A SINGLE ARM, MULTICENTRE PHASE II TRIAL OF SELUMETINIB MONOTHERAPY IN THE TREATMENT OF ADULTS AND ADOLESCENTS WITH NEUROFIBROMATOSIS TYPE 1-RELATED INOPERABLE AGGRESSIVE PLEXIFORM NEUROFIBROMAS (EXCLUDING MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR)

ABBREVIATED TITLE: SELUMETINIB FOR AGGRESSIVE PLEXIFORM NEUROFIBROMAS IN NEUROFIBROMATOSIS 1

SeluNF

Full title	A single arm, multicentre phase II trial of selumetinib monotherapy in the treatment of adults and adolescents with neurofibromatosis type 1-related inoperable aggressive plexiform neurofibromas (excluding malignant peripheral nerve sheath tumour)
Acronym	SELU-NF
Coordinating Investigator	Professor Pierre Wolkenstein National Referral Center for Neurofibromatoses Henri-Mondor Hospital Créteil
Sponsor	Assistance Publique-Hôpitaux de Paris (AP-HP)
Scientific justification	Selumetinib is an oral selective inhibitor of mitogen-activated protein kinase (MAPK) kinase (MEK) 1 and 2 that has been shown to be effective in children with neurofibromatosis type 1 with inoperable plexiform neurofibromas. A similar effect could be expected in a population of adults/adolescents with neurofibromatosis type 1 with similar tumours.
Main objective and primary endpoint	To determine whether selumetinib reduces the volume of inoperable plexiform neurofibromas in adult and adolescent patients with neurofibromatosis type 1. The primary endpoint will be a reduction of the volume of the target lesion of at least 20% at 1 year compared with baseline (assessed by volumetric magnetic resonance imaging [MRI]).
Secondary objectives and endpoints	To determine whether selumetinib has durable efficacy, and an effect on pain, functional outcomes and quality of life (QoL) in patients with neurofibromatosis type 1 with inoperable plexiform neurofibromas. Secondary endpoints are: - Persistence (duration) of response or on/off effect assessed by MRI analysis using a volumetric criterion at baseline and 6 months after discontinuation of treatment

	(if discontinuation occurs before month 18 within the 2-year study period). - Patient reported outcomes: • Physical functioning scale (PF) of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients (EORTC QLQ-C30); • Global health status/QoL scale (QL) score of the EORTC QLQ-C30; • Other EORTC QLQ-C30 dimensions; • Pain measured with Numeric Rating Scale 11 (NRS11); • International Index of Erectile Function 5 (IIEF5) for erectile dysfunction in men and Index of Sexual Life (ISL) in women. • These outcomes will be measured at baseline, month 3, month 6 and then every 6 months on treatment, and 6 months after discontinuation that occurs within the 2-year study period.
Design of the trial	Multicentre, non-randomised, open-label, single-arm, phase II study.
Population of trial subjects	Male and female adult and adolescent patients (aged >15 years) with neurofibromatosis type 1 who have plexiform neurofibromas that cannot be removed by surgery.
Inclusion criteria	1. Patients must be aged >15 years. 2. Patients must have neurofibromatosis type 1 according to the NIH Consensus conference diagnostic criteria or have a positive genetic test for neurofibromatosis type 1. 3. Patients must have inoperable plexiform neurofibromas that have the potential to cause significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g. orbital lesions) or significant cosmetic problems, lesions of the extremity that cause limb hypertrophy or loss of function, and painful histologically confirmed dysplastic lesions. Note: histological confirmation of tumour is not necessary in the presence of consistent clinical and radiological findings, but should be considered if malignant degeneration of a plexiform neurofibroma is suspected clinically or by fluorodeoxyglucose positron emission tomography (FDG-PET) scan or FDG-PET MRI. The targeted lesion(s) should be measurable (≥3 cm in one dimension) and inoperable (i.e. complete resection of plexiform neurofibroma is not considered feasible without substantial risk of morbidity). 4. Patients should have a Karnofsky performance status of >70%.

	5. Patients should have adequate bone marrow function as indicated by absolute neutrophil count ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L and haemoglobin >9 g/dL. 6. Patients should have adequate liver function as indicated by serum bilirubin ≤1.5 x upper limit of normal (ULN), and ALT and AST ≤2.5 x ULN. 7. Patients should have adequate renal function as indicated by serum creatinine ≤1.5 x ULN. 8. Patients should have a life expectancy of ≥24 months. 9. Women of child-bearing potential must have had a negative serum pregnancy test within 7 days prior to start of study treatment administration. 10. Patients should be able to undergo MRI examinations. 11. Patients must provide written informed consent, obtained according to local guidelines, prior to any study-specific procedures being performed.
Exclusion criteria	1. Patients with a malignant peripheral nerve sheath tumour (MPNST). In patients with lesions with FDG-PET standardized uptake value (SUV) max >4, a biopsy should be performed to exclude a MPNST. 2. Patients who have previously received MEK inhibitors. 3. Patients with a known hypersensitivity to MEK inhibitors or any excipient of selumetinib or a history of an allergic reaction attributed to compounds of similar chemical or composition to selumetinib. 4. Patients with a known history of HIV seropositivity or active viral hepatitis. 5. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study, such as: – unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia, uncontrolled arterial hypertension despite medical treatment; severe valvular heart disease; previous moderate or severe impairment of left ventricular (LV) systolic function (LV ejection fraction [EF] <45% on echocardiography or equivalent on multigated angiogram [MuGA]) even if full recovery has occurred; baseline LVEF <55% on echocardiography or below institution's lower limit of normal for MuGA, atrial fibrillation with a ventricular rate >100 bpm on ECG at rest; – active (acute or chronic) or uncontrolled infection/disorders that impair the ability to evaluate the patient or the ability of the patient to complete the study; – liver disease such as cirrhosis, decompensated liver disease, chronic active hepatitis or chronic persistent hepatitis; – fatal or life-threatening disorders.

	6. Female patients who are pregnant or breast-feeding, or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes. Oral contraceptives are not acceptable alone. 7. Patients with a contraindication to MRI. 8. Patients who have undergone major surgery or radiotherapy ≤3 weeks prior to starting study treatment or who have not recovered from the side effects of such procedure; 9. Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumour, immunotherapy or biological therapy. 10. Patients who are receiving other investigational agents or who have received investigational drugs ≤4 weeks prior to study treatment start. 11. Patients unwilling or unable to comply with the protocol. 12. Inability to swallow selumetinib capsules whole (since capsules cannot be crushed or broken).
Investigational medicinal product(s)	Phase II. Selumetinib hydrogen sulfate will be supplied in 10 mg and 25 mg capsules. Selumetinib will be administered orally twice daily (approximately every 12 hours) continuously for 28-day cycles with no rest period between cycles. Patients should be instructed to take the dose on an empty stomach (either 1 hour before or 2 hours after meals) with water. The capsules cannot be crushed and must be swallowed whole. The dose for adults (and adolescents with body surface area (BSA) ≥1.8 mg/m^2) will be 50 mg bid continuously (i.e. on days 1–28 of each 28-day treatment cycle). Adolescents aged 15 to <18 years with BSA <1.8 mg/m^2 will receive a dose of 25 mg/m^2 bid continuously (days 1–28 of each 28-day treatment cycle). Treatment will be administered for 2 years (or until disease progression or unacceptable toxicity if either occurs earlier). In case of response, treatment can be continued beyond the 2-year study period.
Comparator treatment	Not applicable.
Interventions added for the trial	Treatment with selumetinib, visits, MRI, blood tests, ophthalmological examinations, cardiac evaluations
Expected benefits	Reduction of the volume of neurofibromas Reduction of the morbidity associated with these tumours Improvement of general health
Risks added by the trial	Level of risk D: - Toxicity due to selumetinib treatment: the most common toxic effects associated with selumetinib in previous studies in neurofibromatosis type 1 included acneiform rash, gastrointestinal effects, asymptomatic creatine kinase elevation and paronychia.

	- Risks associated with the study procedures: injected MRI; adverse events due to the injection.
Practical implementation	Patients with be screened (pre-included) as outpatients by the investigators, after validation during one of the monthly French national multidisciplinary boards. If they meet the inclusion criteria, without any exclusion criteria, they will be included by the investigator. Baseline MRI and paraclinical examinations will be performed. Patients will be treated orally with selumetinib, until toxicity or progression. Follow up will be performed to assess efficacy and toxicity, as well as the secondary endpoints
Number of subjects included	35
Number of sites	5 sites (all in France)
Duration of the trial	Inclusion period: 12 months Participation period (treatment): 24 months Total duration: 36 months
Number of enrolments expected per site and per month	7 enrolments per site in total. Total 2–3 enrolments (across all sites) per month.
Statistical analysis	The main analysis will be performed using the intention to treat population (all patients who received at least one dose of study drug).
Sources of funding for the trial	AstraZeneca (selumetinib and funding for the trial analysis)
Trial will have a Data Monitoring Committee	Yes