Title: Pilot Study of the MEK1/2 inhibitor selumetinib (AZD6244 hydrogen sulfate) for adults with neurofibromatosis type 1 (NF1) and Cutaneous neurofibromas (CN)

Table of changes

This protocol has been updated to reflect the selumetinib pharmaceutical information regarding the capsule appearance and the product in-use period from the Pharmaceutical Management Branch. The specific changes to the protocol are described in the table below (page numbers refer to the clean pdf version of the study; additions are noted in ***bold italics*** and deletions are noted with a ~~strikethrough~~):

Protocol:

#	Section	Change	Rationale
1	Title page and Header	The version number and version date have been updated. Protocol Type / Version # / Version Date: Amendment / v***9***~~8~~.0 / ***1***~~0~~6 ***July*** ~~December~~ ***2021*** ~~2019~~	Administrative update
2	8.1 Selumetinib, Other Names 8.1 Selumetinib, Solubility	Correct current list of "Other Names" from Selumetinib hydrogen sulfate; ARRY-142886 to KOSELUGO, Selumetinib Hydr-sulfate; selumetinib sulfate; ARRY-142886. Other Names: ***KOSELUGO, Selumetinib Hydr-sulfate;*** ***s***~~S~~elumetinib ~~hydrogen~~ sulfate; ARRY-142886 Correct "Solubility" from 2.5 to 2.4. Solubility: Very low aqueous solubility (2.***4***~~5~~ mcg/mL at pH 7.4).	Updates to sub-section consistent with the PMB Pharmaceutical Data Sheet.

3	**8.1 Selumetinib, Section 8.1.1, Mode of Action**	Addition of (AZD6244 Hydrogen Sulfate) x2 to subsection paragraph. 8.1.1 Mode of Action: Selumetinib ***(AZD6244 hydrogen sulfate)*** is a selective mitogen-activated protein kinase (MEK) inhibitor. By inhibiting MEK, selumetinib ***(AZD6244 hydrogen sulfate)*** inhibits ERK phosphorylation, which may inhibit oncogenic growth signaling in tumor cells by targeting the RAS/RAF/MEK/ERK pathway. The RAS/RAF/MEK/ERK pathway is an important mediator of many cellular processes including proliferation, survival, differentiation, apoptosis, motility, and metabolism.	Updates to sub-section consistent with the PMB Pharmaceutical Data Sheet.

4	**8.1 Selumetinib, Section 8.1.2, How Supplied**	The How Supplied sub-section updates the supply of 10 mg and 25 mg capsules as banded and marked with "SEL 10" or "SEL 25" respectively. There is no change in formulation. Formatted as appropriate. 8.1.2 How Supplied: Astra~~-~~Zeneca supplies and ***PMB,*** CTEP, ~~NCI,~~ DCTD distributes selumetinib (AZD6244 hydrogen sulfate). The agent is supplied as ~~size 4~~ hydroxypropylmethylcellulose (HPMC) capsules available in 10 mg ~~(plain white)~~ and 25 mg ~~(blue)~~ strength***s,*** expressed as free base. Capsules are packaged in ~~white,~~ high density polyethylene (HDPE) containers with induction-seals and child-resistant closures. Each bottle contains 60 capsules with desiccant. • ***10 mg: white, opaque, size 4 hard capsule, banded and marked with "SEL 10" in black ink. The capsule shell contains hypromellose, carrageenan, potassium chloride, titanium dioxide, carnauba wax, and purified water. The capsule is imprinted with black ink that contains shellac, iron oxide black, propylene glycol and ammonium hydroxide.*** • ***25 mg: blue, opaque, size 4 hard capsule, banded and marked with "SEL 25" in black ink. The capsule shell contains hypromellose, carrageenan, potassium chloride, titanium dioxide, FD&C blue 2, ferric oxide yellow, purified water, carnauba wax, and/or corn starch. The capsule is imprinted with black ink that contains ferric oxide red, ferric oxide yellow, FD&C Blue 2***	The PMB has updated selumetinib pharmaceutical information for NCI protocols using PMB-supplied Selumetinib (AZD6244 hydrogen sulfate), regarding the capsule appearance and the product in-use period. Thus, updates to sub-section consistent with PMB Pharmaceutical Data Sheet.

		aluminum lake, carnauba wax, shellac, and glyceryl monooleate. Selumetinib (AZD6244 hydrogen sulfate) capsules contain ***vitamin E as the excipient*** ~~a dispersion of drug in~~ D-***alpha***~~α~~-tocopheryl polyethylene glycol 1000 succinate (TPGS~~; a water soluble form of vitamin E~~)***)***. Each 10 mg capsule contains 32~~.~~4 mg ***vitamin E as*** TPGS and each 25 mg capsule contains ***36***~~5.9~~ mg ***vitamin E as*** TPGS.	
5	**8.1 Selumetinib, Section 8.1.3, Storage**	Addition of (AZD6244 hydrogen sulfate) and addition of "controlled." Addition of paragraph regarding storage temperature excursion. Formatted as appropriate. 8.1.3 Storage: Store the selumetinib ***(AZD6244 hydrogen sulfate)*** capsules at ***controlled*** room temperature (20°C-25°C). Brief excursions are permitted between 15°C and 30°C. ***If a storage temperature excursion is identified, promptly return selumetinib (AZD6244 hydrogen sulfate) to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.***	Updates to sub-section consistent with the PMB Pharmaceutical Data Sheet.

6	**8.1 Selumetinib, Section 8.1.4, Stability**	The Stability sub-section updates the product in-use period to provide moisture protection over the storage period. Deletion of current paragraph with exception of first sentence and replaced with updates consistent with PMB Data Sheet. Addition of paragraph about repackaging. Formatted as appropriate. 8.1.4 Stability: ***Shelf-life s***~~S~~tability studies are ongoing. ***Dispense selumetinib (AZD6244 hydrogen sulfate) capsules in the manufacturer's HDPE container. Do not remove desiccant. Protect from moisture. Once the container induction seal is broken the water vapor transmission rate is higher than the intact induction sealed bottle. Significant increase in the moisture content can affect the drug product. The current stability data for selumetinib (AZD6244 hydrogen sulfate) capsules supports an in-use period of up to 60 days.*** ***If repackaging into a pharmacy-supplied HDPE bottle is necessary for patient dispensing, provide a detailed description of the bottle to PMBAfterHours@mail.nih.gov for determination of suitability. The container must be repackaged with desiccant. A 60 day in-use period from the point at which the patient reopens the bottle is permitted.*** ~~If a storage temperature excursion is identified, promptly return selumetinib (AZD6244 hydrogen sulfate) to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the~~	The PMB has updated selumetinib pharmaceutical information for NCI protocols using PMB-supplied Selumetinib (AZD6244 hydrogen sulfate), regarding the capsule appearance and the product in-use period. Thus, updates to sub-section consistent with PMB Pharmaceutical Data Sheet.

		~~excursion) to PMBAfterHours@mail.nih.gov for determination of stability.~~	
7	**8.1 Selumetinib, Section 8.1.5, Route of Administration**	Formatted as appropriate. Oral. Do not eat or drink (except water only) for 2 hours prior to dosing and 1 hour after dosing selumetinib (AZD6244 hydrogen sulfate) capsules.	Updated format of sub-section.

8	**8.1 Selumetinib, Section 8.1.6, Potential Drug Interactions**	Multiple additions and deletions as needed to match PMB Pharmaceutical Data Sheet. Formatted as appropriate. 8.1.6 Potential Drug Interactions: ***Avoid concomitant intake of supplemental vitamin E.*** High vitamin E doses may potentiate warfarin's anticoagulant activity. Monitor PT/INR more frequently in patients receiving both warfarin and selumetinib capsules. ~~Avoid concomitant intake of supplemental Vitamin E.~~ Selumetinib ***(AZD6244 hydrogen sulfate)*** is primarily metabolized by CYP ***3***~~1~~A~~4~~***2*** ~~2~~ ***and to a lesser extent by CYP2C19, CYP1A2, CYP2C9, CYP2E1, and CYP3A5. Selumetinib (AZD6244 hydrogen sulfate) also undergoes glucuronidation by UGT1A1 and UGT1A3. The active human Phase I metabolite, N-desmethyl selumetinib, is approximately 3- to 5-times more potent than selumetinib (AZD6244 hydrogen sulfate) and metabolized through the same routes as selumetinib (AZD6244 hydrogen sulfate). Co-administration of selumetinib (AZD6244 hydrogen sulfate) with the potent CYP3A4 inducer rifampicin decreased selumetinib (AZD6244 hydrogen sulfate) AUC by ~50%. The potent CYP3A4 and 2C19 inhibitors, itraconazole and fluconazole, increased the AUC of selumetinib (AZD6244 hydrogen sulfate) by ~49% and 53%, respectively. It is therefore recommended that patients should avoid taking strong CYP3A4 inhibitors/inducers or fluconazole (strong CYP2C19 inhibitor and***	Updates to sub-section consistent with the PMB Pharmaceutical Data Sheet.

		moderate CYP3A4 inhibitor). Moderate inducers and inhibitors of CYP3A4 should be avoided as well, unless considered clinically indicated. ~~to form the active N-desmethyl metabolite; in addition, UGT1A1 and 1A3 form glucuronide conjugates. CYP 2C8, 2C19, 3A4/5 can also metabolize the parent agent to form N-desmethyl selumetinib; however, as observed during in vitro studies using a pan-CYP inhibitor, other available pathways contribute to selumetinib and N-desmethyl selumetinib metabolism. Use caution in patients who are taking strong inducers or inihibitors of these CYP or UGT enzymes.~~ ***Selumetinib (AZD6244 hydrogen sulfate) is a substrate of BCRP (breast cancer resistance protein) and is a low affinity substrate for P-gp transporters. Selumetinib (AZD6244 hydrogen sulfate) does not inhibit BCRP, P-gp, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2K transporters.*** ~~Selumetinib is also a substrate of BCRP (breast cancer resistance protein) and P-gp transporters. Use caution in patients who are taking strong inducers or inhibitors of either transport protein.~~ ~~Selumetinib does not inhibit CYP 1A2, 2C8, 2C19 and 3A4 or UGT isoforms 1A1 and 2B7. It is a weak inducer of CYP enzymes 3A, 1A and 2C9 and a weak inhibitor of CYP 2C9, 2B6 and 2D6. *In vitro* studies demonstrate selumetinib is an inhibitor of BCRP, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 transporters. It does not~~	

		~~inhibit OCT1, MATE1, MATE2K or P-glycoprotein (MDR1). The N-desmethyl metabolite is a weak inhibitor of CYP3A4 and 1A2. *In vitro* data suggest that selumetinib is unlikely to cause clinically relevant drug-drug interactions by these mechanisms.~~ Patient Care Implications: Study participants should be counseled to avoid excessive sun exposure and use adequate sun protection measures if sun exposure is anticipated during the study.	

9	**13 Statistical Considerations**	Added additional information In all patients, ***when possible, ≥3 areas will be chosen, but only one area for a patient is required minimally because of the difficulty in obtaining patients with multiple areas***. The effect of selumetinib will be separately evaluated ***in up to 3-5 smaller*** (longest neurofibroma diameter 4-7 mm) and 3-5 larger (longest neurofibroma diameter ≥8 mm) neurofibromas in each of the 3 regions. ***Any patient with at least two lesions classified as smaller and/or 2 classified as larger in a single area will be considered evaluable and included in the appropriate analyses. The analyses will be supplemented by a description of the numbers of tumors of each type and number of areas evaluated per patient, which will be used to further interpret the findings. Sub-analyses, which may largely be descriptive, and based on the numbers of areas included may also be done to further interpret the results***. ***With 16 evaluable patients with measurements available at pre cycle 13*** who have continued to receive selumetinib for the same duration, this would provide 90% power to detect a 1.0 effect size (1 SD of the difference in volume from pre to post treatment), using a 0.025 two-sided paired t-test in order to allow for a Bonferroni adjustment for two tests to hold the overall significance level to 0.05. In practice, the two comparisons ***(one for smaller and one for larger tumors)*** may be reported using a less overly conservative Hochberg adjustment.	Updates to sub-section consistent with the GrossCutaneousNeurofibromasRevision 072720.doc

10	Multiple sections and sub-sections within table of contents	Table of contents. Multiple field code changes and deletions/additions to update page numbers post amendment changes. Would not let me hyperlink changes to table of contents on the left column but they are tracked for reference. Thus, only changes were several page numbers across multiple sections and sub-sections.	Table of contents, page numbers updated.

Abbreviated Title: Pilot Selumetinib Cutaneous NF
UAB Protocol #: NCI Protocol #: 9990
Protocol Type / Version # / Version Date: *Amendment/ v9.0 / 16 July 2021*
ClinicalTrials.gov Identifier: NCT02839720

TITLE: PILOT STUDY OF THE MEK1/2 INHIBITOR SELUMETINIB (AZD6244 HYDROGEN SULFATE) FOR ADULTS WITH NEUROFIBROMATOSIS TYPE 1 (NF1) AND CUTANEOUS NEUROFIBROMAS (CNF)

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Jennifer DeSanto, R.N., Leidos Biomedical Research, Inc.

**** Not responsible for direct patient care**
[+] Responsible for selumetinib prescription
***Pharmacology & Experimental Therapeutics Section**
[&] Receiving samples for analysis; non-enrolling sites

Referral Contact: Shaila Handattu, Ph.D., P.M.P., UAB, Trish Whitcomb, RN, OD, CCR, NCI

Investigational Agents:

Drug Name:	Selumetinib (AZD6244 hyd sulfate)
NSC#	748727
Sponsor:	CTEP
Manufacturer:	Astra-Zeneca

KEY WORDS: Neurofibromatosis type 1, cutaneous neurofibromas, tumor response

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PRÉCIS:

Background:

- Neurofibromatosis 1 (NF1) is an autosomal dominant disorder with an incidence of 1:3500 in the US. One of the hallmark features of NF1 is the development of histologically benign peripheral nerve sheath tumors called cutaneous neurofibromas in most individuals with NF1. Some patients develop hundreds to thousands of cutaneous neurofibromas. While cutaneous neurofibromas have not been described to undergo malignant transformation, they can be debilitating, affecting emotional and social quality of life, especially when they occur in large numbers in visible body areas.
- Selumetinib (AZD6244) is a novel orally bioavailable mitogen activated protein kinase inhibitor, is a specific inhibitor of MEK 1, which may mediate anti-tumor effects in NF1 related tumors by inhibition of downstream signaling of Ras. Selumetinib is currently undergoing evaluation in adult cancers and children with brain tumors and in children and adults with NF1-related plexiform neurofibromas (PN).
- In an NCI phase I trial of selumetinib for children and young adults with NF1 and inoperable PN we have observed preliminary activity with PN volume decrease in 71% of patients enrolled. This degree of activity has not been observed in prior trials directed at PN. We observed shrinkage in progressive and non-progressive PN, and a subset of patients also experienced an improvement in function and decrease in pain. Selumetinib has been tolerated well over multiple treatment cycles, and all dose-limiting toxicities were reversible.
- We hypothesize that selumetinib will result in shrinkage of existing cutaneous neurofibromas in individuals with NF1 and may prevent or delay the development of new cutaneous neurofibromas.

Objectives:

- The primary objective will be to determine if selumetinib can result in shrinkage of cutaneous neurofibromas.
- Secondary objectives will include the assessment of the effect of selumetinib on:
  - Target inhibition in cutaneous neurofibroma(s) excised prior treatment and on treatment with selumetinib for analysis of percent inhibition of pERK and changes in pAKT;
- Exploratory objectives will include the assessment of the effect of selumetinib on:
  - The development on new cutaneous neurofibromas while on treatment with selumetinib;
  - Target inhibition in cutaneous neurofibroma(s) excised prior treatment and on treatment with selumetinib for analysis of the tumor kinome.
  - Skin related morbidity and pain using the Skindex, the Global Impression of Change Scale and Numeric Rating Scale, all of which are patient reported outcome measures.
  - Quantify the development of new cutaneous neurofibromas on treatment with selumetinib; and
  - Detailed pathologic analysis of cutaneous neurofibromas pre-treatment and on treatment with selumetinib for changes in cell composition (including macrophage and mast cell infiltration).
  - Alterations that correlate with cNF response to selumetinib treatment with pilot genomic, DNA methylation, and transcriptomic studies.

Eligibility:

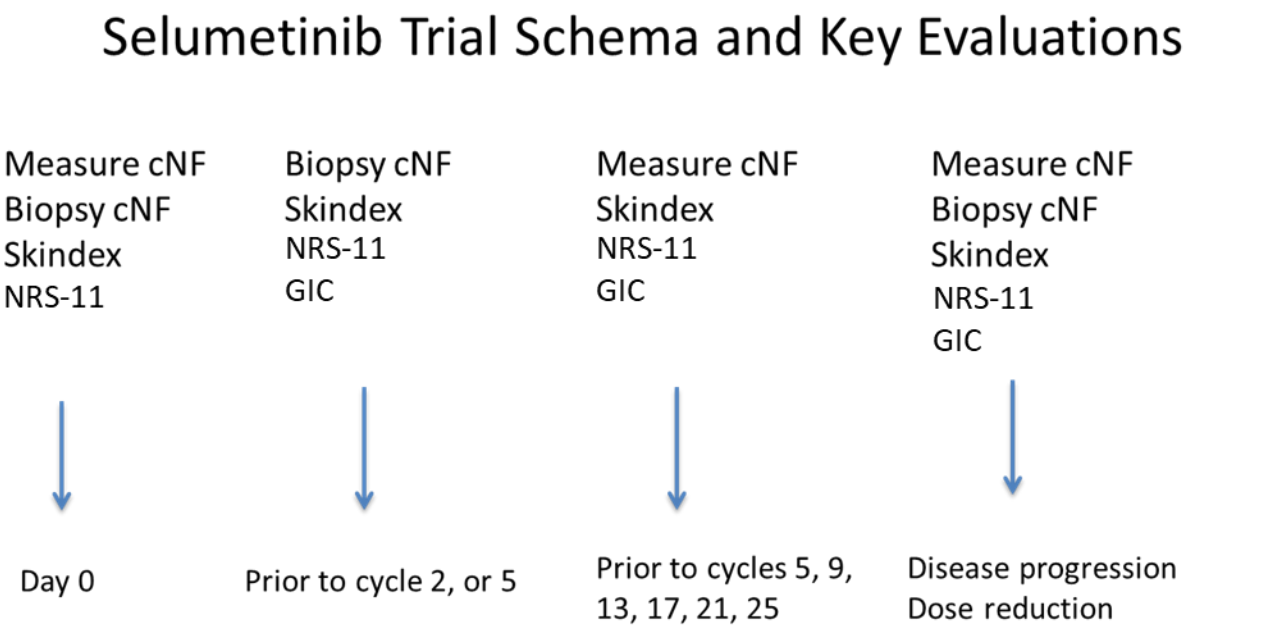
- Patients must be at least 18 years of age with a diagnosis of NF1, must have measurable cutaneous neurofibromas, and substantial neurofibroma burden causing distress, disfigurement, or itching.

- Patients must have adequate organ function, and have recovered from acute toxicity of all prior NF1 tumor directed treatment.

Design:

- This is a limited institution open label pilot study in which all subjects will receive selumetinib orally at the recommended phase II dose for NF1 PN (50 mg/dose) approximately every 12 hours (one cycle = 28 days). If tolerated, the dose may be escalated after cycle 1 to 75 mg every 12 hours.
- Patients will undergo regular evaluation for selumetinib related toxicities. In absence of treatment limiting toxicity, or progression of disease, patients may remain on treatment for a maximum of 24 cycles unless they experience a volume decrease in the target cutaneous neurofibromas, in which case treatment may continue for additional 12 cycles. Patients who discontinue treatment with selumetinib will be monitored after every 4 months for 12 months off treatment for changes in cutaneous neurofibroma volume and number. Volume decrease will be defined as a $\geq$ 20% decrease in the sum of the volumes of the smaller and/or larger target cutaneous neurofibromas.
- For response evaluation, the average volume of 3-5 small (longest neurofibroma diameter 3-7 mm) and 3-5 larger (longest neurofibroma diameter $\geq$8 mm) target cutaneous neurofibromas in 3 different body regions will be calculated at each response evaluation (baseline, and then after every 4 cycles). Cutaneous neurofibromas will be measured with calipers, and volumes will be calculated by multiplying length, width, and height of each target neurofibroma. At each response evaluation the sum of the on-treatment volumes for the smaller tumors will be subtracted from the pre-treatment volumes of the same tumors to arrive at an overall percentage change in tumor size for each patient. This will be repeated for the larger tumors. Then, the average percentage change for each size category will be reported along with its 95% confidence interval, and other associated statistics. A maximum of 24 patients will be enrolled, and 16 evaluable patients will be required to have 90% power to detect a 1.0 effect size. Enrollment will proceed over approximately 12 months.
- In order to assess changes in skin related morbidity and pain, patients will complete both the Skindex and the Global Impression of Change Scale along with the Numeric Rating Scale, all of which are patient reported outcome measures.
- In order to evaluate the pharmacodynamic effects of selumetinib, patients will undergo mandatory excisions of $\geq$ 1 cutaneous neurofibroma prior to treatment and once on treatment with selumetinib to assess percent inhibition of pERK and changes in pAKT and other molecular markers such as tumor kinome.

SCHEMA



- Selumetinib at 50 mg every 12 hours continuous dosing schedule (1 cycle -28 days)
- Selumetinib dose may be escalated to 75 mg every 12 hours after cycle 1, if tolerated (no toxicities of grade 2 or greater).
- Dose determined by pediatric phase I study in NF1 PN
- Regular safety evaluations including physical exam, laboratory evaluations, ophthalmology evaluation, echocardiogram, EKG

cNF= cutaneous neurofibroma

Table of Contents

1 STUDY OBJECTIVES

1.1 PRIMARY OBJECTIVE:

1.1.1 Determine if selumetinib can result in shrinkage of cutaneous neurofibromas.

1.2 SECONDARY OBJECTIVE:

1.2.1 Assess the effect of selumetinib on target inhibition in cutaneous neurofibroma(s) excised prior treatment and on treatment with selumetinib for analysis of percent inhibition of pERK, and changes in pAKT.

1.3 EXPLORATORY OBJECTIVE(S):

1.3.1 Assess the effect of selumetinib on the development on new cutaneous neurofibromas while on treatment with selumetinib.

1.3.2 Assess the effect of selumetinib on target inhibition in cutaneous neurofibroma(s) excised prior treatment and on treatment with selumetinib for analysis of the tumor kinome.

1.3.3 Assess the effect of selumetinib skin related morbidity and pain using the Skindex, the Global Impression of Change Scale and Numeric Rating Scale, all of which are patient reported outcome measures.

1.3.4 Quantify the development of new cutaneous neurofibromas on treatment with selumetinib

1.3.5 Detailed pathologic analysis of cutaneous neurofibromas pretreatment and on treatment with selumetinib for changes in cell composition (including macrophage and mast cell infiltration).

1.3.6 Investigate alterations that correlate with cNF response to selumetinib treatment with pilot genomic, DNA methylation, and transcriptomic studies.

2 BACKGROUND AND RATIONALE

2.1 PATHOGENESIS AND CLINICAL PRESENTATION OF CUTANEOUS AND PLEXIFORM NEUROFIBROMAS IN NEUROFIBROMATOSIS TYPE 1:

Neurofibromatosis 1 (NF1) is an autosomal dominant disorder caused by mutations in the *NF1* tumor suppressor with an incidence of 1:3500 in the US(1). NF1 is characterized by diverse, progressive cutaneous, neurological, skeletal, and neoplastic manifestations with no standard drug treatment options available. The neurofibroma is the defining clinical feature of NF1 and is responsible for much of the medical burden of the disorder. Although the fundamental pathology is similar, neurofibromas come in a variety of forms and in various locations. Ratner and Carroll(2) distinguished five distinct forms of neurofibromas: localized cutaneous, diffuse cutaneous, localized intraneural, plexiform, and massive soft tissue.

2.1.1 Cutaneous neurofibromas:

Localized cutaneous neurofibromas occur either on the surface of the skin or within the dermis and are easily visible in adults with NF1. In her 1988 population-based survey in Wales, Huson(3) found cutaneous neurofibromas in >99% of adults with NF1, making this the most common medically significant manifestation of the condition in adults. This study described an increase in the number of cutaneous neurofibromas with increasing age in individuals with NF1(3). This study also reported that 10/30 (33%) parous women described an increase in size and number of cutaneous neurofibromas during pregnancy. Most reports in the literature quantified cutaneous neurofibromas by counting them at a single time point, and longitudinal measurements in individual patients have not been reported. Spontaneous shrinkage of cutaneous neurofibromas has not been described to date. The growth and increasing number of these lesions can cause substantial cosmetic burden and may cause symptoms of bleeding and itching. Treatment of cutaneous neurofibromas has been limited to surgical excision or extirpation using a laser(4-9) or by electrodessication. Some individuals have hundreds of skin tumors removed in a single session, but it is usually impossible to remove all of the tumors. Also, all of these approaches leave a scar and additional tumors will reappear over time. There have been very few efforts to test non-surgical treatment.

2.1.2 Plexiform neurofibromas:

Another cardinal feature of NF1 the development of histologically benign peripheral nerve sheath tumors called plexiform neurofibromas (PN) in 25-40% of individuals with NF1. Unlike discrete neurofibromas, PN grow along the length of nerves and involve multiple branches of a nerve (10). They are a major source of morbidity(11-13), causing disfigurement, impairment of nerve function, pain, and in some cases development of malignant peripheral nerve sheath tumors (14, 15). Many PN are thought to be congenital or occur at early age, have a complex shape, and can become very large. Currently, there are no standard treatment options other than surgery for these tumors. Complete resection is often not feasible due to the extensive growth of the tumor, rich vascular supply, and invasion of the surrounding tissues, and regrowth after surgery is common (16, 17).

2.1.3 Pathogenesis of cutaneous and plexiform neurofibromas:

Histologically, cutaneous neurofibromas and PN are composed of neoplastic Schwann cells, which lack *NF1* gene expression, accompanied by a varying number of cellular and non-cellular components including fibroblasts, perineurial cells, mast cells, and collagen (18). The gene responsible for NF1 encodes a protein called neurofibromin. Although the function of neurofibromin is not completely understood, it is known to include a GTPase activating protein (GAP) domain that regulates hydrolysis of Ras-GTP to Ras-GDP. Therefore, loss of neurofibromin is associated with Ras activation (18). Activated Ras results in the initiation of a cascade of signaling events such as activation of Raf and MAPK that lead to increased cell proliferation (19, 20). In addition, activation of the mTOR pathway has been identified in benign and malignant NF1 tumors (21-23), and the tumor microenvironment contributes to the pathogenesis of PN. Schwann cells have been shown to secrete kit ligand, which recruits mast cells, and results in abnormal growth properties (24-26). Blocking Ras activity or Ras signaling provides thus a rational approach towards the treatment of PN.

These insights into the pathogenesis of neurofibromas have opened the door towards development of therapies that that target the pathogenetic mechanisms. Various inhibitors of Ras or its downstream effectors have been tested in preclinical models or clinical trials, reviewed by Gutmann et al.(27) and described in more detail below. Extracellular signaling proteins, especially those involving mast cells

that are abundant in neurofibromas, have also been targeted. Several agents have been shown to be effective in reducing the rate of growth or even shrinking neurofibromas in mouse models, and have subsequently been advanced to clinical trials in humans with NF1. All of these recent clinical trials have targeted plexiform neurofibromas, rather than cutaneous neurofibromas. This is due to the significant morbidity of these tumors, including their propensity to cause major disfigurement, pain, or compression of critical structures. These complications often occur in children and are typically beyond the reach of surgical treatment, lending urgency to the development of non-surgical therapies.

Although the rationale for focusing on plexiform neurofibromas in clinical trials is understandable, the morbidity of cutaneous neurofibromas should not be underestimated. These tumors are not life-threatening, but they can be highly disfiguring, prone to bleeding and infection, itch, and can be painful by rubbing against clothing. As such, they are responsible for major negative effects on quality of life for patients with NF1, typically adults. Wolkenstein et al.(28) surveyed 128 adults in France with NF1 for quality of life measures and found that visibility of lesions was associated with negative effects on emotions, physical symptoms, and functioning. Similar findings were reported by Kodra et al.(29) in an Italian cohort and Page et al.(30) in U.S. cohort. Although the number and size of cutaneous neurofibromas varies widely from one person to the next, some individuals have thousands of visible neurofibromas, including on areas of the body that cannot be covered up, such as the hands and face.

2.1.4 Imaging and measurement of cutaneous neurofibromas:

The development of clinical trials directed at cutaneous neurofibromas has been hampered by the difficulty in measuring and counting cutaneous neurofibromas. We recently developed and validated an approach to quantification of number and size of cutaneous neurofibromas that will provide a reliable outcome measure. This is through the combined use of a method to document the number of tumors and a caliper-based measurement to determine surface volume. We have developed paper frames with a 100 cm^2 cut-out area that is used to guide the assessment (Figure 1). The frames are made from paper that is sticky on the back and are adhered to areas of skin, typically on the back, the abdomen, and the thigh. Visible landmarks are used to align the frames consistently when measurements are done at different times, using photographs to insure similar positioning from one time to the next (the neurofibromas themselves provide clear landmarks). Counts can be done manually in "real time," marking neurofibromas with a washable marker to avoid counting a tumor more than once; counts can also be done on a photograph. We have shown that different observers obtain similar counts(31), provided there is prior agreement on the threshold size of tumors to be counted; we typically set a lower size threshold of 4 mm in longest diameter for counting.

We have also developed an approach to measure the size of cutaneous neurofibromas. In our first test, we compared measurements done with a calipers to measurements done with a 3-D laser scanner using a set of 16 plaster model "tumors" of known volume that were placed on the skin. The models ranged from 1.18-452.39 cubic mm in volume and from 2 to 12 mm in longest diameter, and 1 to 6 mm in height. Three different observers measured the models with a caliper, measuring two perpendicular diameters and height above the skin, and results were compared with the results of the laser scanner calculated volumes. Table 1 only shows data indicating Pearson correlation coefficients of the volumes calculated from measurements made by the three observers (H1, H2, and H3) as compared with the true volumes of the models. Data on the use of the laser scanner are not shown, as we concluded that the manual measurements were more accurate than those obtained with the scanner and therefore manual measurements with a caliper will be used in this clinical trial. We have used this approach to monitor tumor size in a cohort of 24 patients with NF1 followed over a two-year period, with measurements

done every 4 months, for a total of seven visits. A minimum of six and maximum of 18 tumors were monitored for each patient, for a total of 1980 tumors measured cumulatively across all patients and all seven time points. Aggregate data for all tumors is shown in Figure 2. Tumor growth was significant ($p = 0.0185$) over the period of observation, although the trend of increased volume was very slight.

Figure 1 Counting neurofibromas in a 100 cm^2 frame; counting was done manually and neurofibromas were marked with a washable marker to identify those that were counted. Targets for measurement were marked in green.

	H1	H2	H3
H1	1.00000	0.99599	0.99799
H2	0.99599	1.00000	0.99706
H3	0.99799	0.99706	1.00000

Table 1. Pearson correlation coefficients of volumes calculated from caliper measurements of plaster model tumors as compared with the true volume of the models.

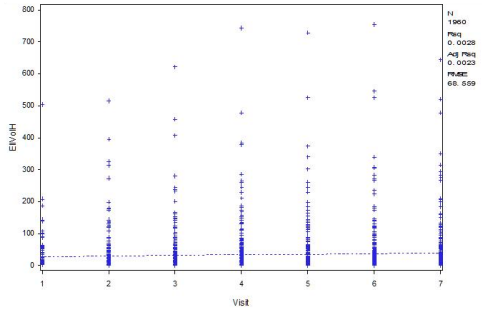


Figure 2 Plot of tumor volumes (y-axis) at each of 7 visits (x-axis) for all tumors measured in 24 patients with trend line showing slight overall increase in volume over the two-year time period.

We believe that these studies provide the basis for meaningful evaluation of targeted agents in trials for cutaneous neurofibromas.

2.1.5 Clinical trials directed at cutaneous neurofibromas:

Riccardi conducted a trial with the antihistamine ketotifen in the 1980s(32) and reported improvement in neurofibroma-related itching and pain, but not in tumor size or number. A search of clinicaltrials.gov (July 20, 2015) reveals several entries of clinical trials for cutaneous neurofibromas, including ranibizumab, imiquimod 5% cream, erbium-YAG laser vaporization, topical rapamycin, and photodynamic therapy. No current information is posted about the ranibizumab, imiquimod, or topical rapamycin studies and there is no published information on these trials in PubMed. There is substantial literature on the effectiveness of laser therapy. The photodynamic therapy trial involves use of delta aminolevulinic acid as a photosensitizer with subsequent illumination with 630 nm light; this trial is indicated as ongoing in clinicaltrials.gov.

2.1.6 Clinical trials directed at PN

In contrast to cutaneous neurofibromas, multiple clinical trials targeting plexiform neurofibromas have been conducted to date (27) including the farnesyltransferase inhibitor tipifarnib(33), the antifibrotic agent pirfenidone(34-36), the mTOR inhibitor sirolimus(37, 38), the antiangiogenic and immune modulatory agent peginterferon alfa-2b (39, 40), and the c-kit inhibitor imatinib. The tipifarnib trial was double-blinded and included a placebo control group (29 patients), and the median time to progression (TTP) of progressive PN treated with placebo was 10. 6 months. Tipifarnib did not result in a doubling of the TTP compared to the placebo arm. Three subsequent open label phase II trials used the tipifarnib trial placebo group to evaluate if the agent of interest would result in an increase in the TTP compared to the placebo control group. Of all phase II trials performed to date, the following agents have demonstrated activity: Compared to the tipifarnib placebo control group, peginterferon alfa-2b achieved a doubling in the TTP (39) and sirolimus achieved a statistically significant increase in the median TTP

by 3.5 months(37). PN volume decreases by ≥20% have been infrequently observed in clinical trials utilizing volumetric MRI analysis at the NCI for response evaluation: In 60 patients enrolled on the tipifarnib phase II trial (29 placebo, 31 tipifarnib) the maximum volume decrease observed was 11.3% in one patient(33). On the pirfenidone phase II trial (36 patients) the maximum volume decrease observed was 12% (36). On the peginterferon alfa-2b phase II trial 3 of 80 patients had a volume decrease of >20% (21, 22, and 27%) (unpublished, confidential information, Regina Jakacki). On the sirolimus phase II trial of 58 patients, no PN volume decrease ≥20% was observed, and 3 patients had a maximum decrease of >15%, <20%(37). In a phase II trial of the c-kit and PDGFR inhibitor imatinib conducted by Kent Robertson, PN volume decrease ranging from 20 to 40% was observed in 6 of 23 response evaluable patients(41). This trial used a different method of volumetric analysis and responses were only observed in very small PN (≤20 mL). In contrast, most target PN enrolled on NCI clinical trials have much larger volumes: Tipifarnib median PN volume 364 mL (range 20.5-5573 mL); pirfenidone: median PN volume 349 mL (range 12-5629 mL).

Recently, in a CTEP sponsored phase I clinical trial of selumetinib for children with NF1 and inoperable plexiform neurofibromas (NCT01362803), preliminary activity has been observed (See section 2.2.3). Decreases in plexiform neurofibroma volumes Have been observed in >71% of patients enrolled. This degree of activity has not been observed in prior trials directed at PN. We observed shrinkage in progressive and non-progressive PN, and a subset of patients also experienced an improvement in function and decrease in pain. Selumetinib has been tolerated well over multiple treatment cycles, and all dose-limiting toxicities were reversible.

Based on a strong unmet need for the development of effective medical therapies for cutaneous neurofibromas in NF1, the preliminary activity of selumetinib in NF1 related plexiform neurofibromas, the tolerability of selumetinib over multiple treatment cycles, and the availability to measure the number and size changes of cutaneous neurofibromas, we are proposing a pilot study of selumetinib for patients with NF1 and substantial cutaneous neurofibroma burden that is causing distress to the patient.

2.2 SELUMETINIB [AZD6244 (ARRY-142886; SELUMETINIB)]

All preclinical information provided in this protocol is from the Investigator's Brochure.

AZD6244 (ARRY-142886; selumetinib) is a potent, selective, orally (PO) available, and non-ATP competitive small molecule inhibitor of the mitogen-activated protein (MAP) kinase kinase, MEK1/2 (Investigator's Brochure, 2015)(42). AZD6244 inhibits the activity of purified MEK by 50% at 10-14 nmol/L (IC_{50}), and is inactive or only minimally active at 10 mcmol/L against epicutaneous growth factor receptor (EGFR), ERB2, p38α, ERK2, and MAPKK 6 kinases. AZD6244 is metabolized to biologically active N-desmethyl AZD6244, which is approximately 3- to 5-fold more active than the parent compound.

The RAS/RAF/MEK/ERK signaling pathway plays a central role in the regulation of many cellular processes including proliferation, survival, differentiation, apoptosis, motility, and metabolism (43, 44). This pathway is one of the most important and best understood MAP kinase signal transduction pathways, activated by a diverse group of extracellular signals including integrins, growth factor receptors (*i.e.,* EGFR, platelet-derived growth factor receptor [PDGFR], and insulin-like growth factor-1 receptor), and cytokines (45). Activated RAS triggers the phosphorylation and activation of RAF kinase, which then phosphorylates MEK1 and MEK2 on two serine residues (46). Activated MEK phosphorylates its only known substrates, ERK1 and ERK2. Phosphorylated ERK (pERK) dimerizes

and translocates to the nucleus (47) where it is involved in several important cellular functions, including cell proliferation.

Overexpression of growth factors or growth factor receptors involved in the RAS/RAF/MEK/ERK pathway and activating genetic mutations of the signaling proteins may lead to uncontrolled proliferation and tumor formation. For example, RAS genes are the most frequently mutated oncogenes detected in human tumors(45). 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. In addition to being found in almost all pancreatic adenocarcinomas, RAS mutations are found in ~40% of colorectal carcinomas (CRC), 20-25% of lung adenocarcinomas, and also in some breast or ovarian cancers. *BRAF* mutations have also been observed in many human cancers, particularly melanoma (30-60%), thyroid cancer (30-50%), CRC (5-20%), and ovarian cancer (~30%) (42, 44). These mutations in *BRAF* usually involve gain-of-function substitutions that render the kinases constitutively active. Also, studies of primary tumor samples and cell lines have shown constitutive activation or overactivation of the kinase pathways in cancers of the pancreas, colon, lung, ovary, biliary tract, and kidney (48). Therefore, agents targeting the RAS/RAF/MEK/ERK pathway may inhibit oncogenic signaling in tumor cells.

2.2.1 Nonclinical Studies

2.2.1.1 Efficacy

In vitro studies have shown that AZD6244 is a potent and selective inhibitor of MEK with IC_{50} of 10-14 nM (Investigator's Brochure, 2015). Significant biochemical activity has not been detected when tested at 10 mcmol/L against a diverse panel of >300 other molecules, including enzymes, receptors, kinases, transporters, and ion channels. The effects of AZD6244 on ERK phosphorylation and cell viability were determined in a panel of cell lines with known RAF and RAS mutant status. AZD6244 inhibited ERK1 and ERK2 phosphorylation with IC_{50} 0.0018-0.0408 mcmol/L. In cell viability assays, IC_{50} values ranged from <10 nM to >10 μM and most of the cell lines that were sensitive to selumetinib contained either a BRAF or RAS gene mutation. Two metabolites of AZD6244 (N-desmethyl AZD6244 and an amide AZD6244) have been identified. The N-desmethyl metabolite was found to be 3-to 5-fold more potent inhibitor than the parent compound in cellular ERK phosphorylation and cell viability inhibition assays. In contrast, the AZD6244 amide metabolite was up to 50-fold less active than AZD6244 and therefore is unlikely to significantly contribute to biological activity of AZD6244. In tumor cell viability inhibition assays, N-desmethyl metabolite was ≥5-fold more potent than AZD6244 in inhibiting cell viability.

Significant suppression of tumor growth in response to AZD6244 treatment was observed in several xenograft mouse models derived from a range of tumor types including melanoma, breast, pancreatic, lung, colon, and hepatocellular carcinomas (49-52). In papillary thyroid cancer models, AZD6244 effectively inhibited tumor growth, both *in vitro* and *in vivo*, particularly in tumor cells carrying activating *BRAF* gene mutations (53). In the Calu-6 lung cancer xenograft model, AZD6244 suppressed tumor growth at doses of 10, 25, or 100 mg/kg given twice daily (BID), and the minimal effective dose was identified as 0.75 mg/kg administered BID (50). In this model, MEK activity was inhibited as assessed by determination of pERK levels in tumor. Studies using human CRC xenograft models demonstrated that AZD6244 inhibited tumor growth by inhibition of cell proliferation in SW620 model and by induction of apoptosis in Colo205 model. *In vivo* studies with mutant *KRAS* positive ($KRAS^+$) human cancer xenografts have demonstrated the potential for using AZD6244 in combination with a

number of cytotoxic and targeted agents, including docetaxel, irinotecan, gemcitabine, pemetrexed, gefitinib, cediranib, rapamycin, cisplatin, and temozolomide (Investigator's Brochure, 2015).

2.2.1.2 Pharmacokinetic/Pharmacodynamic Studies

Two oral formulations of AZD6244 have been tested in preclinical pharmacology studies: the original mix-and-drink formulation (AZD6244 free-base), and the AZD6244 hydrogen sulfate salt (capsule) formulation (AZD6244 Hyd-Sulfate) (Investigator's Brochure, 2015). The former requires reconstitution of the AZD6244 free-base crystalline powder in the 25% (w/v) Aqueous Captisol®(sulfobutyl ether β-cyclodextrin) (SBE-CD) solution. While systemic exposure was demonstrated in the rat and monkey studies with AZD6244 free-base, the exposure was not dose-proportional; bioavailability was decreasing with increasing dose. This is likely a reflection of dose-limited absorption due to limited solubility of AZD6244 free-base. However, AZD6244 hydrogen sulfate produced approximately proportional exposures with dose in the mouse and monkey, and allowed higher exposures than AZD6244 free-base. There was no/minimal accumulation of AZD6244, whether dosed with AZD6244 free-base or AZD6244 hydrogen sulfate on multiple dosing in the mouse, rat, or monkey. N-desmethyl metabolite was not detectable in rat and at only trace levels in the monkey, but was produced in mouse at circulating levels around 2-12% of parent compound. Studies in rats and mice indicate that AZD6244 is widely distributed, although concentrations were generally lower in tissue than blood. High levels of protein binding (93.7%-99.7%) were observed in all preclinical species tested and in humans (98.4%). There was no evidence of AZD6244-related material binding to melanin and minimal penetration into the central nervous system (CNS).

AZD6244 is metabolized in human hepatocytes by cytochrome P450 (CYP enzymes) 1A2, 2C19 and 3A4, with CYP1A2 being the enzyme primarily responsible for the formation of the N-desmethyl metabolite. Glucuronidation appears to be a significant clearance mechanism for AZD6244 and the N-desmethyl metabolite. It is a weak inducer of CYP 3A, 1A, and 2C9. AZD6244 does not inhibit CYP 1A2, 2C8, 2C19, 2D6, and 3A4. It was a weak inhibitor of CYP2C9 (IC_{50} 44.7 mcM). N-desmethyl AZD6244 does not inhibit CYP 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, but is a weak inhibitor of 1A2 (IC_{50} of 18.9 mcM). In the rat, mouse, and monkey, fecal excretion was the predominant route after oral and intravenous dosing.

2.2.1.3 Toxicologic Studies

Toxicity of AZD6244 was evaluated in the acute dosing (one or two doses on a single day) and continuous daily dosing studies (for a 1month and 6 months) in Sprague-Dawley rats and cynomolgus monkeys (Investigator's Brochure, 2015). 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. Tissue mineralisation was not apparent in cynomolgus monkeys when dosed for up to 1 month with AZD6244 free-base or for up to 6 months with AZD6244 hydrogen sulfate. However, mineralization was seen in multiple tissues (cornea, kidney, liver, myocardium, skeletal muscle, and glandular stomach) in mice dosed with AZD6244 hydrogen sulfate for up to 1 month, and in the liver of a small number of mice dosed up to 6 months. Physeal dysplasia was observed at a dose level of selumetinib 10 mg/kg/day (arithmetic mean AUC 546 uM.h) in 4 of 10 male rats receiving 13 weeks treatment at substantially greater drug exposure than that achieved in children or adults receiving selumetinib at the recommended doses: For total selumetinib AUC, there is a 43.3-fold exposure margin in comparison to adult patients with advanced cancer receiving selumetinib 75 mg BID (arithmetic mean AUC_{0-12} 12.62 uM.h) and a 64.2-fold exposure margin in comparison to pediatric patients with low grade glioma receiving selumetinib 25 mg/m^2 BID

(arithmetic mean AUC_{0-12} 8.5 uM.h). Focal decreased cellularity of the femoral bone marrow adjacent to the physis was observed at a dose level of selumetinib 25 mg/kg/day (arithmetic mean AUC 806 uM.h) in 4 of 10 female rats receiving 30 days treatment (all terminated before planned 13 weeks due to skin lesions). For total selumetinib AUC, there is a 63.9-fold exposure margin in comparison to adult patients with advanced cancer receiving selumetinib 75 mg BID (arithmetic mean AUC_{0-12} 12.62 uM.h) and a 94.8-fold exposure margin in comparison to paediatric patients with low grade glioma receiving selumetinib 25 mg/m^2 BID (arithmetic mean AUC_{0-12} 8.5 uM.h).Physeal dysplasia and decreased bone marrow cellularity were not observed at lower dose levels of selumetinib (5 mg/kg/day in male rats; 12.5 mg/kg/day in female rats).

Twice daily (BID) oral dosing with AZD6244 free-base for 1 month in monkeys produced diarrhea, dehydration, and electrolyte imbalance, in some animals associated with renal toxicity. Dosing with AZD6244 hydrogen sulfate (0.5, 1.5, and 4 mg/kg BID) for up to 6 months in monkeys was also associated with fluid and/or red-colored feces, but with no notable gastrointestinal (GI) tract or renal pathology.

AZD6244 and its N-desmethyl metabolite showed no evidence of mutagenic potential, but AZD6244 produced an increase in micronucleated immature erythrocytes in mice, predominantly via an aneugenic mode of action. AZD6244 showed enhanced cytotoxicity in the presence of ultraviolet (UV) light. Reproductive toxicology data in mice indicate that AZD6244 can have adverse effects on embryofetal development and survival at dose levels that were not toxic to mothers.

In summary, preclinical studies demonstrated that AZD6244 exposures can be significantly enhanced by using AZD6244 hydrogen sulfate, compared to AZD6244 free-base. In 6-month toxicology studies, AZD6244 exposures, expressed as area under the concentration-time curve from time 0 h to 12 h (AUC_{0-12}), achieved with AZD6244 hydrogen sulfate at high dose levels (4 mg/kg BID in monkeys and 20 mg/kg BID in mice) were approximately 3-fold and 15-fold higher in primates and mice, respectively, when compared with those achieved in man at 75 mg BID AZD6244 hydrogen sulfate. At the NOAEL of 1.5 mg/kg BID from 1-month and 6-month studies in primates, exposures were generally similar to those seen in man after dosing at 75 mg BID AZD6244 hydrogen sulfate. Exposure achieved in the 6-month mouse study at the low dose level of 1 mg/kg BID was slightly below that seen to date in man after dosing with AZD6244 hydrogen sulfate (75 mg BID). Preclinical pharmacology studies suggest an acceptable safety profile for administering AZD6244 free-base or AZD6244 hydrogen sulfate to cancer patients.

2.2.2 Clinical Experience

2.2.2.1 Pharmacokinetics

AZD6244 plasma PK parameters of AZD6244 hydrogen sulfate were similar after single and multiple dosing, suggesting a minimal accumulation over time after BID dosing (Investigator's Brochure, 2015). The AZD6244 exposure parameters, *i.e.,* the maximum plasma concentration (C_{max}) and the AUC were approximately dose-proportional across the 25- to 100-mg BID dose range after single (day 1) or multiple dosing studied on days 1, 8, 15, and 22. The geometric mean values of exposure parameters were: C_{max}=369-1483 ng/mL and AUC_{0-12}=1361-7055 ng·h/mL on day 1, and C_{max}=458-1365 ng/mL and AUC_{0-12}=1515-4758 ng·h/mL on day 8. AZD6244 was absorbed relatively quickly across all dose levels, with a median time-to-reach C_{max} (t_{max}) of 1.5 hours. Following the peak, AZD6244 concentration declined multi-exponentially with a mean terminal elimination half-life ($t_{1/2}$) ranging from 5 to 7 hours, which was consistent across dose levels. The apparent volume of distribution at steady

state (V_{ss}/F) and apparent clearance (CL/F) also remained largely consistent across the dose range, with mean values ranging from 87 to 126 L and 12 to 19 L/h, respectively. The plasma PK profile of the AZD6244 active metabolite, N-desmethyl AZD6244, was similar to that of AZD6244, although exposure was much lower, achieving C_{max} and AUC values generally <15% of the parent compound, in each patient. The median t_{max} was approximately 1.5 hours and $t_{1/2}$ ranged from 9-13 hours. The AZD6244 amide metabolite showed increased exposure on multiple dosing indicating some accumulation. Given the 3-to 5-fold greater potency of the N-desmethyl metabolite compared to AZD6244 shown by the *in vitro* cell-based ERK phosphorylation assay, the N-desmethyl AZD6244 is likely to contribute to pharmacodynamic effects. In contrast, AZD6244 amide, which was approximately 40- to 50-fold less active than AZD6244 in this assay, is unlikely to contribute significantly to AZD6244 biological activity.

The capsule formulation significantly improved oral bioavailability compared the free-base formulation, although large inter-patient variability was noted. The estimated oral bioavailability of capsule relative to the free-base suspension based on a dose-normalized AUC_{0-24} was 263% (90% confidence interval [CI]=214%-322%). The geometric mean values of exposures obtained for AZD6244 hydrogen sulfate at the maximum tolerated dose (MTD) of 75 mg BID (AUC_{0-24}=6335 and 5448 ng·h/mL on day 1 and 8, respectively, and C_{max}=1207 and 1439 ng/mL on day 1 and 8, respectively) were statistically significantly higher than those obtained at the MTD of AZD6244 free-base (100 mg BID); the relative estimated exposures by hydrogen sulfate *vs.* free-base were 197% (90% CI=161 to 242%) for $AUC_{0–24}$ and 252% (90% CI=182 to 348%) for C_{max}.

A food effect study involving administration of AZD6244 hydrogen sulfate to patients with advanced solid malignancies under fasting conditions and with a high-fat meal indicated a statistically significant effect of food on the exposure of AZD6244. Geometric mean C_{max} and AUC values were reduced by approximately 62% and 19%, respectively, under fed conditions. Therefore for further clinical studies, it is recommended that AZD6244 be taken on an empty stomach (*i.e.*, no food other than water can be taken) at least 2 hours after a meal and 1 hour before the next meal. AZD6244 capsule should be taken with water.

At a population level, plasma exposure of AZD6244 (C_{max} and AUC) appeared to be increased in healthy volunteers of Asian descent by approximately 1.5- to 2-fold, in non-Japanese Asians and Japanese Asians, respectively, compared with Western healthy volunteers. However, the AZD6244 PK was highly variable and there was overlap in the range of exposure experienced by Asian and Western subjects.

There is no evidence of PK interactions between docetaxel, dacarbazine, temsirolimus, or erlotinib and AZD6244.

2.2.2.2 Efficacy

Four randomized phase 2 monotherapy studies comparing efficacy of AZD6244 free-base formulation (100mg BID) to standard chemotherapy regimens in patients with solid tumors (melanoma, pancreatic cancer, CRC, and NSCLC) did not demonstrate superior efficacy of AZD6244 over standard chemotherapy agents (Investigator's Brochure, 2015). Several objective responses were observed in melanoma patients with mutant BRAF tumors and in patients with mutant KRAS NSCLC.

Although statistical significance in overall survival (OS) was not achieved, a statistically significant improvement was seen in progression-free survival (PFS) for AZD6244 in combination with docetaxel in patients with mutant KRAS NSCLC (P=0.014)(54) and for AZD6244 in combination with

dacarbazine in patients with mutant BRAF cutaneous melanoma (P=0.021) (55), when compared to the respective chemotherapy/placebo groups. Clinical activity of AZD6244 hydrogen sulfate monotherapy was demonstrated in uveal melanoma (56).

2.2.2.3 Safety

The tolerability profile of AZD6244 free-base at 100 mg BID was similar to that of AZD6244 hydrogen sulfate at 75 mg BID (Investigator's Brochure, 2015). The most common AEs associated with AZD6244 are acneiform rash, diarrhea, nausea, vomiting, peripheral edema, and fatigue. Stomatitis, dry skin, and pyrexia have also been commonly reported in the AZD6244 studies. Dose escalation of selumetinib was limited mainly by the occurrence of rash and diarrhea.

Events consistent with central serous retinopathy/retinal pigment epithelial detachment have been reported in a small number of patients receiving treatment with AZD6244, generally in combination with other novel targeted anticancer agents.

Mild (generally grade 1) elevations in serum liver transaminases have been recorded within the first week of starting treatment with AZD6244 and levels tend not to increase further beyond the first month of continued dosing. Mild increases in serum phosphate and in calcium phosphate product have been reported.

Dyspnea and exertional dyspnea have been reported in patients receiving AZD6244. The majority of these events have occurred in patients with lung or pleural disease due to their underlying malignancy. There have been reports of pneumonitis-type events, including symptoms of shortness of breath, fatigue, cough and/or fever, in a small number of patients receiving AZD6244, but pneumonitis-AZD6244 association has not been established. Studies of AZD6244 should include guidance for the management and investigation of new or worsening dyspnea or symptoms of pneumonitis-type events that are not attributed to the patient's underlying cancer.

Increases in systolic or diastolic blood pressure, sometimes exceeding the threshold for therapeutic intervention, have been observed in studies with AZD6244. Asymptomatic reductions in left ventricular ejection fraction (LVEF) to below 55% have been observed in a small number of patients during AZD6244 treatment and evidence of reversibility while on continuous dosing was demonstrated in some patients. Studies of AZD6244 should include baseline and symptom-triggered echocardiography assessments and guidance for the management and investigation of decreases of LVEF. Review of electrocardiogram (ECG) parameters has shown no evidence of QT interval corrected according to Fridericia's formula (QTcF) prolongation during treatment with AZD6244.

Increased creatine phosphokinase (CPK) levels have been reported in a small number of patients with advanced cancer receiving AZD6244. A relationship between selumetinib and increased CK levels has not been established.

2.2.3 Clinical trials of selumetinib in adults with refractory cancers and children with NF1 and PN:

Selumetinib is an oral specific MEK1/2 inhibitor with activity in adult cancers characterized by activation of the Ras pathway at the adult recommended dose of 75 mg BID (capsules) (54, 55, 57). In an adult phase I trial using a powder for reconstitution formulation paired tumor biopsies were obtained prior to treatment with selumetinib and 2-4 hours after the day 15 dose during cycle 1. Tumor samples were analyzed for inhibition of pERK using immunohistochemistry (58). Of 24 paired biopsies 19 had pretreatment pERK expression. Strong inhibition of pERK with a gmean of 79% (90% CI 50%-91%)

was seen with most patients having received 100 mg selumetinib per dose. At the 100 mg dose level the gmean for the day 1 C_{max} was 807 ng/mL, and the AUC was 3124 ng•h/mL.

In adults, selumetinib is being evaluated in multiple malignancies, including uveal melanoma, non-small cell lung cancer, and radioiodine refractory differentiated thyroid cancer. In patients with advanced uveal melanoma, patients treated with selumetinib demonstrated modestly improved progression-free survival and response rate; however, no improvement in overall survival was observed. In addition a high rate of adverse events was noted. A randomized phase II trial of docetaxel with and without selumetinib in NSCLC demonstrated improved overall survival and a statistically significant improvement in progression-free survival and objective response rate with combination therapy. Selumetinib produced increases in iodine uptake and retention in a subgroup of patients with thyroid cancer that is refractory to radioiodine. Of 8 patients treated with radioiodine and selumetinib, 5 had confirmed partial responses and 3 had stable disease; all patients had decreases in serum thyroglobulin levels (mean reduction, 89%). As 5 of these patients had NRAS mutations, the authors postulate that the effectiveness may be greater in patients with RAS-mutant disease.

The Pediatric Brain Tumor Consortium is conducting a phase I/II trial with selumetinib in recurrent or refractory low grade gliomas based on the finding of activation of the Ras-MAP kinase signaling pathway in these tumors. The maximum tolerated dose in this trial was 25 mg/m^2/dose BID on a continuous dosing schedule. Thus far there have been 8/38 sustained responses (1 complete and 7 partial). Of 5 with available biologic data, 3 demonstrated BRAF fusion, 1 had BRAFV600E mutation and 1 displayed neither (59).

In our CTEP sponsored phase I clinical trial of selumetinib for children with NF1 and inoperable PNs (NCT01362803), preliminary activity has been observed. The primary objectives of this trial are to determine the maximum tolerated dose (MTD) and plasma pharmacokinetics (PK) of selumetinib in patients 3-18 years old with NF1 and inoperable PNs. Selumetinib is administered twice daily as capsules (10 mg and 25 mg) on a continuous dosing schedule (1 cycle = 28 days). The MTD is determined based on cycle 1-3 toxicities. Three dose levels have been evaluated: dose level 1 (20 mg/ m^2/dose, 50% of the adult recommended dose), dose level 2: (30 mg/ m^2/dose, 75% of the adult recommended dose), and dose level 1.5 (25 mg/m^2/dose, 60% of the adult recommended dose). Response evaluation with volumetric MRI analysis occurs after cycles 5, 10, and then after every 6 cycle. A partial response is defined as a ≥20% decrease in the PN volume compared to baseline at enrollment.

As of January 2016: This trial has completed the primary objectives. Twenty-four patients (13 M:11 F, median age 10.9 years, range 3-18) with a median target PN volume of 1,205mL (range 29-7,210mL) have enrolled. Dose level 2 (30 mg/m^2/dose) exceeded the MTD with dose-limiting toxicity (DLT) in 2/6 patients: grade (gr) 3 creatine kinase (CK) elevation (n=1), and gr 3 decrease in left ventricular ejection fraction (n=1). DL1 (20 mg/m^2/dose) was tolerated with DLT in 2/12 patients: gr 3 cellulitis (n=1), and grade 3 urticaria (n=1). All DLTs were reversible. No other patients developed a decrease in LVEF requiring holding selumetinib. The DL1 dose of 20 mg/m^2/dose is similar to the MTD of 25 mg/m^2/dose determined in the Pediatric Brain Tumor Consortium (PBTC) study of selumetinib for low grade gliomas. For consistency in treating pediatric patients, we therefore evaluated the PBTC MTD of 25 mg/m^2/dose in the NF1 PN trial as dose level 1.5. Of six patients enrolled at this dose level, one patient experienced a gr 3 rash as DLT during cycle 2. No other DLTs were observed during cycles 1-

3, and the 25 mg/m^2 dose level is thus the MTD and the recommended phase II dose for children with NF1 and PN.

The most frequent selumetinib toxicities (all grades) are acneiform rash, asymptomatic CK elevation, nausea, vomiting, abdominal pain, diarrhea, and fatigue. Preliminary median (range) selumetinib C1 day 1 PK parameters were: $AUC_{0\text{-}24h}$ DL1 (n=8) 2118 (1872-3240) ng•h/mL, DL2 (n=5) 2702 (2088-6008) ng•h/mL; half-life DL1 6.8 h (5.6-14.3), DL2 7.6 h (5.4-9.8). Five patients developed paronychia that was deemed possibly related to selumetinib; 2 had grade 1 and 3 experienced grade 2, paronychia.

One patient enrolled on the phase I selumetinib trial developed asymptomatic grade 1 cataract in both eyes, not interfering with vision, which were not appreciated at prior exams. The patient had previously been treated with imatinib and retinoid acid, both of which are associated with cataracts. This patient also experienced clinical benefit with reduction in PN related pain; celebrex, which was administered at trial entry for PN related pain, could be discontinued on treatment. As the patient derived clinical benefit, selumetinib was continued. A review by Astra Zeneca of development of cataract in studies with selumetinib identified 4 cases, all of which had confounding factors (>60 years old, hypertensive, previous exposure to steroids). Based on the information in the most relevant clinical studies, cataract was reported for very few patients on selumetinib therapy, and due to the presence of alternative risk factors like hypertension, older age and steroid therapy, a causal link with selumetinib could not been established. Decreased LVEF was seen in only one patient, who did not experience recurrent decreased in LVEF after dose reduction. Reversible, asymptomatic reductions in LVEF have been recorded in a small number of patients receiving selumetinib in studies with scheduled echocardiography assessments. Evidence of reversibility of LVEF changes on continuing selumetinib, often without therapeutic treatment, has been demonstrated in patients with follow-up assessments available.

Decrease in PN volumes (median -31%, range -5.8 to -47.7%) was observed in all patients and occurred slowly over time. The maximum response was reached after a median of 20 (range 5-42) cycles. Seventeen of 24 patients (71%) met criteria for confirmed partial response. These responses have been maintained for a median of 23 cycles (range 6 to 42). No patients have experienced disease progression to date, but slow regrowth has been observed in some cases, most notably following dose reductions, and in the case of one patient, who required prolonged interruption of selumetinib dosing for toxicity.

Anecdotal evidence of clinical improvement included: decrease in PN related pain in 8 of 13 patients, improvement in motor function in 5 of 8 patients, and decreased disfigurement based on photography in 5 of 18 patients.

Selumetinib thus has preliminary activity in children and adolescents with NF1 PN at doses as low as 50% of the adult recommended dose (75 mg BID) and a phase II trial was developed and is now ongoing to assess objective response rate by 3D MRI, pain, QOL, and functional changes prospectively.

2.3 RATIONALE FOR THE PROPOSED PILOT STUDY:

As described in this protocol, cutaneous neurofibromas cause substantial morbidity in individuals with NF1, and there is a strong unmet need for the development of effective medical therapies.

Preclinical studies in an NF1 mouse model have shown significant reduction in the size of plexiform neurofibromas in animals treated with a MEK inhibitor or in human neurofibroma cell cultures(60). Selumetinib has been evaluated in clinical trials for adult[54, 55, 57, 58] and pediatric tumors[59, 61]. In a phase I trial of selumetinib for children with NF1 and inoperable plexiform neurofibromas, selumetinib has been well tolerated over multiple treatment cycles and has resulted in shrinkage of progressive and non-

progressive plexiform neurofibromas (> 20% reduction in tumor volume) in 67% of subjects. A subset of patients also experienced an improvement in function and decrease in pain. This is the most impressive response that has been seen to date in medical treatment of plexiform neurofibromas.

We are proposing herein a pilot study for treatment of cutaneous neurofibromas with the oral MEK1/2 inhibitor selumetinib for the following reasons:

First, as noted above, cutaneous neurofibromas impose a significant emotional burden on adults with NF1 and there are no existing medical treatments or current clinical trials.

Second, although inhibition of MEK has not been tested in a preclinical model for cutaneous neurofibromas (because there is only one such model which does not mirror the human tumors precisely and it is not used in the preclinical consortium), cutaneous tumors are similar to plexiform neurofibromas histologically, and both are derived from Schwann cells in which biallelic *NF1* mutation has been seen.

The third factor that has led us to propose this trial is that we have developed an approach to quantification of number and size of cutaneous neurofibromas that will provide a reliable outcome measure as described above. This method will not only allow to monitor the size of cutaneous neurofibromas over time, but also to assess changes in the number of cutaneous neurofibromas.

We hypothesize that selumetinib will result in shrinkage of existing cutaneous neurofibromas and may prevent or delay the development of new cutaneous neurofibromas. In the absence of validated response measured for cutaneous neurofibromas we are proposing a small pilot study of selumetinib to evaluate the potential utility of selumetinib in individuals ≥ 18 years old with NF1 and cutaneous neurofibromas.

The primary objective will be to determine if selumetinib can result in shrinkage of cutaneous neurofibromas. Secondary objectives will include the assessment of the effect of selumetinib on target inhibition, on the tumor microenvironment, and on skin related morbidity. We will also quantify the development of new cutaneous neurofibromas.

As cutaneous neurofibromas are predominantly a problem in adults, we plan to limit enrollment for this pilot study to patients ≥ 18 years old. In addition, as no validated response criteria are available for cutaneous neurofibroma trials we will focus on assessing changes in the size (percent change in volume) of target cutaneous neurofibromas. We hope that findings from our trial will allow for the development of response criteria in future trials directed at cutaneous neurofibromas. In order to allow for consistent in the measurements we will have only three sites participating in the study, which will be trained in the measurement of cutaneous neurofibromas at UAB so that consistent measurements will be obtained.

2.4 CORRELATIVE STUDIES BACKGROUND

2.4.1 Effect of selumetinib on target inhibition in cutaneous neurofibroma(s)

Proposed studies from cutaneous neurofibroma biopsies/ excision: We hypothesize that inhibition of pERK is required for cutaneous neurofibroma shrinkage and that lack of response is a result of insufficient inhibition of pERK (integrated biomarker), or of upregulation of another pathway, such as AKT (exploratory biomarker). Our goal in this study will be to analyze this relationship by determining the percent decrease in pERK in paired biopsies/excisions of cutaneous neurofibromas obtained prior to treatment and on treatment with selumetinib. pAKT and changes in the tumor kinome will also be analyzed.

Evaluation of skin related morbidity using the skindex:

Cutaneous neurofibromas can severely affect the quality of life of individuals with NF1. As a

exploratory endpoint this study therefore aims to evaluate changes in patient reported outcomes (Skindex) during treatment with selumetinib. Skindex was chosen because the scale is validated for dermatologic skin diseases and has very good psychometric properties. The primary diagnoses in the validation paper were eczematous dermatitis, psoriasis, non-melanoma skin cancer, benign growths, warts, alopecia, acne rosacea, etc.(62), and the author says it can be used by patients with any skin condition. It also has been used in clinical trials, even as a primary endpoint (in a study evaluating treatments for basal cell carcinoma and squamous cell carcinoma), and it has been found to be sensitive to change(63). The Skindex has been used in individuals with NF1 in several studies and was found to "measure most of the dermatologic effects of NF1(28, 29, 64)." It assesses the domains of symptoms (e.g., itching, pain, burning, irritation, bleeding), functioning (e.g., relationships, daily living activities, work, and sleep), and emotions (e.g., worried, embarrassed, ashamed, frustrated, depressed), so it covers the areas that would seem to be affected by cutaneous neurofibromas and that may improve with effective treatment. Since this is a specific trial evaluating a treatment for cutaneous neurofibromas, which is a skin condition, it seems like the content of Skindex items is appropriate.

The Skindex will also be utilized to establish efficacious cutaneous neurofibroma volume reduction. A 20% reduction in average cutaneous neurofibroma volume has been established as the minimum response criterion; however, we are unable to know a priori the size reduction a patient considers to be significant. Therefore, surveys will be completed by study participants before selumetinib treatment (Day 0) after the first cycle and then after every 4 cycles of the clinical trial. Skindex measurements will be related to the cutaneous neurofibroma volume measurements collected at the same study visit to qualitatively determine an efficacious cutaneous neurofibroma volume reduction.

Evaluation of skin related morbidity using the Global Impression of Change Scale:

The patient Global Impression of Change (GIC) Scale is a single item scale that evaluates the clinical significance of changes in pain intensity or other morbidities. We will administer an adapted version of the GIC Scale at the follow-up PRO evaluations only (it should not be given pre-study because it assesses change from baseline). On the adapted GIC, patients will give their overall impression of change in cutaneous neurofibroma size. Patients will also be given the opportunity to describe any noticeable changes in a follow-up free text response.

Evaluation of pain using the Numeric Rating Scale:

The NRS-11 Pain Scale is a simple and commonly used numeric scale in which patients rate pain from 0 (no pain) to 10 (worst pain).This information will help evaluate the effects of the study drug on pain as well as provide data on clinically meaningful changes in pain.

2.4.2 Investigate genomic alterations that correlate with cNF size response to selumetinib treatment:

Clinical observation of patients with cutaneous neurofibromas reveal tumors of various sizes and our experience in measuring tumors suggests that different tumors in the same patient may grow at different rates. The cause of this heterogeneity is not known, but we hypothesize that tumors with faster growth or larger growth have a different genomic composition, such as more deleterious NF1 somatic mutation, other driver mutation(s), or epigenetic changes may underlie these differences. In addition, it is possible that different tumors will respond differently to selumetinib, and we will also be in a position to explore genetic or epigenetic factors that contribute to such differences, if they occur.

Biallelic inactivation of the NF1 gene is known to be required for tumorigenesis but several genes associated with mismatch repair (MMR) and regulatory cell cycle (e.g. TP53, CDKN2A, and RB1) have been implicated as modifiers of NF1-related tumors, especially malignant peripheral nerve sheath tumors [19, 20]. Thomas and colleagues (2010) analyzed 89 cNF from 3 unrelated patients and found that 64% had a detectable NF1 somatic mutation; 24% of these were due to NF1 loss of heterozygosity (LOH), and 24% had microsatellite instability (MSI)[21]. This group also analyzed TP53, CDKN2A, and RB1 and found no pathogenic mutations; however, 1 cNF had RB1 LOH and 4 DNs had TP53 LOH. These results suggest other genes may influence cNF development.

For this exploratory objective, genomic analyses of cNFs will be performed under the direction of Dr. Ashley Cannon to identify somatic mutations that are driving tumorigenesis as well as mutations that may be influencing tumor response to selumetinib. These are pilot genomic studies that may not have sufficient statistical power and will likely warrant more comprehensive analyses and larger sample sizes in future studies. Prior to selumetinib treatment, ≥1 cNF will be biopsied from each patient. If a decrease in cNF size is observed by cycle 12 of selumetinib treatment, two types of tissue will be collected from patients: at least 1 cNF with no change in size and at least 1 cNF with a substantial size decrease.

These exploratory investigations will be performed solely for research purposes, the results of which may not be directly interpretable to the clinical setting. There is no plan for looking for incidental findings that are relevant to other diseases. Therefore results will not be shared with patients or referring physicians.

3 ELIGIBILITY ASSESSMENT AND ENROLLMENT

3.1 ELIGIBILITY CRITERIA

3.1.1 Inclusion Criteria

3.1.1.1 Patients must be ≥ 18 years old at the time of enrollment and have a documented germline *NF1* mutation in a CLIA certified laboratory or a diagnosis of NF1 based on clinical NIH consensus criteria(65). In addition to substantial cutaneous neurofibroma burden as defined below, at least one of the criteria below have to be present:

- Six or more café-au-lait macules (≥0.5cm in prepubertal subjects or ≥1.5 cm in post pubertal subjects)
- Freckling in axilla or groin
- Optic glioma
- Two or more Lisch nodules
- A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex)
- A first-degree relative with NF1

Histologic confirmation of tumor is not necessary in the presence of consistent clinical findings.

3.1.1.2 Measurable disease: Patients must have substantial cutaneous neurofibroma burden causing distress to the patient by disfigurement or itching. Patients must have ≥ 9 measurable cutaneous neurofibromas. For the purpose of this study measurability will be defined for each of the

lesions selected as target lesions as a neurofibroma with a longest diameter ≥ 4 mm in the longest diameter.

3.1.1.3 ECOG performance status ≤2

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

3.1.1.4 Patients must have normal organ and marrow function as defined below:

- hemoglobin ≥10 g/dL (not requiring RBC transfusions)
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL (not requiring platelet transfusions)
- total bilirubin ≤ 1.5 X upper limit of normal (ULN), with the exception of patients with Gilbert Syndrome who are required to have ≤ 3 X ULN
- ALT(SGPT) ≤3.0 X ULN
- creatinine within normal institutional limits

OR

- creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.1.5 Ability of subject or Legally Authorized Representative (LAR)) to understand and the willingness to sign a written informed consent document.

3.1.1.6 Willingness to avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.

3.1.1.7 Willingness to avoid the ingestion of grapefruit and Seville oranges (as well as other products containing these fruits, e.g. grapefruit juice or marmalade) during the study.

3.1.1.8 Prior therapy:

- Since there is no standard effective chemotherapy for patients with NF1 and cutaneous neurofibromas, patients may be treated on this trial without having received prior medical therapy directed at their PN.

- Since selumetinib is not expected to cause substantial myelosuppression, there will be no limit to number of prior myelosuppressive regimens previously received for NF1 related or other tumor manifestations.
- Patients who have received previous investigational agents or biologic therapy, such as tipifarnib, pirfenidone, Peg-Intron, sorafenib, or other VEGFR inhibitors are eligible for enrollment.
- Growth factors that support platelet or white cell number or function must not have been administered within the past 7 days and are not permitted while on the study.
- At least 6 weeks must have elapsed prior to enrollment since the patient received any prior radiation therapy, and the target cutaneous neurofibromas have to be in areas outside of a prior radiation field.
- At least 4 weeks must have elapsed since receiving medical therapy directed at NF1 related tumor manifestations.
- At least 4 weeks must have elapsed since any surgeries, with evidence of completed wound healing.
- Patients who received prior medical therapy for a NF1 related tumor must have recovered from the acute toxic effects of all prior therapy to ≤ grade 1 CTCAE version 5.0 before entering this study.

3.1.1.9 The effects of selumetinib on the developing human fetus at the recommended therapeutic dose 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, for the duration of study participation, and for 4 weeks after dosing with selumetinib ceases. Women of child-bearing potential must have a negative pregnancy test prior to entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, the patient should inform her treating physician immediately. Please note that the selumetinib manufacturer recommends that adequate contraception for male patients should be used for 12 weeks post-last dose due to sperm life cycle.

3.1.1.10 Informed Consent: Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent from all patients, which can be accomplished using the study specific informed consent or another consent, such as the NCI, POB screening protocol. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for screening or baseline values even if the studies were done before informed consent was obtained, if the patient agrees.

3.1.2 Exclusion Criteria

3.1.2.1 Patients who are receiving any other investigational agents, or have received an investigational agent within the past 30 days.

3.1.2.2 May not have a NF1 related tumor such as optic pathway glioma or malignant peripheral nerve sheath tumor, which requires treatment with chemotherapy, radiation, or surgery.

3.1.2.3 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, active

bleeding diatheses or renal transplant, including any patient known to have hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements. Patients with HIV who have adequate CD4 counts and who have no requirement for antiviral therapy will be eligible.

3.1.2.4 Pregnant or breast-feeding females are excluded due to potential risks of fetal and teratogenic adverse events of an investigational agent. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method. Abstinence is an acceptable method of birth control.

3.1.2.5 Prior treatment with selumetinib or another specific MEK 1/2 inhibitor.

3.1.2.6 No supplementation with vitamin E is permitted.

3.1.2.7 Inability to swallow capsules, since capsules cannot be crushed or broken.

3.1.2.8 Refractory nausea and vomiting, chronic gastrointestinal diseases (e.g., inflammatory bowel disease), or significant bowel resection that would preclude adequate absorption.

3.1.2.9 Strong inhibitors or inducers of hepatic microsomal isoenzymes

3.1.2.10 While not an exclusion criterion, unless 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 known to be strong inhibitors or inducers of hepatic microsomal isoenzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5, UGT1A1, UGT1A3 and transporters BCRP and P-gp. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Section 17.1.1 is the Patient Drug Information Handout and Wallet Card that should be provided to patients. Known Cardiac Disorder, including:

- Uncontrolled hypertension (blood pressure [BP] of ≥150/95 despite medical support/management)
- Acute coronary syndrome within 6 months prior to starting treatment
- Uncontrolled angina – Canadian Cardiovascular Society grade II-IV despite medical support/management
- Heart failure NYHA Class II or above (for the NYHA Classification refer to Appendix II)
- Prior or current cardiomyopathy including but not limited to the following:
  - Known hypertrophic cardiomyopathy
- Known arrhythmogenic right ventricular cardiomyopathy
- Baseline left ventricular ejection fraction (LVEF) ≤ 53%
- Previous moderate or severe impairment of left ventricular systolic function (LVEF <40% on echocardiography or equivalent on Multi-Gated Acquisition Scan [MUGA]) even if full recovery has occurred.
- Severe valvular heart disease
- Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest
- QTcF interval >450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (*e.g.*, heart failure, hypokalemia, family history of long QT interval syndrome) are excluded. The use of medication(s) that can prolong QTc interval is

prohibited while treated on this study. For a comprehensive list of agents that prolong QTc refer to a frequently-updated medical reference, such as https://www.crediblemeds.org/everyone/composite-list-all-qtdrugs.

3.1.2.11 Known Ophthalmologic conditions, such as:

a. Current or past history of retinal pigment epithelial detachment (RPED)/central serous retinopathy (CSR)
b. Current or past history of retinal vein occlusion
c. Known intraocular pressure (IOP) > 21 mmHg (or ULN adjusted by age) or uncontrolled glaucoma (irrespective of IOP); patients with controlled glaucoma and increased IOP who do not have meaningful vision (light perception only or no light perception) may be eligible after discussion with the study chair.
d. Subjects with any other significant abnormality on ophthalmic examination (performed by an ophthalmologist) should be discussed with the Study Chair for potential eligibility
e. Ophthalmological findings secondary to long-standing optic pathway glioma (such as visual loss, optic nerve pallor or strabismus) or long-standing orbito-temporal PN (such as visual loss, strabismus) will NOT be considered a significant abnormality for the purposes of the study

3.1.2.12 Known severe hypersensitivity to selumetinib or any excipient of selumetinib or history of allergic reactions attributed to compounds of similar chemical or biologic composition to selumetinib

3.1.2.13 Have had recent major surgery within a minimum of 4 weeks prior to starting study treatment, with the exception of surgical placement for vascular access.

3.1.2.14 Have any unresolved chronic toxicity with CTC AE grade ≥ 2, from previous anti-NF1 therapy, except for alopecia.

3.1.2.15 Clinical judgment by the investigator that the patient should not participate in the study

3.2 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4 REGISTRATION PROCEDURES

4.1 Registration with the Coordinating Center

Authorized staff will register eligible candidates through a web-based data entry system called OnCore. OnCore is the UAB Comprehensive Cancer Center's Clinical Trial Management System. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol

before treatment begins will be considered ineligible and registration will be denied. A physician on the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist. Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the protocol Principal Investigator (PI).

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.
3. Enrollment and exclusion criteria will be entered through OnCore after receiving email confirmation from the Protocol PI (or his designee) that consented subject is eligible for study entry.
4. OnCore will send enrollment confirmation via automated email alerts to study protocol team, coordinating center, site PI, and site study coordinator.
5. Following registration, participants should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. The coordinating center should be notified of participant status changes as soon as possible by email.

4.2 SCREENING EVALUATION

Eligibility will be determined during a pre-study evaluation period after subjects have signed a screening consent or the protocol specific consent. Subject information must be entered onto a screening log and for subjects not enrolled; a brief reason will be entered onto the screening log.

Eligibility blood tests should be performed within 2 weeks (14 days) prior to enrollment on the trial unless otherwise stated (Appendix III). If greater than 7 days elapses between eligibility blood tests and starting therapy, blood tests should be repeated. If test results are outside the window of eligibility, they must be corrected prior to started therapy.

1. History and physical examination: Complete history, including prior and concurrent therapy; physical examination including performance status, blood pressure, height, weight, signs and symptoms. Documentation of substantial cutaneous neurofibroma burden, the presence of ≥ 9 measurable cutaneous neurofibromas, and the presence of distress to the patient should be documented prior to enrollment.
2. Hematology: Complete blood count with differential and platelets.
3. Chemistries: Electrolytes (including sodium, potassium, chloride, CO_2), calcium, phosphorus, magnesium, creatinine, BUN, glucose, ALT, bilirubin, urinalysis, total protein, albumin, amylase, lipase and CPK.
4. EKG/Echo: Electrocardiogram and echocardiogram to be performed within 8 weeks prior to enrollment on the trial.
5. Urine or serum pregnancy test for all females of childbearing potential. This test is to be performed within 72 hours prior to enrollment.

6. Ophthalmology evaluation: A complete ophthalmology evaluation will be performed pretreatment. Particular emphasis will be given to the evaluation of corneal opacification and retinal changes.

5 TREATMENT PLAN

5.1 STUDY DESIGN OVERVIEW

This is a limited institution open label pilot study in which all subjects will commence treatment with selumetinib orally at 50 mg /dose approximately every 12 hours (one cycle = 28 days). This dose corresponds approximately the pediatric phase II dose of selumetinib for children with NF1 and plexiform neurofibromas or for children with low-grade gliomas, which is 25 mg/m^2 BSA per dose. The recommended phase II dose of selumetinib for adults with refractory solid tumors is 75 mg per dose twice daily. This dose was evaluated in a phase II trial of selumetinib for adult with inoperable PN. The first 2 patients enrolled on this trial experienced toxicities requiring dose modification including skin rash and scalp pain. This adult trial was thus amended to initiate treatment at a dose of 50 mg per dose with an option to increase the dose to 75 mg per dose, provided the 50 mg dose is well tolerated. We will use the same strategy in this trial directed at cutaneous neurofibromas. Patients will be able to escalate to 75mg every 12 hours [BID], if the medication is tolerated well for the first cycle, with no toxicities of grade 2 or greater.

Patients will undergo regular evaluation for selumetinib related toxicities. In absence of treatment limiting toxicity, or progression of disease, patients may remain on treatment for a maximum of 24 cycles unless they experience a volume decrease in the target cutaneous neurofibromas, in which case treatment may continue for additional 12 cycles.

For response evaluation, the average volume of 3-5 small (longest neurofibroma diameter 4-7 mm) and 3-5 larger (longest neurofibroma diameter ≥8 mm) target cutaneous neurofibromas in 3 different body regions will be calculated at each response evaluation (baseline, and then after every 4 cycles). Cutaneous neurofibromas will be measured with calipers as developed by Dr. Korf, and volumes will be calculated by multiplying length, width, and height of each target neurofibroma. At each response evaluation the sum of the on-treatment volumes for the smaller tumors will be subtracted from the pre-treatment volumes of the same tumors to arrive at an overall percentage change in tumor size for each patient. This will be repeated for the larger tumors. Then, the average percentage change for each size category will be reported.

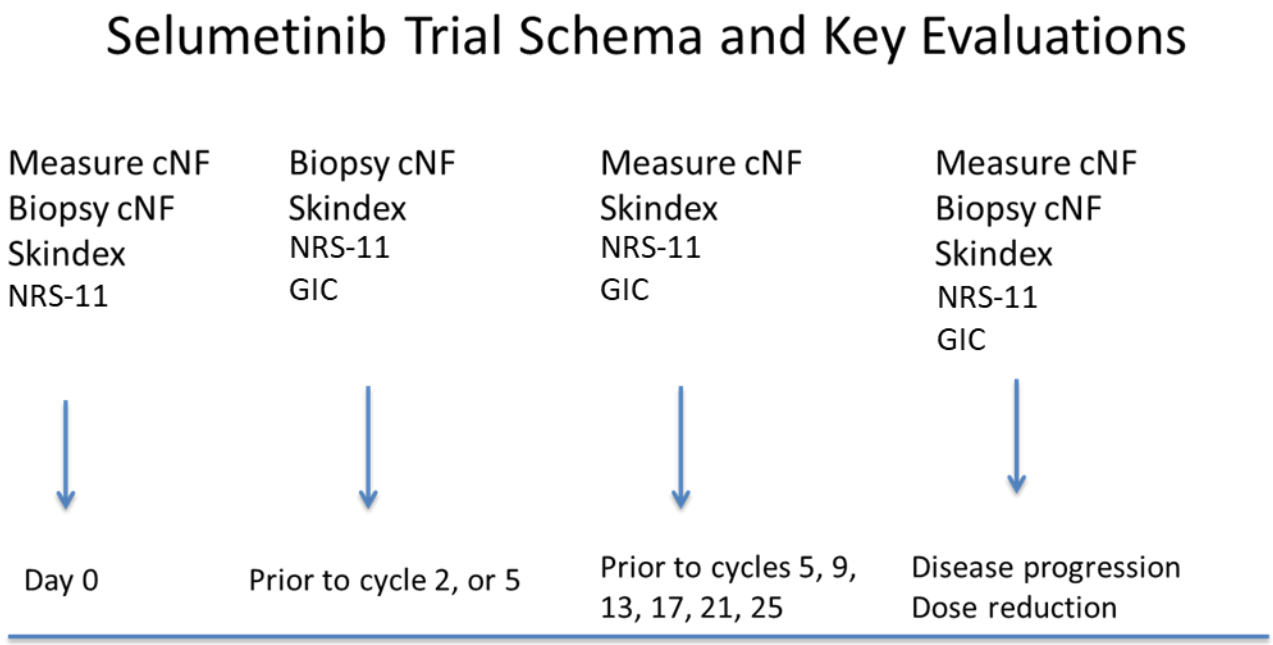
In absence of validated response criteria for cutaneous neurofibromas for the purpose of determining the duration of treatment with selumetinib, responsive disease will be defined as a ≥20% decrease in the average volume of the smaller or larger cutaneous neurofibromas compared to the baseline volume. Progressive disease will be defined as a ≥ 20% increase in the average volume of smaller or larger cutaneous neurofibromas compared to the baseline volume. Stable disease will be defined as measurements not meeting criteria for responsive or progressive disease.

In order to assess changes in skin related morbidity and pain, patients will complete both the Skindex (Appendix IV) and the Global Impression of Change Scale (Appendix X) along with the Numeric Rating Scale (Appendix XI), which are all patient reported outcome measures..

In order to evaluate the pharmacodynamic effects of selumetinib, patients will undergo mandatory excisions of ≥ 1 cutaneous neurofibroma prior to treatment and once on treatment with selumetinib to

assess percent inhibition of pERK and changes in pAKT and other molecular markers such as tumor kinome (Appendix VI).

The study schema is as follows:



- Selumetinib at 50 mg every 12 hours continuous dosing schedule (1 cycle -28 days)
- Selumetinib dose may be escalated to 75 mg every 12 hours after cycle 1, if tolerated (no toxicities of grade 2 or greater).
- Dose determined by pediatric phase I study in NF1 PN
- Regular safety evaluations including physical exam, laboratory evaluations, ophthalmology evaluation, echocardiogram, EKG

cNF= cutaneous neurofibroma

5.2 AGENT ADMINISTRATION

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. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Selumetinib will be supplied in in 10 mg (plain white) and 25 mg blue capsules. Selumetinib will be administered orally twice daily (approximately every 12 hours) at a dose of 50 mg per dose on a continuous dosing schedule (1 cycle =28 days) with no rest periods between cycles. Patients will be able to escalate to 75 mg BID if the medication is tolerated well for the first cycle, with no toxicities of grade 2 or greater.

Patients should be instructed to take the dose of selumetinib on an empty stomach (no food or drink other than water for 2 hours before and 1 hour after dosing) with water only. The capsules cannot be crushed and have to be swallowed whole.

Patients will be instructed to keep a diary of medication taken (Section **17.7** Appendix VI) to document intake of each dose of selumetinib and potential side effects. The patient diary will be reviewed at the time of study visits.

Patients should avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.

5.3 DURATION OF TREATMENT

In absence of treatment limiting toxicity, or progressive disease, patients may remain on treatment for a maximum of 24 cycles unless they experience a volume decrease in the target cutaneous neurofibromas, in which case treatment may continue for additional 12 cycles.

Patients who discontinue treatment with selumetinib will be monitored after every 4 months for 12 months off treatment for changes in cutaneous neurofibroma volume and number. Patients who are permanently removed from treatment with selumetinib will also continue to be followed for 30 days after the last dose of selumetinib until toxicities have resolved to baseline or stabilized, OR they no longer meet criteria for reporting (whichever is later).

5.4 SUPPORTIVE THERAPIES

Appropriate antibiotics, blood product support, anti-emetics, and general supportive care will be used as indicated.

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

- Patients experiencing **edema** should have cardiac ejection fraction (EF) measurements, serum chemistry (including electrolytes and albumin), and routine urinalysis.
- Patients with symptoms consistent with **cardiac** impairment (e.g., congestive cardiac failure, edema, or dyspnea) should have EF measurements (MUGA scan or echocardiography) at the time of the event as well as other routine investigations. Decreases in left ventricular ejection fraction (LVEF) from baseline (if known) may be investigated according to the algorithm described in Section 6.3.
- **Respiratory** events (pulmonary edema) should be followed up with an electrocardiogram, EF measurement, and chest X-ray. All new dyspnea AEs or worsening of pre-existing dyspnea AEs should be followed according to the dyspnea management algorithm (Appendix V).
- Oxygen saturation will be measured at baseline and again following any respiratory event.
- Patients experiencing visual disturbances should undergo a complete ophthalmologic examination, including a slit lamp examination.

5.4.2 Dermatologic adverse events:

The use of medications for the supportive care of rash is permitted, provided that compliance with Appendix I regarding concomitant medications is observed(66). Early initiation of treatment for rashes is strongly recommended to minimize the duration and severity of the adverse event. For pediatric subjects, the following guidelines have been found to be useful:

Acneiform rash:

Experience with acneiform rash suggests that topical clindamycin gel or lotion applied BID, rather than steroids, is the most helpful for pustular rash. In severe cases, semisynthetic oral tetracyclines such as doxycycline or minocyline may also be useful.

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.

For any questions regarding management of skin toxicity, please contact: Dominique Pichard (Email: picharddc@nih.gov, phone 301-594-3457).

5.4.3 Visual adverse events:

All patients will have a detailed ophthalmologic evaluation at baseline. In patients who develop visual symptoms, a repeat ophthalmologic evaluation will be performed to include: best corrected visual acuity, intraocular pressure, slit lamp fundoscopy (photograph if abnormal); consider optical coherence tomography.
If a diagnosis of retinal pigment epithelial detachment (PRED) or central serous retinopathy (CSR) is made, treatment with selumetinib will be held and repeat ophthalmologic evaluations will be performed until resolution. Treatment may be restarted after a dose reduction using the criteria described in Section 6.
If a diagnosis of retinal vein occlusion (RVO) is made, selumetinib will be discontinued permanently. For the development of cornea or lens opacification see Section 6.1.

5.4.4 Gastrointestinal adverse events: Diarrhea

Patients should be made aware that they may experience diarrhea, and should be encouraged to record the number of stools and possible associated symptoms in the patient diary (Section 17.7, Appendix VII). Patients should be given loperamide to take home and should start taking loperamide immediately after the first episode of unformed, loose stool (in accordance with local regulations and practice). Additional agents may be used concurrently if loperamide is not adequate to control diarrhea as a single agent.

In addition, the following dietary advice should be considered: BRAT diet (bananas, rice, apple sauce, toast, plain pasta), readily digestible food, avoidance of lactose-containing products and fried, fatty or spicy foods, increased fluid intake (8-10 glasses of clear fluids/day (including water, clear broth, fluids containing salt and sugar). Patients should be encouraged to seek advice early from their physician or study nurse if they have persistent diarrhea, diarrhea complicated by vomiting, or inability to take oral liquids.

5.4.5 Gastrointestinal adverse events: Oral mucositis

Patients should be encouraged to follow a daily oral health care regime, both before and during treatment with selumetinib.

Patients with a healthy mouth may use nonalcoholic mouthwash 4 to 6 times daily (e.g. after each meal), or according to the instructions, during the study.

Saline mouthwashes (Sodium chloride 0.9%) are preferred in cases of stomatitis, and should be used at a different time than 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.

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. The toothbrush should be replaced regularly (at least every 3 months). Patients with stomatitis should change their toothbrush every 4 - 6 weeks.

Consider treating stomatitis at an early stage (CTCAE grade 1) or as soon as the patient complains of a sore mouth. Consider using an oral topical analgesic, with or without topical steroids, depending on the patient's clinical condition and the local standard medical practice.

Consider culture to rule out herpes simplex.

5.4.6 Pulmonary adverse events: Dyspnea

Patients who develop dyspnea while receiving selumetinib should undergo standard clinical evaluations to rule out infectious etiology and pneumonitis. Selumetinib will be held for grade ≥2 pneumonitis, and may be restarted at a reduced dose following criteria for dose reduction in Section 6.

5.4.7 Surgical procedures

Major surgery will require holding selumetinib 1 week prior to surgery and until wound has healed completely.

5.5 CONCURRENT THERAPIES

1) Other cancer chemotherapy, radiation, immunotherapy, biologic therapy, hematopoietic growth factors, or investigational agents cannot be administered to patient while receiving selumetinib.

2) Doses of vitamin E greater than the 100% daily recommended doses are contraindicated.

   Selumetinib capsules contain vitamin E in the form of D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-soluble form of vitamin E which acts as a formulation excipient.

Capsule	Ingredient	Maximum amount of Vitamin E per capsule
10 mg	Active	32.4 mg
25 mg	Active	35.9 mg

The maximum daily dose of vitamin E that a study subject may receive from selumetinib is approximately 143.6 mg/day (patients who receive 50 mg BID) or 215.4 mg (patients who receive 75 mg BID) or 136.6 mg/day (patients who receive 35 mg BID) or 71.8 mg/day (patients who receive 25 mg BID). Therefore:

   a. Patients should not take any supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interfere with blood coagulation processes.
   b. Selumetinib should be administered with caution in patients who are also receiving concomitant coumarin anticoagulant medications, e.g. warfarin. These patients should have their INR monitored / anticoagulant assessments conducted more frequently and the dose of the anticoagulant should be adjusted accordingly.

3) The use of corticosteroids for control of symptoms related to the underlying NF1 or for other reasons will be allowed.

4) Patients should avoid medications that are known to be strong inhibitors or inducers of hepatic microsomal isoenzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5, UGT1A1. UGT1A3 and transporters BCRP and P-gp. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. Refer to the patient drug interaction handout and wallet card in Appendix 1.

5.6 Criteria for Removal from Protocol Therapy and Off Study Criteria

5.6.1 Criteria for removal from protocol therapy

1. A patient may be removed from the protocol treatment for the following non-medical or administrative reasons:
   a. Patient refusal of further treatments (reasons must be noted on the patient's CRF).
   b. It is deemed in the best interest of the patient. In this instance the PI should be notified and the reasons of withdrawal should be noted in the CRF.
   c. Serious protocol deviation or serious non-compliance as determined by the PI.
2. Any patient who develops treatment-limiting toxicity, which does not resolve to meet study parameters within 21 days of drug discontinuation or within the time frame defined in Section 6.1.

3. If treatment-limiting toxicity recurs in a patient who has resumed treatment after two dose reductions.
4. Any patient with clinical evidence of progressive disease on treatment following any treatment cycle will be removed from study treatment.
5. A patient who develops a concurrent serious medical condition that might preclude or contraindicate the further administration of selumetinib will be removed from the study. A patient who becomes pregnant will be immediately taken off therapy.
6. Patients who initiate another cutaneous neurofibroma directed therapy will be removed from therapy.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent is withdrawn.

Toxicities must be followed until stabilization or resolution prior to a subject being taken 'off study'.

5.6.2 Off-Study Criteria

- Completed study follow-up period. Patients will be followed for 30 days after the last dose of selumetinib, when treatment related toxicities have returned to baseline or stabilized, OR they no longer meet criteria for restarting treatment as outlined in Section **6.2**(whichever is later).
- Withdrawal of consent for any further data submission
- Noncompliance with study requirements
- Death

Authorized staff must notify OnCore when a subject is taken off-study.

6 DOSING DELAYS/DOSE MODIFICATIONS

6.1 TREATMENT LIMITING TOXICITIES

Selumetinib will be held for selumetinib related toxicities requiring dose modifications: Any ≥ grade 3 hematologic or non-hematologic toxicities with the specific **exclusion** of:

- Skin rash, which can be managed successfully with supportive intervention including initiation of oral doxycycline or minocycline.
- Asymptomatic grade 3 creatine kinase elevation, which remains <10 x ULN.
- Gastrointestinal toxicity, such as grade 3 diarrhea, nausea, or vomiting, which can be managed successfully with supportive intervention within 72 hours.
- Grade 3 elevation of ALT or AST that return to levels to meet initial eligibility criteria within 14 days of selumetinib interruption and that do not recur upon re-challenge of selumetinib.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation.
- Grade 3 cataracts will be considered on a case by case basis with consultation with the PI and ophthalmology.

In addition, selumetinib may be held for any ≥ grade 2 related toxicities of ≥7 days if they are intolerable to the patient and cannot be controlled with standard supportive measures.

6.2 DOSE MODIFICATIONS

If the toxicity resolves to meet study parameters or ≤ grade 1 within 21 days of drug discontinuation or the toxicity resolves to meet study parameters or ≤ grade 1 within 3 months and the patient was receiving clinical benefit as defined below, the patient may resume treatment at a dose reduced by 30%, which is a dose of 35 mg/dose (See Figure 3).

Subjects with AEs that are manageable with supportive therapy may not require dose reductions (*e.g.*, nausea/vomiting may be treated with antiemetics, diarrhea may be treated with loperamide, electrolyte abnormalities may be corrected with supplements rather than by dose reduction).

Dose reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose. Selumetinib doses held while the patient is recovering from toxicity should not be made up and the cycle remains 28 days.

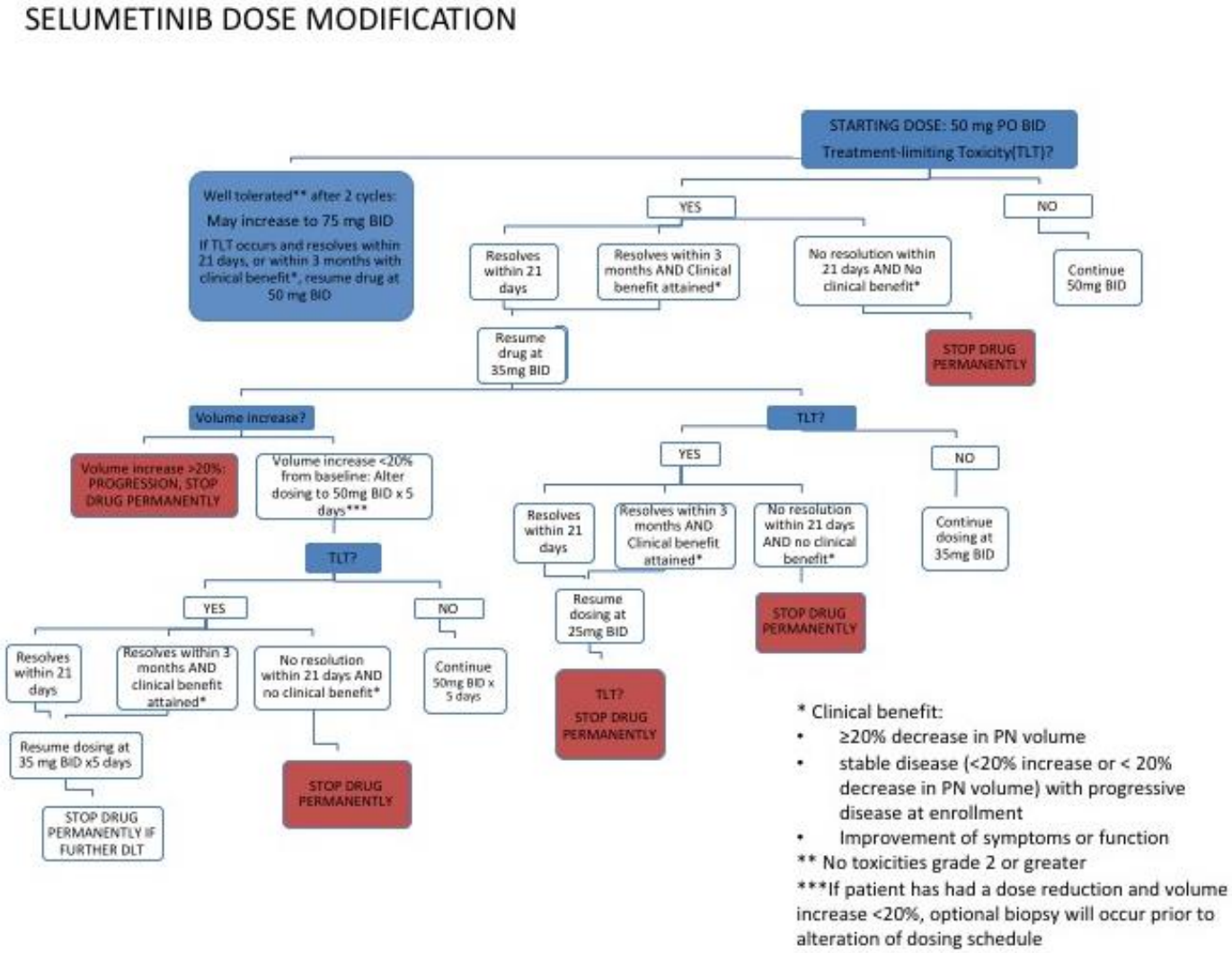
If disease progresses after dose reduction to > 20% increase in tumor volume, the patient will be removed from study treatment, but if volume increases ≤ 20%, the patient may resume dosing at 50 mg BID for 5 days each week (2 day rest/week). If the treatment limiting toxicity recurs on this schedule, the same rules will apply (if the toxicity resolves to meet study parameters or ≤ grade 1 within 21 days of drug discontinuation or the toxicity resolves to meet study parameters or ≤ grade 1 within 3 months and the patient was receiving clinical benefit), the patient may resume treatment at a dose of 35 mg/dose BID X 5 days per week.

Subjects will be withdrawn from the study if they fail to recover to CTCAE Grade 0-1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related AE within 21 days OR they experience agent-related AEs requiring dose modification despite two previous dose reductions (*i.e.*, would require a third dose reduction) unless the investigator and CTEP monitor agree that the subject should remain in the study because of evidence that the patient is/may continue deriving benefit from continuing study treatment (*i.e.*, patient has partial response [PR], complete response [CR], or stable disease [SD] for ≥3 months). The appropriate reduced dose will be determined after discussion between the principal investigator and CTEP monitor. Benefit will be defined as either responsive disease (≥20% decrease in the average volume of smaller or larger cutaneous neurofibromas), or stable disease (<20% increase or < 20% decrease in the average volume of smaller or larger cutaneous neurofibromas) in a patient who enrolled on the trial with progressive disease, or improvement of symptoms or function. For example, patients who experience dose limiting cardiotoxicity (decreased LVEF) and whose LVEF recovers to meet study parameters within >21 days but ≤3 months, may upon recovery continue protocol therapy at the reduced dose provided they have previously experienced clinical benefit while receiving selumetinib.

If treatment-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose, the dose may be reduced a second time from 35 mg per dose to 25 mg per dose if administered on a twice daily continuous dosing schedule using the same criteria, i.e., toxicity resolves to meet study parameters or ≤ grade 1 within 21 days of drug discontinuation, dose may not be re-escalated, doses held will not be made up. If treatment-limiting toxicity recurs after two dose reductions, the patient must be removed

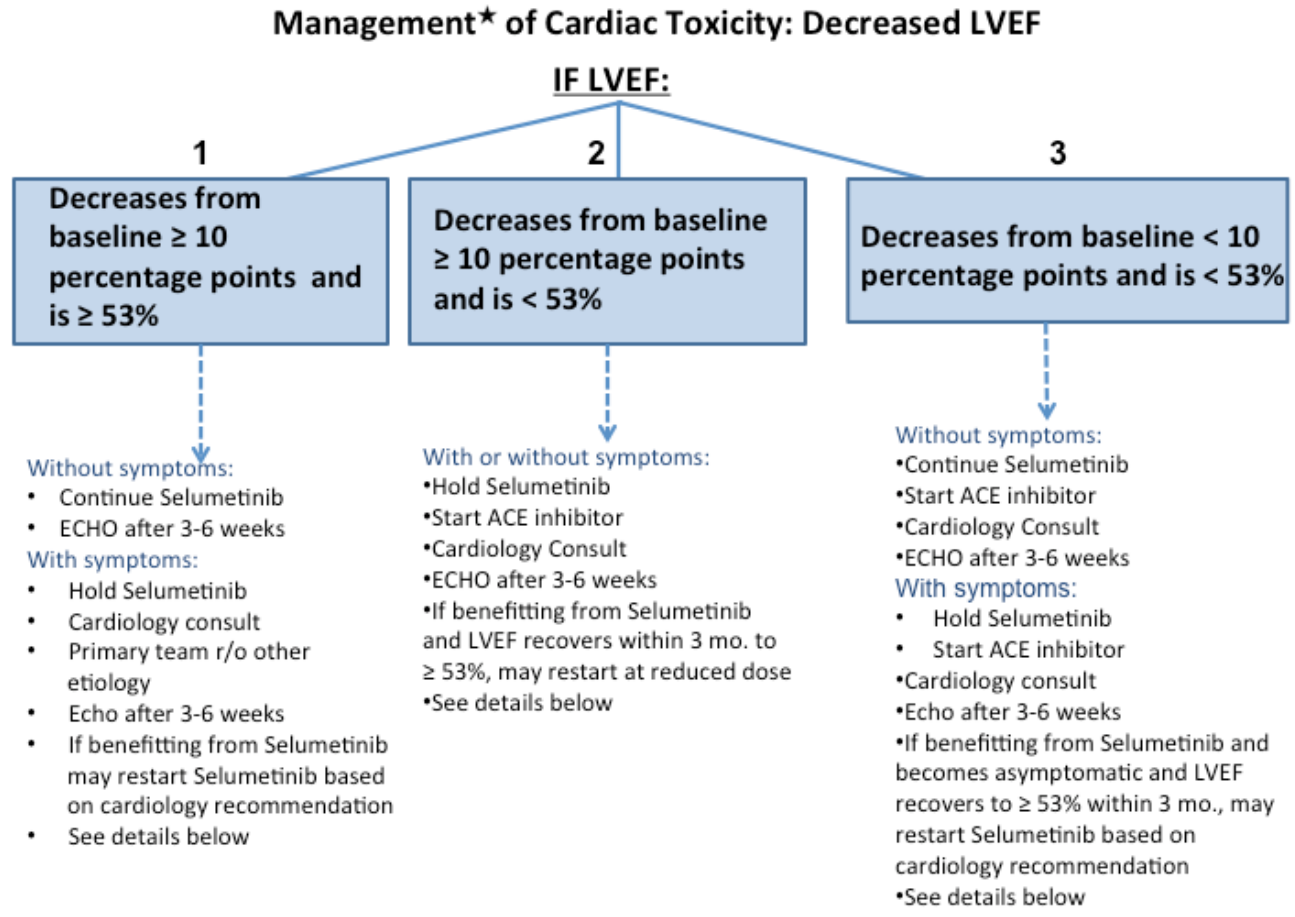
from protocol therapy. Patients removed from study therapy for toxicity will be followed until resolution of toxicity and off study criteria are met.

Figure 3: Selumetinib Dose Modification Schema



6.3 CARDIAC TOXICITY

Cardiac toxicity will be managed as described below in the figure below:



*Management can be modified as directed by consulting cardiologist.

1) Decline in LVEF from baseline of ≥ 10 percentage points but with a normal EF of ≥ 53%

- Patients who have an asymptomatic decline in LVEF from baseline of ≥ 10 percentage points but continue to have a normal EF of ≥ 53% (if a range is given then the upper limit of the range will be used) will continue on treatment with selumetinib and have a repeat ECHO 3-6 weeks later.
- Patients who have a symptomatic decline in LVEF from baseline of ≥ 10 percentage points but continue to have a normal EF of ≥ 53% (if a range is given then the upper limit of the range will be used) selumetinib will be held. A cardiology consult will be initiated to determine the etiology of the symptoms and direct management. At the same time the primary team will investigate other possible etiologies of the symptoms. The ECHO will be repeated in these patients after 3-6 weeks and as recommended by cardiology. If the patient is receiving benefit from selumetinib (see Section 6.2), and if symptoms were found to be related to heart failure selumetinib will be

restarted at reduced dose. If symptoms were unrelated to heart failure, selumetinib may be resumed at full dose.

2) Decline in LVEF from baseline of ≥ 10 percentage points with an EF < 53%

- For patients who have a symptomatic or asymptomatic decline in LVEF from baseline of ≥ 10 percentage points to < 53% (if a range is given then the upper limit of the range will be used), selumetinib will be held. Treatment with an ACE inhibitor should be initiated as soon as possible, and these patients will be referred to cardiology for additional evaluation and treatment. The ECHO will be repeated on these patients after 3-6 weeks, and as recommended by cardiology until recovery from toxicity (LVEF ≥ 53%). ECHOs will then be performed as described in Figure 3. If the LVEF returns to ≥ 53% within 3 months of discontinuation of selumetinib, and the patient is receiving benefit from selumetinib (see Section 6.2), and symptoms have resolved, selumetinib may be restarted at a reduced dose.

3) Decline in LVEF from baseline of < 10 percentage points with an EF < 53%

- For patients who have an asymptomatic decline in LVEF from baseline of < 10 percentage points to < 53% (if a range is given then the upper limit of the range will be used), selumetinib will be continued. Treatment with an ACE inhibitor should be initiated as soon as possible, and these patients will be referred to cardiology for additional evaluation and treatment. An ECHO will be performed after 3-6 weeks and as directed by cardiology. Treatment with selumetinib can be continued for as long as the decrease in LVEF remains less than 10 percentage points from baseline in these patients and patients remain asymptomatic.
- Patients who have a symptomatic decline in LVEF from baseline of < 10 percentage points to < 53% (if a range is given then the upper limit of the range will be used), selumetinib will be held. Treatment with an ACE inhibitor should be initiated as soon as possible, and these patients will be referred to cardiology for additional evaluation and treatment. The ECHO will be repeated in these patients after 3-6 weeks and as recommended by cardiology until recovery of LVEF to ≥ 53%. ECHOs will then be performed as described in Figure 3. If the LVEF returns to ≥ 53% within 3 months of discontinuation of selumetinib, and the patient is receiving benefit from selumetinib (see Section 6.2) and symptoms resolve, selumetinib may be restarted based on cardiology recommendation. If symptoms were related to heart failure selumetinib will be restarted at reduced dose. If symptoms were unrelated to heart failure, selumetinib may be resumed at full dose.

Recommendations for treatment with ACE inhibitors:

For patients meeting criteria to start an ACE inhibitor the following suggestions for choice and dosing of ACE inhibitors before cardiology consultation are made. These can be modified by institutional guidelines or cardiology.

1) Enalapril: start at 2.5 mg PO once daily.
2) Lisinopril: start at 2.5 mg PO once daily.
3) Captopril: start 6.25-12.5 PO mg TID.
4) The above doses are starting doses. ACE inhibitor doses should be titrated upwards if tolerated by blood pressure and renal function; doses should be reduced by 50% in patients with hypovolemia, hyponatremia, or decreased renal function, or if receiving diuretics.
5) After initiation, treatment with an ACE inhibitor should be continued for the duration of the study unless otherwise directed by cardiology.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. 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).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LIST (CAEPR)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 986 patients. Below is the CAEPR for Selumetinib (AZD6244).

NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Adverse Events with Possible Relationship to Selumetinib (AZD6244 hydrogen sulfate), AZD6244 (CTCAE 5.0 Term) [n= 986]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Febrile neutropenia[2]	
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	***Left ventricular systolic dysfunction (Gr 2)***
EYE DISORDERS			
		Blurred vision	
		Eye disorders - Other (central serous retinopathy)	
		Eye disorders - Other (retinal pigment epithelial detachment)	
		Eye disorders - Other (retinal vein occlusion)	
	Periorbital edema		

Adverse Events with Possible Relationship to Selumetinib (AZD6244 hydrogen sulfate), AZD6244 (CTCAE 5.0 Term) [n= 986]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea[3]			***Diarrhea[3] (Gr 3)***
	Dry mouth		
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema face		***Edema face (Gr 2)***
Edema limbs			***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Pain		
INFECTIONS AND INFESTATIONS			
		Folliculitis	
		Nail infection	
		Papulopustular rash	
	Paronychia		
		Skin infection	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	CPK increased		***CPK increased (Gr 3)***
		Ejection fraction decreased	
	Neutrophil count decreased		
	Platelet count decreased		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Hyperphosphatemia	
		Hypoalbuminemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
		Growth suppression	
		Musculoskeletal and connective tissue disorder - Other (neck extensor muscle weakness)	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		

Adverse Events with Possible Relationship to Selumetinib (AZD6244 hydrogen sulfate), AZD6244 (CTCAE 5.0 Term) [n= 986]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dry skin		***Dry skin (Gr 2)***
	Pruritus		
Rash acneiform			***Rash acneiform (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
VASCULAR DISORDERS			
	Hypertension		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Febrile neutropenia/neutropenic infection has been observed primarily in trials combining Selumetinib (AZD6244) and docetaxel.

[3]SBE-CD (Captisol®, vehicle) in the mix and drink formulation is known to cause soft stools and/or diarrhea in rats and dogs; however, it is possible that some of these findings might be related to exacerbation of the vehicle effect by Selumetinib (AZD6244).

Adverse events reported on Selumetinib (AZD6244) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Selumetinib (AZD6244) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hemorrhagic anemia)

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Atrioventricular block first degree; Cardiac disorders - Other (Takotsubo cardiomyopathy syndrome); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Heart failure; Myocardial infarction; Palpitations; Pericardial effusion; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia

EYE DISORDERS - Dry eye; Eye disorders - Other (bilateral macular edema); Eye disorders - Other (black haze in line of vision); Eye disorders - Other (chalazion); Eye disorders - Other (diplopia); Eye disorders - Other (retinal bleeding); Eye disorders - Other (spotty vision; itchy vision); Flashing lights; Floaters; Glaucoma; Optic nerve disorder; Papilledema; Photophobia; Retinal detachment; Retinopathy; Uveitis; Vision decreased

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Bloating; Cheilitis; Colitis; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastric hemorrhage; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (pneumatosis coli); Gingival pain; Ileal stenosis; Oral hemorrhage; Rectal hemorrhage; Stomach pain; Upper gastrointestinal hemorrhage

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Disease progression; Facial pain; Flu like symptoms; Generalized edema; Localized edema; Malaise; Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (liver dysfunction/ failure [clinical])

INFECTIONS AND INFESTATIONS – Infection[4]

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin I increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Electrocardiogram T wave abnormal; Hemoglobin increased; INR increased; Investigations - Other (ECG signs of myocardial ischemia); Lipase increased; Lymphocyte count decreased; Lymphocyte count increased; Serum amylase increased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (electrolyte abnormalities); Metabolism and nutrition disorders - Other (elevated calcium phosphorus product); Metabolism and nutrition disorders - Other (sensation of warmth)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Joint range of motion decreased; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (bilateral stiffness hands and feet [intermittent]); Musculoskeletal and connective tissue disorder - Other (muscle weakness neck); Musculoskeletal and connective tissue disorder - Other (neck myopathy); Myalgia; Myositis; Neck pain; Pain in extremity; Rhabdomyolysis

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain

NERVOUS SYSTEM DISORDERS - Amnesia; Cognitive disturbance; Concentration impairment; Depressed level of consciousness; Dysarthria; Dysgeusia; Dysphasia; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Leukoencephalopathy; Memory impairment; Oculomotor nerve disorder; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Seizure; Spinal cord compression; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delusions; Depression; Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Nephrotic syndrome

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal inflammation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchopulmonary hemorrhage; Epistaxis; Hoarseness; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleural effusion; Pulmonary edema; Sore throat; Voice alteration; Wheezing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Erythroderma; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Scalp pain; Skin and subcutaneous tissue disorders - Other (skin fissures); Skin ulceration; Stevens-Johnson syndrome; Urticaria

VASCULAR DISORDERS - Flushing; Hypotension; Lymphedema; Thromboembolic event

Note: Selumetinib (AZD6244) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 DEFINITIONS

7.2.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

7.2.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.2.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected” also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure 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

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.2.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- 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 this definition.

7.2.6 Disability

A substantial disruption of a person’s ability to conduct normal life functions.

7.2.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.2.8 Protocol Deviation:

Any change, divergence, or departure from the IRB-approved research protocol.

To accommodate changes in patients’ schedules, holidays, and provide flexibility for long term follow up, any change or divergence in the scheduling or conduct of examinations, tests and scans described in this protocol will NOT be considered a protocol deviation and will not require reporting to the IRB unless it meets the definition of unanticipated problem or non-compliance. Similarly, 1) isolated missed

lab values or missed selumetinib doses will be documented, but not be reported as a protocol deviation, and 2) isolated missing lab values will be noted, but not reported as protocol deviation.

7.2.9 Non-compliance

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.2.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3 COORDINATING CENTER AND IRB REPORTING

In addition to the requirements below, the responsibilities of the protocol chair and the coordinating center are listed in Section 17.10, Appendix IX. The PI of each site will report AE, SAEs and IND safety reports to their respective IRB(s) according to the institutional policies and procedures.

7.3.1 IRB Expedited Reporting of Unanticipated Problems and Deaths

The Coordinating Center PI will be responsible for reporting all SAEs to the IRB of the Coordinating Center. The PI of the Coordinating Center will report to the IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received by the IRB within 7 working days of PI awareness according to the institution's procedures.

7.3.2 IRB Requirements for PI Reporting at Continuing Review

The Coordinating Center PI is responsible for reporting all AEs occurring on this study to the IRB of the Coordinating Center at the time of the continuing review. The PI of the Coordinating Center will report to the IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

- All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.3.3 IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the UAB IRB.

7.4 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS TO CTEP A

All observed or volunteered adverse events, regardless of treatment group or suspected causal relationship to study drug, will be recorded on the Adverse Event page(s) of the case report form. Adverse events will be identified and graded using the NCI Common Toxicity Criteria version 5.0 (CTCAE version 5.0). Next it will be determined if the adverse event is related to the medical treatment (attribution). If so, it will be determined whether the adverse event is expected or unexpected. Using the guidelines outlined in this section, adverse events will then be reported to the NCI using a routine report (CDUS), and if required, the CTEP Adverse Event Reporting System (CTEP-AERS), an electronic system for expedited submission of adverse event reports. Information regarding CTEP-AERS and instructions for training is available on the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

The adverse event page will contain information if the reported event was expected or unexpected, and if the reported toxicity is included in the informed consent. A justification will be provided on the adverse event page if the observed toxicity in not included in the informed consent. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the sponsor. Follow-up of the adverse event, even after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.

7.4.1 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).

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section

10.1.2.

- **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.

7.4.2 Expedited Adverse Event Reporting to CTEP

Expedited AE reporting for this study must use CTEP Adverse Event Reporting System (CTEP-AERS), accessed Information regarding CTEP-AERS and instructions for training is available on the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm. The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below.

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.4.3 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.4.4 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions. 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.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via electronic submission within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
1. Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.

- "10 calendar days" – A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Hospitalization for management of NF1 related complications unrelated to study drug will not require expedited reporting.

7.4.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through** CTEP-AERS **must <u>also</u> be reported in routine study data submissions.**

7.4.6 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). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia (27))
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.4.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

7.5 DATA SAFETY MONITORING PLAN

7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. The UAB and NCI study teams will have bi-weekly conference calls to discuss the study progress, adverse events, and any potential problems.

The OnCore trial management system electronically integrates patient demographics, study-specified visits, and procedures/activities. This data is easily accessible to study investigators by electronic case report forms. Severe adverse events and adverse events are also captured within the system. OnCore utilizes several reporting tools for the generation of numerous customized reports utilized by management and leadership staff. The system and all clinical patient data is secure behind the UAB firewall and secure server with access only granted to staff with an approved ID and Password

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB and to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.5.2 Sponsor Monitoring Plan

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

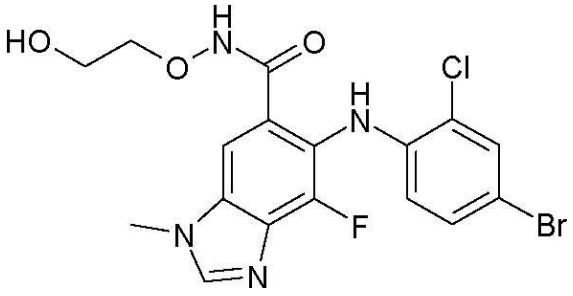
8 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

8.1 SELUMETINIB

Chemical name (IUPAC): 5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-6-[(2-hydroxyethoxy)carbamoyl]-1-methyl-1H-benzimidazol-3-ium hydrogen sulfate

Other Names: KOSELUGO, Selumetinib Hydr-sulfate; selumetinib sulfate; ARRY-142886

Chemical Structure:



Classification: Mitogen-activated protein kinase (MEK) inhibitor

CAS Registry Number: 606143-52-6

Molecular Formula: $C_{17}H_{15}BrClFN_4O_3.H_2SO_4$ **M.W.:** 555.76

Solubility: Very low aqueous solubility (2.4 mcg/mL at pH 7.4).

8.1.1 Mode of Action:

Selumetinib (AZD6244 hydrogen sulfate) is a selective mitogen-activated protein kinase (MEK) inhibitor. By inhibiting MEK, selumetinib (AZD6244 hydrogen sulfate) inhibits ERK phosphorylation, which may inhibit oncogenic growth signaling in tumor cells by targeting the RAS/RAF/MEK/ERK pathway. The RAS/RAF/MEK/ERK pathway is an important mediator of many cellular processes including proliferation, survival, differentiation, apoptosis, motility, and metabolism.

8.1.2 How Supplied:

AstraZeneca supplies and PMB, CTEP, DCTD distributes selumetinib (AZD6244 hydrogen sulfate). The agent is supplied as hydroxypropylmethylcellulose (HPMC) capsules available in 10 mg and 25 mg strengths, expressed as free base. Capsules are packaged in high density polyethylene (HDPE) containers with induction-seals and child-resistant closures. Each bottle contains 60 capsules with desiccant.

- 10 mg: white, opaque, size 4 hard capsule, banded and marked with "SEL 10" in black ink. The capsule shell contains hypromellose, carrageenan, potassium chloride, titanium dioxide, carnauba wax, and purified water. The capsule is imprinted with black ink that contains shellac, iron oxide black, propylene glycol and ammonium hydroxide.
- 25 mg: blue, opaque, size 4 hard capsule, banded and marked with "SEL 25" in black ink. The capsule shell contains hypromellose, carrageenan, potassium chloride, titanium dioxide, FD&C blue 2, ferric oxide yellow, purified water, carnauba wax, and/or corn starch. The capsule is imprinted with black ink that contains ferric oxide red, ferric oxide yellow, FD&C Blue 2 aluminum lake, carnauba wax, shellac, and glyceryl monooleate.

Selumetinib (AZD6244 hydrogen sulfate) capsules contain vitamin E as the excipient D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Each 10 mg capsule contains 32 mg vitamin E as TPGS and each 25 mg capsule contains 36 mg vitamin E as TPGS.

8.1.3 Storage:

Store the selumetinib (AZD6244 hydrogen sulfate) capsules at controlled room temperature (20°C-25°C). Brief excursions are permitted between 15°C and 30°C.

If a storage temperature excursion is identified, promptly return selumetinib (AZD6244 hydrogen sulfate) to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

8.1.4 Stability:

Shelf-life stability studies are ongoing. Dispense selumetinib (AZD6244 hydrogen sulfate) capsules in the manufacturer's HDPE container. Do not remove desiccant. Protect from moisture. Once the container induction seal is broken the water vapor transmission rate is higher than the intact induction sealed bottle. Significant increase in the moisture content can affect the drug product. The current stability data for selumetinib (AZD6244 hydrogen sulfate) capsules supports an in-use period of up to 60 days.

If repackaging into a pharmacy-supplied HDPE bottle is necessary for patient dispensing, provide a detailed description of the bottle to PMBAfterHours@mail.nih.gov for determination of

suitability. The container must be repackaged with desiccant. A 60 day in-use period from the point at which the patient reopens the bottle is permitted.

8.1.5 Route of Administration:

Oral. Do not eat or drink (except water only) for 2 hours prior to dosing and 1 hour after dosing selumetinib (AZD6244 hydrogen sulfate) capsules.

8.1.6 Potential Drug Interactions:

Avoid concomitant intake of supplemental vitamin E. High vitamin E doses may potentiate warfarin's anticoagulant activity. Monitor PT/INR more frequently in patients receiving both warfarin and selumetinib (AZD6244 hydrogen sulfate) capsules.

Selumetinib (AZD6244 hydrogen sulfate) is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C19, CYP1A2, CYP2C9, CYP2E1, and CYP3A5. Selumetinib (AZD6244 hydrogen sulfate) also undergoes glucuronidation by UGT1A1 and UGT1A3. The active human Phase I metabolite, N-desmethyl selumetinib, is approximately 3- to 5-times more potent than selumetinib (AZD6244 hydrogen sulfate) and metabolized through the same routes as selumetinib (AZD6244 hydrogen sulfate). Co-administration of selumetinib (AZD6244 hydrogen sulfate) with the potent CYP3A4 inducer rifampicin decreased selumetinib (AZD6244 hydrogen sulfate) AUC by ~50%. The potent CYP3A4 and 2C19 inhibitors, itraconazole and fluconazole, increased the AUC of selumetinib (AZD6244 hydrogen sulfate) by ~49% and 53%, respectively. It is therefore recommended that patients should avoid taking strong CYP3A4 inhibitors/inducers or fluconazole (strong CYP2C19 inhibitor and moderate CYP3A4 inhibitor). Moderate inducers and inhibitors of CYP3A4 should be avoided as well, unless considered clinically indicated.

Selumetinib (AZD6244 hydrogen sulfate) is a substrate of BCRP (breast cancer resistance protein) and is a low affinity substrate for P-gp transporters. Selumetinib (AZD6244 hydrogen sulfate) does not inhibit BCRP, P-gp, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2K transporters.

Patient Care Implications: Study participants should be counseled to avoid excessive sun exposure and use adequate sun protection measures if sun exposure is anticipated during the study.

8.1.7 Agent Ordering and Agent Accountability:

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email anytime.

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record Form (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.8 Useful links and Contacts

CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/

NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov

PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm

PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx

CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp

CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov

PMB IB Coordinator: IBcoordinator@mail.nih.gov

PMB email: PMBAfterHours@mail.nih.gov

PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

Investigator Brochure Availability:

The current version of the IB for this agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

8.1.9 Selumetinib Administration

Patient Precautions:

- Patients should avoid donating blood whilst participating in studies of selumetinib and for at least 1 weeks after receiving the last dose of the study medications or for longer if required in accordance with the prescribing information for the comparator / concomitant / compulsory administered medications.
- Reproductive toxicology data indicate that selumetinib has the potential for adverse effects on embryofoetal development and survival. Therefore:

- Females of child-bearing potential must use acceptable, effective and reliable methods of contraception from the time of screening until at least 4 weeks after discontinuing study treatment or longer if required, depending on the prescribing information of the combination or concomitantly administered medications. Selumetinib must not be administered to pregnant or breast-feeding women. Conception while on treatment must be avoided.
- 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.
- Male and females of childbearing potential: reliable methods of contraception should be used consistently and correctly.

  − Acceptable effective methods of contraception for women include implants, injectables, combined oral contraceptives, some intrauterine devices/systems and sterilization including vasectomy of the partner, all being used in combination with barrier methods of contraception (e.g. condoms).

  − Acceptable methods of contraception for men include the use of condoms with spermicidal foams/gels or prior vasectomy.

  − True sexual abstinence is also an acceptable method of contraception (for both men and women).

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 CORRELATIVE STUDIES FOR RESEARCH

Biomarker name (Lead PI and Site)	**Assay**	**Tissue/Body Fluid Tested and Timing of Assay**
pERK and pAKT, total ERK and AKT: Robert Kinders, NCI Frederick	Quantitative ELISA	Cutaneous neurofibroma biopsy: • baseline, and as in Appendix III and Appendix VI
Kinome analysis: Gary Johnson, University of North Carolina	Multiplexed kinase inhibitor beads and mass spectrometry (MIB/MS)	Cutaneous neurofibroma biopsy: • baseline, and as in Appendix III and VI
Whole genome analysis: Ashley Cannon, UAB/HudsonAlpha	Whole genome sequencing	Cutaneous neurofibroma biopsy: Baseline and 12 months on treatment
Transcriptome analysis: Ashley Cannon, UAB/HudsonAlpha	RNA sequencing	Cutaneous neurofibroma biopsy: Baseline and 12 months on treatment

DNA methylation studies: Ashley Cannon, UAB/HudsonAlpha	Genome-wide methylation testing	Cutaneous neurofibroma biopsy: Baseline and 12 months on treatment

9.1.1 Biopsies (See Appendix VI)

The primary analyses for target inhibition to be performed in cutaneous neurofibroma excisional biopsies will be surgical pathology and quantitative analysis of pERK and pAKT. If feasible, the tumor kinome will be analyzed in collaboration with Gary Johnson and Wade Clapp(72).

Biopsies obtained will be processed and analyzed following the priorities outlined below:

1) Flash frozen for pERK and pAKT determination (to be analyzed by Bob Kinders from ½ core)
2) Surgical pathology formalin fixed and paraffin embedding
3) Flash frozen for tumor kinome

Optional biopsies obtained for whole genome sequencing, transcriptome analysis, and DNA methylation studies will be performed by Ashley Cannon at UAB and HudsonAlpha.

9.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Tissue collected during the course of this study will follow NIH guidelines for the research use of human samples and OHRP Issues to Consider in the Research Use of Stored Data or Tissues. Samples will be ordered and tracked through the Institution's ordering system.

9.2.1 Tumor Collection

Tumor samples for PD studies will be collected as outlined in Appendix VI. Tumor samples for optional genomic studies will be collected as outlined in Appendix VI. Samples will be labeled with the study Id number, but no information that could identify the patient.

9.2.2 Sample Storage and Destruction

Samples will be stored until shipment. It is the responsibility of the institutional Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample with patient ID are linked to patient demographics and clinical information. This information will only be provided to investigators listed on this protocol. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

The study will remain open and status reported to the IRB until all samples have been analyzed, reported or destroyed. Any use of these samples for purposes not described in this protocol will require prospective IRB review and approval.

The amount of blood drawn from adults (those 18 years of age) for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, in an 8 week period.

Samples distributed to the testing site at Indiana University for bone marrow progenitor cells and cytokine analysis (Dr. W. Clapp's Laboratory), and for kinome analysis (Dr. Johnson's laboratory) will be sent with only sample identifiers. No personal information will be linked to patient samples. The record of personal information and sample identifiers will be stored in a secure computer database/locked PI or AI file. Samples will not be sent outside NIH or UAB to non-AI investigators without IRB notification and an executed MTA.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or destruction of samples to the NCI or UAB IRB as soon as he is made aware of such loss.

If the patient withdraws consent, the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will report destroyed samples to the local IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the institutional IRB.

10 STUDY CALENDAR

10.1 ON-STUDY EVALUATIONS (SEE APPENDIX III)

Evaluations performed during screening may also be used as baseline assessment where applicable.

1. History and Physical Examination: History and physical examination with vital signs, will be performed every other week during cycle 1, and then according to the schedule in Appendix III and when the patient comes off treatment regardless of the reason. Weight will be recorded at the time of response evaluations.
2. Performance status: ECOG Performance status will be recorded as described in Appendix III.
3. Hematology: Complete blood count, differential and platelets will be performed as described in Appendix III and when the patient comes off treatment regardless of the reason.
4. Chemistries: Electrolytes (including sodium, potassium, chloride, CO_2), calcium, phosphorus, magnesium, creatinine, BUN, glucose, ALT, bilirubin, total protein and albumin, and CPK will be performed as indicated in Appendix III, and when the patient comes off treatment regardless of the reason. Urinalysis will be performed at the time of response evaluations (cutaneous neurofibroma measurements)

5. Urine or serum pregnancy test to female subjects of childbearing potential at the time of response evaluations (cutaneous neurofibroma measurements).
6. Ophthalmology evaluation for corneal and lens opacifications and retinal changes prior to starting treatment with selumetinib and according to Appendix III.
7. EKG will be performed at baseline and if clinically indicated. An ECHO will be performed at baseline and according to Appendix III. Upon recovery from toxicity (to a LVEF of ≥ 53%), patients should be monitored with an ECHO every 2 – 3 cycles or as directed by the cardiologist (see algorithm in Section 6.3.)
8. Response evaluation: Target cutaneous neurofibromas will be measured as described in Section 17.9, Appendix VIII according to the schedule in Appendix III.
9. Patient reported outcomes: This study will assess changes in skin related morbidity and pain using both the Skindex and the Global Impression of Change Scale along with the Numeric Rating Scale. Patients will complete the Skindex as described in Appendix IV, the Global Impression of Change Scale as described in Appendix X and the Numeric Rating Scale as described in Appendix XI.
10. Patient diary (Section 17.7, Appendix VII) will be completed by all patients daily to monitor drug intake and adverse events; medication adherence should be reviewed per Section 17.8, Appendix VIIA. If diary review OR capsule count indicates that the administered dose deviates by ≥ 20 % from the prescribed dose, the study staff will review adherence with the patient and initiate interventions to improve adherence. The adherence intervention session will try to identify any barriers to medication adherence and engage the patient in collaborative problem-solving to minimize problems with taking the study medication.
11. Excisional biopsy of cutaneous neurofibromas: Patients who have cutaneous neurofibromas that can be excised with minimal morbidity will have mandatory biopsies of ≥ 1 cutaneous neurofibroma at baseline, prior to staring treatment with selumetinib, prior to cycles 2 or 5 and if progression or dose reduction. A voluntary biopsy will be obtained by cycle 12 if a decrease in the cutaneous neurofibroma is observed.
    1) In order to correlate the measured response of cutaneous neurofibromas with target inhibition in cutaneous neurofibromas, the percent change in pERK and pAKT will be evaluated comparing pretreatment and on treatment levels. The timing of the on-treatment biopsy will be approximately 4-6 hours after administration of the preceding selumetinib dose, which correlates with the expected peak selumetinib concentrations. Only percutaneous biopsies will be performed.
    2) At time of Progression: In addition, a voluntary biopsy will be obtained at the time of progression (Cutaneous neurofibroma volume increase ≥20%).
    3) After dose reduction: In addition, a voluntary biopsy will be obtained following dose reduction and will be performed after 1-2 cycles at the lower dose.
12. Excisional biopsy of cutaneous neurofibromas (OPTIONAL): Patients who have cutaneous neurofibromas that can be excised with minimal morbidity will be asked to allow a biopsy of a cutaneous neurofibroma at baseline, prior to staring treatment with selumetinib according to **Section 9.1.1**.

1) If a decrease in cNF size is observed by cycle 12 of selumetinib treatment, two types of tissue will be collected from patients: at least 1 cNF with no change in size and at least 1 cNF with a substantial size decrease.

10.2 Off Therapy Evaluations

The following tests and procedures should be performed, if possible, at the time a patient comes off treatment regardless of the reason for coming off treatment, unless the test or procedure has been performed in the past 2 weeks or within a time period described below.

1. History and physical examination, vital sign including blood pressure, and performance status.
2. Laboratory: Complete blood count, differential, and platelet count, electrolytes (including sodium, potassium, chloride, CO_2), calcium, phosphorus, magnesium, creatinine, BUN, glucose, ALT, bilirubin, urinalysis, total protein, and albumin.
3. Measurement of cutaneous neurofibromas unless performed within the last 4 weeks within the past 4 weeks.
4. Skindex should be done.
5. Global Impression of Change should be done.
6. Numeric Rating Scale should be done.

10.3 Study Calendar

See Appendix III

11 MEASUREMENT OF EFFECT

There are no validated response criteria for cutaneous neurofibroma, and the primary goal of this study will be to determine if selumetinib is able to result in a measurable degree of tumor shrinkage of NF1 cutaneous neurofibromas.

Cutaneous neurofibromas will be measured as described in Section 17.9, VIII.

For the purpose of determining the duration of treatment with selumetinib, responsive disease will be defined as a ≥20% decrease in the average volume of the smaller or larger cutaneous neurofibromas compared to the baseline volume. Progressive disease will be defined as a ≥ 20% increase in the average volume of smaller or larger cutaneous neurofibromas compared to the baseline volume. Stable disease will be defined as measurements not meeting criteria for responsive or progressive disease.

As a secondary endpoint this study aims to evaluate changes in PRO and outcomes (Skindex, Global Impression of Change Scale and Numeric Rating Scale) during treatment with selumetinib. Changes will be recorded and documented, but as there are, at present, no validated response criteria for the evaluations to be performed, no response criteria have been defined a priori and the analysis will be descriptive (see statistical section).

12 DATA REPORTING / REGULATORY REQUIREMENTS

12.1 DATA COLLECTION

All data will be kept secure. The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All human subjects personally identifiable information (PII) as defined in accordance to the Health Insurance Portability and Accountability Act, eligibility and consent verification will be recorded. Primary data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant. Clinical and toxicity data will be entered into the electronic OnCore Trial Management System.

End of study procedures: Data will be stored according to HHS and FDA regulations as applicable.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

12.2 DATA SHARING PLANS

12.2.1 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

12.3 CTEP MULTICENTER GUIDELINES

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Section 17.10, Appendix IX.

The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.4 COLLABORATIVE AGREEMENTS LANGUAGE

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator"

(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to

CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13 STATISTICAL CONSIDERATIONS

This limited site, open label pilot study will be conducted at the University of Alabama and the NCI as a collaboration between Bruce Korf (UAB) and Brigitte Widemann (NCI).

The primary objective of this pilot study is to determine if selumetinib is able to result in a measurable degree of tumor shrinkage of NF1 cutaneous neurofibromas.

Patients with NF1 and measurable cutaneous neurofibromas as defined in Section 3.1 will be eligible to enroll.

Patients will undergo standardized documentation and counting of cutaneous neurofibromas. In brief:

Patients with NF1 and measurable cutaneous neurofibromas will undergo standardized documentation and counting of cutaneous neurofibromas (Section 17.9, Appendix VIII). In brief: Digital photography will be performed in all patients prior to treatment with selumetinib, and after every 4 cycles. A 10 x 10 cm picture frame is placed on predefined areas, which will be chosen for each patient to represent areas of cutaneous neurofibroma burden. In all patients, when possible ≥3 areas will be chosen, but only one area for a patient is required minimally because of the difficulty in obtaining patients with multiple areas. A fourth area may be used to monitor cNFs that will be biopsied so not to disrupt the areas being used for cNF size and number response outcomes. Digital photographs will be transferred to a computer, and all cutaneous neurofibromas in the frame ≥4 mm in diameter will be marked and counted as described by Cunha et al (31). Within each picture frame target cutaneous neurofibromas will be measured with calipers as previously described by Korf et al (unpublished data). The width, length, and height will be measured, and the volume of each of the neurofibromas measured will be calculated. The effect of selumetinib will be separately evaluated in up to 3-5 smaller (longest neurofibroma diameter 4-7 mm) and 3-5 larger (longest neurofibroma diameter ≥8 mm) neurofibromas in each of the 3 regions. Any patient with at least two lesions classified as smaller and/or 2 classified as larger in a single area will be considered evaluable and included in the appropriate analyses. The analyses will be supplemented by a description of the numbers of tumors of each type and number of areas evaluated per patient, which will be used to further interpret the findings. Sub-analyses, which may largely be descriptive, and based on the numbers of areas included may also be done to further interpret the results.

At the time of each response evaluation the number of neurofibromas will be counted in the picture frames, and the volume of the target neurofibromas will be measured. The sum of the on-treatment volumes for the smaller tumors will be subtracted from the pre-treatment volumes of the same tumors

to arrive at an overall percentage change in tumor size for each patient. This will be repeated for the larger tumors. Then, the average percentage change for each size category will be reported along with its 95% confidence interval, and other associated statistics.

With 16 evaluable patients with measurements available at per cycle 13 who have continued to receive selumetinib for the same duration, this would provide 90% power to detect a 1.0 effect size (1 SD of the difference in volume from pre to post treatment), using a 0.025 two-sided paired t-test in order to allow for a Bonferroni adjustment for two tests to hold the overall significance level to 0.05. In practice, the two comparisons(one for smaller and one for larger tumors) may be reported using a less overly conservative Hochberg adjustment. As well, if the paired differences are not normally distributed ($p<0.05$ by a Shapiro-Wilks test), then a Wilcoxon signed rank test may be used instead of a paired t-test. In order to allow for some patients who may not complete all evaluations, an additional 8 patients may be enrolled to ensure there will be 16 fully evaluable patients. Plans are to enroll adults of different ages so that changes in neurofibroma size can be evaluated in different age groups.

Exploratory analyses may also be performed restricted to just the patients who have both small and large tumors measured, if appropriate. In addition, the resulting changes in average volume for tumors of a given size per patient may be compared against other measures related to qualitative assessment such as changes in the Skindex to determine if a potentially valid level of response/non-response can be developed in at least a preliminary fashion on the basis of the interpretation of the qualitative consequences of a volume decline of an observed magnitude.

Toxicities will be summarized descriptively and tabulations on the type, severity, and relationship to study treatment will be performed. Changes in both the Skindex and Global Impression of Change Scale along with the Numeric Rating Scale evaluations, will be exploratory and summarized using descriptive statistics and when feasible compared using Wilcoxon rank test or pairwise t-test.

Tumor biopsies: In all patients for whom paired cutaneous neurofibroma biopsies can be obtained mechanisms of response and resistance will be assessed by analyzing pathways in addition to pERK: pAKT, and kinome analysis will be performed.

The changes from baseline for both tumor volume and pathway biomarkers will be determined and tested for statistical significance using a Wilcoxon signed rank test. The correlation of tumor volume changes and levels and changes of levels of pERK in PNs will be determined using Spearman rank correlation. The inhibition of pERK and levels of pAKT will be compared between patients with a tumor response and those without a response using a Wilcoxon rank sum test, although it is understood that such a comparison is exploratory and does not establish causality.

13.1 SAMPLE SIZE ACCRUAL

A maximum of 24 patients will be enrolled, and 16 evaluable patients will be required to have 90% power to detect a 1.0 effect size. Approximately 2 patients will be enrolled per month. Thus enrollment should be complete within 1 year.

PLANNED ENROLLMENT REPORT

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	

DOMESTIC PLANNED ENROLLMENT REPORT					
American Indian/ Alaska Native					
Asian					
Native Hawaiian or Other Pacific Islander					
Black or African American	3	2			5
White	10	9			19
More Than One Race					
Total	13	11			24

14 HUMAN SUBJECTS PROTECTIONS

14.1 RATIONALE FOR SUBJECT SELECTION

Neurofibromatosis type 1 is a genetic disorder with a worldwide incidence of 1:3500 individuals. No groups, in regards to gender, and racial and ethnic groups, are being excluded from participation in the trial. Females who are pregnant or breastfeeding will not be eligible for the trial due to risks of fetal and teratogenic adverse events as seen animal studies.

14.2 PARTICIPATION OF CHILDREN

This trial is designed to if selumetinib is able to result in a measurable degree of tumor shrinkage of NF1 cutaneous neurofibromas in adults. As cutaneous neurofibromas are predominantly a clinically problem in adults, this trial will not enroll children. However, a separate trial with selumetinib for children with plexiform neurofibromas will be ongoing and provide a mechanism for children to receive treatment.

14.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

14.3.1 Risks of Selumetinib

The primary risk to patients participating in this research study is from toxicity of selumetinib, an investigational agent, and from the uncommon risks of tumor biopsies. The protocol provides for detailed and careful monitoring of all patients to assess for toxicity. Selumetinib will be administered at the recommended phase II dose and therefore toxicity data from this dose level has been established without severe (dose-limiting) toxicities. Also, in order to minimize potential risk due to long-term and cumulative toxicity, treatment will be limited according to Section 6. All patients entered on the trial will have NF1 and substantial cutaneous neurofibroma burden causing distress to the patient, which is a manifestation that this agent is hypothesized to benefit. Selumetinib offers a potential for direct benefit although the likelihood of this may be small. The potential benefits from this therapy are disease stabilization or shrinkage of cutaneous neurofibromas, prevention of development of new neurofibromas, and a reduction in symptoms caused by the cutaneous neurofibromas. Furthermore, by just entering the study, patients will be followed very carefully, in an organized coherent manner, which may also benefit their overall healthcare.

Patients of Asian descent may experience a higher exposure of selumetinib than the majority of subjects of non-Asian descent receiving an equivalent dose of selumetinib. These patients will receive standard dosing but will be counselled regarding this higher drug exposure and urged to contact investigators if

they are experiencing any side effects. If, during the course of the selumetinib development program the dosing regimen being evaluated in this study is found not to be tolerated in a specific ethnic group, this ethnic group may later be excluded from this study. Investigators will be notified, and the protocol will be amended to reflect such findings. The data so far do not suggest a safety concern in any specific population.

14.3.2 Risk of cutaneous neurofibroma biopsy

The rare risks of the cutaneous neurofibroma biopsies include risk of pain, bleeding, bruising or infection. Every effort will be made to ensure the patient's comfort during biopsy, minimize risk of bleeding and infection. Patients will be monitored after biopsy for the occurrence of any of these side effects, and clinically indicated interventions initiated as needed.

Therefore, overall this study involves greater than minimal risk but presents the prospect of direct benefit to individual subjects.

14.4 Consent and Assent Process and Documentation

The investigational nature and research objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts and benefits, and potential alternative therapies will be carefully explained to the patient, and a signed informed consent document will be obtained prior to entry onto the study. The PI or an associate investigator of the trial will obtain consent.

15 MULTI-INSTITUTIONAL GUIDELINES

Please also refer to Section 17.10, Appendix IX. The PI of the Coordinating Center for a trial is responsible to ascertain that no patients are entered on the trial at a participating institution without full IRB approval. Thus, the UAB IRB must approve the addition of each participating institution to the protocol and will require a copy of the local IRB approval from each participating institution before UAB IRB approval will be granted.

In addition, this protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines.

15.1 IRB Approvals

The PI will provide the UAB IRB a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the UAB IRB.

15.2 Amendments and Consents

The PI will provide the UAB IRB with copies of all amendments, consents and local IRB approvals from each participating institution.

15.3 IND Action Letters or Safety Reports

The PI is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

15.4 DRUG ORDERING

Each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov).

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67. This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

68. Febrile neutropenia/neutropenic infection has been observed primarily in trials combining AZD6244 (selumetinib) and docetaxel.

69. SBE-CD (Captisol®, vehicle) in the mix and drink formulation is known to cause soft stools and/or diarrhea in rats and dogs; however, it is possible that some of these findings might be related to exacerbation of the vehicle effect by AZD6244 (selumetinib).

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17 APPENDICES

17.1 APPENDIX I: MEDICATIONS TO AVOID

17.1.1 PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **selumetinib (AZD6244 hydrogen sulfate)**. This clinical trial is sponsored by the National Cancer Institute (NCI). This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

Selumetinib (AZD6244 hydrogen sulfate) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 1A2, 2C8, 2C9, 2C19, 3A4/5 and UGT 1A1 and 1A3. Selumetinib (AZD6244 hydrogen sulfate) is metabolized by these enzymes and may be affected by other drugs that inhibit or induce these enzymes.
- The proteins in question are P-gp and BCRP. Selumetinib (AZD6244 hydrogen sulfate) is a substrate of BCRP and P-gp transporters and may be affected by other drugs that inhibit or induce these transporters.

March 2016

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Selumetinib (AZD6244 hydrogen sulfate) interacts with many drugs which can cause side effects. Because of this, it is very important to tell your study doctors about all of your medicines before you enroll on this clinical trial. It is also very important to tell them if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care prescribers can write prescriptions. You must also tell your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Selumetinib (AZD6244 hydrogen sulfate) must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 1A2, 2C8, 2C9, 2C19, 3A/5, UGT 1A1 and 1A3, P-gp and BCRP."

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
- Avoid taking extra vitamin E found in vitamins or supplements.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

_____ and he or she can be contacted at

_____.

March 2016

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental drug **selumetinib (AZD6244 hydrogen sulfate).** This clinical trial is sponsored by the NCI. AZD6244 hydrogen sulfate (selumetinib) interacts with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistant, nurse practitioners, pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	➢ Selumetinib (AZD6244 hydrogen sulfate) interacts with CYP 1A2, 2C8, 2C9, 2C19, 3A4/5, UGT 1A1 and 1A3, P-gp, and BCRP, and must be used very carefully with other medicines that interact with these enzymes and proteins. ➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered "strong inducers/inhibitors of CYP 1A2, 2C8, 2C9, 2C19, 3A4/5, UGT 1A1 and 1A3, P-gp and BCRP." ➢ You should avoid taking extra vitamin E found in vitamins or supplements. ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

17.2 APPENDIX II: NEW YORK HEART ASSOCIATION CLASSIFICATIONS

Clinical Evaluation of Functional Capacity of Patients
with Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability to work**
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.

Reference: Bruce, R. A.: Mod. Concepts Cardiovasc. Dis. 25:321, 1956. (Modified from New York Heart Association, 1953).

17.3 APPENDIX III: REQUIRED STUDY EVALUATIONS

Studies to be obtained	Pre study	Prior to Subsequent Cycles[3]	End of Therapy Evaluation
History[1]	X	2, 5,9,13, etc	X
Physical Exam, vital signs[2]	X	2, 5,9,13, etc	X
Height, weight	X	2, 5,9,13, etc	X
Performance Status	X	2, 5,9,13, etc	X
EKG	X	As clinically indicated	As clinically indicated
Echocardiogram[3]	X	5, 9, then every 4 cycles	As clinically indicated
CBC, differential, platelets	X[5]	2, 5,9,13, etc	X
Urinalysis	X	5,9,13, etc	X
Electrolytes including Ca++, PO_4, Mg++, BUN, creatinine, glucose, ALT, bilirubin, Total protein/albumin, amylase, lipase, CPK	X[5]	2, 5,9,13, etc	X
Ophthalmology toxicity evaluation	X	5, 13, then yearly	As clinically indicated
Pregnancy Test	X	5,9,13, etc	X
Patient diary and capsule count Appendix VIII		2, 5,9,13, etc	X
Adherence Questionnaire Appendix VIIIA		Only if pill count discrepancy >20%	-
Cutaneous neurofibroma disease evaluation with caliper and photography, Appendix VIII	X	5,9,13, etc	X
Skindex, Appendix IV	X	2, 5, 9, 13, etc	X
Global Impression of Change Scale, Appendix X		2, 5, 9, 13, etc	X
Numeric Rating Scale, Appendix XI	X	2,5,9,13, etc	X
Cutaneous neurofibroma biopsy For kinome and pERK Appendix VI	X	2 or 5 and if progression or dose reduction	-
Cutaneous neurofibroma biopsy (OPTIONAL): For whole genome sequencing, transcriptome analysis, and DNA methylation	X	By cycle 12[6]	

[1]Baseline history includes prior treatment for PN with dates. Interval history includes events and changes since last visit, review of all medications and allergies

[2]A complete standard physical examination will be performed at baseline, subsequent physical exams will be targeted based on signs and symptoms of presenting patient. Vital signs: Heart rate, temperature, blood pressure, respiratory rate, O_2 saturation by pulse oximetry at baseline and then as indicated.

[3]Patients who stop selumetinib for cardiac toxicity should be monitored by ECHO every 3 to 6 weeks. Upon recovery from toxicity, patients should be monitored with an ECHO every 2-3 cycles as directed by the cardiologist

[4]Study evaluation frequency with "etc." denotes every subsequent 4 cycles

[5] If greater than 7 days elapses between eligibility blood tests and starting therapy, blood tests should be repeated. If test results are outside the window of eligibility, they must be corrected prior to started therapy.

[6] If a decrease in cNF size is observed by cycle 12 of selumetinib treatment, two types of tissue will be collected from patients: at least 1 cNF with no change in size and at least 1 cNF with a substantial size decrease.

17.4 APPENDIX IV: SKINDEX

Participant's ID:_____
Date:_____

The Skindex will be completed prior to treatment with selumetinib, and prior to cycles 2, 5, 9, 13, etc.

Select one:

Baseline

Prior to: Cycle 2 Cycle 5 Cycle 9 Cycle 13

Other (Please specify):_____

DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past four weeks.

These questions concern your feelings over the past 4 weeks about **the cutaneous neurofibromas that have bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My cutaneous neurofibromas hurt	☐1	☐2	☐3	☐4	☐5
2. My cutaneous neurofibromas affect how well I sleep . . .	☐1	☐2	☐3	☐4	☐5
3. I worry that my cutaneous neurofibromas may be serious .	☐1	☐2	☐3	☐4	☐5
4. My cutaneous neurofibromas make it hard to work or do hobbies	☐1	☐2	☐3	☐4	☐5
5. My cutaneous neurofibromas affect my social life	☐1	☐2	☐3	☐4	☐5
6. My cutaneous neurofibromas make me feel depressed . .	☐1	☐2	☐3	☐4	☐5
7. My cutaneous neurofibromas burn or sting	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my cutaneous neurofibromas.	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my cutaneous neurofibromas.	☐1	☐2	☐3	☐4	☐5
10. My cutaneous neurofibromas itch	☐1	☐2	☐3	☐4	☐5
11. My cutaneous neurofibromas affect how close I can be with those I love	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my cutaneous neurofibromas.	☐1	☐2	☐3	☐4	☐5
13. I worry that my cutaneous neurofibromas may get worse .	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my cutaneous neurofibromas.	☐1	☐2	☐3	☐4	☐5
15. I am angry about my cutaneous neurofibromas.	☐1	☐2	☐3	☐4	☐5

16. Water bothers my cutaneous neurofibromas (bathing, washing hands)	☐1	☐2	☐3	☐4	☐5
17. My cutaneous neurofibromas makes showing affection difficult	☐1	☐2	☐3	☐4	☐5

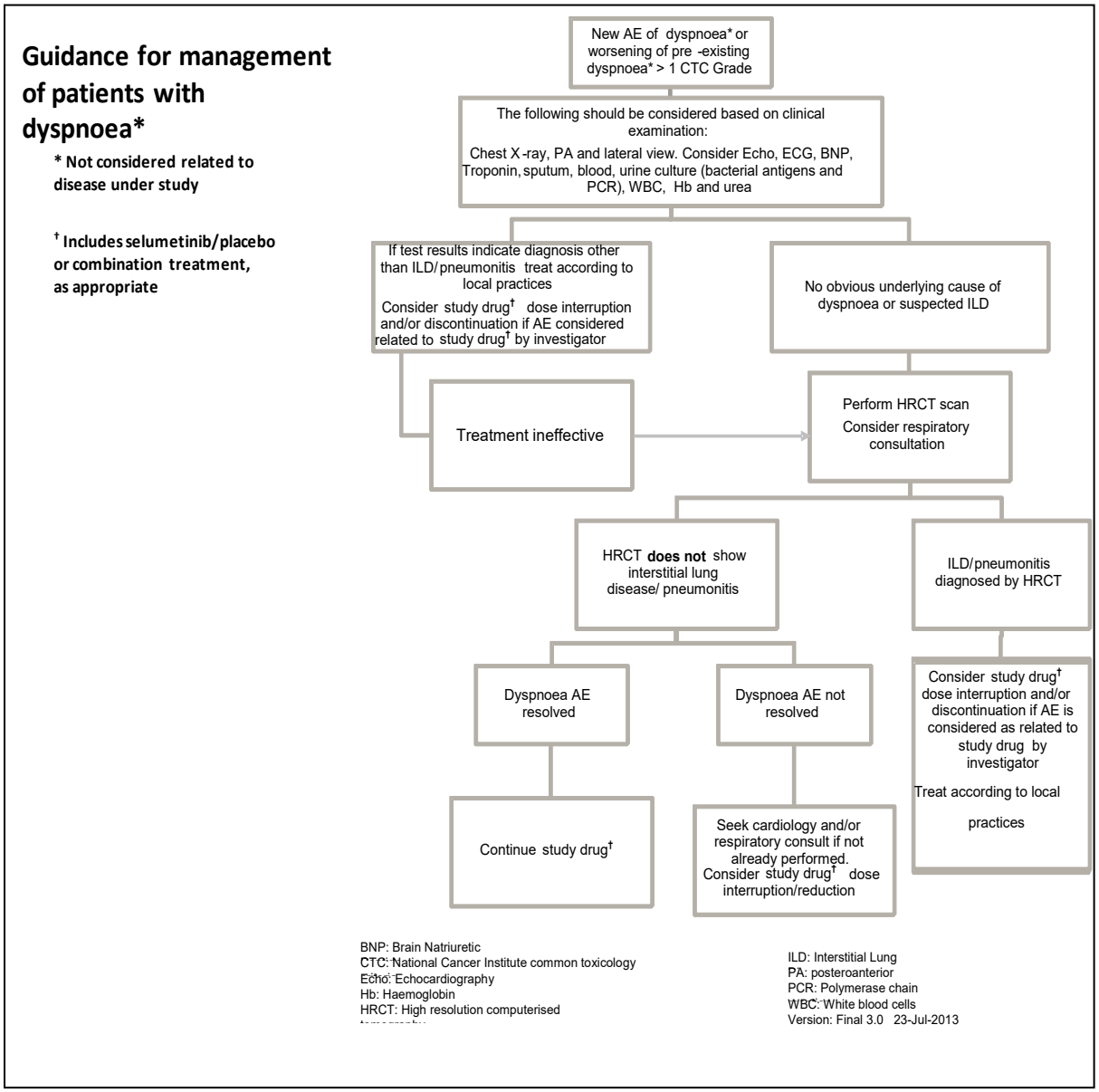
Please turn to next page

These questions concern your feelings over the past 4 week about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST 4 WEEK DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
18. I worry about side-effects from cutaneous neurofibromas medications / treatments	☐1	☐2	☐3	☐4	☐5
19. My cutaneous neurofibromas are irritated	☐1	☐2	☐3	☐4	☐5
20. My cutaneous neurofibromas affect my interactions with others	☐1	☐2	☐3	☐4	☐5
23. I am frustrated by my cutaneous neurofibromas.	☐1	☐2	☐3	☐4	☐5
24. My cutaneous neurofibromas are sensitive	☐1	☐2	☐3	☐4	☐5
25. My cutaneous neurofibromas affect my desire to be with people	☐1	☐2	☐3	☐4	☐5
26. I am humiliated by my cutaneous neurofibromas.	☐1	☐2	☐3	☐4	☐5
27. My cutaneous neurofibromas bleed	☐1	☐2	☐3	☐4	☐5
28. I am annoyed by my cutaneous neurofibromas.	☐1	☐2	☐3	☐4	☐5

29. My cutaneous neurofibromas interfere with my sex life . .	☐1	☐2	☐3	☐4	☐5
30. My cutaneous neurofibromas make me tired	☐1	☐2	☐3	☐4	☐5

17.5 APPENDIX V: SAFETY MANAGEMENT ALGORITHM FOR DYSPNEA



AstraZeneca Guidance for selumetinib studies (March 2015)

17.6 APPENDIX VI: BIOPSY COLLECTION AND TRANSPORT FOR ANALYSIS

17.6.1 Biopsies for pAKT/pERK analysis, pathologic analysis, and kinome analysis.

A. Samples will be obtained by excisional biopsy.

B. Order of priority for biopsy specimens after removal of sample for pathology:

1) pERK/pAKT (frozen)
2) Pathology (formalin)
3) Kinome analysis (frozen)

Samples for pERK/pAKT (Priority #1)

Description:

The optimal level of inhibition of pERK/pAKT required for antitumor activity is not known. In this study pERK, pAKT, total ERK and AKT by Quantitative ELISA will be assessed in Dr. Robert Kinders' Laboratory (NCI Frederick) in cutaneous neurofibroma biopsies obtained prior to cycle 2 compared to baseline, and percent inhibition will be correlated with response as evaluated by volumetric cutaneous neurofibroma measurement. Additional biopsies may be obtained at time of progression or after dose reduction.

Handling:

Part of a specimen (5 mg) will be **snap frozen immediately (see below)**.

Biopsies will be maintained frozen in designated monitored freezers (-70°C). Samples will be batched for analysis upon completion of sample collection.

Labeling:

Samples for pERK/pAKT will be labeled with CTEP protocol number, patient study number, sample ID, and collection point (pre-dose, etc). Samples will be documented on a Chain of Custody Form for each patient.

Shipment of Batched Samples:

Contact Dr. Kinders lab and arrange for shipment. Samples will be transported on dry ice.

Samples must be accompanied with this appendix and full Standard Operating Procedure guidelines, which provides more details regarding the samples.

Contact information for Dr. Robert Kinders (pERK/pAKT analysis)

Dr. Bob Kinders (PADIS/LHTP/FNLCR)
Bldg. 431, Rm. 129
Frederick, MD 21702-1201
Phone: 301-846-6410
kindersr@mail.nih.gov

Pathology, Formalin Fixed Specimens (Priority #2)

Specimen Collection Guidelines: Recommendations for processing of formalin fixed specimens:

1) Place the specimens into the cell safe biopsy capsule and immerse immediately into 10% neutral buffered formalin pot for fixation.
2) Leave sample(s) for exactly 24 hours in formalin at room temperature, to allow for adequate fixation of the samples.

   Remove the cell safe biopsy capsule (containing the biopsy) from the formalin.
3) Place the fixed biopsy sample/s inside the block cassette and immediately process to paraffin using the preferred Routine Biopsy Paraffin Processing Schedule identified in Table 1: (NOTE, if multiple core biopsies are collected then they should be placed into the same cassette block and processed together).
4) Pathology: Samples for pathology will be placed in formalin and delivered to pathology as per standard clinical procedure.

Kinome Analyses (Priority #3)

Samples for Kinome Analysis (Wade Clapp, Indiana University)

Description:

Cutaneous neurofibroma kinome analysis will be performed using multiplexed kinase inhibitor beads and mass spectrometry (MIB/MS) at baseline, prior to cycle 2, and if available, at time of progression or dose reduction

Handling:

From a biopsy specimen, sample will be **snap frozen immediately**.

Biopsies will be maintained frozen in designated monitored freezers (-70°C). Samples will be batched for analysis upon completion of sample collection.

Labeling:

Samples will be labeled with CTEP protocol number, patient study number, sample ID, and collection point (pre-dose, etc). Samples will be documented on a Chain of Custody Form for each patient.

Transport of samples to Indiana University

Contact Dr. Clapp's lab and arrange for shipment. Samples will be transported on dry ice.

17.6.2 Optional biopsies for whole genome sequencing, transcriptome analysis, and DNA methylation studies (To be performed by Ashley Cannon at UAB and HudsonAlpha).

A. Samples will be obtained by excisional biopsy.

B. These biopsies will be optional.

Samples for genomic analyses of cNFs

For this exploratory objective, genomic analyses of cNFs will be performed under the direction of Dr. Ashley Cannon to identify somatic mutations that are driving tumorigenesis as well as mutations that may be influencing tumor response to selumetinib. These are pilot genomic studies that may not have sufficient statistical power and will likely warrant more comprehensive analyses and larger sample sizes in future studies.

1. Collection time points and procedures:
    a. Prior to selumetinib treatment, ≥1 cNF will be biopsied from each patient.
    b. If a decrease in cNF size is observed by cycle 12 of selumetinib treatment, two types of tissue will be collected from consenting patients: at least 1 cNF with no change in size and at least 1 cNF with a substantial size decrease.
2. Procedures:

At the time of tissue collection, samples will be divided in half, with one half being placed in media and the other half will be flash frozen.

The media samples will be sent to the UAB Molecular Genetics Laboratory (MGL) for Schwann cell culture and detection of the somatic *NF1* mutation. Schwann cell cultures from each biopsied cNF will reduce variability due to cellular heterogeneity.

All frozen samples as well as a portion of the cultured Schwann cells will be sent to the HudsonAlpha Genomic Services Lab for DNA extraction, whole genome sequencing, RNA-seq, and genome-wide methylation testing.

Whole genome sequencing will be performed using the Illumina HiSeq X Ten System. The WGS alignment and initial analysis will be accomplished with HudsonAlpha's established pipeline. Genomic variant analysis will be performed with Cartagenia software to confirm the germline mutation (control tissue) and identify acquired mutations that correlate with cNF response to selumetinib, if a decrease is observed. Candidate genes for the variant analysis will include those involved in cell cycle, apoptosis, and DNA repair (e.g. MMR genes, *TP53*, *CDKN2A*, and *RB1*) but the entire genome will still be included in the analysis.

RNA sequencing will be performed by an rRNA reduction process followed by 50M paired reads at PE75 on the HiSeq 4000 System. Transciptome analysis will be performed at HudsonAlpha to determine whether transcripts are differentially expressed in tumors that respond to selumetinib versus those that are unchanged.

17.7 APPENDIX VII: PATIENT DAILY MEDICATION DIARY FOR SELUMETINIB

NF1 Patient Diary for Selumetinib NCI CTEP Protocol # ___

ID #: _____ Institution: _____
Cycle Number: _____ Dose: Twice a Day
Cycle Start Date: _____

		Time (M = missed)		Number of Capsules Taken		Comments (Please note reason if dose is missed)
Day	**Date**	**AM**	**PM**	**10 mg (am/pm)**	**25mg (am/pm)**	
1				# taken: ____/____	# taken: ____/____	
2				# taken: ____/____	# taken: ____/____	
3				# taken: ____/____	# taken: ____/____	
4				# taken: ____/____	# taken: ____/____	
5				# taken: ____/____	# taken: ____/____	
6				# taken: ____/____	# taken: ____/____	
7				# taken: ____/____	# taken: ____/____	
8				# taken: ____/____	# taken: ____/____	
9				# taken: ____/____	# taken: ____/____	
10				# taken: ____/____	# taken: ____/____	
11				# taken: ____/____	# taken: ____/____	
12				# taken: ____/____	# taken: ____/____	
13				# taken: ____/____	# taken: ____/____	
14				# taken: ____/____	# taken: ____/____	
15				# taken: ____/____	# taken: ____/____	
16				# taken: ____/____	# taken: ____/____	
17				# taken: ____/____	# taken: ____/____	
18				# taken: ____/____	# taken: ____/____	
19				# taken: ____/____	# taken: ____/____	
20				# taken: ____/____	# taken: ____/____	
21				# taken: ____/____	# taken: ____/____	
22				# taken: ____/____	# taken: ____/____	
23				# taken: ____/____	# taken: ____/____	
24				# taken: ____/____	# taken: ____/____	
25				# taken: ____/____	# taken: ____/____	
26				# taken: ____/____	# taken: ____/____	
27				# taken: ____/____	# taken: ____/____	
28				# taken: ____/____	# taken: ____/____	

Number of Pills Returned: 10 mg:_____25mg:_____

Patient Signature: _____ Date:_____

NF1 Patient Diary for Selumetinib NCI CTEP Protocol # ____

ID #: Institution:

SIDE EFFECTS: (Please describe in detail to include location of rash, # of stools, # of times vomited in 24 hrs, highest temperature etc)	**Start Date**	**Stop Date**	**Medication Taken** (please include dose)

Severity: 1=mild 2=moderate 3=severe

Patient Signature: _____ Date:_____

17.8 APPENDIX VIIA: ADHERENCE

Selumetinib Capsule Count Form: Complete one form for each cycle at the time Selumetinib is prescribed/dispensed and then when capsules/bottles are returned.

Study ID #:_____ Cycle number: _____

Cycle start date:_____ Current dose (mg/dose): _____

Number doses per day:_____

If there is a discrepancy >20% between total mg returned (actual) and total mg that should have been returned (expected) the Adherence Intervention will be implemented. For questions please contact Staci Martin at 301-435-3964.

Date	**No. of capsules prescribed** **10 mg 25 mg**	**No. of capsules returned** **10 mg 25 mg**	**Total mg returned**	**Total mg should have been returned**	**% Adherence**

Comments:

Signature: _____ Date: _____

17.9 APPENDIX VIII: MEASUREMENT AND COUNTING OF CUTANEOUS NEUROFIBROMAS

A) Measurement of cutaneous neurofibromas

Cutaneous neurofibromas will be measured as described below at the following time points:

Select One:

☐ Baseline

Prior to: ☐ Cycle 5 ☐ Cycle 9 ☐ Cycle 13

☐ Other (Please specify): _____

Date/Time counting performed: _____

For response evaluation, the average volume of 3-5 small (longest neurofibroma diameter 4-7 mm) and 3-5 larger (longest neurofibroma diameter ≥8 mm) target cutaneous neurofibromas in 3 different body regions will be calculated at each response evaluation (baseline, and then after every 4 cycles). Cutaneous neurofibromas will be measured with calipers as developed by Dr. Korf, and volumes will be calculated by multiplying length, width, and height of each target neurofibroma. At each response evaluation the sum of the on-treatment volumes for the smaller tumors will be subtracted from the pre-treatment volumes of the same tumors to arrive at an overall percentage change in tumor size for each patient. This will be repeated for the larger tumors. Then, the average percentage change for each size category will be reported

Area 1: Location				
Area 1	Length (mm)	Width (mm)	Height (mm)	Volume (mm^3)
1 large				
2 large				
3 large				
4 large				
5 large				
1 small				
2 small				
3 small				
4 small				
5 small				
Area 2: Location				
Area 2	Length (mm)	Width (mm)	Height (mm)	Volume (mm^3)
1 large				
2 large				
3 large				
4 large				
5 large				
1 small				
2 small				

3 small				
4 small				
5 small				
Area 3: Location				
Area 3	Length (mm)	Width (mm)	Height (mm)	Volume (mm^3)
1 large				
2 large				
3 large				
4 large				
5 large				
1 small				
2 small				
3 small				
4 small				
5 small				
Area 4: Location				
Area 4	Length (mm)	Width (mm)	Height (mm)	Volume (mm^3)
1 large				
2 large				
3 large				
4 large				
5 large				
1 small				
2 small				
3 small				
4 small				
5 small				

B) Counting of cutaneous neurofibromas

Photography of cutaneous will be performed in all patients to count the cutaneous neurofibromas as described below:

Photograph Timing:

Select One:

☐ Baseline

Prior to: ☐ Cycle 5 ☐ Cycle 9 ☐ Cycle 13

☐ Other (Please specify): _____

Date/Time photography performed: _____

Digital photography will be performed in all patients with cutaneous neurofibromas at the time points noted.

- Digital photography/ Paper frames: A 10 x 10 cm picture frame is placed on predefined

areas, which will be chosen for each patient to represent areas of cutaneous neurofibroma burden. Three areas will be chosen. All cutaneous neurofibromas in the frame ≥4 mm in diameter are marked. Multiple digital photographs of the area in the frame are obtained before and after marking; in addition, photographs with a larger view which demonstrate the location of the lesions on the body will be taken. These photographs will be used to ensure that the same areas are photographed longitudinally. This method will determine the number of lesions in a prescribed area, but not their volume. The photographs can be taken in the clinic and take about 15 minutes to complete. The cutaneous neurofibromas will be then be counted; only cutaneous and not subcutaneous lesions will be counted for the purposes of this analysis.

- Number of Cutaneous Neurofibromas counted area 1: _____
- Number of Cutaneous Neurofibromas counted area 2: _____
- Number of Cutaneous Neurofibromas counted area 3: _____
- Number of Cutaneous Neurofibromas counted area 4: _____

Signature: _____ Date:_____

17.10 APPENDIX IX: CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP-sponsored research protocol, then the guidelines below must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

17.11 APPENDIX X: GLOBAL IMPRESSION OF CHANGE SCALE

The Global Impression of Change Scale will be completed prior to cycles 2, 5, 9, 13, etc.

Select One:

Prior to: ☐ Cycle 2 ☐ Cycle 5 ☐ Cycle 9 ☐ Cycle 13

☐ Other (Please specify): _____

Global Impression of Change Scale - cNF

1. Think about your cutaneous neurofibromas. Compared to before you started taking the medicine for this study, would you say the size of your cutaneous neurofibromas are:

- ☐ 1 Very Much Improved
- ☐ 2 Much Improved
- ☐ 3 Minimally Improved
- ☐ 4 No Change
- ☐ 5 Minimally Worse
- ☐ 6 Much Worse
- ☐ 7 Very Much Worse

(Please check only one box)

2. Think about how your cutaneous neurofibromas affect you physically (for example, itching, pain, appearance). Compared to before you started taking the medicine for this study, would you say the physical effects of your cutaneous neurofibromas are:

- ☐ 1 Very Much Improved
- ☐ 2 Much Improved
- ☐ 3 Minimally Improved
- ☐ 4 No Change
- ☐ 5 Minimally Worse
- ☐ 6 Much Worse
- ☐ 7 Very Much Worse

(Please check only one box)

3. Think about how your cutaneous neurofibromas affect you emotionally (for example, worry, embarrassed, depressed). Compared to before you started taking the medicine for this study, would you say the emotional effects of your cutaneous neurofibromas are:

- ☐ 1 Very Much Improved
- ☐ 2 Much Improved
- ☐ 3 Minimally Improved
- ☐ 4 No Change
- ☐ 5 Minimally Worse
- ☐ 6 Much Worse
- ☐ 7 Very Much Worse

(Please check only one box)

4. Think about how your cutaneous neurofibromas affect your daily life (for example, work or school, social life, sleep). Compared to before you started taking the medicine for this study, would you say the effects of your cutaneous neurofibromas on you daily life are:

- ☐ 1 Very Much Improved
- ☐ 2 Much Improved
- ☐ 3 Minimally Improved
- ☐ 4 No Change
- ☐ 5 Minimally Worse
- ☐ 6 Much Worse
- ☐ 7 Very Much Worse

(Please check only one box)

Please describe any changes you have noticed in your cutaneous neurofibromas or changes in how these tumors affect you since you started taking the study drug:_____

_____

_____

_____

17.12 APPENDIX XI: NUMERIC RATING SCALE

The Numeric Rating Scale (NRS-11) will be completed prior to treatment with selumetinib, and prior to cycles 2, 5, 9, 13, etc.

Select One:

☐ Baseline

Prior to: ☐ Cycle 2 ☐ Cycle 5 ☐ Cycle 9 ☐ Cycle 13

☐ Other (Please specify): _____

Numeric Rating Scale (NRS-11)

Below is a line with numbers from 0 to 10 where 0 means no pain and 10 means the worst pain you can imagine.

Please circle the one number that best describes your pain at its **worst** during the past week.