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CADTH Reimbursement Recommendation

Selumetinib (Koselugo)

Indication: For the treatment of pediatric patients aged 2 years and above, with neurofibromatosis type 1 who have symptomatic, inoperable plexiform neurofibromas

Sponsor: Alexion Pharma GmbH

Final recommendation: Reimburse with conditions

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Summary

What Is the CADTH Reimbursement Recommendation for Koselugo?

CADTH recommends that Koselugo be reimbursed by public drug plans for the treatment of pediatric patients aged 2 years and above, with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PNs), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Koselugo should only be covered to treat patients who are aged between 2 and 18 years with a diagnosis of NF1 with PNs that are causing symptoms and cannot be completely removed by surgery.

What Are the Conditions for Reimbursement?

Koselugo should only be reimbursed if prescribed by specialists with experience in managing NF1 and PNs, and the cost of Koselugo is reduced. To continue treatment with Koselugo longer than 18 months, the treating physician must provide proof that the patient is responding to treatment, including but not limited to reductions in symptoms of pain, improved motor function, and/or stabilization of disease, or proof of shrinking of tumours.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial suggested that treatment with Koselugo caused tumours to shrink, and resulted in lasting responses to treatment. Additionally, Koselugo may improve patient-reported symptoms of pain, motor function, and health-related quality of life (HRQoL).
- Koselugo meets some needs identified by patients. It is a new treatment option that reduces tumour size and has manageable side effects.
- Based on CADTH's assessment of the health economic evidence, Koselugo does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Koselugo is estimated to cost the public drug plans approximately $65 million over the next 3 years. However, the actual budget impact is uncertain given that the proportion of patients with NF1 with symptomatic PNs is unknown and the estimates are highly sensitive to this parameter input.

Summary

Additional Information

What Are NF1-Associated PNs?

NF1 is a rare, progressive, genetic disease that affects multiple systems of the body, and results in noncancerous tumours that grow in and under the skin, as well as other complications. In up to 50% of patients with NF1, larger noncancerous tumours called PNs grow along the nerves anywhere in the body, causing pain, discomfort, and limiting mobility. NF1 affects 1 out of every 2,500 to 3,000 infants; however, the number of people with PNs due to NF1 that cannot be removed by surgery in Canada is unknown.

Unmet Needs in NF1-Associated PNs

Prior to the approval of Koselugo, there were no drug treatments available for patients with PNs that cannot be removed by surgery. There is a need for new treatments options that reduce tumour sizes and improve quality of life (QoL).

How Much Does Koselugo Cost?

Treatment with Koselugo is expected to cost approximately $268,678 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that selumetinib be reimbursed for the treatment of pediatric patients aged 2 years and above, with NF1 who have symptomatic, inoperable PNs only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from a phase II, single-arm study (SPRINT phase II) that included 50 pediatric patients with NF1 with inoperable PNs reported that after a median treatment duration of 4.3 years, 68.0% of patients (95% confidence interval [CI], [redacted]) achieved an objective response rate (ORR) that was determined by a reduction from baseline in PN volumes of 20% or more. In addition, treatment with selumetinib resulted in an improvement in patient-reported pain (Numerical Rating Scale 11 [NRS-11] = [redacted] points [95% CI, [redacted]]; Pain Interference Index [PII] = [redacted] points [95% CI, [redacted]]), motor function (mobility = [redacted] points [95% CI, [redacted]], upper extremity = [redacted] points [95% CI, [redacted]]) as well as improvements in strength and range of motion (ROM). However, the magnitude of clinical benefit is uncertain due to the lack of minimal important difference (MID), or the change did not exceed the estimated clinically meaningful threshold of 2 points for the NRS-11 or 0.75 points or more for the patient-reported PII.

Patients identified a need for treatments that reduce pain and tumour size, improve physical function, and improve overall HRQoL. CDEC concluded that selumetinib addresses some of these important unmet needs as nearly all patients (95.8%) experienced a reduction in target PN volume during the SPRINT phase II trial, with 77.1% experiencing a maximum reduction of 20% or more. CDEC recognized that there is significant unmet need for patients with NF1-associated symptomatic, inoperable PNs for which no other effective treatments are currently available. CDEC concluded that selumetinib might address an unmet need for patients diagnosed with NF1-associated symptomatic, inoperable PNs.

The committee considered analyses conducted by CADTH that evaluated the cost-effectiveness of selumetinib with best supportive care (BSC) relative to BSC. CADTH could not address uncertainties associated with the lack of comparative treatment effects and limitations with the model's structural assumptions that led to selumetinib substantially delaying disease progression compared to BSC. CDEC concluded that, based on the sponsor's submitted price for selumetinib and publicly listed prices for all other drug costs, the most likely estimated incremental cost-effectiveness ratio (ICER) is $426,286 per quality-adjusted life-year based on the CADTH reanalysis that assumed a smaller residual benefit. In all reanalyses, a price reduction would be required for selumetinib to achieve an ICER of $50,000 per quality-adjusted life-year.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. In pediatric patients aged 2 to 18 years with NF1 with symptomatic, inoperable PNs	The SPRINT phase II study enrolled patients between the ages of 2 to 18 years; no information was identified for patients who turned 18 years of age while on study treatment. Additionally, there is no evidence available for the initiation of therapy after 18 years of age. Evidence from the SPRINT phase II trial suggested that treatment with selumetinib resulted in overall improvement, including reductions in pain (NRS-11, PII), improvements in motor function (strength and ROM MMTs), with most patients demonstrating response to treatment (ORR) and reductions in tumour volume, in pediatric patients aged 2 to 18 years with NF1 with symptomatic, inoperable PNs.	In the SPRINT phase II trial, morbidity was defined as any PN-related clinical signs or symptoms, while inoperable PNs were defined as those that are unable to be completely surgically removed without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, or invasiveness or high vascularity of the PN. CDEC also noted that patients whose surgical removal did not result in amelioration of symptoms could be eligible for treatment with selumetinib.
2. The maximum duration of initial authorization is 18 months.	The clinical experts noted to CDEC that based on their experience, in the absence of disease progression or toxicity, patients should initially be treated with selumetinib for 18 months before deciding whether to continue treatment with selumetinib.	—
Renewal		
3. For renewal after initial authorization, the physician must document the beneficial clinical effect when requesting continuation of reimbursement. Patients on therapy should be monitored for response (e.g., a reduction in pain, improved function, reduction in tumour volume, disease stabilization) using clinical judgment and/or standard imaging.	There are no standardized metrics for defining treatment response for NF1-associated PNs. Based on clinical expert opinion, assessing response should be multifaceted, relying heavily on clinical judgment of symptomatology in combination with standard imaging techniques. Volumetric MRI was used in the SPRINT phase II study to determine response to treatment; however, volumetric MRI is not available in Canadian clinical practice, and only standard imaging techniques remain available; these may be subject to capacity constraints and additional challenges due to the pediatric population.	—
4. Subsequent renewals should be assessed annually.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	—
Discontinuation		
5. Selumetinib should be discontinued upon disease worsening or progression (e.g.,	Discontinuation criteria from the SPRINT phase II trial included AEs that were unable to be resolved within 21 days of selumetinib interruption (or up	—

Reimbursement condition	Reason	Implementation guidance
worsening of motor function or pain).	to 2 dose reductions), and evidence of clinical or imaging progressive disease on treatment (i.e., an increase in the volume of the target PN by 20% or more compared with baseline or the time of best response after documenting a partial response). Based on clinical expert opinion, patients whose disease is not responding (i.e., tumour growth, lack of stabilization, or lack of improvement of symptoms), or in patients with severe AEs that are unable to be managed should be discontinued from treatment with selumetinib.	
Prescribing		
6. The patient must be under the care of either a neurooncologist or a pediatrician with expertise in neurooncology.	Carefully considered diagnosis and follow-up of patients with NF1 is important to ensure that selumetinib is prescribed for the most appropriate patients, and that adverse effects are managed appropriately.	—
Pricing		
7. A reduction in price	The cost-effectiveness of selumetinib is highly uncertain. CADTH undertook price reduction analyses that differed in the magnitude of residual benefit assumed following treatment discontinuation. Assuming a smaller residual benefit, the price reduction analysis indicated that an 89% reduction in price for selumetinib is required to achieve an ICER of $50,000 per QALY. As outstanding uncertainty remains, it was noted that a higher price reduction may be required.	—
Feasibility of adoption		
8. The feasibility of adoption of selumetinib must be addressed.	The magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption. There remains considerable uncertainty regarding the epidemiologic inputs that would inform the size of the target population. As such, there is uncertainty regarding the potential budget impact of reimbursing selumetinib.	—

AE = adverse event; ICER = incremental cost-utility ratio; MMT = manual muscle test; NF1 = neurofibromatosis type I; NRS-11 = Numerical Rating Scale 11; ORR = objective response rate; PII = Pain Interference Index; PN = plexiform neurofibroma; QALY = quality-adjusted life-year; ROM = range of motion.

Discussion Points

- CDEC considered the patient population, severity of the condition, potential for rapid progression, and lack of therapeutic options available, all of which represent a significant unmet need for this population. CDEC discussed that despite the evidence suggesting that treatment with selumetinib improves pain and function, and reduces tumour volume, the clinical experts noted that the correlation between PN volume changes and improvements in symptoms or function remains

uncertain, and that tumour size may not always be reflective of morbidity. CDEC were advised by the clinical experts that, because of the poor correlation between tumour volume and symptoms, decisions about initiation and response to therapy are primarily determined by a comprehensive, interdisciplinary assessment of symptoms.

- Overall, CDEC discussed the nonrandomized design of the SPRINT phase II trial, which made interpreting the results and overall magnitude of treatment effect attributable to selumetinib challenging mainly because of the open-label design and the absence of a comparator influences patient selection, patient-reported outcomes (PROs), and reporting of harms.
- CDEC discussed an array of nuanced ethical and equity considerations related to selumetinib. Those considerations included HRQoL impacts on patients with NF1 who have symptomatic, inoperable PNs and access challenges related to the need for a specialized care teams for timely diagnosis and management. CDEC also discussed the unique vulnerabilities of the NF1 pediatric population, including the impacts of appearance on children, as well as challenges with reliance on parents to advocate and support these patients, and the potential for caregiver burden, especially in circumstances where parents also have NF1. CDEC also discussed the ethical challenges of uncertainties in the evidence, including those related to long-term safety and the use of outcomes that may not be meaningful to patients, as well as the challenges that this might raise for informed consent. Access to selumetinib may also be hampered by geographic inequities in access to treatment and challenges in transitions between pediatric and adult care settings; mitigating these access barriers may lead to additional health system costs.
- Though the committee considered the outcomes of the SPRINT phase II trial to be clinically relevant in this setting, the lack of standardized, objective measures of response represents an inherent challenge in measuring and interpreting clinical outcomes in NF1-associated PNs. Additionally, CDEC considered the unavailability of volumetric MRI in Canadian clinical practice and noted that it is unclear how this may impact the magnitude of response observed.
- The clinical experts noted to CDEC that given the heterogeneity in the disease and the individualized approach to treatment, decisions often involve a multidisciplinary team of pediatricians, NF1 experts, neurooncologists, and nurse practitioners. The clinical experts also emphasized the importance of consulting with other specialists, including surgeons, cardiologists, ophthalmologists, and pharmacists, for the management of alternative treatment options, adverse effects, and drug interactions. CDEC recognizes that some jurisdictions might not have access to enough specialists to implement this recommendation, so public drug plans should consider whether a pan-Canadian approach would be feasible. This could include leveraging clinical expertise in larger jurisdictions through the establishment of a centralized panel or committee of NF1 specialists who could assess response to treatment.
- The SPRINT phase II trial enrolled patients aged 2 to 18 years. CDEC discussed the lack of available evidence for treating patients older than 18 years. However, the clinical expert noted to CDEC that patients who initiated treatment with selumetinib before the age of 18 and whose disease responded to treatment could continue treatment with selumetinib after they turned 18.

- Given that NF1-associated PNs may require lifelong treatment, CDEC discussed that there is uncertainty regarding the long-term efficacy and safety of selumetinib. CDEC noted that despite the longer follow-up at the second data cut-off (DCO) (5.6 years), the duration of the treatment effect and safety remain unknown.
- CDEC discussed an indirect treatment comparison (ITC) submitted by the sponsor that compared selumetinib with natural history and the placebo arm of an external study that suggested improvements in mean annual change in target PN volume and progression-free survival (PFS), as well as improvements in the propensity score matched analysis of PFS. However, the results of the indirect evidence were associated with important limitations, and no conclusions could be drawn by CDEC.
- CDEC discussed that improvement of HRQoL is important as the impact of NF1-associated symptomatic, inoperable PNs on HRQoL can be significant. However, no definitive conclusion could be reached regarding the effects of selumetinib on QoL because of attrition, small sample size, and the absence of MID thresholds.
- CADTH could not address the limitations associated with the structural assumption of the submitted economic model. It was assumed that all patients on BSC automatically begin in the "progressed" state, and CDEC noted that this assumption contradicts the available clinical evidence and favours selumetinib. As such, all analyses likely underestimate the true ICER, and a higher price reduction may be required.
- CDEC discussed that the budget impact estimates were highly sensitive to the epidemiological inputs used to derive the target population eligible for treatment. If the proportion of patients with NF1 who have PNs is expected to be higher, the expected budget impact would be more aligned with the sponsor's submitted results, with a 3-year total budget impact of $107,836,511 (year 1 = $26 million; year 2 = $38 million; year 3 = $44 million).

Background

NF1 is an autosomal dominant genetic disorder associated with progressive cutaneous, neurologic, skeletal, and neoplastic manifestations. Approximately half of all NF1 cases are familial, while half arise from spontaneous mutations in the NF1 gene. Currently, the incidence of NF1 in Canada is unknown, though it is estimated to occur in 1 in 2,500 to 3,000 births. The patient group input received by CADTH for this review highlighted that there are currently over 12,000 cases of NF1 in Canada. The most common manifestations of NF1 include abnormally coloured patches of skin (café-au-lait macules [CALMs]), freckling under the arms and in the inguinal region, and benign tumours predominantly in the skin and nerves, known as neurofibromas. Other manifestations may include bone dysplasia, scoliosis, ocular problems, and neurologic complications with impacts such as cognitive impairments and learning disabilities. Neurofibromas are histologically benign nerve sheath tumours, typically originating in the terminal nerve branches of the skin. PNs are the most common type of tumour in patients with NF1, occurring in up to 50% of patients. One or multiple PNs may grow along large nerves and plexuses anywhere in the body, with varying manifestations

that continue to develop to early adulthood, and multiple PNs may be both symptomatic and asymptomatic in the same individual. Additionally, PNs have a complex shape and can reach large sizes, resulting in clinical symptoms such as disfigurement, motor dysfunction (weakness and restricted ROM), pain, and neurologic dysfunction. The severity of symptoms from PNs may range from mild to severe; however, the presence of symptoms may depend on their location and impact on surrounding structures. PNs grow most rapidly during the early childhood, though growth rate is highly variable between patients.

Treatment and clinical management options for NF1-associated PNs are extremely limited and are dependent on symptomatology. For symptomatic patients, treatments aim to relieve symptoms caused by the individual PNs. Currently, the only available options to treat and manage NF1-associated PNs include pain management and surgical excision to remove as much of the tumours as possible. However, for many patients, surgery is not a viable option as most PNs are not amenable to complete resection due to encasement of, or proximity to, vital structures.

Selumetinib has been approved by Health Canada for the treatment of pediatric patients aged 2 years and older with NF1 who have symptomatic, inoperable PNs. Selumetinib is a selective inhibitor of mitogen-activated protein kinase (MEK) 1 and 2. It is available as 10 mg or 25 mg oral capsules and the dosage recommended in the product monograph is 25 mg/m^2 twice daily based on body surface area.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase II, open-label, single-arm study in pediatric patients with NF1 and inoperable PN
- patients' perspectives gathered by patient groups, the Tumour Foundation of BC (TFBC) and the Canadian Organization for Rare Disorders (CORD)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 3 clinical specialists with expertise diagnosing and treating patients with NF1
- input from 1 clinician group, including the Canadian Pediatric Brain Tumour Consortium (CPBTC)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to selumetinib.

Stakeholder Perspectives

Patient Input

CADTH received input from 2 patient groups: the TFBC and CORD. The TFBC provides essential information and support services to patients with neurofibromatosis and their families. CORD works with governments, researchers, clinicians, and industry to promote research, diagnosis, treatment, and services for all rare disorders in Canada.

Both patient groups conducted online surveys in November 2022, recruiting patients with NF1 and their caregivers. Additionally, the TFBC conducted a Zoom focus group. The TFBC group recruited 25 patients and caregivers, and CORD recruited 8 caregivers. Key themes identified by patients and caregivers with NF1 included limitations on daily living, functional, and social activities; moderate to severe chronic pain; dependency on caregivers into adulthood; financial stress because of the diagnosis; and lack of treatment options, which negatively impacts the emotional well-being of patients and families.

Respondents from both patient and caregiver groups described difficulties in obtaining a diagnosis of NF1, as well as significant impacts on both affected children and their families in terms of managing the physical and mental aspects of the disease. Additionally, substantial negative mental health impacts were reported, with most patients living with anxiety and fear over their diagnosis, and some patients experiencing suicidal feelings or actions. Respondents to both surveys and interviews emphasized surprise and disappointment in the lack of treatment options or support available, with 46% of respondents not having been offered any kind of treatment, and only 17% of those who were offered treatment indicating that they experienced minimal improvement in symptoms.

No patients in the TFBC survey had experience with selumetinib. Half (n = 4) of the CORD respondents had experience with selumetinib through clinical trials and described it as “miracle drug” that was “life-changing” because of substantial improvements in pain levels; functional abilities, including speaking clearly and chewing food; and softening and shrinking tumours that were previously disabling and/or disfiguring.

Numerous outcomes were identified as important to patients, reflecting the heterogenous nature of the disease, but common themes included an overall improved QoL, a desire for reduction in pain and reduction or prevention in tumour size or growth, improved function and emotional well-being, greater independence from caregivers, and a reduced number of health care visits.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The information in this section is based on input received from a panel of 6 clinical specialists consulted by CADTH for the purpose of this review.

The clinical experts indicated that the main limitations and unmet needs of pediatric patients with NF1 with symptomatic PNs is the lack of access to disease-modifying medical interventions that can reduce the burden of disease or stabilize symptomatic PNs. The clinical experts noted that there are currently no established practice guidelines for this heterogenous disease. For patients with symptomatic PNs, surgery is the only available treatment option, which is either aimed at excising tumours, if possible, or debulking, if complete excision is not achievable. The experts noted that surgery is not curative for most large or extensive PNs and is associated with significant risks of secondary injuries based on the number, location, size, and vascularity of the tumours, particularly for PNs involving large arteries or nerves. Additionally, the experts cited that multiple invasive surgeries may be required, as tumours may regrow, or increase in size, thereby further increasing the risks to patients. Aside from surgery, current treatment strategies consist of “watch and wait” for patients with PNs that are not currently symptomatic. Otherwise, treatment for patients

with symptomatic PNs focus on relieving pain, reducing functional impairment, and improving overall QoL. The panel highlighted the availability of MEK inhibitors through managed access programs, noting that selumetinib is the first, and only, Health Canada–authorized MEK inhibitor available outside of clinical trials for the treatment of PNs. The panel concluded that selumetinib is expected to cause a shift in the current treatment paradigm given the absence of other medications available for this population. The experts stated that should selumetinib be recommended for reimbursement, it would likely be the initial therapy of choice.

The clinical experts noted that only a minority of patients with NF1 have symptomatic PNs. Patients with NF1 are diagnosed based on standard, well-established, and recently updated clinical diagnostic criteria that include clinical characteristics such as CALMs and presence of neurofibromas. Although the recently updated diagnostic criteria include genetic testing, the experts noted that genetic testing is not required for diagnosis of NF1. The experts highlighted that results of genetic testing do not impact treatment decisions once a clinical diagnosis of NF1 has been established. The clinical diagnosis of NF1 is relatively straightforward in older children, adolescents, and adults, but can be challenging in younger children due to the absence of clinical characteristics such as CALMs or PNs. However, the updated diagnostic criteria, which includes genetic testing in patients without a family history, has improved confirmatory diagnosis in young children before they manifest other clinical features of NF1. The diagnosis of large, extensive, or rapidly growing PNs generally require more clinical expertise, and may require more complex tumour characterization, including MRI and sometimes biopsy if there is concern for malignant transformation.

The experts also highlighted that in terms of natural history, there is a trend for tumours to appear and grow rapidly in early childhood (before ages 6 to 8 years), and then slow down or remain static in adulthood. Rapid growth of a PN is a concern for transformation to a malignant peripheral nerve sheath tumour. The experts also discussed the uncertainty regarding treatment decisions for patients who are asymptomatic, which have not been established. In addition, there is no evidence available related to whether treatment with MEK inhibitors such as selumetinib prevent growth of new PNs.

The experts emphasized the heterogeneity of the disease in patients with NF1, with cutaneous neurofibromas and PNs often occurring throughout the body and ranging in severity from asymptomatic to severely debilitating due to pain, functional impairment, or disfigurement. One clinical expert highlighted that disfigurement due to large, visible PNs is a source of anxiety and concern due to public fear and social stigmatization. The panellist also highlighted the potential for ongoing problems into adulthood due to large PNs, which may result in severe disfigurement and displacement of joints and bones; however, it was also emphasized that there is no clear evidence that treating asymptomatic PNs with selumetinib in children will prevent the development of symptoms in adults. Other concerns raised by the experts for the NF1 population include deficient social skills, frequent learning disabilities, autism, and attention-deficit/hyperactivity disorder (ADHD), further highlighting the challenges these patients face.

Treatment with selumetinib offers the only available medical treatment for patients with NF1 whose extensive inoperable PNs are causing significant pain, functional impairment, and/or disfigurement. Although it is difficult to determine which patients are most likely to respond to treatment, 1 clinical expert currently treating pediatric patients via compassionate access to selumetinib stated that about 80% of patients will

respond to treatment. The experts noted that most patients with NF1 with PNs are asymptomatic, and the benefit of treatment for these patients has not yet been established. Clinical trials are currently being conducted for selumetinib in the adult population, which will provide insight into similarities or differences in effectiveness by age. The experts agreed that there is a concern regarding the lack of knowledge about both the potential benefits and harms associated with long-term selumetinib treatment, given that NF1 is a lifelong disease. The experts also noted that the life expectancy of patients with NF1 has been reported to be reduced by 10 to 15 years, although estimates of life expectancy with currently available medical management are unknown.

The clinical experts noted that current clinical trials aim to address important outcomes; however, given the heterogeneity of the disease, standardizing subjective measures (such as pain perception) across this population is an issue, which means that interpreting the results relies heavily on clinical judgment. The clinical experts agreed that the most important outcomes in the management of pediatric patients with NF1 and symptomatic, inoperable PNs is the reduction or improvement in symptoms (i.e., reduced pain, improved function), as well as overall improvements in QoL and disease stabilization. The experts noted that volumetric MRI, though used in the clinical trial to define disease progression, is only used by the National Institute of Health (NIH) for research studies and is not available in Canadian clinical practice. The experts considered a change in planar tumour size of 20% to 25% to be indicative of response to treatment. One expert discussed the potential for symptomatic disease progression despite no evidence of progression on imaging studies and for improvement in symptoms without reduction of tumour size on imaging studies. In addition, the panellists emphasized that it is not always clear which tumours are the cause of symptoms when patients have large numbers of PNs, thereby making it difficult to know when the disease is progressing. The experts also highlighted that tumours are frequently irregular in shape, making measurements about changes in size difficult. As a result, the panel noted that response to treatment is multidimensional and must consider reductions in tumour sizes, changes in symptoms, and improvements in function and disfigurement.

The experts stated that young children with NF1 and symptomatic PNs may initially be followed with an MRI every 3 months, in addition to annual follow-ups with NF1 specialists to assess other features of the disease. Upon initiating treatment, the experts stated that patients would be seen weekly for a month, then monthly, and if treatment is well tolerated, or disease stabilizes, then follow-ups would be prolonged to every 6 months. The experts also noted that imaging in young children often requires a general anesthetic. The experts noted that no firm treatment duration for selumetinib has been determined but suggested that similar to the SPRINT phase II trial, in clinical practice patients would continue treatment until disease progression or toxicity. The experts considered that the initial treatment authorization for selumetinib should be 18 months. The clinical experts agreed that selumetinib would be discontinued in patients whose disease is not responding (i.e., tumour growth, lack of stabilization, or lack of improvement of symptoms), or in patients with severe adverse events (AEs) that are unable to be managed. The experts also noted that the need for surgery to further debulk tumours might be indicative that the treatment is not working and should therefore be discontinued. One clinical expert, however, highlighted that selumetinib may be used in conjunction with debulking surgery, though there is currently no evidence for this.

The experts indicated that expertise in using selumetinib is sparse and limited to pediatric oncologists and neurooncologists in tertiary care hospitals in Canada. Currently, only pediatric oncologists are prescribing treatment with selumetinib, as they have the experience and know-how to manage these patients. However, the experts highlighted that with further insight and growing experience, NF1 experts who are pediatricians could continue and manage this oral treatment. Given the heterogeneity in the disease and the individualized approach to treatment, decisions often involve a multidisciplinary team of pediatricians, NF1 experts, neurooncologists, and nurse practitioners. The experts also emphasized the importance of consulting with other specialists, including surgeons, cardiologists, ophthalmologists, dermatologists, and pharmacists, for the management of selumetinib, adverse effects, and drug interactions. The expert panel also highlighted that for patients in remote areas, access to specialty clinics may be a limiting factor, emphasizing that patients would be required to attend in-person appointments for treatment initiation and imaging follow-up as well as to assess safety.

Clinician Group Input

Input for this review was received through shared clinical experiences from 1 clinician group: the CPBTC, which included 27 pediatric neurooncologists across Canada.

Overall, the clinician group input was aligned with that given by the clinical expert panel convened by CADTH, highlighting that no systemic therapies exist for treating NF1-associated PNs, which represents the major unmet need in this patient population, with surgical resection, if feasible, as the only option currently available for patients. The clinician group emphasized that selumetinib has clearly shifted the current treatment paradigm and emerged as the standard of care as first-line therapy for patients with inoperable, symptomatic PNs, with those most in need of intervention including those for whom PNs are invading critical structures, causing a deformity, or causing functional impairment in activities of daily living such as walking, swallowing, or eating. The clinician group also noted that in Canada, treatment initiation with selumetinib is currently limited to neurooncologists, pediatric oncologists, or pediatric neurologists with an expertise in neurooncology. The CPBTC suggested that treatment with selumetinib in Canada could be initiated by oncologists and followed remotely in conjunction with local clinicians.

Finally, the CPBTC noted that many parents of children with NF1 also have NF1 themselves and are likely to have lower socioeconomic standing, in part because of the disease. It was therefore the CPBTC's opinion that many patients and parents of patients are more likely to lack private insurance to cover selumetinib, which could result in unequitable access in some parts of the country. The CPBTC emphasized that children without private insurance who are also not eligible for the provincial public drug plans will need special consideration and that the drug in question urgently requires reimbursement and equitable access as a standard of care treatment for patients with NF1 and symptomatic PNs.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for selumetinib:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Treatment options include pain management (supportive care) and surgical excision to reduce or remove PN tumours (current standard of care). There is a lack of appropriate comparators in this population. Are there medications marketed in Canada that are used for this condition off-label that would have been appropriate comparators in this population?	CDEC agreed with the clinical experts that surgical excision is the only treatment option to reduce the number and size of PNs; however, it is associated with numerous risks due to the number, size, location, and vascularity of PNs. Most large or extensive PNs cannot be completely excised. Although other MEK inhibitors are available, they have not been used to treat PNs. No other treatment options are available to patients; thus, selumetinib monotherapy would be the first and only medication available to treat patients with NF1 who have symptomatic inoperable PNs
Is there evidence to suggest that monotherapy with selumetinib will prevent or successfully treat MPNST?	CDEC agreed that there is no evidence to support the use of selumetinib in preventing the transformation to or treating MPNST.
Considerations for initiation of therapy	
Is NF1 genetically screened in newborns? How is it diagnosed?	NF1 is currently not part of any Canadian newborn screening program. CDEC and the clinical experts highlighted that because treatment is initiated based on the presence of symptoms, genetic testing results would not affect treatment decisions for PNs once a clinical diagnosis of NF1 has been established. CDEC and the experts noted that diagnosis of NF1 is established using clinical and/or symptomatic features, including the presence of CALMs, axillar and inguinal freckling, and the presence of neurofibromas. The diagnosis of PNs

Implementation issues	Response
	must often be confirmed by clinicians with expertise and may be aided by imaging (e.g., MRI), and in some cases, biopsy is necessary to rule out malignancy.
What is the proportion of operable vs. inoperable PNs seen in your practice? In an individual patient, would there be PNs that are operable and also those that are inoperable? Another criterion in the SPRINT study was the ability to swallow intact capsules. What are your thoughts regarding this criterion and practicality? What happens when patients who are younger are unable to swallow capsules? Would you use this medication in asymptomatic, growing, inoperable PN?	CDEC and the experts agree that most large or extensive PNs cannot be completely excised surgically. Surgery is associated with many complications (e.g., bleeding risk, proximity to vital structures, secondary injury), and due to the extensive and progressive nature of the disease, multiple surgeries may be required. Though there may be many PNs in a patient, most do not cause symptoms; therefore, most PNs are not eligible for treatment via surgery, and it is not always clear which PNs are symptomatic. Selumetinib is currently provided as capsules that must be swallowed; however, another formulation (oral suspension) is currently being developed for patients who are unable to swallow capsules. CDEC and the clinical experts noted that the majority of patients with NF1 who have PNs are asymptomatic, and the role of selumetinib in these patients remains unknown. However, this population remains of critical importance because of the progressive nature of NF1. There are many implications regarding the scope of selumetinib use in this population given the greater number of patients with asymptomatic PNs (e.g., resource use, monitoring). Selumetinib is currently not being used in these patients.
Considerations for continuation or renewal of therapy	
How widely is centrally read volumetric MRI accessible and available in the jurisdictions?	CDEC and the clinical experts highlighted that access to volumetric MRI is not available as a standard of care for patients with NF1 in Canada and is limited worldwide. Volumetric MRI is currently limited to clinical trials.
Considerations for discontinuation of therapy	
Are there situations in which selumetinib is discontinued, and then restarted? How long should patients be on this medication to see response clinically and/or radiographically? How else would clinical benefit be defined apart from PN volume (e.g., improvement in pain, airway, or motor function in PN)? How is radiographic benefit defined? When is clinical and/or radiographic response seen in patients while on this medication? Are there any predictors of response for this medication? Is there an ideal treatment duration, or treatment range for patients? Is there any information on acquired resistance while on this medication?	CDEC and the clinical experts noted that treatment with selumetinib may be discontinued in the presence of AEs, and then restarted once resolved. Patients and clinicians may also choose to discontinue treatment if there is evidence of disease stabilization, and then restart treatment at tumour progression or presence of symptoms. Typically, in clinical trials, a 20% to 25% reduction in tumour volume is considered a response to treatment; however, given the lack of availability of volumetric MRI, measurement of treatment response is difficult and multidimensional. It considers tumour growth on imaging, the worsening of symptoms such as pain, or deterioration in function (e.g., motor, airway, bowel). There are no predictors of response in this population; however, it is estimated that up to 80% of patients will respond, while 20% will not, for unknown reasons. No end date for selumetinib treatment has been determined as, inherent in phase II trial concepts, treatment continues until progression or unacceptable toxicity. In the absence of clinical

Implementation issues	Response
	benefit or toxicity, selumetinib could be initially given for 18 months. The decisions about stopping treatment are discussed on a case-by-case basis with patients and families. There is no evidence or information available on acquired resistance to selumetinib.
While on this medication, is there any time during the treatment course a "drug holiday" could happen? Can a patient restart and resume on this medication and obtain benefits after a treatment interruption for whatever reason?	CDEC and the experts agreed that there is no evidence to support any benefits from a drug holiday; however, if patients achieve disease stabilization, the experts were of the opinion that treatment could be stopped and then restarted at radiographic progression or worsening of symptoms. There are no biologic markers to determine whether the treatment needs to be continued, so clinical judgment and discussion with patients and families will be used.
Considerations for prescribing of therapy	
The product monograph states that selumetinib should be discontinued if patients are unable to tolerate treatment after 2 dose reductions for AEs. What is the prevalence of discontinuation in practice with this medication? Are there any alternate dosing schedules for patients using this medication (e.g., intermittent dosing)?	CDEC acknowledged that the experts noted that approximately 20% of patients will not respond to treatment and will discontinue due to nonresponse. Dose reductions will occur per the product monograph, and if patients are still not tolerating treatment after 2 dose reductions, treatment will be discontinued. CDEC also noted that up to [redacted] of patients discontinued treatment with selumetinib due to AEs or lack of effect in the SPRINT phase II trial. CDEC and the experts noted that there is no evidence on intermittent dosing of selumetinib.
The product monograph states that treatment should be initiated by a physician experienced in the diagnosis and treatment of patients with NF1-related tumours. However, based on the potential toxicities, the patient would be managed by a multidisciplinary team (i.e., in a specialized settings) for optimal management. How are pediatric patients with this condition screened and managed, including follow-up, monitoring, and evaluating toxicities with regards to access points to the health care system?	CDEC agreed with the clinical experts that patients with NF1 may be under the care of specialists in the management of NF1 but prescribing of selumetinib is currently limited to pediatric oncologists and neurooncologists. The clinical setting for administering and monitoring patients is still evolving. Given the heterogeneity in the disease, and the individualized approach to treatment required, decisions often involve a multidisciplinary team of pediatricians, surgeons, NF1 experts, neurooncologists, dermatologists, nurse practitioners, cardiologists, ophthalmologists, and pharmacists to properly monitor the safety and toxicity of selumetinib. Remote monitoring, blood work, eye exams, and other follow-up are possible; however, patients would be required to attend in-person appointments for treatment initiation and imaging needs.
Are there any situations in which selumetinib is combined with any other medication for this indication?	CDEC agreed with the clinical experts that there is no evidence to support the use of selumetinib in combination with other therapies for this indication, as there are no other medications for this indication.
Generalizability	
The clinical trials presented included patients aged 2 to 18 years old. Can selumetinib be started in patients older than 18 years? Though not as common as NF1, would patients with NF2 and	CDEC and the clinical experts agreed that given that the SPRINT trial was conducted in patients 2 to 18 years old, there is currently no evidence for using selumetinib in patients older than 18 years. However, selumetinib is currently provided

Implementation issues	Response
schwannomatosis related to genetic variants other than NF1 benefit from treatment with selumetinib?	off-label via compassionate access in Ontario through philanthropic efforts. There is an ongoing RCT to determine the efficacy of selumetinib in patients who are older than 18 years. Other MEK inhibitors are also available, though not necessarily for the treatment of NF1 and PNs. There is also no evidence to support the use of selumetinib in patients with NF2 or schwannomatosis. NF2 and schwannomatosis are very rare genetic conditions that are entirely distinct from NF1. There are alternative treatments available for patients with NF2, and schwannomatosis is rarely, if ever, diagnosed in children.
Care provision issues	
Are supportive medications continued while on therapy?	Selumetinib is provided as monotherapy; however, supportive medications to manage side effects of treatment (e.g., diarrhea, paronychia) would be used, as needed.
How often do patients undergo MRIs for PNs? How often is imaging conducted for screening and follow-up?	Imaging is generally conducted every 3 months initially, based on local standards, though may be extended to every 6 months, or annually, based on response to treatment.
Selumetinib also includes vitamin E (e.g., 10 mg capsules contain 32 mg of vitamin E as the excipient, TPGS, while 25 mg capsules contain 36 mg of vitamin E as TPGS). Is there a clinical relevance (e.g., bleeding risk) for this excipient in this population?	The use of natural health supplements is high in patients with NF1 and symptomatic PNs, and there is a risk of inadvertent toxic levels of natural supplements. Consultation with a pharmacist for patient counselling is required due to the numerous drug interactions associated with selumetinib to ensure patients do not take contraindicated medications.
System and economic issues	
The incidence of NF1 is 1 in 2,500 to 3,000 births. The following outline the costs per patient for the maximum and minimum doses of selumetinib. These would be in addition to the costs of supportive care. Maximum dose: 50 mg b.i.d. cost, $306.50 × 2 x 365 days per year = $223,745 per patient Minimum dose: 10 mg b.i.d. cost, $122.60 × 3 x 365 days per year = $134,247 per patient	This was a comment from the drug programs to inform CDEC deliberations.
There is a patient support program available by the manufacturer.	This was a comment from the drug programs to inform CDEC deliberations.

AE = adverse event; b.i.d. = twice daily; CALM = café-au-lait macule; CDEC = CADTH Canadian Drug Expert Committee; MEK = mitogen-activated protein kinase; MPNST = malignant peripheral nerve sheath tumour; NF1 = neurofibromatosis type 1; NF2 = neurofibromatosis type 2; PN = plexiform neurofibroma; RCT = randomized controlled trial; TPGS = alpha-tocopherol polyethylene glycol succinate; vs. = versus.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

SPRINT phase II is a phase II, open-label, single-arm, multicenter study that aimed to evaluate the efficacy of 25 mg/m^2 selumetinib twice daily in 50 pediatric patients with NF1 and inoperable PNs. The primary outcome of the SPRINT phase II study was ORR determined by change in PN volumes through volumetric MRI. Secondary outcomes included PROs and functional evaluations to determine the effect of selumetinib on pain, motor function, and HRQoL. Two DCOs were submitted for the SPRINT phase II trial. The primary DCO occurred on June 29, 2018, and an updated DCO on March 31, 2021, providing a maximum follow-up of 5.6 years.

At baseline, patients included in the SPRINT phase II trial were mostly white (42; 84.0%) males (30; 60.0%) with a mean age of 10.3 years (standard deviation [SD] = 3.92 years). The median number of target PNs causing morbidity was 3 (range = 1 to 4), and the mean target PN volume was 837.11 mL (SD = 925.011), ranging from 5.6 mL to 3,820.0 mL. Pain was present in the target PNs in 26 (52.0%) patients. The most common location of target PNs was the neck and trunk, and the trunk and extremity (12 each; 24.0%), and [redacted] patients had had at least 1 prior PN-related or NF1-related surgical procedure.

Efficacy Results

Pain

Evaluation of pain was a secondary end point of the SPRINT phase II trial. Pain intensity was measured by the NRS-11, a self-evaluation of pain in patients 8 years or older consisting of 4 questions scored on a scale 0 (no pain) to 10 (worst pain you can imagine). A threshold of 2 points was suggestive of clinically meaningful change, per the literature. The interference of pain on daily functioning was measured by the PII, a 6-item scale that assesses the extent to which pain has interfered with daily activities in the past 7 days (0, meaning not at all, to 6, meaning completely). Higher scores for both scales indicate greater impact of pain on patients.

At the June 29, 2018, DCO, the mean adjusted change from baseline score for target tumour pain intensity measured by the NRS-11 was reduced at precycle 13 by −2.07 points (95% CI, −2.84 to −1.31). At the March 31, 2021, DCO, representing a longer follow-up period, the NRS-11 target tumour pain was reduced at precycle 13 with an adjusted mean change from baseline of [redacted] points (95% CI, [redacted]).

For the PII, the self-reported adjusted mean change from baseline score at precycle 13 was reduced by −0.65 points (95% CI, −0.89 to −0.42), and the adjusted mean change from baseline in parent-reported PII score at precycle 13 was reduced by −0.82 points (95% CI, −1.17 to −0.47) at the June 29, 2018, DCO. At the March 31, 2021, DCO, the results were consistent with the primary analysis, with a reduction in the adjusted mean change from baseline at precycle 13 of [redacted] (95% CI, [redacted]) for the self-report total score, and [redacted] (95% CI, [redacted]) for the parent-reported score.

Motor Function

Motor function was evaluated in patients with motor morbidity using the strength of muscle groups and ROM tests, as well as the Patient-Reported Outcomes Measurement Information System (PROMIS) mobility and upper extremity domains. The PROMIS was completed by both the patient and the parent. Higher scores indicate better physical functioning.

The baseline score for the self-reported and parent-report assessments in the mobility domains of PROMIS were 46.57 (SD = [redacted]) and 37.43 (SD = [redacted]), respectively, while the baseline scores for the self-reported and parent-report assessments in the upper extremity domain were 45.95 (SD = [redacted]) and 38.15 (SD = [redacted]), respectively, with higher scores indicating better physical functioning. At the March 31, 2021, DCO, self-reported mobility and self-reported upper extremity improved with an adjusted mean change from baseline at precycle 13 by [redacted] points (95% CI, [redacted]) and [redacted] points (95% CI, [redacted]), respectively. In the parent-reported assessments, the adjusted mean change from baseline at precycle 13 improved in the mobility and upper extremity domains by [redacted] points (95% CI, [redacted]) and [redacted] points (95% CI, [redacted]), respectively.

Strength using the manual muscle test (Medical Research Council 5-point Likert scale) was assessed in the 33 patients who had motor morbidity in any body quadrant at enrolment. At the March 31, 2021, DCO, [redacted] patients had evaluable strength assessments at baseline and precycle 13, with a mean strength score of [redacted] (SD = [redacted]) at baseline, and an adjusted mean change from baseline increased by [redacted] points (95% CI, [redacted]). For ROM, the mean ROM sum of all joints was [redacted] degrees (SD = [redacted]), and the adjusted mean change from baseline at precycle 13 was an increase of [redacted] degrees (95% CI, [redacted]).

Health-Related Quality of Life

HRQoL was a secondary end point of the SPRINT phase II study and was measured using the Pediatric Quality of Life Inventory (PedsQL) tool, which assesses function in 4 domains: physical (8 items), emotional (5 items), social (5 items), and school (5 items) on a 5-point Likert scale (0 = never a problem; 4 = almost always a problem), with scores revere-transformed to a 0 to 100 scale, so that higher scores indicated better HRQoL. No MID threshold was identified in the literature. The observed mean score at baseline was 73.91 (SD = [redacted]) in the self-reported version and 60.79 (SD = [redacted]) in the parent-reported version. At the March 31, 2021, DCO, the adjusted mean change from baseline in the self-reported version of the PedsQL was [redacted] points (95% CI, [redacted]) and [redacted] points (95% CI, [redacted]) in the parent-reported version, suggesting improvements in HRQoL.

Objective Response Rate

ORR was the primary end point of the SPRINT phase II study. At the June 29, 2018, DCO, 33 patients (66.0%; 95% CI, 51.2 to 78.8) achieved ORR per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. The ORR achieved in the sensitivity analysis based on independent central review (ICR) was [redacted]. Differences in ORR between the primary central analysis and the ICR analysis were primarily due to differences in categorization of confirmed partial response (PR) versus stable disease (based on the chosen threshold of 20% shrinkage to determine response), where [redacted] patients were considered to have confirmed

PR despite reductions in tumour size being slightly below the threshold of 20%. At the later, March 31, 2021, DCO, the ORR was 68.0% (95% CI, [redacted]). At both DCOs, ORR was based on confirmed PRs.

An exploratory ICR analysis using modified Response Evaluation Criteria in Solid Tumours (RECIST) criteria that used a 30% volume reduction for PR as opposed to 20% with REiNS was also conducted at the June 29, 2018, DCO. Based on RECIST 1.1 assessment, the ORR was only [redacted], with [redacted] patients having an unconfirmed PR, and [redacted] patients having stable disease.

Change in target PN volume was also assessed as part of the volumetric MRI and application of the REiNS criteria. At the March 31, 2021, DCO, the mean percent change from baseline in target PN volume at precycle 13 was [redacted] (SD = [redacted]), corresponding to a mean absolute change of [redacted] mL ([redacted]). The proportion of patients with a maximum reduction from baseline of at least 20% was identical to the June 29, 2018, DCO, at 77.1%, and [redacted] had a maximum reduction from baseline of 40% or more.

Harms Results

Nearly all patients in the SPRINT phase II trial experienced a treatment-emergent adverse event (TEAE) (49; 98.0%). The most frequent TEAEs reported at the March 31, 2021m, DCO were vomiting [redacted], increased blood creatine phosphokinase [redacted], diarrhea [redacted], nausea [redacted], and dry skin [redacted]. Grade 3 or higher TEAEs were reported in [redacted] patients, with the most frequent consisting of [redacted]. Overall, [redacted] patients had at least 1 TEAE leading to dose interruption.

At the March 31, 2021, DCO, [redacted] patients experienced serious AEs, the most frequently occurring being [redacted]

A total of [redacted] patients discontinued selumetinib due to AEs; [redacted] of which were grade 3 [redacted] and [redacted] were grade 4 [redacted] experiencing a grade 3 and grade 4 AE leading to withdrawal.

No AEs with a fatal outcome were reported in the SPRINT phase II study; however, after the March 31, 2021, DCO, [redacted] patients died due to progressive neurofibrosarcoma after selumetinib treatment was terminated. These deaths were not attributed to treatment with selumetinib.

The most frequent notable harm associated with selumetinib was [redacted], occurring in [redacted] patients. The majority of cases were grade 1, [redacted] were grade 2, and [redacted] grade 3. One patient had discontinued treatment due to grade 3 paronychia at the earlier (June 2018) DCO. Other notable harms included [redacted].

Critical Appraisal

SPRINT phase II was a phase II, open-label, single-arm, multicenter study. The choice to conduct a single-arm study also has implications on the overall strength and interpretability of the results. In a single-arm study, there is an increased risk of bias in the estimation of treatment effects due to the potential for confounding

related to natural history, and other unidentified prognostic factors that could affect all study outcomes. The noncomparative design of the SPRINT phase II trial precludes the ability to assess the therapeutic benefit or safety of selumetinib. Because all patients received the same treatment in this single-arm study, the treatment effect on time-to-event end points are uninterpretable and were only considered as exploratory and supportive. Awareness of treatment assignment by both patients and parents and/or caregivers increases the risk of detection bias and performance bias and may lead to systematic overestimation or underestimation of the overall treatment effect. As such, the open-label trial design limits interpretability of the clinical outcome assessments such as the PRO and functional end points, as well as AEs. The already small sample size (N = 50) was further restricted for secondary end points, including PROs and functional evaluations, as these were based on patients with target PNs in specific locations or limited to patients of a certain age. The outcome of the SPRINT phase II study was ORR, which was considered appropriate by the clinical experts consulted by CADTH and the CADTH review team as an objective measure to assess the activity of selumetinib. Secondary clinical outcome assessments (PROs and functional evaluations) were considered appropriate to evaluate the wide range of PN-related morbidities; however, based on the design of the SPRINT phase II study, and the lack of statistical tests or imputation of missing data, the results should only be viewed as supportive of the overall effect of selumetinib.

There is a lack of standardized end points for trials in NF1. As previously noted, multiple outcomes were included in the SPRINT phase II trial, including response and time-to-event outcomes based on volumetric MRI using the REiNS imaging criteria. The clinical experts consulted by CADTH highlighted that volumetric MRI is not used in routine clinical practice as it is not standard of care in Canada, and that evidence of disease progression is multifactorial, based on standard imaging techniques, though they emphasized the importance of clinical symptomatology and physical assessment in determining progression and response. As such, patients in Canadian clinical practice would be evaluated for progression slightly differently than in the SPRINT phase II trial, potentially impacting the generalizability of the results. PROs (i.e., NRS-11, PII, PROMIS, PedsQL) and functional outcomes (i.e., strength, ROM) were also evaluated in the SPRINT phase II trial. The clinical experts consulted by CADTH noted that the outcome scales reported in the trial were not used in routine clinical practice and may not be generalizable to the typical patient in Canada. They also noted that a gestalt-type approach is considered in clinical practice for overall improvement or deterioration in symptomatology overall, as opposed to specific changes in certain domains (e.g., grooved pegboard test, key pinch grip), though variation and heterogeneity by the patient and/or caregivers is significant in this population.

Indirect Comparisons

There are no appropriate comparators to conduct a standard ITC and a placebo-controlled trial design was considered unethical by National Cancer Institute (NCI) Pediatric Oncology Branch (POB) investigators due to significant PN-related morbidity and promising results shown in the phase I trial. Indirect comparisons were therefore necessary to estimate the relative benefit of selumetinib. The NCI POB has conducted 2 additional studies, a natural history (NH) study to develop a better understanding and quantification of NF1 manifestations, and to allow more sensitive end points to be developed for clinical studies, and Study 01-C-0222, which is a phase II, randomized, crossover, double-blinded, placebo-controlled study of tipifarnib

in children and young adults with NF1 and progressive PN. Given the lack of direct comparative evidence for selumetinib, the sponsor conducted naive qualitative comparisons of the results from the SPRINT phase II study with the NH study and the placebo arm of Study 01-C-0222 to serve as external control arms. The sponsor also conducted a propensity score modelling analysis of PFS compared to the NH study.

Description of Studies

The sponsor conducted a naive, side-by-side comparison of results from SPRINT phase II, stratum 1, versus patients with PNs from the NH study using the outcomes of tumour growth (absolute and annual rates) based on the full NH cohort as well as an age-matched NH cohort. The age-matched NH cohort included patients who were aged 3 to 18 years and had at least 1 volumetric MRI within this age and at least 1 subsequent volumetric MRI. A naive, side-by-side qualitative comparison was also conducted for the outcome of PFS between SPRINT phase II, stratum 1, and the placebo arm of Study 01-C-0222.

In the propensity scoring analysis, PFS from SPRINT phase II, stratum 1, was compared to the age-matched cohort of the NH study. Prognostic factors were identified based on data from the NH study. The univariate Cox model and multivariate Cox model (covariates: study, sex, race, target PN location, PN status, age, weight, height, and target PN volume) were fitted to estimate an unadjusted and adjusted hazard ratio, respectively. Age, weight, height, and target PN volume were kept as continuous variables in the model. Three different matching algorithms were explored (matching 1:1 without replacement, inverse probability of treatment weighting [IPTW], and matching 1:2 with replacement).

Efficacy Results

PN Growth Rate, Naive Comparison: SPRINT Phase II, Stratum 1, Versus NH Study

Data on the natural history of NF1-related PNs, based on the patients from the selected external controls, demonstrated that the majority of PNs grow continuously over time or, at best, remain stable in size (i.e., < 20% increase in volume from baseline). In contrast to the median annual volume change of [redacted] or [redacted] seen in the SPRINT study (2018 and 2021 DCO, respectively), the median annual volume change in the NH study (age-matched cohort with maximum follow-up aligned to each DCO of the SPRINT study) was [redacted] and [redacted], respectively.

Over the full duration of the studies, the mean percentage change from baseline in the SPRINT trial was [redacted] compared to [redacted] in the NH study. The follow-up duration and included patients differ notably in these populations.

Patients who enrolled in the NH study and later went on to participate in SPRINT phase II, stratum 1 (n = [redacted]), experienced PN growth before selumetinib (median = [redacted] per year; maximum = [redacted] per year), and a median volume reduction of [redacted] per year after selumetinib treatment (median follow-up = [redacted] years; range, [redacted] years). Of these patients, [redacted] had a reduction of at least 20% in their target PN and the response was sustained for [redacted] patients at the latest DCO.

PFS, Naive Comparison: SPRINT Phase II, Stratum 1, Versus NH Study

At the time of the March 31, 2021, DCO, disease progression was experienced by [redacted] of patients in the NH study compared to [redacted] of patients in SPRINT phase II, stratum 1, over a [redacted]-year period. Median PFS in the NH age-matched cohort was [redacted] years (95% CI, 1.1 to 1.6) and was [redacted] in SPRINT phase II, stratum 1. The probability of remaining without progression in SPRINT phase II, stratum 1, and the NH study was [redacted] (95% CI, [redacted]) and [redacted] (95% CI, [redacted]), respectively.

PFS, Naive Comparison: SPRINT Phase II, Stratum 1, Versus Study 01-C-0222

Because Study 01-C-0222 required progressive disease for enrolment, a subgroup analysis was conducted for the earlier DCO (i.e., 2018) of SPRINT phase II, stratum 1, including only those with progressive PNs at enrolment. In this subgroup, the probability of remaining without progression at 2 years was 94.7% (95% CI, 80.6% to 98.7%), compared to 20.6% (95% CI, 7.7% to 37.8%) in the placebo arm of Study 01-C-0222. The sponsor did not update this comparison for the later DCO (i.e., 2021).

PFS, Propensity Scoring Analysis: SPRINT Phase II, Stratum 1, Versus NH Study

The univariate Cox analysis identified age, weight, height, and PN status at baseline (i.e., progressive, nonprogressive, or unknown) were associated with PFS; younger patients with progressive PNs at baseline had a higher risk of progression. The multivariate analysis identified only PN status as correlated with PFS.

After matching, the sample sizes were small, and some standardized differences remained unbalanced (> 0.1 to > 0.2) in the 1:1 and 1:2 matching analyses. In the IPTW analysis, no baseline characteristics differed by a standardized difference of more than 0.1. However, the effective sample size after IPTW was not reported. Across all 3 methods of propensity scoring analysis, the hazard ratios for PFS ranged from [redacted] in favour of selumetinib with P values of less than 0.001.

Harms Results

Safety outcomes were not assessed in the ITCs.

Critical Appraisal

Because it was deemed unethical to conduct placebo-controlled trials in this population by the NCI POB investigators, only unanchored ITCs were possible. There are substantial limitations inherent to unanchored naive comparisons as there is no method of control for inherent differences in the study design and patient populations, so differences seen in clinical outcomes may be confounded by underlying differences in the compared trials.

In the naive comparison, results were only reported for mean annual change in target PN volume, absolute and percent change in target PN volume from baseline, and PFS. In the propensity scoring analysis, only PFS was assessed. Patient and clinician input suggests that tumour volume or change in volume does not always directly correlate with symptomatology, in part because it is highly dependent on the location of the PNs with respect to important structures. Outcomes related to symptoms, morbidity, disability, HRQoL, and disfigurement were not assessed. No safety outcomes were evaluated.

There were notable differences between the patient populations of the 2 external controls in comparison to the SPRINT trial with regards to baseline age, race, target PN location, PN status (i.e., progressive, nonprogressive, or unknown), target PN volume, and treatment history. Additionally, the study designs differed with respect to follow-up and frequency of imaging. The risk of bias and imprecision is inherently high as a result of small study sizes, observed clinical heterogeneity, and the unanchored and naive approach to the comparison, but the direction of potential bias as a result of these differences is unknown. The sample size of the before-after analysis ([redacted]) of patients who participated in both the NH study and the SPRINT trial was especially small, limiting the interpretation of results.

Propensity scoring analysis was conducted using 3 standard methods. Although propensity scoring analysis is an appropriate approach to mitigate the impact of between-trial differences in baseline patient characteristics, it is unknown whether all key treatment effect modifiers and prognostic factors were accounted for. The methodology for selecting baseline characteristics was not explained or justified. Of the 3 methods of propensity score analysis, only IPTW demonstrated balance in every baseline characteristic examined, while in the 1:1 and 1:2 matching analyses, some standardized differences were still greater than 0.1 or greater than 0.2 in important characteristics. The sample size of all analyses were small as a result of the studies informing the comparisons, but the 1:1 and 1:2 matching analyses also resulted in further drops in sample size. The effective sample size of IPTW was not reported, limiting interpretation.

Overall, interpretation of the ITCs is substantially compromised by important limitations. From the naive comparisons and the propensity scoring analyses, the results suggest selumetinib confers a benefit in terms of reduction in the rate of tumour growth and improvement in PFS. However, the magnitude of benefit is uncertain, and there can be no conclusions from the ITCs regarding other clinically important outcomes or harms.

Other Relevant Evidence

No long-term extension studies or other relevant studies were included in the sponsor's submission to CADTH.

Ethical Considerations

Patient group, clinician group, clinical expert, and drug program input gathered during this CADTH review, as well as relevant published literature, were reviewed to identify ethical considerations relevant to the use of selumetinib for the treatment of pediatric patients aged 2 and above with NF1 who have symptomatic, inoperable PNs.

- The current lack of disease-modifying treatment options for pediatric patients with NF1 who have symptomatic, inoperable PNs leads to challenges in pediatric patient QoL related to pain, motor function, cognition, and psycho-social functioning, and the potential for social stigma due to the appearance of PNs.

- Several challenges arose in the evidence used to evaluate selumetinib, including the contrast between the study design of the pivotal SPRINT trial and clinical practice, and challenges related to the use of volumetric MRI to measure tumour size and response to treatment. As this drug is expected to be administered for life, questions remain about long-term effectiveness, safety, and unknown risks to patients, given the absence of long-term data.
- Given the lack of long-term effectiveness and safety data, the use of selumetinib raises ethical considerations related to ongoing consent to a novel treatment for patients who may be incapable of decision-making, as well as their caregivers who may have similar limitations. Access to appropriate NF1 and selumetinib expertise (e.g., pediatric neurooncologists and multidisciplinary care teams) also raises challenges, as such expertise is required to diagnose and treat NF1, and to prescribe, monitor, and follow patients receiving selumetinib. This need for multidisciplinary and specialized care and monitoring raises the potential for equity challenges within the vast geographical disparities of Canada.
- The use of selumetinib for patients with NF1 raises several health system and resource considerations related to how selumetinib will be equitably delivered across Canada, as well as potential challenges related to the treatment of patients who are asymptomatic.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis State transition model
Target population	Pediatric patients 2 years of age and older with NF1 who have symptomatic, inoperable PNs
Treatment	Selumetinib with BSC
Submitted price	$122.60 per 10 mg capsule or $306.50 per 25 mg capsule
Treatment cost	$268,678 per year (assuming mean BSA in the SPRINT trial)
Comparator	BSC, defined as medication used for pain relief and symptomatic disease management; this may include analgesics, antidepressants, and anxiolytics
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs
Time horizon	Lifetime (97 years)
Key data source	SPRINT phase I/II trial
Key limitations	• The submitted model lacked face validity and had an inflexible model structure that precluded CADTH from being able to conduct a thorough assessment of cost-effectiveness. The model did not capture clinical outcomes (i.e., symptom relief and pain management) that are most relevant to patients and clinical experts consulted by CADTH. Rather, the model captured progression, defined as PN growth of at least 20% from baseline or an increase of at least 20% from the best response. The sponsor's submitted model further assumed progression and discontinuation of selumetinib are independent. As

Component	Description
	such, at the age of 18, all patients in the selumetinib group who were progression free would remain in this health state for the remainder of their lifetime regardless of treatment status. The sponsor claimed this reflected the expected residual benefit associated with selumetinib; although, according to clinical experts consulted by CADTH, the expected magnitude of this residual benefit is uncertain. The sponsor further assumed that 100% of patients on selumetinib would start in the "progression free" health state while 100% of patients on BSC would start in the "progressed" health state. This does not align with the available natural history data submitted by the sponsor and is likely to overestimate the benefits of selumetinib associated with progression. • There is no direct evidence comparing selumetinib with BSC. Significant limitations were identified with the evidence submitted from the single-arm trial of selumetinib. Indirect treatment comparisons reviewed by CADTH suggested that a clinical benefit may exist, but the magnitude of the benefit is unknown. • CADTH identified several concerns regarding the model's programming, including the incorrect calculation of annual probability of tumour progression. • The sponsor conducted a preference elicitation study to estimate treatment-specific utility values that were subsequently applied to progression-specific health states. This approach has limited validity. In pediatric patients who have progressed after selumetinib treatment, the sponsor assumed it would take 5 years to return to the utility value for "progressed" disease, despite the fact that this health state should be identical to the "progressed" health state in the BSC arm. • The treatment costs for selumetinib may have been underestimated as drug costs were adjusted to include dose interruptions observed within the trial. A more conservative time-to-discontinuation curve was further selected, which impacted the cost estimation.
CADTH reanalysis results	• Given limitations with the sponsor's model structure and the lack of comparative effectiveness data, CADTH was unable to derive a robust base-case estimate of the cost-effectiveness of selumetinib. CADTH conducted separate analyses involving different assumptions for the magnitude of the residual benefit from selumetinib, alongside revisions to correctly calculate the probability of disease progression, assuming all patients on selumetinib would return to the utility value associated with progression within a year of experiencing disease progression and revising treatment costs assumptions. • CADTH reanalyses aligned with the sponsor results, in that selumetinib is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. In CADTH reanalysis A, whereby a smaller residual benefit was assumed (i.e., the mean duration of progression-free survival for patients on selumetinib would be 22.19 years), the ICER for selumetinib plus BSC was $426,286 per QALY gained compared to BSC alone (incremental costs = $1,177,024 and incremental QALYs = 2.76). In CADTH reanalysis B, the same changes were made as in reanalysis A with the exception that the residual benefit modelled reflected the sponsor's assumption (i.e., the mean duration of progression-free survival for patients on selumetinib would be 33.96 years). The ICER for selumetinib plus BSC was $294,751 per QALY gained compared to BSC alone (incremental costs = $1,177,024 and incremental QALYs = 3.99). • Both analyses assume selumetinib substantially delays disease progression despite a lack of direct clinical evidence to support these assumptions. The clinical benefits predicted within the model are highly uncertain. CADTH could not address limitations associated with the model's structural assumption that all patients on BSC would automatically start in the "progressed" state. This assumption contradicts the available clinical evidence and favours selumetinib. As such, all analyses are likely to underestimate the true ICER.

BSA = body surface area; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NF1 = neurofibromatosis type 1; PN = plexiform neurofibroma; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: uncertainties in the proportion of patients with NF1 who would have PNs; and the proportion of patients with symptomatic PNs would be expected to be smaller than estimated by the sponsor, according to clinical experts consulted by CADTH. CADTH performed reanalyses that aligned with clinical expert opinion by halving the prevalence of symptomatic PNs from the sponsor's original estimate. In the CADTH reanalysis, the 3-year total budget impact from the introduction of selumetinib for the treatment of pediatric patients with NF1 and symptomatic, inoperative PNs was estimated to be $64,702,506 (year 1 = $15,723,217; year 2 = $22,868,414; year 3 = $26,110,875). Given that NF1 is considered a rare disease, there remains considerable uncertainty regarding the epidemiologic inputs needed to obtain a reliable estimate of the budget impact of selumetinib.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Meeting date: March 24, 2023

Regrets: Three expert committee members did not attend.

Conflicts of interest: None