TITLE: Phase 2 trial of selumetinib in patients with Neurofibromatosis type II related tumors

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SCHEMA

Description

This is a single institution, Phase 2 trial for patients with neurofibromatosis type 2 (NF2) with vestibular schwannomas (VS) who exhibit hearing loss. Bilateral vestibular schwannomas (VS) are the hallmark of NF2. As these tumors enlarge, they cause sensorineural hearing loss and, ultimately, complete hearing loss.

Selumetinib (AZD6244) is a highly selective, orally bioavailable, non-ATP competitive small molecule inhibitor of the mitogen-activated protein (MAP) kinase MEK-1/2. MAPK activation in NF2 has been most thoroughly described in schwannomas and elevated MEK1/2 and ERK1/2 have been demonstrated in human schwannoma tissue at both the mRNA and protein levels.

Schema

This is a Phase 2 trial to assess the hearing response rate and radiographic response of VS in children and young adults with NF2 who are treated with selumetinib. Dosing is based on BSA calculated at the beginning of each course.

Selumetinib is taken orally twice a day continuously. One course is equivalent to 28 days. Therapy may continue for up to two years (26 courses) in the absence of disease progression or unacceptable toxicity.

Dose modifications will be based on Body Surface Area (BSA) dose reduction guidelines in Appendix D.
There will be two treatment strata. Stratum 1 is for those patients who have a target vestibular schwannoma which is causing hearing loss. Stratum 2 will be reserved for patients who exhibit growth of a tumor(s) besides vestibular schwannoma and are therefore not eligible for stratum 1.

1 OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the hearing response rate at 24 weeks using word recognition scores in children and young adults with NF2 who are treated with selumetinib on stratum 1

1.1.2 To determine the radiographic response rate of other NF2 related tumors (meningiomas and ependymomas) in patients treated with selumetinib on stratum 2.

1.2 Secondary Objectives

1.2.1 To determine the radiographic response rate of VS (defined as an decrease in VS volume by ≥ 20% compared to baseline) during selumetinib treatment

1.2.2 To describe MRI characteristics of the tumors before and after treatment

1.2.3 To evaluate the feasibility of collecting pre-trial tumor samples in NF2 patients

1.2.4 To determine if pre-trial tumor samples indicate activation of the MAPK pathway:

1.2.5 To evaluate the effect of selumetinib on quality of life using the NFTI-QOL scale for patients ≥ 16 years of age

2 BACKGROUND

2.1 *Neurofibromatosis Type 2*

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder associated with development of multiple types of central nervous system (CNS) and peripheral nervous system (PNS) tumors. The causative genetic event in NF2 is loss of tumor suppressor protein merlin as a consequence of mutations in the NF2 gene located at chromosome 22q12.2. Merlin is a member of the ezrin, radixin, and moesin (ERM) family of membrane-cytoskeletal linker proteins.[1-3] Although merlin is important in many cellular processes and functionally overlaps with ERM proteins, it is distinguished by its tumor suppressor activity, which inhibits several important cancer signaling pathways, including Ras/Raf/MEK/ERK (also called the mitogen-activated protein kinase or MAPK pathway), Rac, and phosphoinositide 3-kinase (PI3K)/Akt.[1,4-6] The incidence of NF2 is approximately 1 in 25,000 individuals.[7] CNS and PNS manifestations of NF2 most commonly include vestibular schwannoma (VS) (previously called "acoustic neuroma"), meningioma, and less commonly, ependymoma and low-grade glioma (LGG) also occur.[8] NF2 represents 2.5% of all newly diagnosed intramedullary spinal tumors.[9] The clinical presentation of patients with NF2 and VS classically includes hearing loss, tinnitus, and ataxia, though patients may present with symptoms related to other CNS tumors before developing VS.[10] A positive family history is present in approximately 50% of cases. Initial screening tests for NF2 include MRI and

audiometry, and genetic testing is available. Due to relative slow growth, standard chemotherapy is generally ineffective in NF2, necessitating the use of surgical resection and radiation therapy, both of which increase morbidity in this patient population. While emphasis is placed on minimizing intervention, those who require therapy are at high risk of functional disability, most commonly hearing loss in the context of VS.

MEK Activation in NF2-Related Tumors

The biology of NF2 has been intensively studied, and the MAPK signaling pathway has been strongly implicated in merlin-deficient tumorigenesis.[4,11-13] MAPK proteins play a key role in the regulation of many cellular processes, including proliferation, survival, differentiation, apoptosis, motility, and metabolism.[14] Activated RAS triggers phosphorylation and activation of the RAF kinase, which in turn phosphorylates MEK1 and MEK2 on two serine residues.[15] Activated MEK phosphorylates its only known substrates, ERK1 and ERK2. Phosphorylated ERK dimerizes and translocates to the nucleus, where it is involved in several important cellular functions, including cell proliferation. Overexpression of growth factors and/or receptors involved in the MAPK pathway activation or activating mutations of genes encoding the signaling proteins may lead to uncontrolled proliferation and tumor formation. In fact, RAS genes are the most frequently mutated oncogenes detected in human tumors.[16] RAS proteins are guanine nucleotide binding proteins that activate RAF proteins when bound to GTP. Cancer-associated mutations in RAS proteins stabilize the GTP-bound form of RAS, thereby providing a constitutive signal downstream in the cascade.

MAPK activation in NF2 has been most thoroughly described in schwannoma, the prototypical NF2 tumor. Several groups have demonstrated elevated MEK1/2 and ERK1/2 in human schwannoma tissue at both the mRNA and protein levels.[12,17] ERK1/2 signaling in rat models has been shown to enhance Schwann cell de-differentiation[18], adhesion[19], and proliferation[20], and MEK inhibition in human schwannoma cell lines has been shown to decrease proliferation and increase apoptosis.[12] Mechanisms underlying MAPK activation in human NF2-driven tumors are multifaceted and largely dependent on activation of growth factors and/or growth factor receptors, including platelet-derived growth factor receptor (PDGFR)[11,21], insulin-like growth factor receptor (IGFR)[22], fibroblasts growth factor (FGF)[13], and ErbB2/B3.[23] Integrin signaling, specifically the focal adhesion kinase (FAK)/Src/Ras pathway, has also been implicated in ERK1/2 activation[11,24], as has p21-activated kinase (PAK), which normally inhibits merlin via a negative feedback loop[25] and cross-talks with the ERK1/2 signaling pathway.[11]

Though much less studied, MAPK activation in other merlin-deficient tumor types may be driven by similar inciting factors to those in schwannoma. MAPK over-activity has been frequently observed in meningioma[26,27], of which 50-60% result from NF2 mutation.[28] MAPK activation in NF1-driven LGG, however, appears to be mediated by a similar mechanism to that seen in NF2 schwannomas, whereby loss of tumor suppressor proteins neurofibromin or merlin stabilizes GTP-bound RAS, leading to constitutive activation. [29]

Evidence of Selumetinib Activity in NF2 schwannomas

Ammoun and colleagues initially revealed a long-lasting activation of ERK1/2 in primary human schwannoma cells basally and with stimulation with PDGF-DD, a relevant mitogen for schwannomas. They then performed the first *in vitro* study of selumetinib in a human

schwannoma cell line and demonstrated complete inhibition of PDGF-mediated ERK1/2 activation and cell proliferation at 1 μM (458 ng/mL)[42].

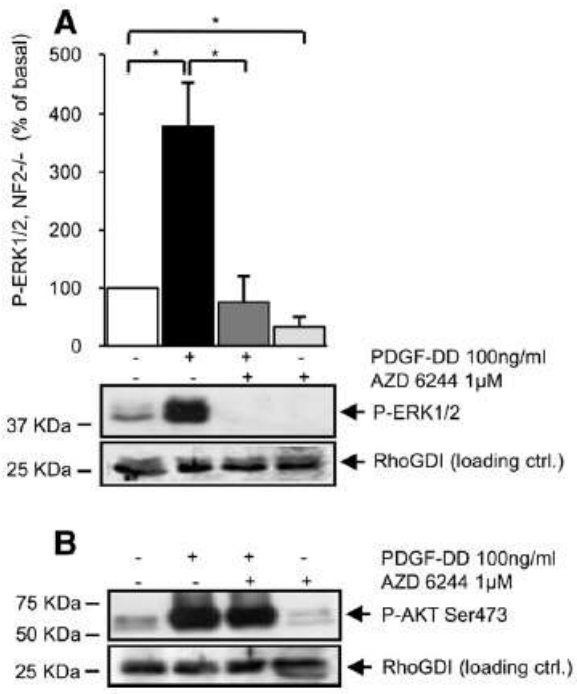


Fig. 1. AZD6244 strongly inhibited basal and PDGF-DD-mediated ERK1/2 (1A) but not AKT (1B) activation in primary human schwannoma cells (NF2−/−). The cells were serum-starved for 24 hours before stimulation, pretreated with AZD6244 1.0 μM (458 ng/ml) for 1 hour and stimulated with PDGF-DD (100 ng/ml) for 10 minutes. The phosphorylated/activated levels of ERK1/2 and AKT were detected by immunoblotting. The data have been corrected to a loading control, RhoGDI.

Figure 1 above shows serum-starved cells selumetinib completely inhibited the PDGF-DD-mediated ERK1/2 activation. Additionally, a significant decrease in the level of basal ERK1/2 activity was also observed (Fig. 1A). The effect of selumetinib seems specific as PDGF-DD-mediated AKT activation was not inhibited (Fig. 1B).

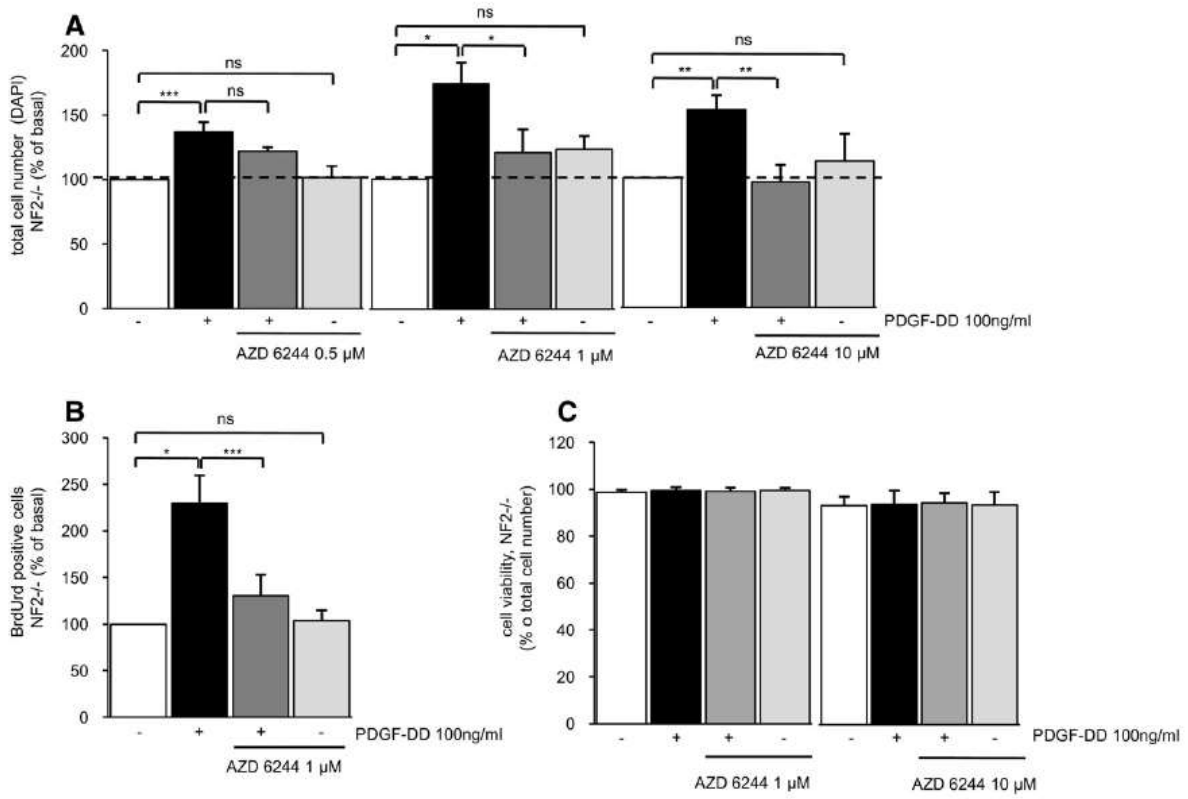


Fig. 2. AZD6244 effects on schwannoma cell proliferation. (A and B) PDGF-DD-mediated schwannoma cell proliferation was strongly inhibited by AZD6244. (C) AZD6244 was not toxic for schwannoma cells at the concentrations used in this assay. The cells were cultured for 72 hours with or without PDGF-DD (100 ng/ml) and AZD6244 0.5 µM (229 ng/ml), 1.0 µM (458 ng/ml), and 10.0 µM (4.58 µg/ml). Total cell number (DAPI-stained), proliferating cells (BrdUrd-positive), and dead cells (PI-positive) were manually counted using fluorescent microscope.

Figure 2 above shows selumetinib strongly reduces PDGF-DD-mediated schwannoma proliferation in a concentration-dependent manner, with full significant inhibition at 1.0 µM (458 ng/ml) (Fig. 2A). These results were confirmed using a BrdUrd incorporation assay; Fig. 2B. Selumetinib does not seem to be toxic in vitro, as it did not influence cell viability at the concentrations tested (Fig. 2C). They also verified that MEK1/2 is a target for schwannomas by staining sections of schwannomas for expression of activated (i.e., phosphorylated) MEK1/2 and its downstream kinase phosphorylated ERK1/2. They found increased levels of both kinases in their active form in schwannoma tissue, thus supporting their current in vitro data.
The concentration used above is well below the maximum serum concentration achieved in an early phase 1 clinical trial of selumetinib in adults with advanced cancer.[33] Ammoun *et al*. also showed *in vitro* efficacy of selumetinib in combination with PDGFR/c-KIT inhibitor nilotinib in human schwannoma cells.[43] Nilotinib alone was effective at inhibiting PDGF-mediated and basal schwannoma cell proliferation at a low concentration of 0.5 µM, though the anti-proliferative effect was even greater with a combination of PDGFR inhibition (0.25 µM nilotinib) and MEK inhibition (0.5 µM selumetinib).

2.2 SELUMETINIB

Selumetinib is a highly selective, orally bioavailable, non-ATP competitive small molecule inhibitor of the mitogen-activated protein (MAP) kinase MEK-1/2.[30] Selumetinib inhibited the

activity of purified MEK enzyme with an IC50 of 10-14 nM, and was found to be inactive or only minimally active at 10 μM against a panel of other kinases, including epidermal growth factor receptor (EGFR), ERBB2, p38α, ERK2, and MKK6 kinases. Because ERK is the only known substrate of MEK, the inhibition of MEK will target only the ERK signal transduction pathway; other signal transduction pathways will not be blocked. *In vitro*, *in vivo*, and preliminary clinical trial results suggest that selumetinib exhibits a favorable pharmacologic and toxicologic profile.

2.2.1 Pre-clinical Studies of Selumetinib

Nonclinical Studies
Efficacy
In vitro studies have shown that selumetinib and its N-desmethyl metabolite are potent and selective inhibitors of MEK.[30] However, significant biochemical activity was not detected when the two compounds were tested against a diverse panel of 305 other molecules, including enzymes, receptors, kinases, transporters, and ion channels. The effects of selumetinib on ERK phosphorylation and cell viability were determined in a panel of cell lines in which the mutational status of RAF and RAS were known. Selumetinib inhibited ERK1 and ERK2 phosphorylation with IC50s ranging from 0.0018 to 0.041 uM. Selumetinib was particularly potent in inhibiting the viability of cell lines with V600E BRAF gene mutation and some with KRAS mutations. The N-desmethyl metabolite was found to be 3-fold more active than the parent compound at inhibiting ERK phosphorylation and 5-fold more potent at inhibiting cell viability. Significant suppression of tumor growth in response to selumetinib treatment was observed in several xenograft mouse models derived from a range of tumor types including melanoma, breast, pancreatic, lung, colon, and hepatocellular carcinomas.[30,31] In the Calu-6 lung cancer xenograft model, selumetinib suppressed tumor growth at doses of 10, 25, or 100 mg/kg given twice daily, and the minimal effective dose was identified as 0.75 mg/kg administered twice daily (BID). In this model, MEK activity was inhibited as assessed by the level of phosphorylated ERK (pERK) in the tumor. Studies using human colorectal xenograft models (SW620, Colo205) demonstrate that selumetinib inhibits tumor growth by inhibition of cell proliferation and by induction of apoptosis.

Pharmacokinetic/Pharmacodynamic Xenograft Studies
Oral bioavailability of selumetinib was favorable in rats (37% at 10 mg/kg) and monkeys (86% at 1 mg/kg), but bioavailability decreased with increasing dose.[30] The declining bioavailability at higher doses may be due to the low aqueous solubility of selumetinib. No accumulation of selumetinib was observed following multiple dosing in rats or monkeys. Studies in rats indicate that selumetinib is widely distributed, although tissue concentrations were lower than blood concentrations. High levels of protein binding (93.7-99.7%) were observed in all preclinical species tested and in humans (98.4%). Selumetinib was excreted rapidly within 48 hours via the feces, mostly as metabolites.

The value of pERK as a biomarker of selumetinib efficacy has been explored in non-clinical studies. In the Calu-6 human lung cancer xenograft model, levels of pERK were determined by both immunohistochemical (IHC) staining of formalin-fixed tissue sections and by Western blot analysis of tumor protein lysates.[30] Following an acute tumor-suppressive dose of 25 mg/kg of

selumetinib, immunostaining for pERK in the cytoplasm was reduced by approximately 90% at 1, 2 and 4 hours post-dose and recovered to >50% of the control by 24 hours. The increase in tumor pERK content by 24 hours correlated with the decrease in plasma concentration of selumetinib. The same trend was observed by Western blot analysis. These data showed that the level of pERK in the tumor is a potential biomarker for selumetinib activity *in vivo*.

A whole blood fluorescence-activated cell sorting (FACS) assay was developed to monitor pERK levels in peripheral blood mononuclear cells (PBMCs) to allow assessment of selumetinib activity without tissue biopsy.[32] Whole blood samples from cynomolgus monkeys at pre-dose and 1, 2, 4, 8, 12 hours post-dose were analyzed for pERK levels. Plasma concentrations of selumetinib correlated with inhibition of TPA-induced ERK phosphorylation. Similarly, the *ex vivo* addition of selumetinib to human whole blood from volunteers resulted in the inhibition of ERK phosphorylation in isolated PBMCs. Data from an ongoing phase 1 study in cancer patients also indicate a strong correlation between plasma drug concentration and inhibition of ERK phosphorylation in blood from these patients, demonstrating the effectiveness of pERK as a mechanistic biomarker for MEK inhibition in the clinical setting.

Toxicologic Studies
The toxicologic effects of selumetinib were evaluated in acute dose (one or two doses on a single day) and at 1-month repeat-dose studies in Sprague-Dawley rats and cynomolgus monkeys.[30] The repeat-dose study in rats indicated that the agent was well tolerated but produced soft stools and gastrointestinal mucosal mineralization associated with increased serum phosphorus and decreased albumin. Diarrhea, dehydration, electrolyte imbalance, and secondary renal changes were observed in monkeys. The vehicle, Captisol® (SBE-CD), used in the formulation is known to cause gastrointestinal disturbances in preclinical studies. A reduction in the volume of Captisol® administration to monkeys was associated with a reduced incidence of diarrhea; however, it is likely that selumetinib exacerbated the vehicle effects. The no observable adverse effect levels (NOAEL) in rats and monkeys in the 1-month studies were identified as 10 mg/kg/day and 20 mg/kg/day (administered twice daily), respectively. Selumetinib and its active metabolite showed no evidence of mutagenic potential, but selumetinib produced an increase in micronucleated immature erythrocytes in mice, predominantly via an aneugenic mode of action.

Safety pharmacology studies were performed to assess the effects of selumetinib and its active metabolite on key organ systems.[30] The agents did not produce any toxicologically significant effect. Evidence of gastric mucosal lesions and minor increases in airway resistance were observed in some rats following a 100 mg/kg dose; however, these effects were not apparent in the 1-month study.

2.1.2 ***Clinical Studies***
As of 31 October 2015, approximately 2880 patients with cancer have received treatment with selumetinib, including 1388 patients in AZ-sponsored studies, 57 patients in the Array-sponsored Study ARRY-0401, 62 patients in the Merck-sponsored Study D1532C00028, and approximately 1375 patients in investigator- or collaborative group-sponsored studies. Of the investigator-sponsored studies, 2 are being conducted in a paediatric population (Studies 8799 (11C0161 [NCT01362803; Phase 1] and PBTC-029 [NCT01089101; Phase 1/2]). In addition, 354 subjects (healthy volunteers or subjects with renal or hepatic impairment) have been exposed to

selumetinib Hyd-Sulfate in clinical pharmacology studies.

Selumetinib was initially dosed as a free-base suspension formulation for the First Time in Man Phase 1 study. An MTD of 100 mg BID was established by this study, and subsequent phase 2 studies were carried out at this dose level using this formulation. A subsequently developed selumetinib Hydrogen-Sulfate salt capsule formulation was found to have an MTD of 75 mg BID in a phase 1 study. Further development of selumetinib will be with the selumetinib Hyd-Sulfate capsule formulation.[30]

Pharmacokinetics
The single dose pharmacokinetics of selumetinib and its active metabolite N-desmethyl were characterized following dosing of the free-base suspension and the Hyd-Sulfate capsule formulation. Selumetinib was rapidly absorbed across all dose levels with a median tmax of 1.5 hrs. Following the peak, selumetinib concentrations declined multi-exponentially, with a mean t1/2 ranging from 5 to 7 hours, consistent across dose levels. Plasma N-desmethyl selumetinib concentrations followed a similar pharmacokinetic profile to selumetinib, although exposure was much lower with Cmax and AUC values generally <10% of parent.

AUC following dosing with the free-base suspension formulation increased with increasing dose in a less than dose proportional manner, although there was a high degree of inter-patient variability. In contrast, following dosing with the Hyd Sulfate capsule formulation there was more of a trend towards increases in exposure (AUC and Cmax) in proportion to increases in dose. In a relative bioavailability study, the Hyd-Sulfate formulation showed significantly improved bioavailability over the free-base suspension. Pharmacokinetic data from a food effect study indicated that both low fat and high fat food decreases the exposure of selumetinib.

Selumetinib plasma pharmacokinetic parameters were similar after single and multiple dosing (days 8, 15 and 22) suggesting minimal accumulation over time after twice daily dosing, consistent with the terminal half-life observed.[30]

Pharmacodynamics
The effect of selumetinib on ERK phosphorylation in peripheral blood mononuclear cells was evaluated in Part A of study ARRY-0401. Using FACS analysis, the magnitude of pERK relative to baseline was determined in TPA-stimulated pre- and post-treatment blood samples. Selumetinib inhibited TPA-induced ERK phosphorylation at an IC50 of approximately 134 ng/mL (total concentration in plasma). The magnitude of inhibition was found to correlate with plasma selumetinib concentrations. Inhibition of pERK as an indirect measure of MEK inhibition by selumetinib was assessed in PBMCs from each patient at 4 time points post single dose administration across dose levels. Inhibition of ERK phosphorylation was observed at all doses, with greatest inhibition generally occurring at the first time point; 73% inhibition seen at 1 hour.

Phase 1

Accrual to the Pediatric Brain Tumor Consortium's (PBTC) Phase 1 study completed in April, 2013, and the maximum tolerated dose in all age groups was 25 mg/m2/dose, BID. 39 patients

were accrued; one was found to be ineligible. Initially, only patients >12 and ≤ 21 years were eligible. Dose levels 1 and 2 (33 and 43 mg/m2/dose, BID) were deemed intolerable with dose limiting toxicities (DLTs) of headache, rash and mucositis. Following de-escalation to dose level 0 (25mg/m2/dose BID), eligibility was extended to patients <12 years. Among the 24 patients treated at dose level 0, no patient <12 years and 3 of 12 patients ≥12 years experienced DLTs of elevated amylase/lipase, rash, and mucositis. There were 8 sustained responses (1 complete and 7 partial) and the phase 2 study through the PBTC is ongoing.

There is also an ongoing trial for patients with neurofibromatosis type 1 who have plexiform neurofibromas (PN). PN are benign nerve sheath tumors that have no standard treatment options other than surgery, which is often difficult due to proximity to vital structures. In this trial, selumetinib will be administered orally BID on a continuous dosing schedule. Limited dose escalations will be performed to define the MTD based on tolerability of selumetinib during the first three treatment cycles. Disease status will be evaluated using volumetric MRI analysis at regular intervals. A phase 2 registration study has started and is ongoing based on the phase 1 data.

Phase 2 –Adult studies

In a phase 2 randomized trial of temozolomide versus selumetinib for high-stage malignant melanoma, 200 patients were randomized. There was no statistically significant difference between the groups for the primary endpoint of PFS. Six of 104 patients treated with selumetinib had a partial response compared with 11 of 96 patients with PR+CR on the temozolomide arm.

In a separate randomized phase 2 study, 70 subjects with previously treated, advanced, or metastatic pancreatic cancer were randomized to receive selumetinib or capecitebine. There was no statistically significant difference between the two treatment groups in the primary endpoint of time to death. Another phase 2 randomized study of selumetinib versus capecitebine for subjects with recurrent/progressive colon cancer also showed no significant difference between treatments in the primary endpoint of time to progression. Overall, the best response reported was stable disease in 11 patients (10 treated with selumetinib and 1 treated with capecitebine). In a phase 2 randomized study of selumetinib versus pemetrexed, 84 subjects with recurrent progressive NSCLC were recruited. No significant difference was seen in the primary endpoint of PFS. Four patients achieved a best overall response of CR (1 pemetrexed treated) or PR (2 selumetinib, 1 pemetrexed treated).[30]

More recently, a phase 2 trial of selumetinib in patients with Iodine-131- resistant papillary thyroid cancer showed 1/32 evaluable subjects with a PR, 21/32 with SD, and 11/32 with PD. Median PFS was 32 weeks, and the most common toxicities were rash, fatigue, diarrhea, and peripheral edema.[34] In a separate pilot study in patients with RAI-refractory differentiated thyroid cancer (DTC), Ho *et al*. demonstrated that iodine avidity could be returned to patients with previously RAI-refractory disease, resulting in a response in a subset of these patients treated with RAI after selumetinib. This effect may, in part, be a function of BRAF/RAS mutation status.[35]

Two trials have examined the activity of selumetinib in “biologically enriched” cohorts. Patel

and colleagues analyzed 18 subjects with metastatic melanoma, treated on a phase 2 study. Nine of 18 had BRAF mutations, and 4 had NRAS mutations. Five of 9 patients with BRAF mutations had a PR, and the remaining 4 of 9 had SD for at least 6 weeks. No responses were seen in the BRAF WT group, and responses did not correlate in the NRAS mutated group.[36] A recently published, randomized phase 2 trial examined the use of selumetinib in combination with docetaxel versus docetaxel with placebo for patients with KRAS mutant, advanced NSCLC. The investigators reported a statistically significant improvement in progression free survival in the selumetinib treated group (5.3 months versus 2.1 months (95% CI 1.4-3.7); HR for progression 0.58, (80% CI 0.42-0.79; one-sided p=0.014).[37]

2.2.2 **Safety Data**

AZD6244 Hydrogen-Sulfate Capsule
Safety data from a phase 1 study of the Hyd-Sulfate capsule formulation are available at dose levels of 25 mg BID (n=6), 50 mg BID (n=7), 75 mg BID (n=7), and 100 mg BID (n=8). One DLT was reported in the first 22 days of dosing in the 75 mg BID cohort (CTCAE grade 3 fatigue that resolved with discontinuation of drug). Two DLTs (pleural effusion and rash, both CTCAE grade 3) were reported in the first 22 days of dosing in the 100 mg BID cohort. The MTD of selumetinib Hyd-Sulfate capsule was determined to be 75 mg BID.

The most frequently reported adverse events were fatigue, dermatitis acneiform, nausea, diarrhea, and peripheral edema. All AEs of dermatitis and fatigue for patients treated in the 75 mg BID cohort were considered treatment-related. The majority of AEs were CTCAE grade 1 or 2 in intensity. However, 33/56 of patients experienced at least one CTCAE grade 3 event during the study, of which 18/56 experienced at least one treatment-related AE > Grade 3. The majority of grade 3 events were reported by only one patient. Events that were reported in more than one patient include left ventricular dysfunction, nausea, vomiting, fatigue, febrile infection, lower respiratory tract infection, increased blood alkaline phosphate, GGT increased, hypoxia, dermatitis acneiform, and hypertension. Fatigue was the most commonly reported CTCAE grade 3 or higher AE. The only grade 4 event in the study was a single episode of hypoglycemia.

Eighteen patients had permanent discontinuation of study treatment due to at least one adverse event. Five patients had AEs of fatigue reported as contributing to discontinuation of treatment. Two patients each had AEs of anorexia, vomiting, nausea and LV dysfunction, also reported as being at least partly contributing to discontinuation of study treatment. Seven patients had at least one SAE that was considered treatment-related, with hypertension being the only SAE reported more than once.[30]

LVEF
Scheduled on-treatment assessments (Week 4 or 8) of LVEF were included in two studies of selumetinib monotherapy to evaluate a possible cardiac etiology for peripheral edema. Small median reductions (<10 percentage points) from baseline were recorded during selumetinib treatment in both studies, although individual patient changes were highly variable (–25 to +19 percentage points). No comparative data are available from these studies. Clinically meaningful reductions in LVEF (≥10 percentage points and to below 55%) in patients receiving selumetinib in combination with chemotherapy have been recorded in two randomized double-blind placebo-

controlled Phase 2 studies with scheduled Week 6 echocardiography assessments (D1532C00006 and D1532C00016). These asymptomatic reductions occurred in 13.6% vs. 7.1% of patients with NSCLC receiving selumetinib or placebo in combination with docetaxel and in 20.5% vs. 11.4% of patients with advanced melanoma receiving selumetinib or placebo in combination with dacarbazine. Evidence of reversibility of LVEF changes on continuing selumetinib (often without therapeutic treatment) has been demonstrated in patients with follow-up assessments available.

Increase in Creatinine Phosphokinase Levels

Increased CPK levels have been reported with MEK inhibitors[38-40], which may suggest a class effect. Scheduled measurement of CPK levels has not been included in studies of selumetinib. However, AEs of increased CPK levels have been reported in a small number of patients. In study D1532C00006, CPK levels were measured at a single investigational site in patients with melanoma believed by the investigator to be receiving selumetinib + dacarbazine. AEs of increased CPK levels were reported in 7 patients (15.9% of the overall selumetinib + dacarbazine group). CPK levels were not measured in the 3 patients at the same site who received placebo + dacarbazine. A causal relationship between selumetinib and increased CPK levels has not been established.

Muscle Weakness

Neck extensor muscle weakness (with mild increase in CPK levels), reversible on selumetinib interruption, has been reported in 3 patients with uveal melanoma treated with selumetinib in a non-AZ-sponsored study.[41] A relationship between selumetinib and muscle weakness has not been established.

Potential Drug Interactions

In vitro metabolic studies of selumetinib using hepatocytes from humans and animals found that the biologically active N-desmethyl derivative was detected in mouse and human hepatocytes, detected minimally in monkeys, and was not detected in rats.[30] CYP3A4 is the predominant isoform responsible for selumetinib oxidative metabolism with CYP2C19, CYP1A2, CYP2C9, CYP2E1 and CYP3A5 involved to a lesser extent. *In vitro* studies indicate that selumetinib also undergoes direct Phase 2 metabolic reactions to form glucuronide conjugates principally involving the enzymes UGT1A1 and UGT1A3. Cytochrome P450 (CYP)1A2 was the enzyme primarily responsible for the formation of the N-desmethyl derivative. CYP2C19 and CYP3A4 were also minimally involved in the transformation to N-desmethyl metabolite. Neither selumetinib, nor its active metabolite, were found to be inhibitors of CYP isoforms 1A2, 2C8, 2C19, 2D6, or 3A4. At the systemic selumetinib concentrations observed following 100 mg selumetinib capsule formulation in man, no significant cytochrome P450 interactions would be expected. Since the formation of N-desmethyl AZD6244 from selumetinib may occur through the CYP1A2 pathway and smoking induces this pathway, the smoking status of the subjects should to be recorded in all studies (i.e., smoker or non-smoker) to investigate whether smoking status influences systemic drug exposures of N-desmethyl selumetinib.

Selumetinib exposure in subjects of Asian ethnicity

Selumetinib exposure appears to be higher in Japanese, non-Japanese-Asian and Indian healthy adult volunteers compared to Western adult volunteers. However, there is considerable overlap with Western subjects when corrected for body weight or BSA. No specific adjustment to the starting dose is recommended for paediatric Asian patients, however these patients should be closely monitored for adverse events.

Vision Changes

Visual disturbances symptoms, including blurred vision have been reported in 10% of patients during treatment with selumetinib. Adverse events of central serous retinopathy/retinal pigment epithelial detachment have been reported in a small number of patients receiving selumetinib. Rare adverse event of retinal vein occlusion have been reported, however a relationship between selumetinib and retinal vein occlusion has not been established.

Rationale

The preclinical work described above, demonstrating the important role of MAPK pathway activation in NF2-driven tumorigenesis, provides strong rationale for targeting the MAPK signaling pathway through selective therapeutic inhibition of MEK1/2 with selumetinib. Therefore, we are initiating a single institution, Phase 2 trial for patients with neurofibromatosis type 2 (NF2). There will be two strata in this clinical trial. Stratum 1 will include patients with NF2 with VS who exhibit hearing loss. Stratum 2 will include for patients who have progressive lesions other than VS (including non-vestibular schwannomas, meningiomas, and spinal cord lesions). Our hypotheses are: 1) selumetinib given orally twice daily will improve hearing in NF2 patients with VS in stratum 1 and 2) selumetinib given orally twice a day will decrease the size of NF2-associated tumors in stratum 2.

3 PATIENT SELECTION

3.1 Inclusion Criteria:

3.1.1 Patients must have a confirmed diagnosis of neurofibromatosis 2 by fulfilling National Institute of Health (NIH) criteria or Manchester criteria, or by detection of a causative mutation in the NF2 gene.
The NIH criteria includes presence of:

- Bilateral vestibular schwannomas, **OR**
- First-degree relative with NF2 and **EITHER** unilateral eighth nerve mass **OR** two of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity.

The Manchester criteria includes presence of:

- Bilateral vestibular schwannomas, **OR**
- First-degree relative with NF2 and **EITHER** unilateral eighth nerve mass **OR** two of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity, **OR**
- Unilateral vestibular schwannoma **AND** any two of: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity, **OR**
- Multiple meningiomas (two or more) **AND** unilateral vestibular schwannoma **OR** any two of: schwannoma, glioma, neurofibroma, cataract.

3.1.2 Patients do not need to have a histologic diagnosis in order to start therapy but must have measurable disease (in 2 dimensions) on MRI scan to be eligible.

3.1.2.1 For Stratum 1: Patients must have a target VS with the following qualities:

Associated with a word recognition score of < 85% and > 0%

AND

Documented progression defined as: Either progressive hearing loss or progressive tumor growth in last 18 months defined as ≥ 20% increase in volume.

3.1.2.2. For Stratum 2: Patients must not meet the eligibility criteria as stated for Stratum 1 and have a target lesion that has exhibited progression. Progression is defined as: ≥ 25% increase in sum of the products of perpendicular diameters of lesions in the preceding 18 months; any new lesion; or clinical deterioration related to disease.

3.1.3 Patients must be able to swallow capsules

3.1.4 Age:

Patients must be ≥ 3 years to ≤ 45 years of age at start of treatment

3.1.5 Prior Therapy
Since there is no standard effective chemotherapy for patients with NF2 and vestibular schwannomas, meningiomas, or ependymomas patients may be treated on this trial without having received prior medical therapy directed at their VS, meningiomas, or ependymomas.

Since selumetinib is not expected to cause substantial myelosuppression, there will be no limit to number of prior myelosuppressive regimen for these NF2 patients.

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, biologic therapy or radiotherapy prior to entering this study except for alopecia.

Myelosuppressive chemotherapy**:** Patients must have received their last dose of known myelosuppressive anticancer chemotherapy at least three weeks prior to study registration or at least six weeks if nitrosourea.

Biologic agent: Patient must have received their last dose of the biologic agent ≥ 7 days prior to study registration. For biologic agents that have a prolonged half-life, at least three half-lives must have elapsed prior to registration

Monoclonal antibody treatment**:** At least three half-lives must have elapsed prior to registration

3.1.6 Corticosteroids:
Patients who are receiving dexamethasone or other corticosteroids must be on a stable or decreasing dose for at least 1 week prior to registration. It is recommended that patients be off all steroid therapy or receive the least dose that will control their neurologic symptoms

3.1.7 Prior radiotherapy
XRT: ≥ 6 months must have elapsed if prior XRT to vestibular schwannoma or other tumor.

3.1.8 Stem Cell Transplant or Rescue without TBI**:**
No evidence of active graft vs. host disease and ≥ 3 months must have elapsed since transplant.

3.1.9 Performance Status:
Karnofsky ≥ 60% for patients > 16 years of age
Lansky ≥ 60 for patients ≤ 16 years of age.

3.1.10 Organ Function Requirements

3.1.10.1 Adequate Bone Marrow Function Defined as:

- Peripheral absolute neutrophil count (ANC) ≥ 1500/µL
- Platelet count ≥ 100,000/µL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to registration)
- Hemoglobin ≥ 9 g/dL (may receive RBC transfusions)

3.1.10.2 Adequate Renal Function Defined as:

- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m2 or
- A serum creatinine ≤1.5×ULN for age and sex

3.1.10.3 Adequate Liver Function Defined as:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- AST(SGOT)/ALT(SGPT) ≤2.5×ULN institutional upper limit of normal for age

3.1.10.4 Central Nervous System Function:

- Patients with seizure disorder may be enrolled if they are receiving non-enzyme inducing anticonvulsants and the seizures are well controlled.

3.1.10.5 Cardiac Function

Adequate cardiac function defined as:

- LVEF ≥55% by ECHO
- QTc interval ≤450 msecs by EKG

3.1.10.6 Hypertension

- Patients, 3 to < 18 years of age must have a blood pressure that is ≤ 95th percentile for age, height and gender at the time of registration.
- Patients who are ≥18 years of age must have a blood pressure that is <140/90 mm of Hg at the time of registration.

  Patients may be on blood pressure medication provided that it is not on the contraindicated list and that the medication has not been adjusted in the previous 3 months.

3.1.11 Growth factors:

All colony forming growth factor(s) have been discontinued for at least one week prior to registration (filgrastim, sargramostim, and erythropoietin). For patients on long acting growth factors, the interval should be two weeks.

3.1.12 Inclusion of Women and Minorities
Both males and females of all races and ethnic groups are eligible for this study.

3.1.13 Informed Consent:
All patients and/or their parents or legal guardians must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

3.2 Exclusion Criteria

3.2.1 Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. The effects of selumetinib on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation, and for four weeks after dosing with selumetinib ceases. The selumetinib manufacturer recommends that adequate contraception for male patients should be used for 16 weeks post-last dose due to sperm life cycle. Women of child-bearing potential must have a negative pregnancy test prior to study registration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

Note: Female subjects are considered "of child-bearing potential" if they are anatomically and physiologically capable of becoming pregnant. For girls of normal reproductive potential, the possibility of becoming pregnant requires ovulatory menstrual cycles and heterosexual intercourse. Although the timing of ovulation relative to menarche is variable, there is consistent evidence that some girls may have ovulatory cycles prior to menarche, and that, in healthy populations, regular ovulation may begin within a few months of menarche. Therefore, menarche is the most feasible clinical indicator of the biological potential for pregnancy.

Male patients with sexual partners who are pregnant or who could become pregnant (i.e. women of child-bearing potential) must use acceptable, effective and reliable methods of contraception during the study and for at least 12 weeks after the last dose of selumetinib or for longer if required, depending on the prescribing information of the combination or concomitantly administered medications.

3.2.2 Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction) that is likely to interfere with the study procedures or results

3.2.3 Patients who are currently receiving another investigational drug within 4 weeks prior to the first dose of study treatment, or within a period during which the investigational drug or systemic anticancer treatment has not been cleared from the body (e.g. a period of 5 'half-lives'), whichever is the most appropriate and as judged by the investigator are not eligible.

3.2.4 Patients who have taken another BRAF inhibitor such as Vemurafenib or Dabrafenib prior to study registration are not eligible. Prior treatment with selumetinib or another MEK inhibitor is not allowed.

3.2.5 Patients with QTc interval of > 450 msec

3.2.6 Patients who require enzyme inducing anti-convulsants to control seizures.

3.2.7 Anticoagulation: Patients receiving coumadin are eligible but must have their PT and INR monitored prior to each 4 week course.

3.2.8 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

3.2.9 Patients with the following cardiac conditions:

a. Uncontrolled hypertension in adults (BP ≥ 140/90 mmHg despite medical therapy)
b. Acute coronary syndrome within 6 months prior to starting treatment
c. Uncontrolled Angina - Canadian Cardiovascular Society grade II-IV despite medical therapy (Appendix H)
d. Symptomatic heart failure NYHA Class II-IV, prior or current cardiomyopathy, or severe valvular heart disease (Appendix I)
e. Prior or current cardiomyopathy including but not limited to the following:
    i. Known hypertrophic cardiomyopathy
    ii. Known arrhythmogenic right ventricular cardiomyopathy
f. Previous moderate or severe impairment of left ventricular systolic function (LVEF <45% on echocardiography or equivalent on MuGA) if known even if full recovery has occurred.
g. Severe valvular heart disease
h. Baseline Left ventricular ejection fraction (LVEF) below the LLN or <55% measured by echocardiography or institution's LLN for MUGA
i. Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest

3.2.10 Ophthalmological conditions as follows:

a. Current or past history of retinal pigment epithelial detachment (RPED)/central serous retinopathy (CSR) or retinal vein occlusion
b. Intraocular pressure (IOP) > 21 mmHg or uncontrolled glaucoma (irrespective of IOP) as defined by ophthalmologist

3.2.11 Major surgery within 4 weeks of starting selumetinib. Portacath insertion, G Tube placement, and insertion of ventriculoperitoneal shunt are not considered major surgeries.

3.2.12 History of allergic reactions attributed to compounds of similar chemical or biologic composition to selumetinib or combination medications or any excipient of these medicinal products

3.2.13 History of a medical or psychiatric illness, that in the investigator's judgment renders the patient incapable of further therapy on this protocol

3.2.14 Patients with progressive disease associated with significant or disabling clinical symptoms requiring immediate intervention with surgery or radiation therapy are not eligible.

3.3 Treatment at Primary Institution

All investigational agent(s) should be dispensed and all imaging studies obtained at Cincinnati Children's Hospital Medical Center.

3.4 Criteria to Start Treatment

3.4.1 Subjects must start therapy within fourteen (14) days of registration.

3.4.2 Imaging evaluations necessary to establish eligibility for study entry must be done within four weeks prior to registration.

All other evaluations necessary to establish eligibility for study entry must be done within 14 days prior to registration.

3.4.3 Laboratory values used to assess eligibility must be no older than seven (7) days prior to the start of therapy. Laboratory tests used to determine eligibility need not be repeated if therapy starts within seven (7) days. If a test that is repeated post registration and prior to the start of therapy is outside the limits for eligibility, it must be rechecked within 48 hours prior to the start of therapy. If the recheck is still outside the limits for eligibility, the patient may not receive protocol therapy and will be considered off study.

4 REGISTRATION PROCEDURES

4.1 IRB Approval

Local IRB/REB approval of this study must be obtained prior to consenting and registration of patients.

4.2 Informed Consent for treatment

Consent should be obtained prior to the initiation of any procedures or assessments performed for the purpose of determining protocol eligibility, which would not otherwise be consistent with the institution's standards of clinical practice.

Prior to consent, the protocol's status should be verified via the CCHMC Phase 1/regulatory teams to ensure the study is open to accrual.

4.3 Patient Registration

Patients must be registered prior to any protocol treatment. Patient registration is only available to authorized personnel at CCHMC. Signing off of the eligibility checklist by Investigator or sub-Investigator completes registration.

5 TREATMENT PLAN

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6.2. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's tumor.

5.1 Drug Administration

For stratum 1 and stratum 2 patients with NF2 dosing will be based on BSA. Dosing is based on BSA calculated at the beginning of each course. Selumetinib will be supplied as 10 mg and 25 mg capsules or currently available formulation. Patients will receive selumetinib orally twice daily approximately 12 hours apart. Four consecutive weeks will constitute one course and subsequent courses will immediately follow, with no scheduled break in the administration of the drug.

The recommended dose of selumetinib is 25 mg/m^2 of body surface area (BSA), taken orally twice daily (approximately every 12 hours).

Dosing is individualised based on BSA (mg/m^2) and rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg). Different strengths of selumetinib capsules can be combined to attain the desired dose (Table 1). selumetinib is not recommended in patients with a BSA <0.55 m^2.

Table 1 Dosing scheme of selumetinib 25 mg/m^2 twice daily

Body Surface Area (BSA)	Dose in mg (twice daily)
0.55 – 0.69 m^2	10
0.70 – 0.89 m^2	20
0.90 – 1.09 m^2	25
1.10 – 1.29 m^2	30
1.30 – 1.49 m^2	35
1.50 – 1.69 m^2	40
1.70 – 1.89 m^2	45
≥1.90 m^2	50

Dosing is based on the BSA calculated at the beginning of each course of therapy for all patients. Dosing reduction tables are available in APPENDIX D. Patients will be provided with a Medication Diary for selumetinib, instructed in its use, and asked to bring the diary and pill bottles with them to each appointment.

Selumetinib capsules must be taken whole (do not crush or chew) and should be taken on an empty stomach (no food or drink other than water) either 1 hour before or 2 hours after meals. Selumetinib capsules should be taken with water only.

Participants should be advised to drink plenty of water or take rehydration fluids to avoid dehydration if diarrhea occurs. Patients who vomit a dose of selumetinib should NOT be re-dosed, and appropriate anti-emetic therapy should be implemented prior to the next scheduled dose.

Participants should avoid excessive exposure to sunlight. Patients should use adequate sunscreen protection if exposure to sunlight is to be anticipated.

During the studies, participants should avoid consuming large amounts of grapefruits, Seville oranges, or any other products that may contain these fruits, e.g., grapefruit juice, as these may affect selumetinib metabolism.

Participants should avoid donating blood while taking selumetinib and for at least 12 weeks after receiving the last dose of selumetinib.

Unless considered clinically indicated, patients should avoid taking other additional non-study medications that may interfere with the study medications. In particular, patients should avoid medications that are strong inhibitors or moderate/strong inducers of CYP3A4 and fluconazole (potent CYP2C19 and moderate CYP3A4 inhibitor), as this may interfere with the metabolism of selumetinib. See Appendix C.

5.2 Dose Modifying Toxicities (DMT)

Toxicities will be graded according to CTCAE version 5.0 of the NCI Common Terminology Criteria for Adverse Events. CTCAE version 5.00 is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of CTCAE version 5.0.

DMT will be defined as any of the events listed in this section that are at least possibly related to the investigational agent that occur regardless of expectedness. Please consult Table 7 for appropriate dose modifications.

5.2.1 The following are Dose-Modifying Toxicities (DMT's)

- Any selumetinib-related adverse event that results in a delay of treatment > 7 days
- Non-hematologic dose modifying toxicity is defined as:
    - Any grade 4 non hematologic toxicity
    - Any grade 3 non-hematologic toxicity with the exception of:
        - Grade 3 nausea and vomiting of < 3 days
        - Grade 3 asymptomatic elevation of transaminases that returns to levels meeting eligibility criteria within 7 days of study drug interruption and does not recur upon restarting drug
        - Grade 3 fever or infection if fewer than 3 days in duration
        - Grade 3 asymptomatic hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation

        - Grade 3 asymptomatic elevation of CPK
    - Any grade 2 non-hematological toxicity that persists for more than 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients as to warrant treatment interruption and/or dose reduction will be considered dose-modifying.

- Hematologic dose modifying toxicity is defined as:
    - Any grade 4 hematologic toxicity with the exception of lymphopenia
    - Grade 3 thrombocytopenia with bleeding

5.3 Criteria for starting subsequent courses

A course may be repeated every 28 days if the patient has at least stable disease and the patient meets the following criteria within seven days of the start of each course:

- ANC ≥ 1,000/μL
- Platelets ≥ 100,000/μL
- Non-hematologic dose modifying toxicity related to selumetinib recovered to < grade 2 or baseline (for rash or diarrhea: tolerable grade 2 or baseline)
- No evidence of progressive disease

5.4 Concomitant Medications and Supportive Care Guidelines

Because there is a potential for interaction of selumetinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Refer to APPENDIX C for a list of medications which should be avoided, if possible. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Data to be recorded for each medication in CRF is Indication, Drug Name, Dose, Start and Stop dates

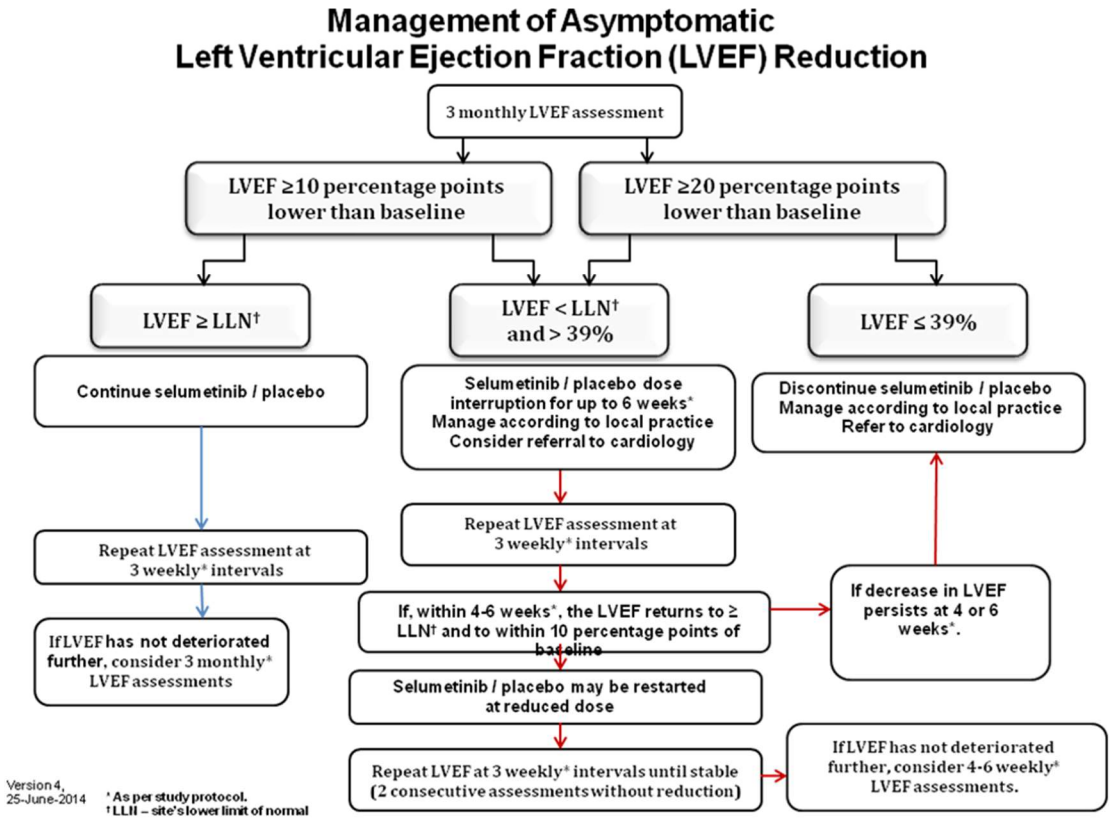
Unless considered clinically indicated, patients should avoid taking other additional non-study medications that may interfere with the study medications. In particular, patients should avoid medications that are strong inhibitors or moderate/strong inducers of CYP3A4 and fluconazole (potent CYP2C19 and moderate CYP3A4 inhibitor), as this may interfere with the metabolism of selumetinib.

High vitamin E doses may potentiate warfarin's anticoagulant activity. Monitor PT/INR more frequently in patients receiving both warfarin and selumetinib hydrogen sulfate capsules.
As selumetinib capsules contain vitamin E, patients should not take any supplemental vitamin E during treatment with selumetinib.

5.4.1 Follow up for certain adverse events should be performed to better characterize the effects of selumetinib therapy

- **Peripheral Edema** - Patients experiencing grade 3 or prolonged grade 2 (> 14 days) edema should have cardiac ejection fraction (EF) measurements, serum chemistry (including electrolytes and albumin), and routine urinalysis as clinically indicated.

- **Cardiac monitoring** - Reversible, asymptomatic reductions in LVEF have been recorded in a small number of patients receiving selumetinib in studies with scheduled echocardiography assessments. Guidance for the investigation and management of decreases of LVEF is described below.
    - ECHO - Patients will have increased monitoring for cardiac function (ECHO) at baseline and every 3 months thereafter during treatment. Patients who develop symptoms consistent with cardiac impairment (e.g., congestive cardiac failure, pulmonary edema, or dyspnea) at any time during treatment should have EF measurements (echocardiography) at the time of the event as well as other routine investigations. Patients who show a ≥10% change in ejection fraction from baseline should be managed according to the recommended management for cardiac adverse events described below and in Table 7. Patients who have a drop in LVEF of ≥10% from baseline and to below 55% at the discontinuation of selumetinib, should have a follow-up ECHO after 30 days to evaluate the potential for reversibility.

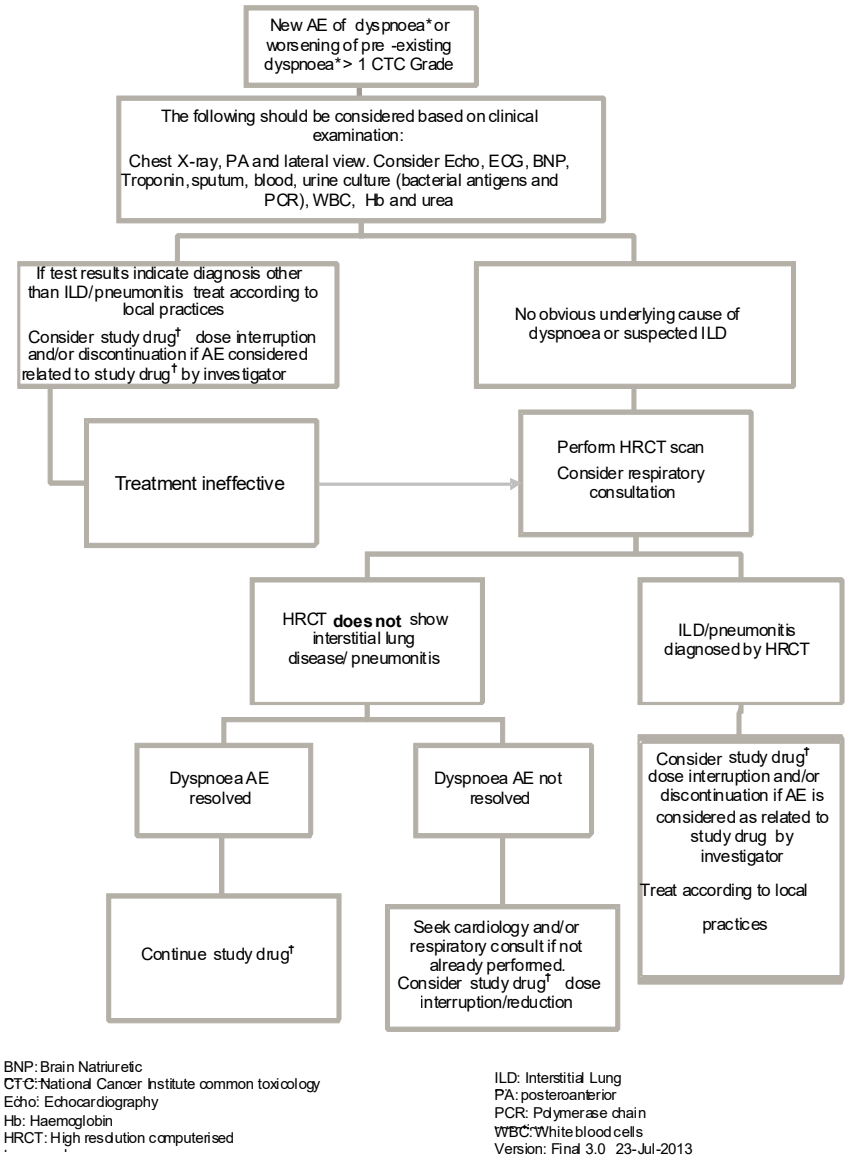


- **Muscle weakness** - Patients should be monitored for CPK elevation and for the development of muscle weakness (refer to management guidelines described in Table 7).
- **Respiratory events** (including dyspnea or pulmonary edema) should be followed up with a chest X-ray (PA and lateral view). See below algorithm for management.

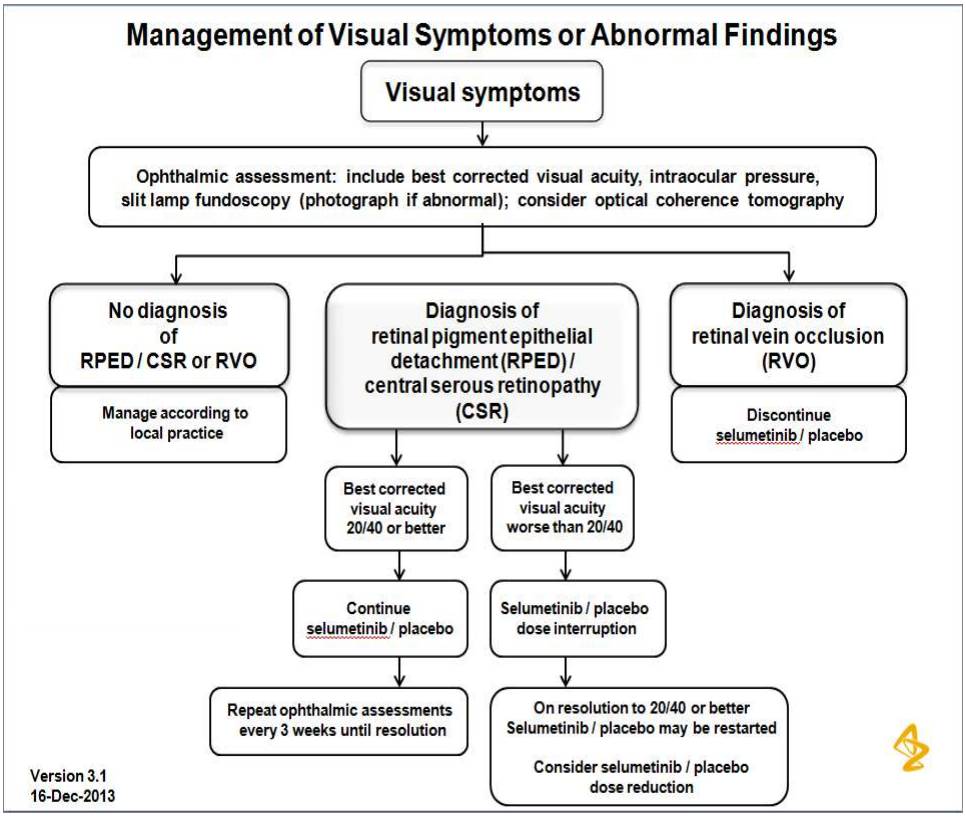
Guidance for management of patients with dyspnoea*

*** Not considered related to disease under study**

† Includes selumetinib/placebo or combination treatment, as appropriate



- **Oxygen saturation** will be measured at baseline and again following any respiratory event.
- **Visual disturbances** - Patients experiencing visual disturbances should undergo a complete ophthalmologic examination which includes the following:
    - Visual acuity
    - Visual fields, if feasible
    - Fundoscopic exam
    - See Table 7 and algorithm below



5.4.2 Febrile Neutropenia

Febrile neutropenia should be managed according to the local institutional guidelines. Measures include laboratory testing, blood and urine cultures, and institution of broad spectrum antibiotics.

5.4.3 Diarrhea

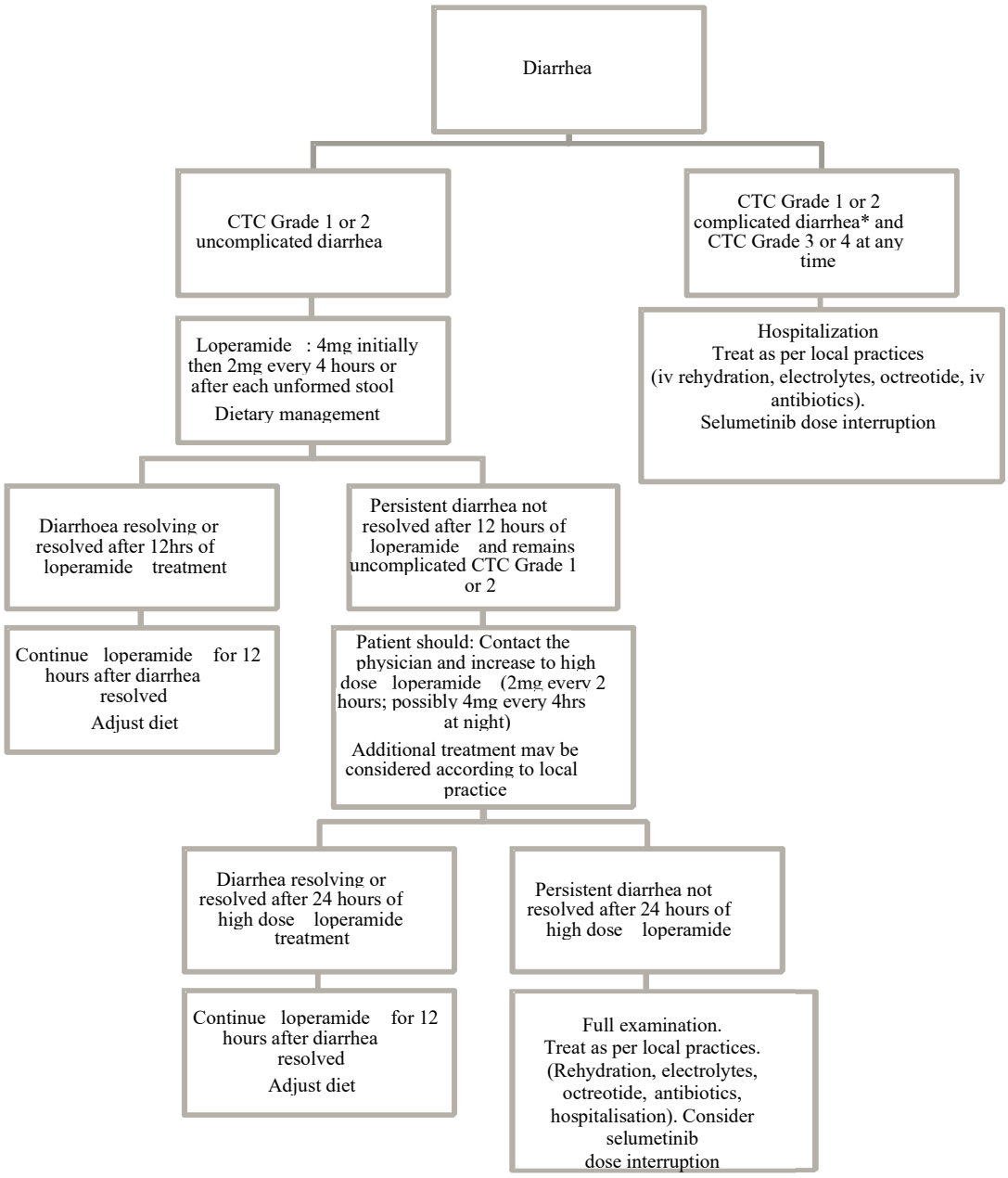
Patients should be advised to drink plenty of water or rehydration fluids to avoid dehydration if diarrhea occurs. Should diarrhea occur follow the loperamide dosing guidelines in Table 6 immediately following first dose of diarrhea. Patients should be given dietary advice in case of diarrhoea (e.g. BRAT [bananas, rice, apple sauce, toast, plain pasta] diet; readily digestible food; avoidance of lactose-containing products, fried, fatty or spicy food) and increase fluid intake. Refer to Table 7, Section 6.2 when modifying the selumetinib dose in response to diarrhea.

Table 6

Weight Specific Guidelines for Therapeutic Use of Loperamide			
Weight (kg)	Initial (Loading) Loperamide dose (mg)	Subsequent daytime loperamide dose	Subsequent nighttime loperamide dose
8-10	1	0.5mg q 3h	0.75mg q 4h
10-20	1	1mg q 3h	1mg q 4h
20-30	2	1mg q 3h	2mg q 4h
30-42	2	1mg q 2h	2mg q4h
> 42	4	2mg q 2h	4mg q 4h

Please see algorithm below when assessing diarrhea:

Guidance for the management of patients with diarrhea



*Diarrhea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension

If Grade 1/2 diarrhea: Full clinical and laboratory evaluation including ruling out infectious causes (Clostridium difficile or viral causes).

If Grade 3/4 diarrhea: Consider hospitalization if needed, full clinical and laboratory evaluation

including infectious evaluation. Consider starting octreotide. Hold selumetinib until < tolerable grade 2. Continue loperamide.

5.4.4 Dermatology/Skin Toxicities/Paronychia

The use of medications for the supportive care of rash is permitted, provided that compliance with Section 5.4 regarding concomitant medications is observed. Early initiation of treatment for rashes is strongly recommended to minimize the duration and severity of the adverse event.

On day 1 of treatment with selumetinib:

- Recommend to use skin moisturizer (alcohol free) at bedtime.
- Avoid excessive exposure to sunlight. Use sunglasses and sunscreen.
- Use of topical retinoids or benzoyl peroxide is not recommended.

For adults with grade 1 rash: Apply a mild / moderate strength topical steroid and/or topical antibiotic.
For adults with grade 2 rash: Apply a moderate strength topical steroid and consider an oral antibiotic.
For adults with ≥ grade 3 rash or a grade 2 rash considered to be intolerable: Hold selumetinib. Apply moderate strength topical steroid and consider an oral antibiotic. If an infection is suspected, consider other broad-spectrum antibiotic cover. Also consider referral to a dermatologist (and manage rash per recommendation). If rash improves to grade 2 or less, restart selumetinib at reduced dose.

For both adult and pediatric subjects, the following guidelines have been found to be useful:

Acneiform rash:
Experience with acneiform rash in the pediatric studies to date suggests that topical clindamycin gel or lotion applied BID, rather than steroids, is the most helpful for pustular rash (typically seen in the older child/adolescent). In severe cases, semisynthetic oral tetracyclines such as doxycycline or minocyline may also be useful for older children and adolescents, but should be avoided in children younger than 8 years old because of risk to tooth development.

Eczematous rash/xerosis:
Eczematous/dry skin rash and other macular (non-acneiform) rash should be treated with a moisturizer such as Cerave or Eucerin. A low potency topical steroid may also be used if symptomatic. Ketoconazole shampoo should be used for any rash involving the scalp.

Paronychia:
For patients who do not undergo drainage, silver nitrate may be used, as well as topical bactroban, steroids, and/or antifungals. Silver nitrate is only of value when there is open inflamed skin or granulation tissue (e.g. pyogenic-granuloma-like lesions). If the periungual skin is swollen but intact (whether infectious or non-infectious), silver nitrate is not recommended. Patients should be cautioned to avoid trauma to the area. Podiatry consult may be considered for partial nail removal.

Patients who undergo incision and drainage and are found to have no infectious organisms on culture, should be treated as above. If infection is identified, patients may be treated with systemic antibiotics (oral tetracyclines).

If paronychia recurs or develops in other fingers or toes, Flurandrenolide (e.g. Cordran) tape or topical steroid cream such as triamcinolone can be used in the morning and Bactroban and Nizoral topical ointments in the evening.

Oral Care:

Prevention, early diagnosis and management of stomatitis may reduce the need for dose interruption and / or reductions of the study medications due to severe stomatitis and so allow the patient to continue on the study drugs. It is strongly recommended that patients receive advice regarding daily oral health care regimes, both before and during treatment.

Patients with a healthy mouth may use non-alcoholic mouthwash several times (4 to 6 times daily, or according to the instructions) daily, e.g. after each meal, during the study.
Saline mouthwashes (Sodium chloride 0.9%) should be preferred in cases of stomatitis, and should be used at a different time to toothbrushing, e.g. after tea.
Use of a mouthwash immediately after selumetinib intake is recommended.
The tongue can be gently brushed (if not sore) with a soft toothbrush.
Patients with, or at risk of stomatitis should not use commercial / over-the-counter mouthwashes because of the alcohol content and astringency. Chlorhexidine mouthwashes are not recommended for the treatment of established stomatitis.
The mouth should be regularly inspected by the patient and healthcare professionals.

Smoking should be strongly discouraged; patients should be offered help with smoking cessation if necessary in the form of nicotine replacement therapy or referral to smoking cessation services.

A high alcohol intake should be discouraged and patients advised to avoid painful stimuli such as spicy foods, hot food and drink.

Teeth should be brushed twice daily with a fluoride toothpaste and soft toothbrush, in the morning before breakfast and last thing in the evening before bed, about 30 minutes after eating. Toothbrush should be replaced regularly at least every 3 months but patients with stomatitis should change their toothbrush every 4 - 6 weeks.

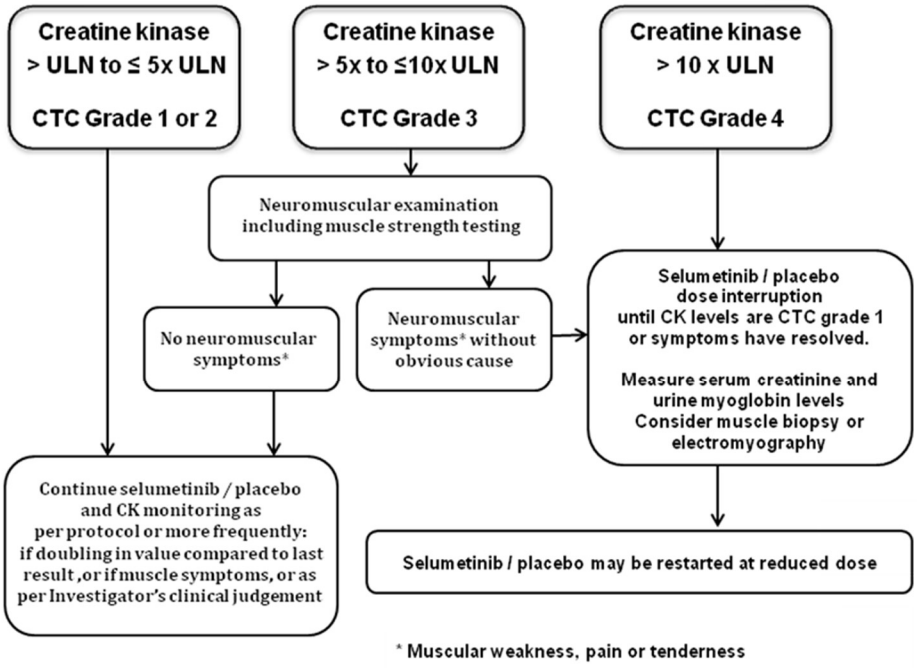
- Use of soft toothbrush is recommended
- Dental floss should be used once daily (caution in patients with coagulopathies including a low platelet count)

In the event of sore mouth or stomatitis:

- Consider treating stomatitis at an early stage (CTCAE grade 1) or as soon as the patient complains of a sore mouth.
- Consider using oral topical analgesic anaesthesia with or without topical steroids,

antiviral and/or antifungal medications depending on the patient's clinical condition and the local standard medical practice.

5.4.5 Elevated CPK: To reduce possible consequences associated with CK elevation that may be arising from a muscular source, the management guideline described below should be followed:



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5.4.6 Pneumocystis jiroveci pneumonia (PJP) prophylaxis
The use of medication (i.e., Bactrim) for PJP prophylaxis in patients is recommended, but is at the investigator's discretion.

5.4.7 Neurosurgical Procedures
If a neurosurgical procedure is required for a reason other than tumor progression (i.e. the onset of hydrocephalus), these procedures should be documented, but will not constitute criteria for declaring the patient "off therapy". Given the potential for the drug to affect wound healing, selumetinib should be held until the patient is clinically stable and has recovered from the acute effects of surgery.

5.4.8 Concomitant Therapy
Other anti-cancer or experimental agents are not permitted.

5.5 Duration of Therapy
In the absence of treatment delays due to adverse event(s) or disease progression, treatment may continue for 26 courses (approximately two years) or until one of the Off Treatment Criteria found

in Section 5.6 applies.

During the second year of treatment, procedures consistent with good clinical care will continue. Patients will be seen monthly for medical history, physical exam (including height, weight, vital signs, and performance status), neurologic exam, dates of drug administration, relevant laboratory evaluations and routine neuro-imaging assessments. Therapy-related events will be recorded per standard assessments, including adverse events, date of disease progression, date of last follow up, date patient goes off treatment and date off study. Please review the table in Section 10 of the protocol for the required assessments and intervals. All patients must discontinue treatment with selumetinib following the completion of 26 courses of treatment.

5.6 Duration of Follow Up

Discontinuation of Treatment

At the discontinuation of treatment, the "Off Treatment Date" is to be recorded in the CRF and is to be consistent with the reason given for going off treatment. The "Last Treatment Date" is defined as the last date that the patient received protocol based therapy. Date of "off treatment" must be the greatest of the date of last treatment, date of procedure, date of patient assessment, notification of patient/family decision, or decision made by the physician that resulted in the patient being taken off protocol treatment. The reason for discontinuation of treatment must be documented by the attending investigator in the medical record and recorded in the CRF. The "Off Treatment Date" and the "Last Treatment Date" should be the same for patients that complete all protocol defined treatment.

Patients will be considered Off Treatment for the following reasons:

5.6.1 Development of unacceptable toxicity as outlined in Section 5.2.1 that does not resolve within 14 days.

5.6.2 Non-compliance with study guidelines

5.6.3 Progressive disease, as outlined in section 11.1 and 11.2

5.6.4 Development of a medical or psychiatric illness, that in the investigator's judgment renders the patient incapable of further therapy on this protocol

5.6.5 The patient, parent or legal guardian refuses further treatment on this protocol

5.6.6 Pregnancy

5.6.7 Completion of maximum number of courses of treatment with selumetinib

Patients will be monitored every 6 months for 2 years after protocol treatment. Ongoing AE's should be monitored as per section 7.4.3. Additionally, patients will be followed for initiation of subsequent therapy for NF2, selumetinib related adverse events (including cardiac toxicities), date of disease progression, date of last follow up, and date of death.

Patients who are off protocol therapy must be followed until an Off Study Criterion is met. Ongoing AE's should be monitored as per section 7.4.3.

5.7 Criteria for Removal from Study

The date and reason for the patient coming off study must be documented in the CRF.

5.7.1 Patient determined to be ineligible (Treatment with selumetinib was never started).

5.7.2 Patient determined to be ineligible (Treatment with selumetinib WAS started).

These patients must be observed for 30 days following date deemed ineligible. All AE's must be recorded in that 30-day period.

5.7.3 Patient, parent, or guardian withdraws consent for continued participation.

5.7.4 Patient death while on study. The IRB, Sponsor, and FDA must be notified as per Section 7

5.7.5 Patients removed from treatment for progressive disease (PD) be observed for 30 days following last dose of selumetinib.

5.7.6 Commencement of additional anti-cancer therapy

5.7.7 Completion of protocol defined follow up

6 DOSING DELAYS/ DOSE MODIFICATION

6.1 Notification of Study Chair

The study chair or co-chair must be notified of any dosage modifications, prior to the implementation of the dose modification

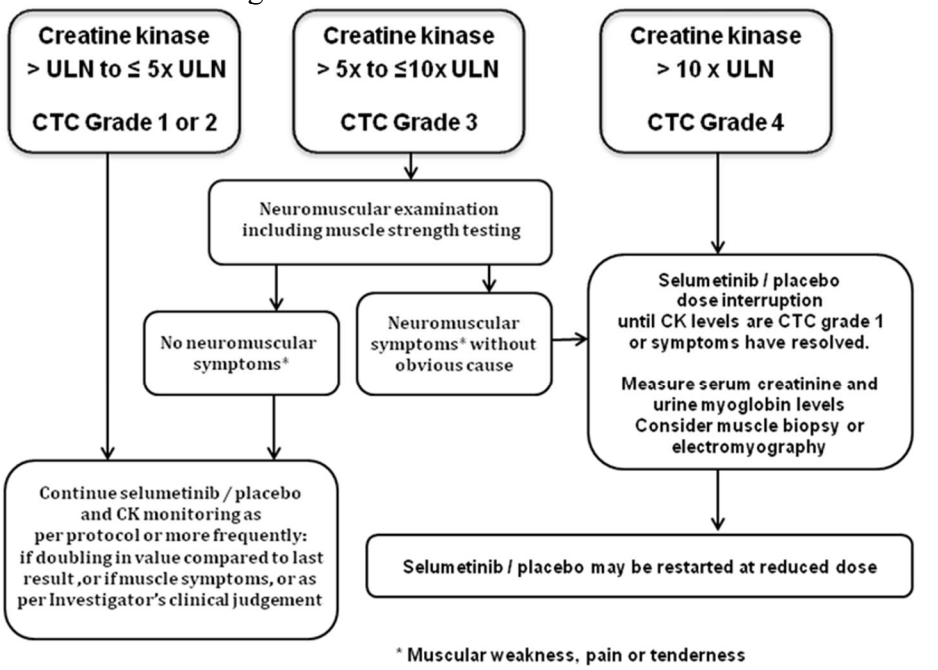
6.2 Hematologic and Non-Hematologic Adverse Events and Management

Table 7

Event	AE Grade or Observation	Dose Modification
Dermatology/Skin	Grade 1 or 2	Maintain dose
	Intolerable Grade 2; Grade 3 or 4	Hold selumetinib until ≤ tolerable grade 2; reduce one dose level and resume treatment. Skin care guidelines are located in Section 5.4.4.
	Grade 4	Patients with grade 4 rash (i.e. life threatening generalized exfoliative ulceration; erythemia multiforme/toxic epidermal necrolysis should be removed from study. Skin care guidelines are located in Section 5.4.4
Diarrhea (if anti-diarrheal treatment is ineffective)	Grade 1 or 2	See algorithm and guidelines in Section 5.4.3.
	Grade 3 or 4	See algorithm and guidelines in Section 5.4 Hold selumetinib until </= tolerable grade 2, on loperamide. Reduce 1 dose level and resume treatment.
Visual Disturbances - for any new or progressive vision problem(including but not limited to the following) Blurred Vision, Flashing Lights, Floater, Photophobia	Grade 1 or 2	Hold selumetinib until Eye exam is completed; If the Ophthalmology exam is normal and the toxicity resolves within 24hrs or an alternate cause for the vision problem is identified – restart selumetinib at the same dose level. See algorithm in 5.4.1
	Grade 3 or 4	Hold selumetinib until Eye exam is completed; If alternate etiology for vision change is identified, contact study chair to discuss restarting of selumetinib. See algorithm in 5.4.1
Hematologic With the exception of	Grade 1, 2, or 3	Maintain dose
	Grade 3 thrombocytopenia	Hold selumetinib until < grade 2, then

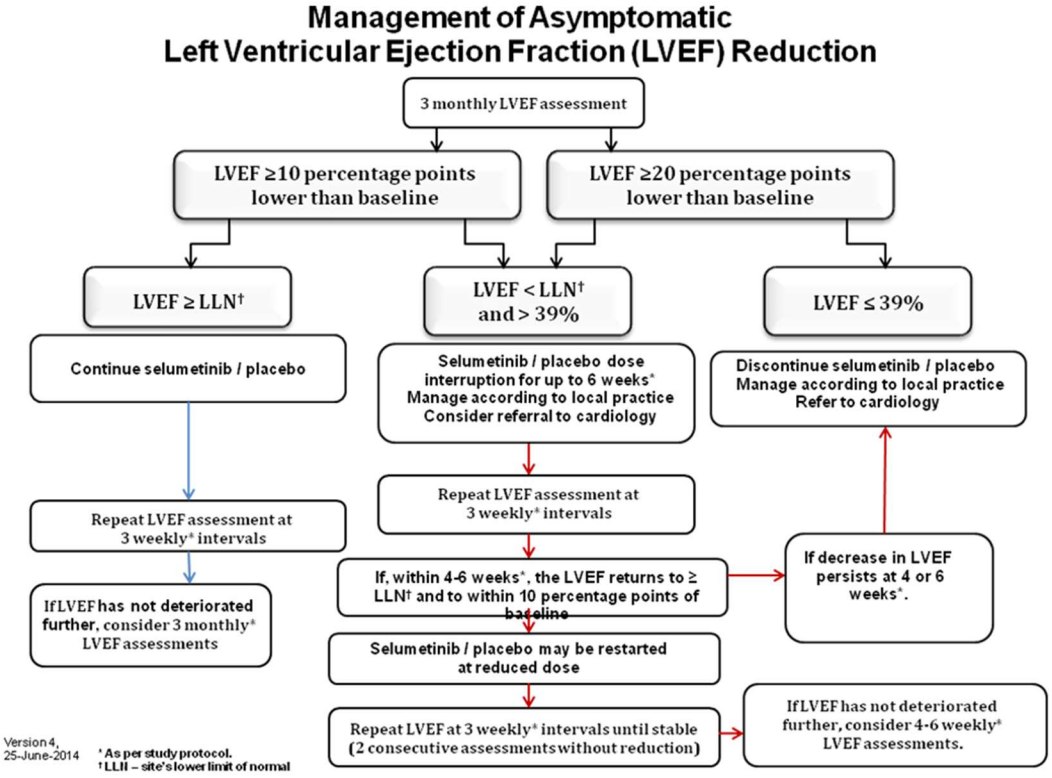
lymphopenia	associated with bleeding	reduce 1 dose level and resume treatment.
	Grade 4	Hold selumetinib until < grade 2, then reduce 1 dose level and resume treatment.
Liver Function • Serum bilirubin, AST, ALT	Grade 1 or 2	Maintain dose
	Grade 3	Hold selumetinib. If returns to levels meeting eligibility criteria within 7 days, then restart at the same dose.
	Grade 3 that does not return to meet eligibility criteria within 7 days , or Grade 4	Hold selumetinib until < grade 2, then reduce 1 dose level and resume treatment.
Other non-hematological toxicity	Grade 1 or 2	Maintain dose
	Grade 2 of concern (e.g., pulmonary, neurotoxicity, or intolerable stomatitis) Grade 2 that persists for >7 days and is considered sufficiently medically significant or intolerable by patients as to warrant treatment interruption and /or dose modifying	Hold selumetinib until < grade 2, then reduce 1 dose level and resume treatment.
	Grade 3 or 4	Hold selumetinib until < grade 1, then reduce 1 dose level and resume treatment.

Elevated CPK: Please see algorithm below



Version 3.0
12-Sept-2013

Cardiac Function: Please see algorithm below



6.2.1 Criteria for continued treatment after toxicity

The study chair or co-chair must be notified of any dosage modification prior to the implementation of the dose modification.

Dose de-escalations to dose level -1 are permitted. See Appendix D.

All patients who require dose de-escalation from dose level -1 must be taken off treatment.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting.

Adverse Events and Potential Risks for Selumetinib are listed below. Investigators may also refer to the most current version of the Selumetinib IB for additional expected AE's.

Adverse events will be managed according to local practice.

Expected Adverse Events

Likely (≥20% of patients)	**Less Likely (<20% to 3%)**	**Rare (<3%)**
• Rashes (all) • Rashes (acneiform) • Diarrhea • Nausea • Vomiting • Asthenic events • Peripheral edema • Dyspnoea • CK increased	• Dry skin • Stomatitis • Dry Mouth • Facial edema • Pyrexia • Blurred vision • Increased blood pressure • ALT/AST increased	• Paronychia • Hyperphosphatemia • Hypoalbuminaemia • Reduced LVEF • Retinal vein occlusion • Central serous retinopathy/ retinal pigment epithelial detachment

Grouped Term	MedDRA Preferred Terms
Rashes (all)	Dermatitis acneiform, Rash, Rash erythematous, Rash exfoliative, Rash macular, Rash papular, Rash maculo-papular, Folliculitis, Acne, Rash pustular, Rash pruritic, Rash follicular, Rash generalised, Rash morbilliform
Rashes (acneiform)	Dermatitis acneiform, Folliculitis, Acne, Rash pustular
Diarrhoea	Diarrhoea, Frequent bowel movements
Stomatitis (oral mucositis)	Stomatitis, Mouth ulceration, Oral mucosa erosion
Asthenic events	Fatigue, Asthenia
Facial and/or peripheral oedema	Oedema peripheral, Periorbital oedema, Face oedema, Oedema
Peripheral oedema	Oedema peripheral, Oedema
Facial oedema	Periorbital oedema, Face oedema, Eyelid oedema
Fatigue/asthenia	Fatigue, Asthenia
Pyrexia	Pyrexia, Body temperature increased
Dyspnoea	Dyspnoea exertional, Dyspnoea, Dyspnoea at rest
Increased blood pressure	Hypertension, Blood pressure increased, Diastolic hypertension, Systolic hypertension, Blood pressure systolic increased, Blood pressure diastolic increased
Increased aspartate aminotransferase or alanine aminotransferase	Alanine aminotransferase increased, Aspartate aminotransferase increased, Hypertransaminaseaemia
Febrile neutropenic events	Febrile neutropenia, Neutropenic infection
Neutropenic events	Neutropenia, Neutrophil count decreased
Retinal vein occlusion	MedDRA SMQ (narrow) Retinal disorders

Physeal dysplasia

A potential risk of effects on bone was identified from a nonclinical experiment. Based on this, pediatric studies of selumetinib should include bone growth assessment at regular intervals including clinical examination, growth chart monitoring and imaging (Section 10 for schedule). Children who show signs of physeal dysplasia at the time of selumetinib discontinuation should have a follow-up assessment after 30 days to evaluate the potential for reversibility.

7.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.2 Definitions

7.2.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

7.2.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.2.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.2.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results

in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

7.3 Documentation and Reporting of non-serious AEs or SARs

- For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.
- Adverse events grades 1 and 2 if the attribution is at least possibly related to selumetinib. Record all adverse events grades 3, 4 or result in death (Grade 5) (while on treatment or within 30 days of treatment), regardless of attribution on the case report forms.
- Baseline abnormalities: Any baseline (pretreatment) abnormalities observed from the time treatment consent is obtained to the start of trial therapy should be recorded on the case report form.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.4 SAEs or Serious SARs

7.4.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected.

7.4.2 Documentation and Sponsor Notification

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued. All SAEs or Serious SAR (including deaths) regardless of attribution will be recorded in the CRF. The Sponsor must be notified of any SAE or Serious SAR within 24 hours of learning of the event. These events (SAEs or Serious SARs) must also be documented within the CRF for that participant within 2 business days of notification of the Sponsor-Investigator/Study Chair or designee.

7.4.3 Documentation and Assessment

Once an AE is detected with a possible causal relationship to selumetinib, it should be followed until its resolution to baseline or until it is judged to be permanent and stable. Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, changes to the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy if documented by use of appropriate method (as in section 11.1) should not be reported as a serious adverse event unless results in death.

Deaths (while on treatment or within 30 days of treatment), regardless of attribution will be recorded on the case report forms and reported as an SAE.

Death due to progressive disease should be reported as Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps)-Other (Progressive Disease)" under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

7.5 Other Malignancy

7.5.1 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy) is to be reported as an SAE. A secondary malignancy is not considered a metastasis of the initial neoplasm.
Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia)
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

7.5.2 A Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy) does not need to be reported.

7.6 Reporting

7.6.1 IRB Reporting Requirements:

CCHMC IRB Reporting Requirements: Unexpected and related adverse events will be reported to the CCHMC IRB per institutional policies. The sponsor-investigator will report any unexpected life threatening event or death (grade 4 or 5) adverse event to the CCHMC IRB within 7 calendar days after the sponsor is made aware of the event.

Reporting of Protocol Violations/ Deviations and Unanticipated Problems: Any protocol violations, deviations, or unanticipated problems should be documented and reported according to CCHMC policy.

7.6.2 FDA Expedited Reporting requirements for studies conducted under an IND:
If the Sponsor- Investigator deems that an event is both a serious SAR AND unexpected, the Sponsor-Investigator is responsible for submitting the event to the IND (FDA) within 15 calendar days. If the Sponsor-Investigator is notified of an unexpected fatal or life-threatening SAR, the FDA is to be notified as soon as possible but in no case later than 7 calendar days after the Sponsor-Investigator's initial receipt of the information. A MedWatch Form 3500A will be completed and submitted to the IND (FDA) for expedited reporting requirements as outlined in 21 CFR 312.32. The MedWatch 3500a form can be accessed at http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

7.6.3 Reporting to Astra-Zeneca:
The IND Sponsor or designee will report all adverse events or adverse drug reactions subject to expedited reporting to Astrazeneca at the same time the report is submitted to the FDA. Astra-Zeneca will also be notified of unexpected, suspected serious adverse event to within 15 days.

8 AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7

Selumetinib (AZD6244)

8.1.1 Agent Information

Chemical Name: 6-(4-Bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide hydrogen sulfate\

Other Names: ARRY-142886; AR00142866; AR-142886-01); Selumetinib Classification: Mitogen-activated protein kinase (MEK) inhibitor

CAS Registry Number: 943332-08-9

Molecular Formula: $C_{17}H_{15}BrClFN_4O_3$. H2SO4 M.W.:555.7

Mechanism of Action: The RAS/RAF/MEK/ERK pathway is an important mediator of many cellular processes including proliferation, survival, differentiation, apoptosis, motility, and metabolism. This pathway is often aberrantly activated in human tumors due to the overexpression of activated K-RAS, mutant b-Raf, or other growth factor receptors. Selumetinib

is a selective mitogen-activated protein kinase (MEK) inhibitor. By inhibiting MEK, selumetinib inhibits ERK phosphorylation. Thus, selumetinib may inhibit oncogenic growth signaling in tumor cells by targeting the RAS/RAF/MEK/ERK pathway.

Formulation: Selumetinib hydrogen sulfate capsules contain 10 and 25 mg of selumetinib (expressed as free base) supplied as a series of size 4, plain, hydroxypropylmethylcellulose (HPMC) capsules in white high density polyethylene (HDPE) containers with foil-lined, induction-sealed, child-resistant closures. Each bottle contains 60 capsules. May be replaced with most current formulations, as determined by Astra-Zeneca.

Each capsule contains a dispersion of selumetinib hydrogen sulfate in d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS; a water soluble form of vitamin E).

Storage: Store the selumetinib hydrogen sulfate capsules at room temperature (20°C-25°C). Brief excursions are permitted between 15°C and 30°C. The temperature of shipments of 10mg capsules must also be monitored to ensure the temperature is within the required limits (below 30C). Data is available to support the 10mg capsule being stored at 30C or less and that performance could be reduced if stored at temperatures higher than 30C.

25mg capsules are stored at room temperature; however temperature monitoring is not necessary for 25mg capsules.

Stability: Stability studies are ongoing.

Availability: Selumetinib hydrogen sulfate capsules are provided to CCHMC by Astra-Zeneca

Route of Administration: Oral. Take selumetinib on an empty stomach either 1 hour before or 2 hours after meals and should be taken with water only.

Potential Drug Interactions: CYP3A4 is the predominant isoform responsible for selumetinib oxidative metabolism with CYP2C19, CYP1A2, CYP2C9, CYP2E1 and CYP3A5 involved to a lesser extent. *In vitro* studies indicate that selumetinib also undergoes direct Phase 2 metabolic reactions to form glucuronide conjugates principally involving the enzymes UGT1A1 and UGT1A3. Selumetinib is primarily metabolized by CYP1A2 to N-desmethyl AZD6244 which is 3-5 fold more pharmacologically active than Selumetinib but circulates at ~7% of the parent. Based on clinical trials, concomitant medications that are strong inhibitors/inducers of CYP3A4 or fluconazole (strong CYP2C19 and moderate CYP3A4 inhibitor) should be avoided, if possible. A list of medications with the potential for interaction with selumetinib is available in APPENDIX C.

In vitro, selumetinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP2E1. In vitro, selumetinib is not an inducer of CYP3A4, CYP1A2 and CYP2B6.

In vitro studies suggest that selumetinib does not inhibit the breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), OATP1B1, OATP1B3, OCT2, OAT1, MATE1 and MATE2K at the recommended paediatric dose. A clinically relevant effect on the pharmacokinetics of concomitantly administered substrates of OAT3 cannot be excluded.

Based on *in vitro* studies, selumetinib is a substrate for BCRP and P-gp transporters but is unlikely to result in clinically relevant drug interactions at the recommended paediatric dose.

Vitamin E intake

Selumetinib capsules contain vitamin E in the form of TPGS, a water-soluble form of vitamin E, which acts as a formulation excipient. The maximum daily dose of vitamin E that a study subject may receive from selumetinib is approximately 270 mg/day. High doses of vitamin E have been reported to potentiate the anticoagulant activity of coumarins such as warfarin. Therefore, selumetinib should be administered with caution in patients who are also receiving concomitant coumarin anticoagulant medications. These patients should have their international normalized ratio [INR] monitored closely/ anticoagulant assessments conducted more frequently, and the dose of the anticoagulant should be adjusted accordingly.

In addition, the concomitant intake of supplemental vitamin E should be avoided in all subjects receiving selumetinib/placebo.

8.1.2 Agent Ordering and Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received using the NCI Drug Accountability Record Form (DARF).

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Correlative Studies

9.1.1 **Required: Assessment for MEK activation in pre-trial tumor material**

10 unstained slides of formalin fixed paraffin embedded tumor tissue will be collected from all patients who have pre-trial tumor material available. No biopsy will be performed for the purpose of this correlative study. This tumor tissue will be used to assess phopho-ERK (Western blot or ELISA), Ki-67 markers, blood vessel density, and MAPK activation markers (by whole-exome and RNA sequencing). With participant consent, tissue will be stored for future research.

Samples will be delivered to the Ratner Lab at Cincinnati Children's Hospital Medical Center.

Ratner Laboratory T7
240 Albert Sabin Way
Cincinnati, OH 45229
Phone: 513-636-3502

9.1.2 NF-QOL studies

NF-QOL will be mandatory for all patients eligible to complete the questionnaire. See Appendix G. For patients under the age of 16 years of age, the patient will complete the NFTI-QOL in

collaboration with the parent proxy. Patients 16 and older will complete the questionnaire independently.

9.1.3 Special Studies - Neuroimaging Studies

Patients will have MRI brain and spine with and without contrast performed prior to initiation of therapy, after courses 3, 6, 9, 12, 16, 20, 26 until progression or end of therapy. MRI spine should be performed at the same time when obtaining MRI Brain when clinically indicated.

Stratum 1 patients: Volumetric measurements of VS: Traditionally, VSs have been measured using either 1-dimensional measurements (in the long axis) or 2-dimensional measurements (calculated by taking the square root of the product of the short axis-long axis measured to the plane perpendicular to the face of the temporal bone). However, the irregular shape of VSs, as determined by the unique anatomy of the IAC and cerebellopontine angle, makes it difficult for linear measurements to accurately and fully represent growth for the entire tumor. As a result, VS growth may be underestimated by linear measurement criteria. Semi-automated volumetric analysis overcomes these limitations since it uses data from 3 dimensions. The coefficient of variation (COV) ranges from 0.6% to 6.8% and is generally below 5% for lesions greater than 1 cc.[12] Volumetric analysis not only better reflects tumor size, but also allows accurate detection of smaller changes in tumor size compared to standard solid tumor response criteria (e.g., RECIST criteria). This ability to detect small changes in size is critical for tumors with slow growth rates such as VS, and, when used in clinical trials, helps limit exposure to potentially toxic and/or inactive agents. Trials for NF- related tumors, such as plexiform neurofibromas, are now routinely using volumetric changes as the primary endpoint, typically choosing a 20% increase for progression and 20% decrease for radiographic response.[45]

10 STUDY CALENDAR

	Pre-therapy	Courses 1-12[H]	Courses 13-26[H]	Completion/ Discontinuation Of Treatment
PHYSICAL ASSESSMENTS				
Medical history	X	X[A]	X	X
Physical exam /height/weight	X	X[A]	X	X
Vital signs	X	X[A]	X	X
Performance status	X	X[A]	X	X
Neurologic exam	X	X[A]	X	X
Smoking Status	X			
Hearing evaluation (stratum 1)[#]	X	X[C]	X[C]	
LABORATORY EVALUATIONS				
CBC - WBC, HgB, Hct, Platelets, ANC, ALC [B]	X	X[A]	X[A]	X
PT and INR for those patients on warfain		X	X	
Serum Chemistry - Sodium, Potassium, Bicarbonate, Chloride, Calcium, BUN, Creatinine, Glucose, Phosphorous, Magnesium, Albumin, Total Protein[B]	X	X[A]	X[A]	X
SGPT (ALT), SGOT(AST), Alkaline phosphatase, Total Bilirubin[B]	X	X[A]	X[A]	X
CPK [**]	X	X[A]	X[A]	
Serum or urine pregnancy test (for females of childbearing potential)	X	X[A]	X[A]	
Echocardiogram (ECHO)	X	X[C]	X[C]	
12-lead EKG	X			
Ophthalmology evaluation	X[D]	X[D]	X[D]	X
Pulse Oximetry	X			
Chest X Ray	X[E]			
Growth plate assessment	X	X[C]	X[C]	
IMAGING ASSESSMENTS				
Brain MRI	X	X[C]	X[C]	X
Spine MRI	X	X[C, F]	X[C, F]	X[F]
CORRELATIVE STUDIES				
NF1-QOL	X	**Every 3 courses**	**Every 4 courses**	
Pre-trial tumor materials (if available)	X			

	Pre-therapy	Courses 1-12[H]	Courses 13-26[H]	Completion/ Discontinuation Of Treatment

A. To be done prior to each course. See Section 5.3. Height does not need to be recorded for patients >18 years of age after initial measurement. Childbearing potential are those female patients who have reached menarche.
- Audiology will include measurement of pure tone thresholds and determination of word recognition scores
B. To be done more frequently throughout the duration of treatment if required to monitor toxicities.
C. To be done prior to initiation of therapy, after courses 3, 6, 9, 12, 16, 20, 26 until progression or end of therapy. The assessment is a tibial x-ray (AP and lateral views) of the right knee. If abnormalities are detected on routine X-rays, MRI scan of both knees should be performed. **Growth plate assessments should be done for patients under the age of 18 only, unless growth plate closure is documented.**
D. Baseline and following any visual disturbance during treatment. See section 5.2
E. To be done if pulse oximetry is < 95% or if clinically indicated during treatment. See section 5.2
F. MRI Spine should be done at the same time points as the standard MRI brain, if clinically indicated.
G. Formalin fixed paraffin embedded tumor tissue will be collected from all patients who have pre-trial tumor material available
H. All evaluations to be completed within 7 days of anticipated start date of the next course.

** Please note that Grade 3 asymptomatic elevations of CPK do not require a dose reduction

11 MEASUREMENT OF EFFECT

11.1 Hearing Response Criteria (Stratum 1 only)

Hearing is monitored in clinical practice by measuring pure tone thresholds, word recognition scores, brainstem auditory evoked responses (BAERs), and otoacoustic emissions (OAEs).

Pure tone thresholds measure the minimum sound level that an ear can perceive. Thresholds are typically measured at octaves and half-octaves from 250 Hz to 8000 Hz. An average of thresholds at 500, 1000, 2000 and 4000 Hz (PTA) is recommended as a standard outcome measure by the American Academy of Otolaryngology, Head and Neck Surgery (AAO-HNS) for reporting in cases of VS.

Word recognition scores measure the ability to recognize (as opposed to detect) auditory information. Patients are presented a list of 50 words at a fully audible level and the percentage identified correctly is the score. This study will use full 50-item monosyllable lists and standardized recordings.

Because tumors associated with NF2 have benign histology, overall survival is not an appropriate endpoint for clinical trials in this condition. Instead, the goal of treatment is to minimize neurologic morbidity (including hearing loss) and to defer surgical treatments that may cause iatrogenic dysfunction. For this reason, hearing function is the most important way to monitor the activity of new agents designed to treat VSs.

Word recognition is the measure most closely associated with daily hearing function since it measures the ability to comprehend speech. If word recognition quality improves, the patient can converse successfully, even if a hearing aid is needed to make sounds sufficiently loud. Statistical methods have been developed to determine significant changes in this measure. Word recognition scores represent summary scores from a collection of binary endpoints (correct/incorrect responses) and thus follow a binomial distribution (e.g., non- Gaussian

distribution). Although it is tempting to use a set change in word recognition score (e.g., fifteen percentage points) as a clinical response, this approach is inappropriate given the binomial model of variance. A more rigorous approach involves the use of the 95% (p=0.05) critical difference table[44]. The 95% critical differences for 50-word lists as proposed here have been used in previous studies[45] and in clinical trials evaluating the effect of drug treatment on hearing.

11.1.1 Hearing Response (HR): **Improvement in word recognition score above the 95% critical difference, taking as reference the baseline word recognition score (APPENDIX E)**

11.1.2 Stable Hearing (SH): **Persistence of word recognition score within the 95% critical difference, taking as reference the baseline word recognition score (APPENDIX E)**

11.1.3 Progressive Hearing Loss (PHL): **Decline in word recognition score below the 95% critical difference, taking as reference the baseline word recognition score (APPENDIX E)**

Duration of hearing response: The duration of hearing response (HR) is measured from the time that measurement criteria are met for HR until the first date that the word recognition score decreases beneath the upper limit of the 95% critical difference of the baseline word recognition score.

Duration of stable hearing: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the word recognition score recorded at baseline

11.2 Radiographic Tumor Response Criteria

11.2.1 Stratum 1

Stratum 1: Response and progression for vestibular schwannomas will be evaluated in this study using the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria proposed by Widemann and colleagues for neurofibromatosis-associated lesions..[46] Response and progression for stratum 1 will not be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) or by MacDonald Criteria, since they may underestimate progression in these irregularly shaped tumors. However, linear measurements utilizing RECIST will be collected as part of the trial for comparison with volumetric measurements. Linear measurements utilizing RECIST will be used for non-target lesions on stratum 1.

Target lesions. Investigators should identify a single target lesion in all subjects. The target lesion in this study is the progressive VS (i.e. the lesion that is enlarging or is associated with hearing loss) that led to registration in the protocol. In cases where subjects have a single ear with hearing, the target lesion should be the enlarging VS ipsilateral to the hearing ear. In cases where subjects have hearing in both ears, the target lesion should be the tumor associated with word recognition score < 85% and is growing the fastest or is causing the most rapid hearing loss. In cases where both VSs are associated with word recognition < 85% and progressing equally rapidly, the target lesion should be the larger of the two tumors on imaging. Target lesions should be identified at baseline and measured using volumetric analysis of the baseline MRI scan. The baseline volumetric MRI scan will be used as reference for comparison of all

future MRI scans to characterize the objective tumor response.

Non-target lesions. Non-target lesions in this study include VSs contralateral to the target lesion (if present).

Volumetric analysis of MRI scans should be performed on sequences with fine cuts through the internal auditory canal

NOTE: Histologic confirmation of tumor type is not required.

11.2.1.1 Evaluation of Target Lesion
Target lesions defined in section 11.2.1 (REiNS criteria)

Radiographic Response (RR)
At least a 20% decrease in the volume of the target lesions, taking as reference the baseline volume.

Progressive Disease (PD)
At least a 20% increase in the volume of the target lesion, taking as reference the lower volume during treatment

Stable Disease (SD)
Does not meet criteria for radiographic response or for progressive disease.

11.2.1.2 Evaluation of Non Target Lesions
Non-Target lesions defined in section 11.2.1 (RECIST criteria)

Complete Response (CR*)*: Disappearance of all non-target lesions and normalization of tumor marker level

Incomplete Response/ Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Duration of radiographic response: The duration of radiographic response is measured from the time measurement criteria are met for RR until the first date that progressive disease is objectively documented (taking as reference for progressive disease the lowest tumor volume during treatment).

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the measurements recorded at baseline.

11.2.2 Stratum 2 Tumor Response Criteria:
Stratum 2 Response and progression for non-VS tumor by MacDonald Criteria.

11.2.2.1 Complete Response

Complete disappearance on MR of all enhancing tumor and mass effect, on a stable or decreasing dose of corticosteroids (or receiving only adrenal replacement doses), accompanied by a stable or improving neurologic examination, and maintained for at least 8 weeks.

11.2.2.2 Partial Response

Partial Response (PR): Greater than or equal to 50% reduction in tumor size by bi-dimensional measurement, as compared with the baseline measurements, on a stable or decreasing dose of corticosteroids, accompanied by a stable or improving neurologic examination, and maintained for at least 8 weeks.

11.2.2.3 Stable Disease

Stable Disease (SD): Neurologic exam is at least stable and maintenance corticosteroid dose not increased, and MR/CT imaging meets neither the criteria for PR nor the criteria for Progressive Disease. If this category is to be reported as of possible clinical benefit, Stable Disease status must be maintained for 6 courses.

11.2.2.4 Progressive Disease

Progressive Disease (PD): Progressive neurologic abnormalities or worsening neurologic status not explained by causes unrelated to tumor progression (e.g., anticonvulsant or corticosteroid toxicity, electrolyte disturbances, sepsis, hyperglycemia, etc.), OR a greater than 25% increase in the bi-dimensional measurement, taking as a reference the smallest disease measurement recorded since the start of protocol therapy, OR the appearance of a new lesion, OR increasing doses of corticosteroids required to maintain stable neurological status or imaging AND/OR unequivocal radiological progression of existing non-target lesions.

12 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

12.1 Regulatory and Compliance Monitoring

Monitoring of clinical studies is a continuous, ongoing review of the conduct of the trial to ensure that it is conducted, documented, and reported in accordance with the IRB-approved protocol, Title 21 CFR, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and applicable regulatory requirements of the sponsor, CCHMC.

Monitoring will include review of central elements defined as:

- Data related to primary study endpoints;
- Appropriateness of consent documentation;
- Protocol eligibility;
- Protocol compliance;
- Timeliness of data entry, including the reporting of adverse events (AE/SAR) and serious

advent events (SAESSAR) as events are reported;
- Appropriateness of treatment delivery;
- Modifications in dose or timing;
- Investigational Drug Service (IDS) compliance (drug accountability);
- Documentation of response assessment measures;
- Essential regulatory documentation; and
- Site Investigator supervision of overall conduct of the study.

Specifically, source document verification of eligibility for all enrolled study participants including verification of appropriate documentation of consent will be performed. 100% Source Document Verification (SDV) of case records will be conducted for the first 2 participants enrolled on the study, as well as, 4 - 5 randomly selected participants thereafter, by comparing data in the source documents to data entered in the Case Report Forms (CRF). In addition, 100% SDV may be performed for pivotal clinical parameters related to primary study endpoints.

Regulatory and compliance monitoring will be a combination of on-site visits (scheduled to occur at least annually or more frequently based on registration, the degree of risk or severity of monitoring findings, and other study management issues) along with off-site continuous (remote) efforts.

12.2 Responsibility for Data Submission
All participant data will be recorded on case report forms by CCHMC study personnel.

12.3 Data and Safety Monitoring Plan
This study will be reviewed in accordance with the CCHMC Cancer Center Data and Safety Monitoring Plan for Phase 1, Pilot, and Phase 2 Studies. In brief, the role of the CCHMC Cancer Center Data and Safety Monitoring Board (DSMB) is to protect the interests of participants and the scientific integrity of clinical trials. The DSMB consists of individuals with recognized expertise in oncology, radiation therapy, conduct of clinical trials, and biostatistics. The DSMB meets a minimum of twice per year. Approximately 4 weeks before each meeting of the DSMB, the study chair and/or designee will be responsible for preparing study reports for review by the DSMB. The DSMB will provide recommendations to change the study or to continue the study unchanged.

12.4 Oversight by the Sponsor Investigator/Study Chair
The Sponsor Investigator/Study Chair along with the CCHMC coordinating center will review trial progress regularly.

This ongoing review by the Sponsor Investigator/Study Chair or designee will include verification of trial eligibility and the appropriateness of documentation of the informed consent process for all patients to confirm registration into the study prior to the first dose of investigational agent. In the event that the study chair is not available, an appointed designee will review eligibility to confirm registration.

In addition, the Sponsor Investigator/Study Chair and/or designee will review participant trial progress in real-time including participant evaluability, dose modifying toxicities, and serious adverse events.

12.5 Privacy and Confidentiality

No information provided from individual patient records may be discussed with anyone other than those individuals involved in the research study or clinical care. Data may not be released in any form except as stated in the agreement or regulations. Each participant enrolled will, from that point forward, be identified by a unique identifier (study number). This study number will also be used for any research specimens collected and shipped to analysts outside CCHMC (if applicable).

All research records generated will be stored in a locked office area, only accessible to study personnel, and/or on a secure CCHMC network drive and/or the coordinating centers clinical trial management system (OnCore). Clinical information will be accessed, according to HIPAA requirements, by study personnel to complete study documents, as needed.

12.6 Record Retention

Study records will be maintained per applicable regulatory requirements and institutional policies and procedures.

13 STATISTICAL CONSIDERATIONS

13.1 Evaluability

13.1.1 Evaluability for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with selumetinib.

13.1.2 Evaluability for Response

All patients who receive study drug will be considered evaluable for response.

Each participant should be assigned one of the following categories: 1) hearing response, 2) stable hearing, 3) progressive hearing loss, 4) progressive disease 5) tumor response 6) early death from NF2-related condition, 7) early death from toxicity, 8) early death because of other cause.

13.2 Study Design/Endpoints

The primary endpoint for the Stratum 1 is hearing response at 24 weeks, defined as an improvement in word recognition score above the 95% critical difference, taking as reference the baseline word recognition score (Appendix E). This primary objective of the efficacy of selumetinib will be addressed according to a Simon two-stage design.[47] The first stage will consist of 9 subjects. If 0 of the 9 subjects have an efficacious response the study will terminate at the end of the first stage and the drug will be deemed ineffective. If 1 or more subjects have an

efficacious response, 8 additional subjects will be enrolled for the second stage. If both stages are completed and there are 3 or more efficacious responses then the drug will be considered successful, in the case of two or fewer desired responses the drug will be deemed ineffective.

The primary endpoint for the Stratum 2 is to estimate the sustained objective response rate (CR+PR). Stratum 2's primary objective of the efficacy of selumetinib will be also addressed according to a Simon two-stage design.[47] The first stage will consist of 9 subjects. If 0 of the 9 subjects have an efficacious response the study will terminate at the end of the first stage and the drug will be deemed ineffective. If 1 or more subjects have an efficacious response, 8 additional subjects will be enrolled for the second stage. If both stages are completed and there are 3 or more efficacious responses then the drug will be considered successful, in the case of two or fewer desired responses the drug will be deemed ineffective.

Using the described design, if the true probability of an efficacy is 0.05, then the probability of terminating at the end of the first stage (9 subjects) is 0.63. The total probability of concluding the drug is effective is 0.05. Under this low probability of efficacy the expected sample size is 12 subjects. If the true probability of an efficacy is 0.25, then the probability of terminating at the end of the first stage (9 subjects) is 0.075. Under this alternative probability of efficacy the power to conclude the drug is effective is 0.81. We anticipate that this trial will complete accrual in two years.

Simon Two-Stage Design

Simon[47] proposed a two-stage design primarily for use in phase 2 clinical trials where a single treatment arm is compared to a historical control. The stated objective of the design is to minimize the expected number of patients treated if the null hypothesis of no treatment effect is in true. Under this framework a design is conducted in two stages as follows. The total number of subjects that under consideration, N, is equal to the sum of the sample sizes from each stage, n_1 and n_2, respectively. After the first n_1 subjects (the first stage) a criteria is set so that if fewer than this pre-specified criteria exhibit a response to treatment the trial is terminated and the treatment is deemed **ineffective**; otherwise, the final n_2 subjects are enrolled. After the second stage a different pre-specified criteria is used such that if fewer than this value exhibit a response the treatment is deemed **ineffective**; if a greater than or equal number of patients exhibit a response to treatment the null hypothesis is rejected and the treatment is declared **effective**. The expected sample size = n_1 * (the probability of termination after the first stage under the null hypothesis) + n_2. The selection of the overall sample size, the sample sizes of each stage and the two pre-specified rejection/acceptance criteria are selected such that the expected sample size is minimized, a minimum power is obtained (usually around 0.8 or 0.90) and a desired level of significance (usual $\alpha \leq 0.05$) is satisfied. This is considered to be an ethical solution to phase 2 trial design since it minimized the number of patients administered an ineffective treatment. Lee and Feng (2005) reviewed 126 phase II trials where the design was reported and found that 25% percent used a Simon two-stage design.

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APPENDIX A Performance Scales

MODIFIED LANSKY SCORE (Score as 0 - 100)

A. Normal Range
- 100 = Fully active
- 90 = Minor restrictions in physically strenuous play
- 80 = Restricted in strenuous play, tires more easily, otherwise active

B. Mild to moderate restriction
- 70 = Both greater restrictions of and less time spent in active play
- 60 = Ambulatory up to 50% of time, limited active play with assistance/supervision
- 50 = Considerable assistance required for any active play; full able to engage in quiet play

C. Moderate to severe restriction
- 40 = Able to initiate quiet activities
- 30 = Needs considerable assistance for quiet activity
- 20 = Limited to very passive activity initiated by others e.g. TV)
- 10 = Completely disabled, not even passive play
- 0 = Unresponsive, coma

KARNOFSKY SCALE
- 100 = Normal; no complaints
- 90 = Able to carry on normal activities; minor signs or symptoms of disease
- 80 = Normal activity with effort
- 70 = Cares for self. Unable to carry on normal activity or to do active work
- 60 = Requires occasional assistance but able to care for most of his/her needs
- 50 = Requires considerable assistance and frequent medical care
- 40 = Disabled; requires special care and assistance
- 30 = Severely disabled; hospitalization indicated though death not imminent
- 20 = Very sick. Hospitalization necessary. Active support treatment necessary.
- 10 = Moribund
- 0 = Dead

APPENDIX B Medications that may cause QTc Prolongation

The following table presents a list of drugs that may prolong the QTc. Patients on these medications are excluded from the study.

Compound	Compound Half Life	Possible Washout Period - Hours	Possible Washout Period - Days
Alfuzocin	~10 hours		7
Amantadine	17 +/- 4 hours (10-25)		4
Amiodarone (cordarone)	58 days (15-142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepridil	42 hr (26-64)		10
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $T_{1/2}$=7-10 hour)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 +/- 7 hours		7
Cisapride	6 – 12 hour, up to 20 hour	60	
Clarithromycin	• Non linear PK3-4 hr (250mg Q12) 5-7 hr (500mg Q12)	36	
Cloroquine	6 to 60 days; mean 20 days		
Desipramine*	> 24 hours, wide interpatient variability		
Disopyramide	6.7 hr (4-10)	36	
Dofetilide	10 hr	48	
Dolesetron	8.1 hr		
Domperidone	7-8 hr	48	
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	
Erythromycin	* Each salt form has different Half life*		
Felbamate	20-23 hr		5
Flecainide	20 hr (12-27)		5
Foscarnet	87.5+/-41.8 hours *distribution and release from bone*		20
Fosphenytoin	12-29 hr		6
Gatifloxacin	7-14 hr	48	
Gemifloxacin	7 hours	48	
Grepafloxacin	16 hr		3
Halofantrine	6-10 days (variable among individual)		45
Haloperidol	18 +/-5 hr		5
Ibutilide	6 hours (2-12) * variable among subject*	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3
Isradipine	8 hours (multiple metabolites)	48	
Levofloxacin	6-8 hours	48	

Levomethadyl	Multiple compartment PK with active metabolite 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		
Compound	**Compound Half Life**	**Possible Washout Period - Hours**	**Possible Washout Period - Days**
Lithium	24 hour (10-50)		7
Mesoridazine	24-48 hours (animal study)		10
Methadone	15-30 hours		7
Moexipril/HCTZ	2-9 hour (include active metabolite) for moexipril; 5.6-14.8 hours for HCTZ	48	
Moxifloxacin	12 +/-1.3 hours		
Naratriptan	6 hours	36	
Nicardipine	~ 2 hour post IV infusion	12	
Nortriptyline*	> 24 hours, wide interpatient variability		
Octreotide	1.7 hours	12	
Ofloxacin	5 to 7.5 hours		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)		1 to 3
Pentamidine	6.4+/-1.3 hours	36	
Pimozide	55 hours		10
Procainamide	3-4 hour for PA and NAPA (active metabolite)	24	
Protiptyline*	> 24 hours, wide interpatient variability		
Quetiapine	6 hours	36	
Quinidine	6-8 hours in adult; 3-4 hours in children	36	
Quinine	4-5 hours		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T ½ =21-30 hours (extensive to poor metabolizer)		4
Salmeterol	5.5 hours (only one datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16-30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~34 hours in healthy; ~19 hours in Kidney transplant		7
Tamoxifen	5-7 days (biphasic)		30
Telithromycin	2-3 hr	24	
Thioridazine	20-40 hours (Phenothiazines)		7
Tizanidine	2.5 hours	12	
Vardenifil	4 to 5 hours		
Venlaflaxine	5 +/-2 hours for parent comp. 11+-2 hours for OVD (active metabolite)	60	
Voriconizole	6 hours; dose dependent		
Ziprasidone	7 hr	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	18	

APPENDIX C Potential Drug Interactions With Selumetinib

Changes to, or addition of, the following medications should be avoided, unless clinically indicated:

Strong inhibitors of CYP3A4 or fluconazole (strong CYP2C19/ moderate CYP3A4 inhibitor)
CYP3A4
Indinavir
Nelfinavir
Ritonavir
Clarithromycin
Itraconazole
Ketoconazole
Nefazodone
Saquinavir
Suboxone
Telithromycin
Aprepitant
Erythromycin
Fluconazole
Grapefruit juice
Verapamil
Diltiazem

Strong / moderate Inducers of CYP3A4
CYP3A4
Efavirenz
Nevirapine
Barbiturates
Carbamazepine
Glucocorticoids
Modafinil
Oxcarbazepine
Phenobarbital
Phenytoin
Pioglitazone
Rifabutin
Rifampin
St John's wort

Strong inhibitors of CYP3A4 or fluconazole (strong CYP2C19/ moderate CYP3A4 inhibitor)
CYP3A4
Troglitazone

When AZD 6244 is co-administered with compounds classified as inhibitors, increased plasma concentration of AZD 6244 is the potential outcome. The co-administration of „inducers“ would potentially lower plasma AZD 6244 concentrations.

(1) Gorski, et al. (2004). Clin Pharmacol Ther. 75:89-100.
(2) Saruwatari, et al. (2003). J Pharm Pharmacol. 55:1553-1559.

APPENDIX D: Dose Reduction Guide for Selumetinib

Body Surface Area (m^2)	**Selumetinib dose (mg)** Dose level 0		**First dose reduction** (mg) Dose level -1	
	am	pm	am	pm
0.55 to 0.69	10	10	10	Zero
0.7 to 0.89	20	20	20	10
0.9 to 1.09	25	25	25	10
1.1 to 1.29	30	30	25	20
1.3 to 1.49	35	35	25	25
1.5 to 1.69	40	40	30	30
1.7 to 1.89	45	45	35	30
1.9 to ≥2.0	50	50	35	35

For all patients, dosing will be based on BSA.

Dosing Table for AZD 6244 20 mg/m2 BID

Dose Level (mg/m^2 BID	BSA Adjusted Total Daily Dose (mg)	BSA Range		Morning Pills Required		Evening Pills Required	
		low	high	10 mg	25 mg	10 mg	25 mg
20 mg/m^2 BID	20	0.50	0.65	1	0	1	0
	30	0.66	0.81	2	0	1	0
	35	0.82	0.93	0	1	1	0
	40	0.94	1.06	2	0	2	0
	45	1.07	1.18	0	1	2	0
	50	1.19	1.31	0	1	0	1
	55	1.32	1.43	3	0	0	1
	60	1.44	1.56	3	0	3	0
	65	1.57	1.68	1	1	3	0
	70	1.69	1.81	1	1	1	1
	75	1.82	1.93	4	0	1	1
	80	1.94	2.06	4	0	4	0
	85	2.07	2.18	2	1	4	0
	90	2.19	2.31	2	1	2	1
	95	2.32	2.43	0	2	2	1
	100	2.44	2.56	0	2	0	2
	105	2.57	2.68	3	1	0	2
	110	2.69	2.81	3	1	3	1
	115	2.82	2.93	1	2	3	1
	120	2.94	3.00	1	2	1	2

APPENDIX E Hearing Response Guidelines:
Clinical criteria for definition of hearing response based on a 50-word hearing test. Upper and lower limits for the 95% critical differences for percentage scores are adapted from Thornton.[REF]

Baseline word recognition score (%)	95% critical difference (%)	Hearing Response (%)	Progressive hearing loss (%)
0	0–4	≥ 6	n/a
2	0–10	≥ 12	n/a
4	0–14	≥ 16	n/a
6	2–18	≥ 20	0
8	2–22	≥ 24	0
10	2–24	≥ 26	0
12	4–26	≥ 28	≤ 2
14	4–30	≥ 32	≤ 2
16	6–32	≥ 34	≤ 4
18	6–34	≥ 36	≤ 4
20	8–36	≥ 38	≤ 6
22	8–40	≥ 42	≤ 6
24	10–42	≥ 44	≤ 8
26	12–44	≥ 46	≤ 10
28	14–46	≥ 48	≤ 12
30	14–48	≥ 50	≤ 12
32	16–50	≥ 52	≤ 14
34	18–52	≥ 54	≤ 16
36	20–54	≥ 56	≤ 18
38	22–56	≥ 58	≤ 20
40	22–58	≥ 60	≤ 20
42	24–60	≥ 62	≤ 22
44	26–62	≥ 64	≤ 24
46	28–64	≥ 66	≤ 26
48	30–66	≥ 68	≤ 28
50	32–68	≥ 70	≤ 30
52	34–70	≥ 72	≤ 32
54	36–72	≥ 74	≤ 34
56	38–74	≥ 76	≤ 36
58	40–76	≥78	≤ 38
60	42–78	≥ 80	≤ 40
62	44–78	≥ 80	≤ 42
64	46–80	≥ 82	≤ 44
66	48–82	≥ 84	≤ 46
68	50–84	≥ 86	≤ 48
70	52–86	≥ 88	≤ 50
72	54–86	≥ 88	≤ 52

Baseline word recognition score (%)	**95% critical difference (%)**	**Hearing Response (%)**	**Progressive hearing loss (%)**
74	56–88	≥ 90	≤ 54
76	58–90	≥ 92	≤ 56
78	60–92	≥ 94	≤ 58
80	64–92	≥ 94	≤ 62
82	66–94	≥ 96	≤ 64
84	68–94	≥ 96	≤ 66
86	70–96	≥ 98	≤ 68
88	74–96	≥ 98	≤ 72
90	76–98	100	≤ 74
92	78–98	100	≤ 76
94	82–98	100	≤ 80
96	86–100	n/a	≤ 84
98	90–100	n/a	≤ 88
100	96–100	n/a	≤ 94

APPENDIX F – Participant Diary

STUDY: **DRUG:** **Amount (mL / # of pills):**

Patient initials/ID number: **Dose:** **Dose Frequency:** **Cycle Number:**

Week # **Date**														
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Time dose taken*														
Indicate reason for missed doses														
SIDE EFFECTS														
Nausea (see scale below)†														
Vomiting (# of times in 24 hr)														
Diarrhea (# of times in 24 hr)														
Constipation∞														
OTHER SIDE EFFECTS (list below)														

OTHER MEDICATIONS (Name)	**Dose**	**Frequency**	**Start Date**	**Stop Date**	**Reason for Use of Medication**

* If you miss a dose write "M" in the box.

† Rate nausea **mild** if you are able to eat and drink a reasonable amount, **moderate** if you can eat and drink but the amount is substantially decreased, or **severe** if you are unable to eat and drink.

∞ Indicate # of bowel movements/day

Parent/patient signature Date

APPENDIX G: NFTI-QOL (Neurofibromatosis 2 impact on quality of life)

SUBJECT IDENTIFIER: _____

INSTRUCTIONS FOR COMPLETING THE NFTI-QOL

Please complete the following information:

Age: _____ years

Gender: Male 1 Female 2 (please tick)

For each of the questions on the next page, please tick the one box that describes how you feel today

Usual activities include: work; housework; study; sport; social; family or leisure activities

Guy's NFTI-QOL

Q1. Do balance or dizziness problems stop you performing your usual activities?

- No balance problems or dizziness ☐0
- Balance or dizziness problems but no difficulties ☐1
- Balance or dizziness problems cause me some difficulties ☐2
- Balance or dizziness problems stop my usual activities ☐3

Q2. Do hearing problems stop you performing your usual activities?

- No hearing problems ☐0
- Hearing problems but no difficulty ☐1
- Hearing problems cause me some difficulty ☐2
- Hearing problems stop my usual activities ☐3

Q3. Does facial weakness stop you performing your usual activities?

- No facial weakness ☐0
- Facial weakness, but no difficulty ☐1
- Facial weakness causes some difficulty ☐2
- Facial weakness stops my usual activities ☐3

Q4. Do problems with your sight stop you performing your usual activities?

- No problems with sight ☐0

Sight problems, but no difficulty	☐1
Sight problems cause me some difficulty	☐2
Sight problems stop my usual activities	☐3

Q5. Do you have any problems in mobility and walking?

No problems in mobility and walking	☐0
Some difficulty but can manage on my own	☐1
Unable to walk around without some help	☐2
Unable to walk at all	☐3

Q6. Has your medical condition affected your role and outlook on life? (*e.g.*, confidence, vulnerability, relationships, caring for family, career, having children)

No effect or positive effect	☐0
Small negative effect	☐1
Moderately negative effect	☐2
Large negative effect	☐3

Q7. Pain; throughout our lives, most of us have had pain from time to time such as mild headaches, sprains and toothaches. Have you had pain *other than this* in the last week?

None	☐0
Mild pain	☐1
Moderate pain	☐2
Severe pain	☐3

Q8. Do you currently suffer from anxiety or depression?

No	☐0
Mild anxiety or depression	☐1
Moderate anxiety or depression	☐2
Extreme anxiety or depression	☐3

APPENDIX H Canadian Cardiovascular Society grading of angina pectoris

Grade	Description
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

Campeau Lucien. Grading of angina pectoris *Circulation* 1976;54:5223

Available on the Canadian Cardiovascular Society Website at www.ccs.ca

APPENDIX I New York Heart Association (NYHA) classification of heart disease

NYHA Class	**Symptoms**
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

New York Heart Association 1994
The Criteria Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th edition. Boston, MA: Little, Brown & Co; 1994:253-256.