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

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	 Patients should have adequate bone marrow function as indicated by absolute neutrophil count ≥1.5 x 10⁹/L, platelets ≥100 x 10⁹/L and haemoglobin >9 g/dL. 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. Patients should have adequate renal function as indicated by serum creatinine ≤1.5 x ULN. Patients should have a life expectancy of ≥24 months. Women of child-bearing potential must have had a negative serum pregnancy test within 7 days prior to start of study treatment administration. Patients must provide written informed consent, obtained according to local guidelines, prior to any
	study-specific procedures being performed.
Exclusion criteria	 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. Patients who have previously received MEK inhibitors. 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. Patients with a known history of HIV seropositivity or active viral hepatitis. 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:
	 tatal or lite-threatening disorders.

Investigational medicinal product(s)	 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. Patients with a contraindication to MRI. 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; Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumour, immunotherapy or biological therapy. Patients unwilling or unable to comply with the protocol. Inability to swallow selumetinib capsules whole (since capsules cannot be crushed or broken). 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 of the method).
	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	7 enrolments per site in total.
per site and per month	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	Yes
Committee	