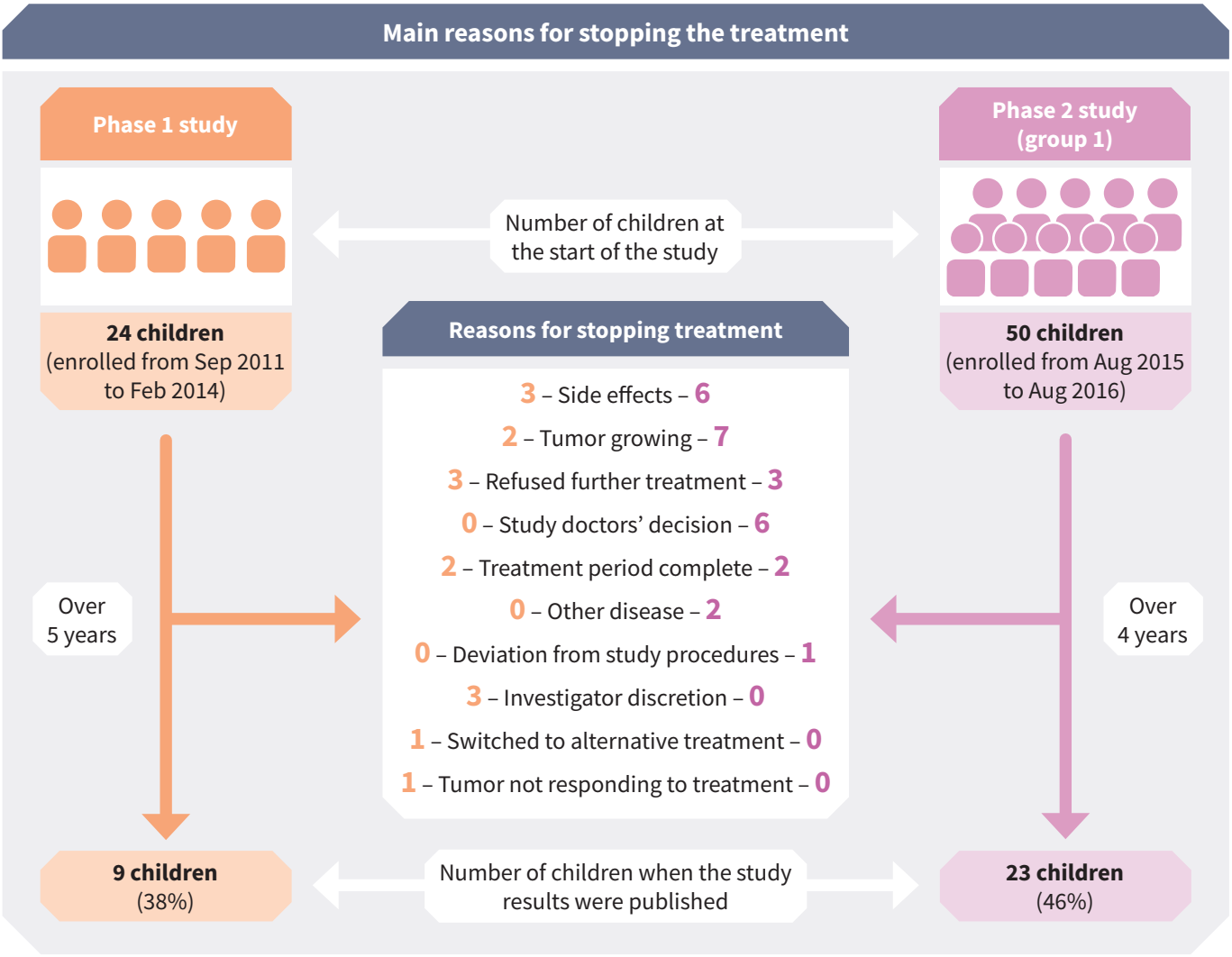


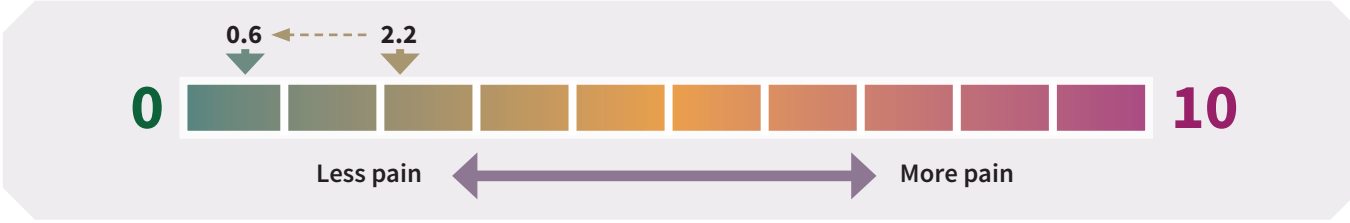
What are the results of the long-term study so far?

- The 24 children who took part in the phase 1 study have received treatment for an average of about 70 months (more than 5 years).
  - 18 out of 24 children (75%) had a 20% or greater reduction in tumor size, lasting for at least 3 months. In 16 of these children (67%), this reduction in tumor size lasted for at least 1 year.
- The 50 children who took part in the phase 2 (group 1) study received treatment for an average of around 52 months (over 4 years).
  - 34 out of the 50 children of this study part 2 (68%) had a 20% or greater reduction in tumor size, lasting for at least 3 months. In 28 of these children (56%), this reduction in tumor size lasted for at least 1 year.
- Overall, a total of 74 children started the long-term follow-up study. Of these, 52 children (70%) had a 20% or greater reduction in tumor size, lasting for at least 3 months. The response was durable, with over 59% of the participants (44 children) having a response that lasted more than 1 year.

Proportion of children achieving tumor volume reduction ≥20% for ≥3 months

Phase 1 study	Phase 2 (group 1) study	Phase 1 + phase 2 (group 1) studies
75%	68%	70%

- After 1 year of treatment:
  - Most children reported a significant decrease in tumor pain intensity, reporting that their tumor-related pain dropped from an average score of 2.2 to 0.6 (on a scale from 0 to 10, with 0 meaning no pain).



  - The children also noted a reduction in how much the pain interfered with their daily activities, meaning it had less of a negative impact on their ability to perform everyday tasks.
- After 4 years of treatment children reported a similar level of improvement: Out of 19 children who completed pain evaluations, 10 (53%) had their pain intensity reduced by two or more points over 4 years.

- Overall, children and their caregivers consistently reported significant and long-lasting improvements in pain.

What were the side effects reported in the long-term study?

Side effects in studies are graded on a scale from 1 to 5

Grade 1	Mild side effects that are generally not bothersome
Grade 2	Side effects that are bothersome and may interfere with some activities but are not dangerous
Grade 3	Severe, very bothersome side effects that significantly interfere with daily activities and may require medical intervention
Grade 4	Life-threatening side effects that require immediate medical attention and intervention
Grade 5	Side effects that result in death

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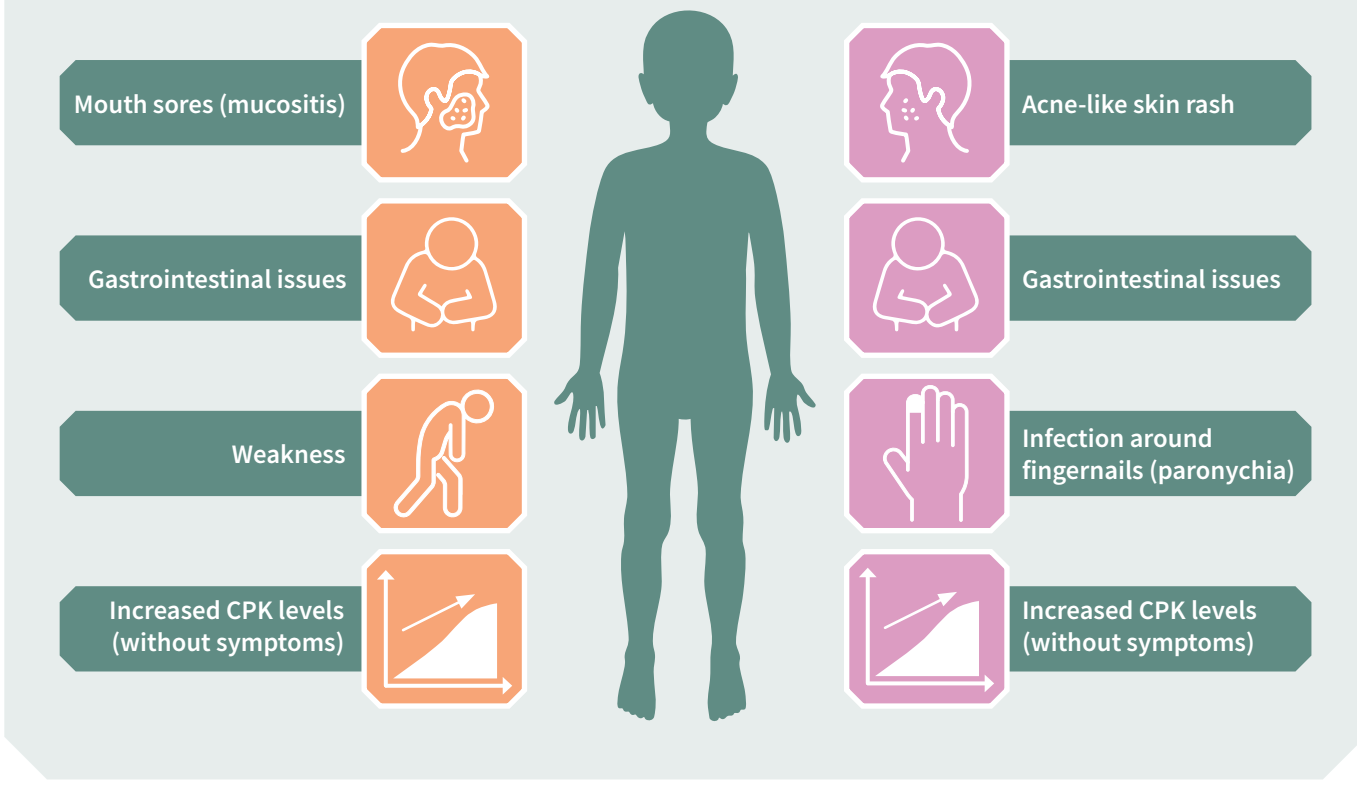
Phase 1 study

- All children had at least one side effect possibly related to selumetinib. Almost all of these (99%) were mild to moderate (grade 2 or lower).
- 3 children stopped treatment due to a side effect possibly related to selumetinib:
  - Mouth sores
  - Weakness/muscle pain
  - Nausea/stomach acid coming up (reflux)

Phase 2 study (group 1)

- Most children (98%) had at least one side effect possibly related to selumetinib. Almost all of these (97%) were mild to moderate (grade 2 or lower).
- 5 children stopped treatment due to a side effects possibly related to selumetinib:
  - Skin ulceration
  - Weight gain
  - infection around a fingernail (paronychia)
  - Sudden worsening of kidney function
  - Diarrhea

Location of the most common side effects



Combined phase 1 and phase 2 (group 1) studies: common side effects linked to selumetinib

Side effects	Cases	Grade 1	Grade 2	Grade 3	Grade 4	% of participants with the side effect
Skin infections	8	3	3	1	0	11%
Abdominal pain	25	18	7	0	0	34%
Constipation	25	20	5	0	0	34%
Increased alanine aminotransferase (a liver proteine) in blood	26	25	0	1	0	35%
Neutrophil count decreased (a type of white blood cell)	26	10	15	1	0	35%
Pruritus (itching)	27	14	13	0	4	37%
Stomach pain	30	25	5	0	0	41%
Anemia	32	29	1	2	0	43%
Increased aspartate aminotransferase (a liver protein) in blood	34	1	2	1	0	46%
Fatigue	42	30	4	0	0	46%
Maculo-papular rash (a rash with flat, red spots and and small reaised bumps on skin)	34	27	5	2	0	46%
Paronychia (infection of the skin around the nails)	36	4	24	8	0	49%
Oral mucositis (inflammation and sores insed the mouth)	39	27	11	1	0	53%
Skin condition that looks like acne (acne-like skin rash)	45	24	18	3	0	61%
Dry skin (xerosis)	49	30	18	1	0	66%
Nausea	49	41	7	1	0	66%
Diarrhea	51	31	11	9	0	69%
Increased CPK (protein found in the heart, brain, and skeletal muscles)	56	37	13	4	2	76%
Other skin issues	58	40	17	1	0	78%
Vomiting	58	41	15	2	0	78%

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Which side effects required special attention in the long-term study?

Selumetinib belongs to a group of medicines known to cause rare but potentially severe eye and heart-related side effects, which require careful monitoring. In the SPRINT study, these side effects were infrequent and mild when they occurred.

1 child had a problem in the back of the eye (retina). They continued selumetinib and the problem was better 3 weeks later.

Some children receiving selumetinib have developed blurred vision. According to the prescribing information, people taking selumetinib should report any new problems with their vision. It also highlights why vision test baselines at the start of the study are important.

16 children had some reduction in the heart's pumping ability. 3 children developed this problem for the first time after being on treatment for several years. Heart functioning has to be monitored when using selumetinib.

Most of the affected children (14 children, 88%) showed improvement or stability of the problem without needing any further intervention and were able to carry on taking treatment. 2 children required dose adjustments to manage the issue, including temporary dose interruption, but neither had to stop treatment, and their heart function returned to within normal limits.

What do the overall results of the SPRINT study mean?

- Selumetinib use in children with NF1 who have plexiform neurofibromas that can't be removed with surgery and cause problematic symptoms stops in most cases tumors from growing and even shrinks them, with effects that can last for years.
- The long-term follow up report shows that for children who continue with the treatment, the relief from tumor-related pain can be sustained over time.
- Children can develop selumetinib-related side effects years after starting treatment, so they need ongoing monitoring while taking the medication.
- Overall, the study results show that treating children with selumetinib for non-removable, symptom-causing tumors linked to NF1 is safe, manageable, and often provides lasting benefits.

What impact does this condition have on caregivers?

- Caregivers of children with NF1 and plexiform neurofibromas face a significant impact on their quality of life.
- In this study, caregivers shared their views and feelings about the difficulties they face while caring for children with NF1 and plexiform neurofibromas:
  - 95 caregivers took part in this data collection part
  - 84 of them were women (around 88%)
  - Their average age was 44 years
  - Each person completed a questionnaire with 22 questions

- The questionnaire looked at different areas of the caregiver's quality of life, including:
  - Relationships
  - Emotional well-being
  - Social and family life
  - Finances
  - Loss of control over one's life

Key findings from this study related caregivers' survey include:

The majority of caregivers reported an impact on their quality of life, with different levels:

- 40% of caregivers experienced mild to moderate impact
- 12% experienced moderate to severe impact
- 1% experienced severe impact

Employed caregivers reported:

- Missing an average of 7% of their working hours
- A reduction of 17% of on-the-job effectiveness due to caring for their child
- A 22% reduction in work productivity in the past week, which includes the inability to fully attend work and be effective during working hours
- An average of 17% of their regular daily activities, other than working, were affected by providing care for their child

In addition, many caregivers had mental and/or physical health conditions:

- Nearly half (50%) reported that they had anxiety
- Around one-third (35%) reported that they had depression

What do the results of this survey to NF1 caregivers mean?

- The survey shows that NF1 caregivers face challenges across many areas of their lives, including their physical, emotional, economic, and social well-being. Caregivers reported significant losses in productivity and limitations in their daily activities.
- Improving quality of life for children with NF1and plexiform neurofibromas, and their caregivers is a key priority for research and medicines development.

10.57264/cer-2024-0184

Where can readers find more information on these studies?

This summary includes information from four published articles and readers can find more information about these publications below.

SPRINT phase 1 study

- This article is called: Activity of Selumetinib in Neurofibromatosis Type 1-Related Plexiform Neurofibromas.
- The full citation of this article is: Dombi E, Baldwin A, Marcus L, *et al.* Activity of Selumetinib in Neurofibromatosis Type 1-related Plexiform Neurofibromas. *N. Engl. J. Med.* 375:2550–2560 (2016).
- You can read the article for free at: https://www.nejm.org/doi/full/10.1056/NEJMoa1605943

SPRINT phase 2 study

- This article is called: Selumetinib in Children with Inoperable Plexiform Neurofibromas.
- The full citation of this article is: Gross AM, Wolters PL, Dombi E, *et al*. Selumetinib in Children with Inoperable Plexiform Neurofibromas. *N. Engl. J. Med*. 382:1430–1442 (2020).
- You can read the article for free at: https://www.nejm.org/doi/full/10.1056/NEJMoa1912735

SPRINT long-term study

- This article is called: Long-term Safety and Efficacy of Selumetinib in Children with Neurofibromatosis Type 1 on a Phase 1/2 trial for Inoperable Plexiform Neurofibromas.
- The full citation of this article is: Gross AM, Dombi E, Wolters PL, *et al.* Long-term Safety and Efficacy of Selumetinib in Children with Neurofibromatosis Type 1 on a Phase 1/2 Trial for Inoperable Plexiform Neurofibromas. *Neuro-Oncology* 25(10):1883–1894 (2023).
- You can read the article for free at: https://academic.oup.com/neuro-oncology/article/25/10/1883/7146403

NF1 caregivers experience study

- This article is called: Burden Among Caregivers of Pediatric Patients with Neurofibromatosis Type 1 (NF1) and Plexiform Neurofibroma (PN) in the United States: A Cross-Sectional Study.
- The full citation of this article is: Yang X, Yoo, HK, Amin S, *et al.* Burden Among Caregivers of Pediatric Patients with Neurofibromatosis Type 1 (NF1) and Plexiform Neurofibroma (PN) in the United States: a cross-sectional study. *Neurol Ther.* 11:1221–1233 (2022).
- You can read the article for free at: https://link.springer.com/article/10.1007/s40120-022-00365-5

Where can I find more information on NF1 and plexiform neurofibromas?

You can find more information at the following websites, which provide resources on the condition:

Neurofibromatosis Type 1

- National Institutes of Health (NIH): https://rarediseases.info.nih.gov/diseases/7866/neurofibromatosis-type-1
- Mayo Clinic: https://www.mayoclinic.org/diseases-conditions/neurofibromatosis-type-1/symptoms-causes/syc-20350490

Plexiform neurofibromas

- Children's Tumor Foundation: https://www.ctf.org/wp-content/uploads/2023/11/Plexiform_Neurofibromas_NF1.pdf

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