Cover Page

NF PROTOCOL 105

A Phase II Study of Cabozantinib (XL184) for Plexiform Neurofibromas in Subjects with Neurofibromatosis Type 1 in Children and Adults

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Neurofibromatosis (NF) Consortium

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A Phase II Study of Cabozantinib (XL184) for Plexiform Neurofibromas in Subjects with Neurofibromatosis Type 1 in Children and Adults

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Protocol Chairs
Michael Fisher, MD, Chair
Jaishri Blakeley, MD, Co-Chair
Amy Armstrong, MD, Co-Chair

Medical Monitor
Alyssa Reddy, MD

Protocol Roster

Study Chair
Michael Fisher, MD
Children's Hospital of Philadelphia
3501 Civic Center Boulevard
Philadelphia, PA 19096
Phone: 215-590-2800
fisherm@email.chop.edu

Study Co-Chairs
Jaishri Blakely, MD
Johns Hopkins University
1550 Orleans Street Suite 1M16
Baltimore, Maryland 21231
Phone: 410-955-8837
Fax: 410-614-9335
Jblakel3@jhmi.edu

Amy Armstrong, MD
Riley Hospital for Children
705 Riley Hospital Dr.
RI 4340
Indianapolis, IN 46202
Phone: 317-948-8568
Fax: 317-944-3107
amyearms@iu.edu

Study Committee
Kent Robertson, MD, PhD
705 Riley Hospital Dr.
RI 4340
Indianapolis, IN 46220
Phone: 417-944-8784
krobert@iu.edu

Brigitte Widemann, MD
National Institutes of Health – NCI
10 Center Drive
Building 10-CRC: Room 1-5750 MSC
Bethesda, MD 20892
Phone: 240-760-6203
Widemanb@mail.nih.gov

Bruce Korf, MD, PhD
University of Alabama at Birmingham
1720 2nd Avenue South - 230 KAUL
Birmingham, Alabama 35294-0024
Phone: 205-934-9411
Fax: 205-934-9488
bkorf@uabmc.edu

Medical Monitor
Alyssa Reddy, MD
University of California, San Francisco
550 16th Street
UC Box 0137
San Francisco, CA 94758
Phone: 415-353-2657
Alyssa.Reddy@ucsf.edu

Study Statistician
Gary Cutter, PhD
Department of Biostatistics
University of Alabama at Birmingham
1667 University Blvd - Ryals 410
Birmingham AL 35243
Phone: 205-975-5048
Fax: 295-975-2531
cutterg@uab.edu

Study Statistician/NFCTC Co-PI (Data)
Lloyd Edwards, PhD
Department of Biostatistics
U. of Alabama at Birmingham
1665 Univ Blvd - Ryals 327D
Birmingham AL 35243
205-975-0687 Phone
ljedward@uab.edu

Clinical Nurse Manager
Lynn Merritt, RN
U. of Alabama at Birmingham
1530 3rd Avenue South – Kaul 230
Birmingham, AL 35294-0024
Phone 205-934-5376
jlynnrn@uab.edu

Program Director
Karen A. Cole-Plourde, BS
University of Alabama at Birmingham
1720 2nd Avenue South – 230 KAUL
Birmingham, AL 35294-0025
Phone: 205-934-5150
Fax : 205-975-3543
kcole@uab.edu

Central Biomarkers
Cytokine analysis
Khadijeh Bijangi-Vishehsaraei, MS, PhD
Children's Clinical Research Center/Translational Research and Integrated Biology, Indiana University
705 Riley Hospital Drive, Room 2641
Indianapolis, Indiana 46202
Phone: 317-278-3050
khbijang@iupui.edu

Endothelial Progenitor Cells
Karen Pollok, PhD
Angio BioCore, Indiana University
Contact: Emily Sims, Core Manager
980 W. Walnut St., R3-343
Indianapolis, IN 46202
Phone: 317-278-7232
ecwillar@iupui.edu

Central Imaging
Eva Dombi, MD
National Cancer Institute
10 Center Drive
Bldg 10-CRC, Rm 1-5750
Bethesda, MD 20892
Phone: 240-858-3852
Fax: 301-402-1734
dombie@mail.nih.gov

Central Quality of Life
Pam Wolters, PhD
Pediatric Oncology Branch
Bethesda, MD 20892-8200
Phone: 301-496-0562
Fax: 301-402-1734
woltersp@mail.nih.gov

Research Compliance Manager
Juliette Southworth, BS, CCRP
The University of Alabama at Birmingham – Kaul 230
Birmingham, AL 35294-0024
205-975-4075 Phone
jsouthworth@uab.edu

Department of Defense
Kimberly Boelte Pope, PhD
Science Officer (General Dynamics IT)
Congressionally Directed Medical Research Programs
1053 Patchel Street
Frederick, MD 21702
Phone: 301-619-4006
Fax: 301-619-7796
kimberly.b.pope2.ctr@mail.mil

Participating Sites

Bruce Korf, MD, PhD University of Alabama at Birmingham 1720 2nd Ave South - KAUL 230 Birmingham, Alabama 35294-0024 Phone: 205-934-9411/Fax: 205-934-9488 bkorf@uabmc.edu	James Tonsgard, MD University of Chicago 5841 South Maryland Avenue, MC 3055 Chicago, IL 60637 Phone: 773-702-6488 tonsgard@midway.uchicago.edu
Michael Fisher, MD Children's Hospital of Philadelphia 3501 Civic Center Boulevard Philadelphia, PA 19096 Phone: 215-590-2800 fisherm@email.chop.edu	David Viskochil, MD, PhD University of Utah 50 North Medical Drive – 2C412 SOM Salt Lake City, UT 84132 Phone: 801-581-8943 dave.viskochil@hsc.utah.edu
Roger Packer, MD Children's National Medical Center 111 Michigan Avenue, NW Washington, DC 20010 Phone: 202-884-2120 rpacker@cnmc.org	David Gutmann, MD, PhD Washington University School of Medicine 660 South Euclid Avenue – Box 811 St. Louis, MO 63110 Phone: 314-362-7379 gutmannd@neuro.wustl.edu
Wade Clapp, MD Indiana University 1044 West Walnut Street Cancer Center, Room 402A Indianapolis, IN 46202 Phone: 317-278-9290 dclapp@iu.edu	Jeffrey Allen, MD New York Univ. Pediatrics 160 E. 32nd Street – 2nd Floor Hassenfeld Children's Center New York, NY 10016 Phone: 212-263-9907 Jeffrey.Allen@nyumc.org
Tena Rosser, MD Children's Hospital Los Angeles 300 Medical Plaza Box 696824 Los Angeles, CA 90095 Phone: 323-361-2471 trosser@chla.usc.edu	Nicole Ullrich, MD, PhD Children's Hospital Boston – Dept. of Neurology 300 Longwood Avenue – Fegan 11 Boston, MA 02115 Phone: 617-355-2066 Nicole.Ullrich@childrens.harvard.edu
Elizabeth Schorry, MD Cincinnati Children's Hospital Medical Center 3333 Burnet Avenue - ML 4006 Cincinnati, OH 45229 Phone: 513-636-4760 elizabeth.schorry@cchmc.org	Brigitte Widemann, MD National Institutes of Health – NCI 10 Center Drive; Building 10-CRC: Room 1-5750 MSC Bethesda, MD 20892 Phone: 301-496-7387 widemanb@mail.nih.gov

Laura Klesse, MD, PhD Childrens Medical Center of Dallas University of Texas Southwestern Medical Center 5323 Harry Hines Blvd. Dallas, Texas 75390-9063 Phone: 214-456-3727 Fax: 214-648-3122	

Affiliate sites

Massachusetts General Hospital (Ullrich; Plotkin)
Dana Farber Cancer Institute (Ullrich; Kieran)
UCLA (Rosser; Silva)
Johns Hopkins (Packer; Blakeley)
Ohio State University (Schorry)
Lurie Children's Hospital of Chicago (Tonsgard; Listernick and Goldman)

Roles and Responsibility of Study Personnel:

Michael Fisher, MD: Study PI, Protocol Chair. Steering Committee Chair of NF Consortium

Jaishri Blakeley, MD: Protocol Co-Chair

Amy Armstrong, MD: Protocol Co-Chair

Kent Robertson, MD: Study Committee

Brigitte Widemann, MD: Study Committee

Bruce Korf, MD, PhD: NF Consortium PI, Study Committee, IND Holder

Gary Cutter PhD: Study Statistician. Biostatistician & Deputy Director of NF Operations Center

Lloyd Edwards, PhD: Biostatistician & Co-PI NF Operations Center

Alyssa Reddy, MD Medical Monitor

Eva Dombi, MD: Volumetric MRI analysis of plexiform neurofibromas on protocol

Pam Wolters, PhD: Quality of life and pain surveys

Khadijeh Bijangi-Vishehsaraei, MS, PhD: Cytokine Biomarkers

Karen Pollok, PhD: Endothelial Progenitor Cell Biomarkers

Lynn Merritt, RN, : Clinical Coordinator – NF Operations Center

Karen Cole-Plourde: Program Director – NF Operations Center

Juliette Southworth, BS, CCRP: Research Compliance Manager – NF Operations Center

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ABSTRACT/SCHEMA

Background

Neurofibromatosis type 1 (NF1) is one of the most common inherited disorders in the general population, affecting approximately 1 in 3500 people with an estimated 100,000 individuals afflicted in the United States alone. NF1 is an autosomal dominant disorder caused by mutations in the *NF1* tumor suppressor gene resulting in a deficiency in a protein called neurofibromin. Deficiency in neurofibromin allows activation of the Ras oncoprotein with resultant cutaneous and plexiform neurofibromas (a complex of Schwann cells, fibroblasts, endothelial cells, and mast cells), which may be disfiguring, painful and life threatening. These tumors are refractory to most therapeutic approaches including chemotherapy, radiation, and surgery. These tumors can result in significant morbidity if located near vital structures, including nerves, blood vessels, and the airway. Thus, in this group of patients, the development of novel treatment interventions is needed.

Receptor tyrosine kinase inhibitors are an emerging class of drugs in the treatment of malignancies. C-kit, in particular, is a tyrosine kinase that has been shown to be essential in the development of plexiform neurofibromas. Preclinical investigation has elucidated the role of c-kit in the activation of mast cells, one of the components of plexiform neurofibromas and a limited number of clinical trials targeting c-kit are underway. Targeting of multiple RTKs may increase efficacy either by synergy or blocking tumor escape pathways. Subsequent screening of clinically relevant c-kit and multiple RTK inhibitors in an *in vivo* model of NF1 plexiform neurofibroma has identified cabozantinib (XL184) as an excellent candidate for clinical testing. Cabozantinib is a small-molecule RTK inhibitor that blocks phosphorylation of c-Met, RET, c-kit and VEGFR2 at nanomolar or subnanomolar concentrations. C-MET and VEGFR2 are strong regulators of tumor angiogenesis. Plexiform neurofibromas are highly vascular tumors and it is postulated that this may be a key mechanism in tumor development and growth. In small animal NF1 models, cabozantinib shows strong biological activity and results in decreased tumor size, number and biologic activity. Preliminary data shows that this molecule may be even more effective than agents currently undergoing clinical evaluation. In preclinical trials, cabozantinib reduced mast cell concentration by greater than 50%. Transgenic mice with plexiform neurofibromas treated with cabozantinib had a 70% reduction in tumor numbers as compared to vehicle controls and 50% reduction in tumor size for residual tumors. Using FDG-PET, tumors in treated mice had significant reduction in metabolic activity. Based on these striking results, we propose cabozantinib for human clinical trials for plexiform neurofibromas.

Primary Objectives

1. **Primary Aim:** To estimate the objective response rate (ORR) as defined by 20% volumetric MRI response of the target lesion to cabozantinib at 12 months in children and adults with NF1 plexiform neurofibromas by volumetric MRI imaging.
2. **Secondary Aims:**
    1. To assess the tolerability and toxicity of cabozantinib in subjects with NF1.
3. **Exploratory Aims:**
    1. To estimate the ORR of up to 2 non-target plexiform neurofibromas to cabozantinib by MRI.
    2. To assess quality of life and pain in subjects with NF1 and plexiform neurofibromas on cabozantinib
    3. To assess the PedsQL NF1 QOL Module, a disease specific QOL scale, and the pain scales for use in this patient population
    4. To assess activity of cabozantinib on mast cell activity by FACS
    5. To describe changes by flow cytometry in peripheral blood monocyte counts, circulating endothelial cells, and plasma angiogenic factors during treatment with cabozantinib (see laboratory correlates section 13.0 C)
    6. To describe the baseline and change in circulating cytokine factors related to proliferating cells (see laboratory correlates section 13.0 C)
    7. To characterize the pharmacokinetic profile of cabozantinib in this population
    8. To determine whether patients who respond (≥20% objective radiographic response of target lesion by 12 cycles) to cabozantinib will maintain that response for 1 year off therapy
    9. To compare the volumetric assessment of plexiform neurofibroma response to therapy performed by two independent analysts using different volumetric analysis methods.

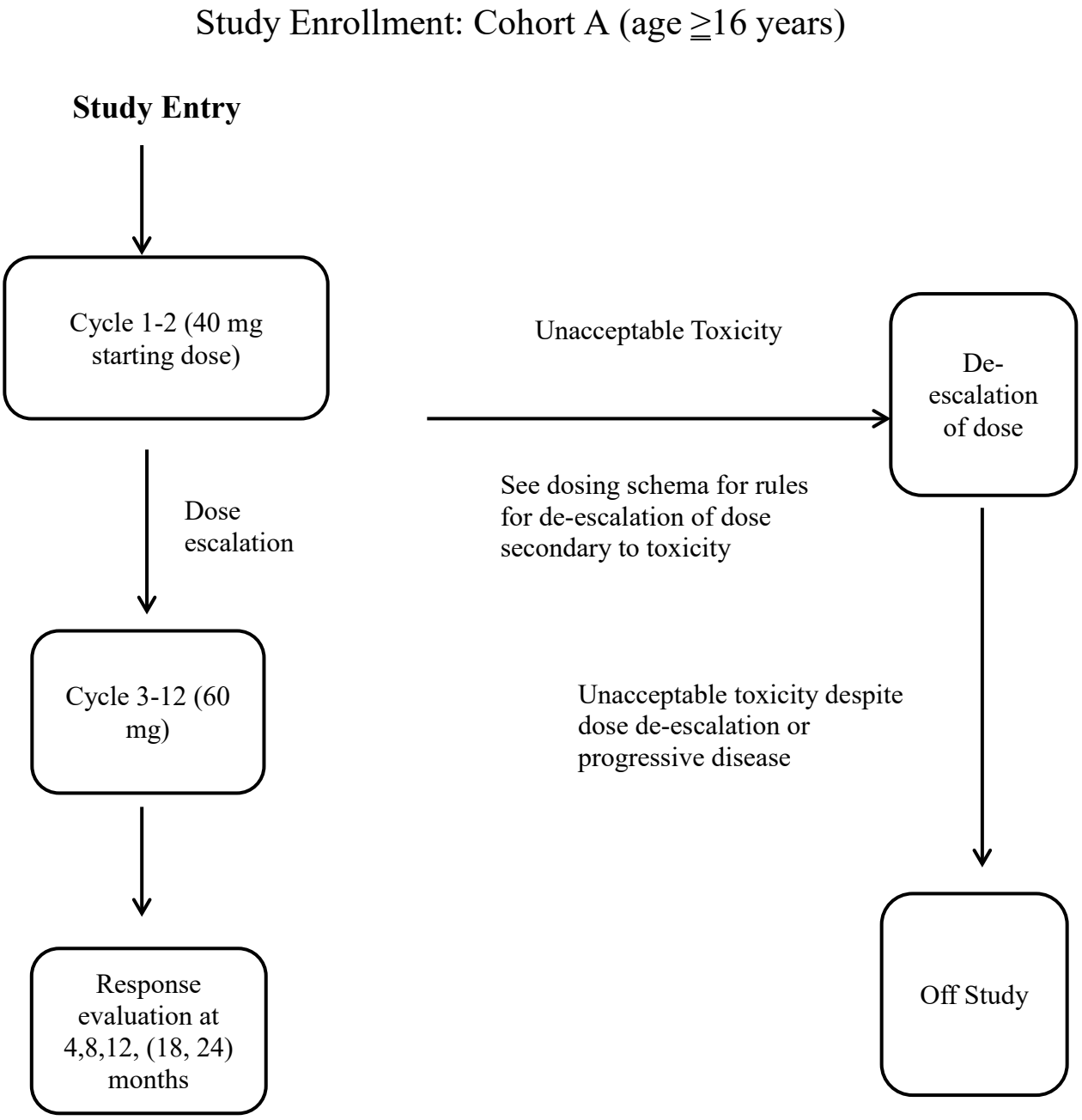
Eligibility

1. Subject ≥ 3 years of age who meet clinical diagnostic criteria of neurofibromatosis type 1 (NF1) or have known pathogenetic *NF1* mutation AND
2. Subjects must have plexiform neurofibroma(s) with a target lesion that has evidence of progression by serial imaging OR known significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Subjects with paraspinal plexiform neurofibromas will be eligible for this trial. Histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a plexiform neurofibroma is clinically suspected.

Design

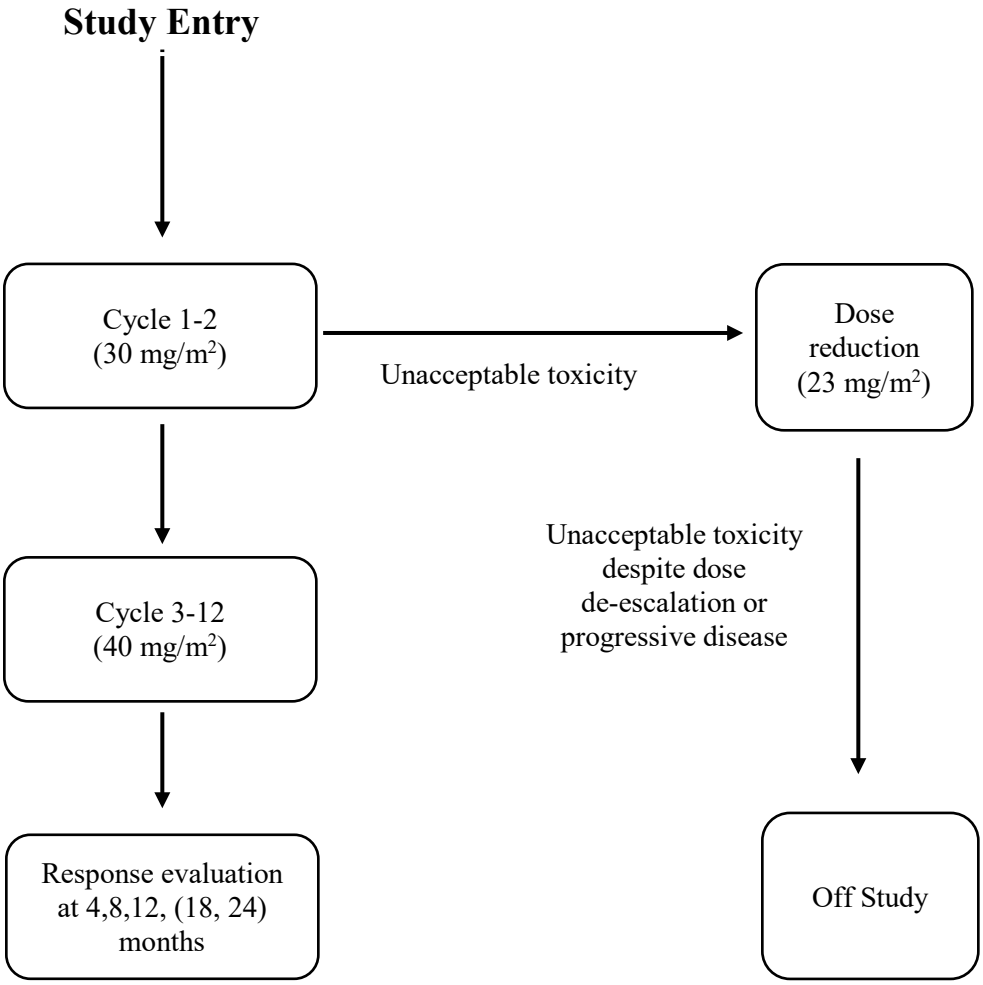
- Cabozantinib will be administered orally daily on a continuous dosing schedule (28 days = 1 treatment cycle).
- Disease status will be evaluated using volumetric MRI analysis at regular intervals.
- Pain reduction and quality of life outcomes will also be assessed.
- Toxicity of chronic cabozantinib administration will be evaluated using physical and laboratory evaluations and adverse event reporting by patients.

EXPERIMENTAL DESIGN SCHEMA



Tumor response will be done by MRI volumetrics at 4, 8, and 12 months (prior to cycle 5, 9 and end of study). Subjects may remain on drug for up to 12 additional cycles and will have MRI done subsequently at 6 months intervals. Subjects who do not achieve at least 15% reduction in volume of the target tumor at the 8 month interval will be considered treatment failure and taken off study.

Study Enrollment: Cohort B (age 3-15 years)



Tumor response will be done by MRI volumetrics at 4, 8, and 12 months (prior to cycle 5, 9 and end of study). Subjects may remain on drug for up to 12 additional cycles and will have MRI done subsequently at 6 months intervals. Subjects in Cohort B who do not have a partial response (>20% reduction in tumor volume) by the end of 12 cycles will be taken off study.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 **Primary Aim:** To estimate the objective response rate (ORR) as defined by 20% volumetric MRI response of the target lesion to cabozantinib at 12 months in children and adults with NF1 plexiform neurofibromas by volumetric MRI imaging.

1.2 **Secondary Aim:**

1.2.1 To assess the tolerability and toxicity of cabozantinib in subjects with NF1.

1.3 **Exploratory Aims:**

1.3.1 To estimate the objective response rate of up to 2 non-target plexiform neurofibromas to cabozantinib by MRI.

1.3.2 To assess quality of life and pain in subjects with NF1 and plexiform neurofibromas on cabozantinib

1.3.3 To assess the PedsQL NF1 QOL Module, a disease specific QOL scale, and the pain scales for use in this patient population

1.3.4 To assess activity of cabozantinib on mast cell activity by FACS

1.3.5 To describe changes by flow cytometry in peripheral blood monocyte counts, circulating endothelial cells, and plasma angiogenic factors during treatment with cabozantinib. (see laboratory correlates section 13.0 C)

1.3.6 To describe the baseline and change in circulating cytokine factors related to proliferating cells (see laboratory correlates section 13.0 C)

1.3.7 To characterize the pharmacokinetic profile of cabozantinib in this population.

1.3.8 To determine whether patients who respond (≥20% objective radiographic response of target lesion by 12 cycles) to cabozantinib will maintain that response for 1 year off therapy

1.3.9 To compare the volumetric assessment of plexiform neurofibroma response to therapy performed by two independent analysts using different volumetric analysis methods.

2.0 BACKGROUND AND RATIONALE

Introduction

Cabozantinib (Exelixis) is a new chemical entity that inhibits multiple RTKs with growth-promoting and angiogenic properties. The primary targets of cabozantinib are MET, VEGFR2, RET, and c-KIT. Cabozantinib is an orally bioavailable compound and marked tumor regression was observed in models tested. In addition, clinical activity with the use of cabozantinib in a variety of tumor settings has been reported. Receptor tyrosine kinases have been implicated in plexiform neurofibroma formation, particularly in the inflammatory response of mast cells, which appear essential in tumor progression. Preclinical evaluation of cabozantinib has shown marked tumor regression in several tumor models, including *Nf1* animal models of plexiform neurofibroma (see below). In addition, cabozantinib has been tested in several Phase 1 and 2 clinical trials and has been FDA approved for medullary thyroid carcinoma and renal cell carcinoma. Cabozantinib has been selected for further human clinical testing for NF1 plexiform neurofibromas because of its

activity in *in vivo* drug screens, including decrease in tumor size, number and metabolic activity by PET imaging. This study will evaluate cabozantinib in a Phase 2 efficacy trial in children and adults with clinically significant NF1 plexiform neurofibromas. To maximize safety and tolerability, there will intra-patient dose escalation starting at a predicted highly tolerable dose with a planned dose escalation to the target dose.

Rationale for Development

Neurofibromatosis type 1 (NF1), is a common human genetic disorder that affects approximately 100,000 people in the United States alone. Individuals afflicted with NF1 develop a wide range of malignant and non-malignant manifestations. Plexiform neurofibromas are benign tumors of the nerve sheath that occur in approximately 40% of patients with NF1. They are a significant cause of morbidity in NF1 by causing pain, disfigurement or impairing function. They are life threatening when they compress vital structures such as the airway or great vessels, or via transformation into malignant peripheral nerve sheath tumors. Based on a series of novel observations made over the past decade, there is an increasing understanding of the requisite NF1 tumor microenvironment required for plexiform neurofibroma formation. *Nf1* heterozygous mast cell infiltration of pre-neoplastic peripheral nerves in association with *Nf1*-deficient Schwann cells has been shown to be critical for tumor development. Further, on the basis that c-kit receptor activation controls the release of mast cells from the bone marrow; mast cells are implicated as active participants in tumor formation. [1] Based on these data, clinically available tyrosine kinase (including c-kit) inhibitors were tested in animal models of neurofibromas to evaluate efficacy on tumor as well as mast cell activation. Of this group of compounds, Cabozantanib has emerged as a drug with significant impact on tumor volume, tumor apoptosis, and mast cell infiltration and as such has been selected for further clinical development.

C-kit dependent microenvironment in *Nf1*-dependent tumors

The notion of targeted therapy against the tyrosine kinase c-KIT for the specific treatment of *Nf1*-dependent tumors stems from careful analysis of models which recapitulate both genetic, as well as the tumor microenvironment, in which these tumors develop.[1]

a. In a series of experiments, Yang et al. showed that *Nf1* loss of heterozygosity in the Schwann cell lineage is *necessary* but *not sufficient* to induce plexiform neurofibromas.[1] In a murine model, animals with germline knockout allele of *Nf1* and a floxed allele susceptible to recombination in the Schwann cell lineage (approximately 10%) Krox20;$Nf1^{flox/flox}$ uniformly develop plexiform neurofibromas; however, animals with wild type bone marrow (WT) with Krox20;$Nf1^{flox/flox}$ do not develop neurofibromas. Animals with heterozygous $Nf1^{+/-}$ bone marrow also do not develop the plexiform neurofibroma phenotype; however, animals with the Schwann cell lineage (Krox20;$Nf1^{flox/flox}$) that are then subsequently transplanted with the bone marrow of animals with *Nf1* +/- bone marrow now develop plexiform neurofibromas. In a series of converse experiments, Yang was able to definitively show that this combination is not just necessary, but is required to form plexiform neurofibromas in mice.

b. Analyses of the tumors from this model demonstrate the presence of the classic histological features of human plexiform neurofibromas including disruption of normal architecture; wavy Schwann cells and infiltrating cells with hyperchromatic nuclei,

excess collagen deposition, angiogenesis, classic ultrastructural abnormalities, and Schwann cell-specific markers.

c. To further validate the model, mast cells were found to infiltrate the peripheral nerves preceding tumor appearance as evidenced by mast cell specific stains. A small population of macrophages and rare B lymphocyte and T-lymphocyte populations were also observed. Mice (Krox20;*Nf1*$^{flox/flox)}$ transplanted with wild type bone marrow showed no elevated mast cell infiltration.

d. The c-Kit receptor tyrosine kinase (RTK) controls many aspects of mast cell development and function. [2] In addition, c-kit activity governs migration, proliferation and survival of *Nf1*$^{+/-}$ bone marrow-derived mast cells.[3] Using two different strains of mice with point mutations in the c-kit receptor resulting in a reduction in receptor tyrosine kinase activity, the concept of c-kit mediated tumor development was tested. The two strains of c-kit mutated mice deficient in mast cell mobilization were intercrossed with *Nf1*$^{+/-}$ mice. These mice then served as bone marrow donors to the *Nf1* LOH Schwann cell lineage mice (Krox20;*Nf1*$^{flox/flox}$). These mice had significantly reduced morbidity and mortality due to progression of plexiform neurofibromas compared to mice that were transplanted without mutations in the c-kit receptor that were able to mobilize their mast cells demonstrating the importance of c-kit signaling in plexiform development.

e. Utilizing a cohort of 8-9-month-old Krox20; *Nf1*$^{flox/-}$ mice with FDG-PET positive tumors, imatinib mesylate, a potent inhibitor of c-kit, PDGFR, and c-abl, was administered orally at 200 mg/kg/day and compared to placebo control. Animals treated with imatinib showed striking decrease in FDG-PET activity. Also, histologic sections of plexiform neurofibromas that develop in the dorsal root ganglia were taken post-mortem showing a clear decrease in dorsal root ganglia plexiform volume in the imatinib mesylate treated group as compared to controls. In the proximal surrounding nerves, mice treated with PBS placebo showed a distinct disruption of the normal nerve architecture and increase in cellularity compared to imatinib mesylate treated mice.

Together these data makes a strong argument for the further clinical development of pharmacologic c-kit targeting for the treatment of *Nf1* dependent plexiform neurofibromas.

RTK inhibition of *Nf1*-dependent tumors by cabozantinib

a. **Activity of cabozantinib as inhibitor of multiple receptor tyrosine kinases (RTKs).**
Data from pharmacodynamic experiments show that, *in vivo*, cabozantinib inhibits several key RTKs that promote tumor cell proliferation and/or angiogenesis including c-Kit, MET, VEGFR2, and RET. There is good correlation between increases in plasma drug concentrations and increased inhibition of receptor phosphorylation at the doses tested. Results from dose-response experiments in mice indicated that the ED_{50} of targets is achieved at well-tolerated doses of cabozantinib at plasma exposure comparable to exposure observed in clinical trials. Cabozantinib produces prolonged inhibition of receptor phosphorylation; such as

sustained inhibition of MET and VEGFR2 for 10 hours after administration of a single dose of cabozantinib.

		Dose Response			Duration of Action		
Target	Model	Maximum Inhibition (%)	Estimated ED_{50} (mg/kg)	Estimated IC_{50} (μM)	Dose (mg/kg)	Maximum Inhibition (%)	Sustained Inhibition > 50% (hours)
MET	Liver (+HGF)	97	5	2	100	99	10
	H441	96	9	7	100	92	10
VEGFR2	Lung (+VEGF)	98	26	2	100	99	10
TIE-2	Lung (basal)	84	86	24	100	58	4
RET	TT	89	11	8	100	79	< 24

MET, hepatocyte growth factor receptor protein; TIE-2, receptor for angiopoietin-1 and -2; VEGFR2, vascular endothelial growth factor receptor 2

ED_{50}, dose associated with 50% inhibition (of receptor phosphorylation); HGF, hepatocyte growth factor; IC_{50}, concentration associated with 50% inhibition (of receptor phosphorylation); TT, medullary thyroid carcinoma cell line; VEGF, vascular endothelial growth factor.

b. **Preclinical drug screen**

Compounds were selected for preclinical in vivo testing that were either undergoing clinical trials and/or commercially available. All of the selected compounds were tyrosine kinase inhibitors. These compounds were tested in 12 week *in vivo* studies in murine Nf1 plexiform neurofibroma models to screen for candidates for further clinical testing. The two compounds shown here were cabozantinib (notated XL184) and XL647. Cabozantinib (inhibitor of c-kit, met, RET and VEGFR2), met all established "success" guidelines for moving forward to human trials. XL647 (inhibits VEGFR2, EGFR, and Her-2) achieved some but not all success criteria and has not been selected to move forward.

i. Criteria for success: The criteria to move a drug forward included reduction in metabolic activity of a cohort by at least 30%, reduction of mast cell cellularity by at least 50%, and decrease in the absolute number of tumors by 25%

ii. Drug toxicity: All compounds selected are currently in clinical trials for other purposes and thus have had extensive preclinical safety and toxicity testing. None of the drugs tested were found to induce weight loss greater than 15%, nor did any drug cause mortality or other observable morbidity.

c. Evaluation of Histologic criteria

Figure 1A shows the results for biological effect of compounds on the reduction in mast cell cellularity of tumors as compared to tumors from mice that received placebo treatment. The defined threshold for success is 50% (as noted by the red line). XL184 (cabozantinib) reduced mast cell cellularity by greater than 50%.

Apoptotic cells in the tumor were evaluated using TUNEL assays (Figure 1B). Each symbol shown indicates the mean number of apoptotic cells scored from

individual tumors. XL184 (cabozantinib) treatment induced a consistent 2-fold increase in the apoptotic cells over the vehicle control group. As a marker of proliferation, the tissue sections were stained with Ki-67, a tumor antigen that is found in growing dividing cells but is absent in the resting phase of cell growth. Both XL184 and XL647 resulted in a reduction in the number of proliferating cells that were scored per high power field (*P<0.01).

Figure 1 A.

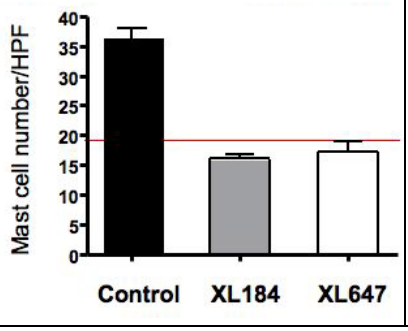


Figure 1B

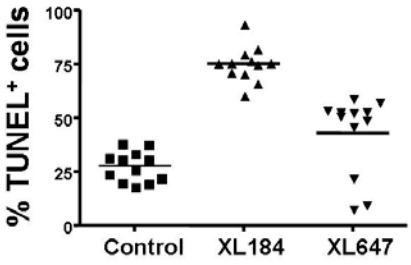


Figure 1C.

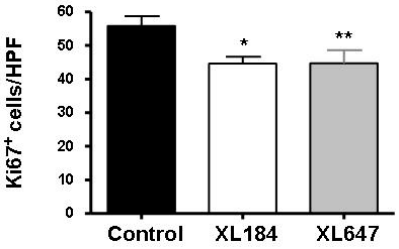


Figure 1. Histologic analysis. (A) Summary data showing the absolute number in mast cells in tumors of mice treated with XL184 and XL647 compared to placebo treated mice. Red line indicates the designated more than 50% decrease in mast cell numbers. *P<0.01 for vehicle control group and both experimental groups. (B) Summary data of TUNEL positive cells observed in tumors of mice treated with XL184 and XL647. *P<0.01 for vehicle control group and XL184 group. (C) Ki67+ cells per high power field. *P<0.01 compared to vehicle control groups.

d. Evaluation of metabolic activity

Small animal PET imaging studies was performed and examined changes in FDG uptake as a biomarker of response to experimental therapy in Krox20; *Nf1*$^{flox/-}$ mice. Imaging studies were performed prior to initiation of therapy and prior to sacrifice. All image data sets were transformed to standardized uptake value units (SUVs) and all voxel values above a threshold of SUV=1.0 within a 3-D volume of interest along the spine was integrated to form an FDG biomarker index. The bar graph in Figure 2 demonstrates the observed results for a representative group of experimental drugs tested. As expected, the placebo groups had an increase in the FDG uptake over the 12-week period. Consistent with the striking cellular changes observed from histologic specimens, following 12-weeks treatment, mice that received XL184 had a significant reduction in SUV uptake.

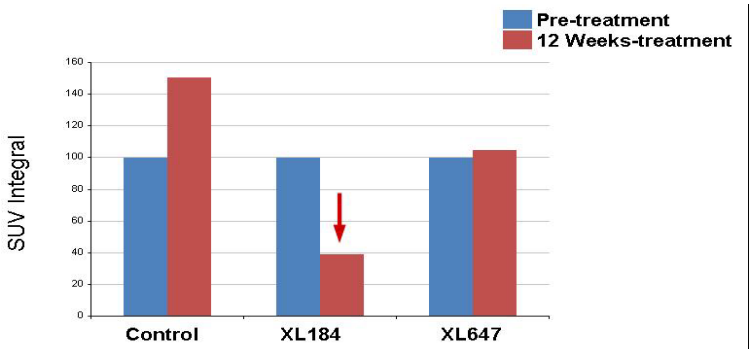


Figure 2. SUV integral. The SUV integral is a measure of the elevated retention of FDG in a 3D volume of interest around the spinal cord. The blue bar represents the pretreatment level, the red bar represent the 12 weeks after the treatment.

e. Tumor number was decreased following long-term treatment with XL 184 (cabozantinib)

To evaluate whether the histologic changes and the metabolic reduction in the XL184 treated mice correlated with the tumor number changes, we measured tumor numbers and tumor size. As shown in Figure 3A, mice treated with XL184 had a 75% reduction in the average number of tumors as compared to that of vehicle controls (* p< 0.01). Of the residual tumors, XL184 treatment reduced the tumor size by greater than 50% compared to control group (*P<0.01) (Figure 3C). Thus this compound meets both go/no go criteria established previously.

Figure 3A.

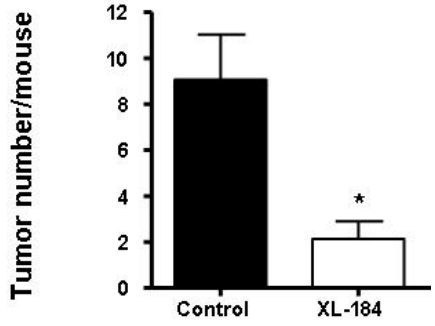


Figure 3B.

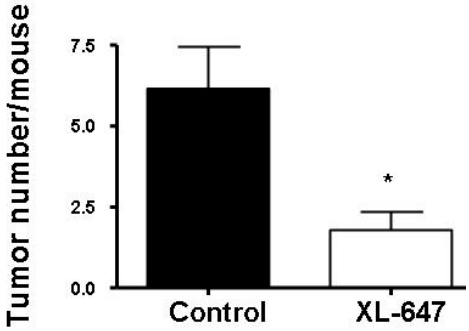


Figure 3C.

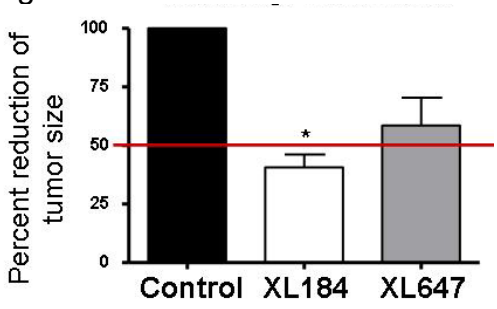


Figure 3. **Measurement of the average tumor numbers following the long-term treatment with Xl184 or XL647.** (A) Mean number of tumors of *Krox20; Nf1$^{flox/-}$* mice treated with vehicle vs. XL184. *p< 0.01 comparing vehicle to XL184. (B) Mean number of tumors of *Krox20; Nf1$^{flox/-}$* mice treated with vehicle vs. XL647. *p< 0.01 comparing vehicle to XL647. (C) Percent tumor size reduction. Mean percent residual tumor size as measured in area (mm2) is shown. *P<0.01. The red line indicates the 50% threshold of tumor size.

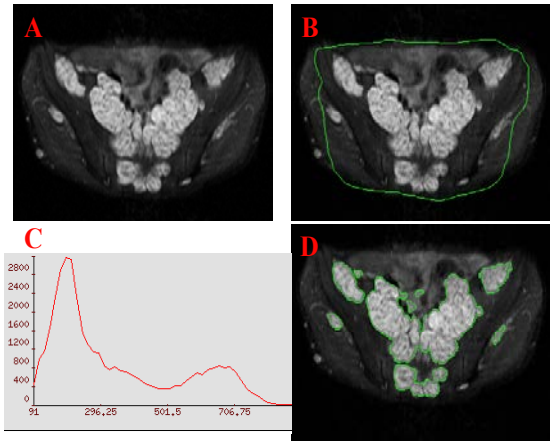
f. Summary

XL184 had a striking reduction in the number of tumors (>70%) and of the few residual tumors that were remaining, a 50% reduction in tumor size was observed. Thus this drug meets both established milestone 2 go/no go criteria and should be considered for a clinical trial. All correlative histologic and imaging data are completely consistent with this striking response.

XL184 has been moved forward and is now in multiple phase 2 clinical trials and also in phase 3 clinical trials.

Imaging and Measurement of Plexiform Neurofibromas

Figure *1: Axial MRI of pelvic plexiform neurofibroma. Steps of automated volumetric analysis A-D.*



Tumor response criteria that are used for cancers are based on one-dimensional (1-D) and two-dimensional (2-D) tumor measurements (Estey, Hoth et al. 1986; Therasse, Arbuck et al. 2000). These methods have limited value in the assessment of treatment outcome for plexiform neurofibromas, which are frequently large, have a complex (non-spherical) shape, and have a slow, erratic growth pattern. In order to reproducibly quantify the size of these complex lesions and detect small changes in the size over time, we used MR imaging characteristics of plexiform neurofibromas to develop an automated method of lesion detection and volume measurement. Short T1-Inversion Recovery (STIR) MR images, on which plexiform neurofibromas are bright lesions compared with normal surrounding tissue, were used to develop a program for automated image analysis within MEDx (v3.41) software (Sensor Systems, Inc. Sterling, VA). Reproducibility and inter-observer variability of this automated method were determined by 2 observers who quantified volumes for plexiform neurofibromas of the orbit (n=2), face/neck (n=3), abdomen (n=1), and pelvis (n=3) on three different days (Solomon, Warren et al. 2004). For each MR image (Figure 1A), the tumor is roughly outlined manually including a rim of low signal intensity normal tissue (Figure 1B). The program then performs a histogram analysis of signal intensity pixel by pixel and a threshold that distinguishes high signal intensity tumor from normal tissue is defined (Figure 1C). Tumor contours are then determined using a gradient image, connected component analysis and automatic edge following operation (Figure 1D). There is an option for re-analysis of MR images using an average or selected threshold. Tumor volume is calculated by summing the results from all images based on the resulting 2-D contours and slice thickness; and a report is generated.

For comparison, the volume of each plexiform neurofibroma was also determined by each observer once by manually tracing the tumor borders on each MR image. The results of the application of the automated method and the correlation with the manual method are shown in the table below.

Automated Volumetric MRI Analysis	Observer 1	Observer 2

Mean tumor volume (ml)	291	290
Median (range)	(80.9-1581)	(75.7-1603)
Median Inter-day CV (%)	3.6	1.6
(range)	(0.7-6.0)	(0.6-5.6)
Difference in volume between observers (%) Median (range)	6.4 (1.4 – 11.9)	6.4 (1.4 – 11.9)
Correlation automated vs. manual method, R	0.999	0.999

This automated volumetric MRI analysis is applicable to most plexiform neurofibromas, has excellent intra- and inter-observer reproducibility and agrees with volumes determined by manual tumor tracing. This method was used in a phase II trial of the farnesyltransferase inhibitor tipifarnib, in the phase I and II trials of pirfenidone, in the phase I trial of peg-interferon alfa-2b, and in the NF Consortium phase 2 trial of Sirolimus for children with NF1 and plexiform neurofibromas to assess changes in tumor size. Imaging studies on these multicenter trials are sent to the NCI, POB, where volumetric MRI analysis is performed. Tumor progression on these trials is defined as an increase in plexiform neurofibroma volume by ≥ 20%.

This volume increase corresponds to much smaller changes in 1-D, or 2-D measurements as outlined in the table below:

Response Criteria	RECIST Diameter, 2r	WHO Product, $(2r)^2$	Current NF1 trials Volume, $4/3\Pi r^3$
Disease progression (Increase)	20	44	73
	12	25	40
	6	13	20

Shaded areas show current criteria used to define disease progression by RECIST, WHO, and the ongoing NF1 trials listed above.

The use of this method of volumetric MRI analysis of PNs in 49 individuals with NF1 who were followed at the NIH for ≥ 18 months resulted in the following observations: 1) Time to disease progression is a realistic trial endpoint, provided progression is present at trial entry, in that progression can be documented within a clinically meaningful time period. The median time to progression on phase A (50% of individuals receive placebo, 50% receive drug) of the tipifarnib phase II trial is 18 months (range 3 to 36+ months). 2) Plexiform neurofibromas appear to grow more rapidly in younger compared to older children (see Figure below), and 3) while the growth rate of PN is variable among patients, the growth rate within patient during the time of observation (median observation period 34 months, range 18-70 months) appeared to be constant (Dombi, Solomon et al. 2007). 4) Given the more rapid growth of PN in younger children, it appears critical that drug development for NF1 PN focuses on young patients.

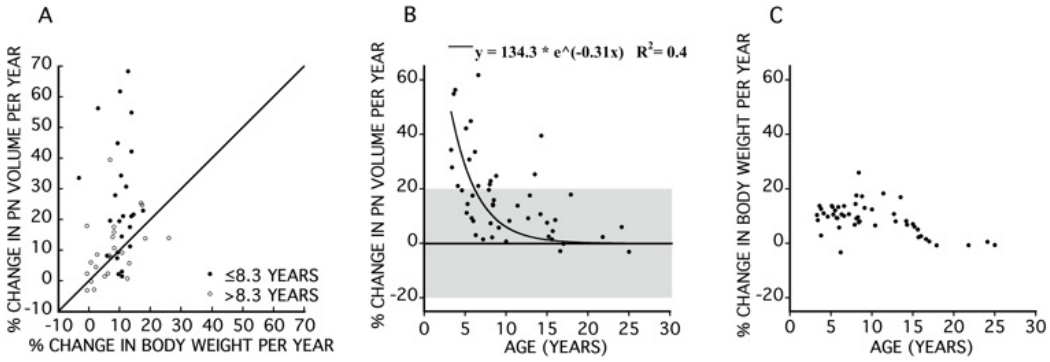


Figure 2: Relationship between the slopes for percent change in plexiform neurofibroma (PN) volume and percent change in body weight per year **(A)**. Values above the 45 degree line represent ratios of percent change in PN volume to percent change in body weight which are greater than 1. Closed symbols represent patients ≤ the median age (8.3 years) at study entry, and open symbols patients > 8.3 years. Percent change in plexiform neurofibroma (PN) volume **(B)** and body weight (**C**) per year as a function of patient age at baseline. The shaded area indicates the 20% change in PN volume required for documentation of disease progression in ongoing clinical trials. The line in **B** represents an exponential fit to the data.

2.1 Cabozantinib tablets

Exelixis internal number: XL184

Chemical Name: Chemical Name: *N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. All tablet strengths are prepared from a common blend and are distinguished by shape. The 20 mg tablets are round and the 60 mg tablets are oval.

Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib malate (25% drug load as cabozantinib)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide,	Glidant	0.3
Magnesium Stearate	Lubricant	0.75
Opadry Yellow Film Coating which includes: - HPMC 2910/Hypromellose 6 cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00

2.2 Cabozantinib Nonclinical Toxicology

Summary of Toxicology
The nonclinical toxicity of cabozantinib was characterized in single- and repeat-dose toxicology studies in rats and dogs (see the current Investigator Brochure for summary tables); in vitro bacterial and mammalian genotoxicity bioassays; an in vivo clastogenic bioassay; reproductive and developmental toxicology studies, and cardiovascular, neurobehavioral, and respiratory safety pharmacology studies. The experimental designs, findings, and conclusions from these nonclinical toxicity studies are discussed in this section.

Single-Dose Toxicology Studies
Toxicity associated with single oral doses of cabozantinib was characterized in rats and dogs by dose-dependent changes in clinical signs, by clinical pathology changes reflective of toxicity to liver and hematopoietic tissues, and by histopathologic findings in multiple tissues.
The NOAELs for the definitive single oral dose toxicity studies of cabozantinib in rats and dogs were considered to be < 100 mg/kg and 2000 mg/kg, respectively. The Cmax and AUC0-t values in rats dosed at 100 mg/kg are approximately 2-fold and 3-fold higher, respectively, than for dogs dosed at 2000 mg/kg; therefore, the higher systemic exposure to cabozantinib in rats correlates with the greater toxicity observed in this species at lower administered doses.

Repeated-Dose Toxicology Studies
Repeated oral administration of cabozantinib, for up to 6 months resulted in dose-dependent toxicity in both rats and dogs.

The NOAELs for the subchronic toxicity studies in rats and dogs administered cabozantinib qd for 14 consecutive days were considered to be 1 mg/kg/day and 10 mg/kg/day, respectively.
Findings from chronic toxicity studies in rats and dogs following qd oral dosing of cabozantinib for 180 days (26 weeks) are summarized in the current Investigator Brochure. In rats, microscopic changes were present only in the kidneys of the 1-mg/kg/day dose group of both sexes, evidenced

by a slight, reversible increase in severity and/or incidence of chronic progressive nephropathy. Based on this, the NOAEL following chronic oral administration of cabozantinib for 180 days was considered to be 0.3 mg/kg/day. There was very little evidence of toxicity.

In dogs, the only microscopic findings possibly related to cabozantinib administration (5 mg/kg qd × 180) were present in testes (hypospermatogenesis) and ovaries (corpora lutea absence). These microscopic findings may reflect a lack of sexual maturation in the young adult animals used in this study, rather than a test article-related change. Therefore, the NOAEL for cabozantinib in this study was considered to be 5 mg/kg/day.

In a second 6-month toxicity study in dogs a higher cabozantinib dose (30 mg/kg) was tolerated for only 10 days due to body weight decreases of up to 11%. Following an 11-day drug holiday, dosing was reinitiated at a lower dose of 20 mg/kg for 122 and 172 days in males and females, respectively ("30/20 mg/kg/day"). The only cabozantinib -related macroscopic finding, which had no microscopic correlate, consisted of mild and/or moderate gray discoloration of the skin or head. Microscopic changes associated with cabozantinib administration were observed only in reproductive tissues (e.g., moderate to severe bilateral hypospermatogenesis in testes, and lack corpora lutea in ovaries), and were correlated with decreased testicular and ovarian weights.

2.3 Clinical Experience

Clinical Summary

As of 28 February 2018, 3017 subjects with cancer treated with cabozantinib in Exelisis sponsored single-agent studies has been performed. Clinical data are available from 18 studies of cabozantinib including four Phase 1 studies, one actively enrolling Phase 1b study, one Phase 1b/2 study, four Phase 2 studies, five Phase 3 study, one ongoing and enrolling Phase 4 study in MTC, one ongoing maintenance "roll-over" study, and one expanded access study.

The most frequently observed adverse events (AEs) were diarrhea, fatigue, decreased appetite, nausea, Palmar-Plantar Erythrodysesthesia (PPE) syndrome, weight decreased, hypertension, vomiting, dysgeusia, and dysphonia. Some of these events resulted in permanent study drug discontinuation, including fatigue, general physical health deterioration, decreased appetite, asthenia, , diarrhea, nausea, and vomiting. The events to monitor of diarrhea, PPES, and hypertension include AEs that were reported in high frequency in previous cabozantinib studies and have been commonly observed with vascular endothelial growth factor – tyrosine kinase inhibitor (VEGFR-TKIs). Less frequent effects but potentially life-threatening AEs that have been reported for subject receiving cabozantinib and other VEGF pathway inhibitors, are GI perforation, fistulas, abscesses, hemorrhage (grade 3), arterial thrombotic events, venous and mixed/unspecified thrombotic events, wound complications, osteonecrosis, proteinuria, and reversible posterior leukoencephalopathy syndrome (RPLS) which have been observed in clinical studies with cabozantinib. There have been 44 subjects in pooled singe-agent studies with Grade 5 events assessed to be related to cabozantinib (note one subject had two Grade 5 AEs): arterial thrombotic event (3 subjects), fistula (5subjects), GI perforation (5 subjects), Hemorrhage (23 subjects), venous and mixed/unspecified thrombotic events (7 subjects), and abscess (1 subject).

Pediatric Experience

The Children's Oncology Group recently completed a Phase 1 trial of Cabozantinib in Children and Adolescents with refractory solid tumors. (Chuk et al. ASCO 2014). In this study, 25

evaluable patients age 4-18 years (median 14) were enrolled. In Part A (dose-finding) of the study (18 subjects), there was 1 DLT of grade 3 fatigue and headache at dose level 55 mg/m^2/day. In Part B (expansion cohort), there was 1 DLT of Grade 2 oral mucositis and Grade 2 palmar-plantar erythrodysesthesia at 40 mg/m^2/day, and 2 DLTs of Grade 3 hypertension and proteinuria, and hypertension and reversible posterior leukoencephalopathy syndrome, respectively, at 55 mg/m^2/day. The toxicity profile in this study was concluded to be similar in adults and in children.

Dose-Limiting Toxicities Beyond Cycle 1 From All Cohorts

Dose level (mg/m²/day)	Patients (n)	DLT	Cycle #
30	2	Gr 3 weight loss	10
		Gr 3 PPE	2
40	4	Gr 3 weight loss	5
		Gr 2 Arthralgia	2
		Gr 4 lipase increase	3
		Gr 3 PPE	6
55	5	Gr 3 Lipase increase	2
		Gr 2 anorexia, weight loss	3
		Gr 4 Neutropenia	2
		Gr 2 fatigue, Gr 3 thromboembolic event	2, 8
		Gr 3 anorexia, dyspnea, & skin ulcer	5

However, in the steady-state pharmacokinetics analysis, cabozantinib exposure was highly variable and did not appear to be dose proportional.

Cabozantinib D21 Steady-State Pharmacokinetics (Average ± SD)

Dose level (mg/m²/day)	Patients (n)	T_{max} (h)	C_{max} (µg/mL)	$AUC_{0\text{-}24h}$ (µg•h/mL)
30	6	5.33 ± 9.18	2.03 ± 0.6	31.9 ± 7.8
40	7	10.3 ± 9.7	1.9 ± 0.7	33.3 ± 11.3
55	6	6.7 ± 8.82	2.0 ± 0.7	33.7 ± 15

Based on comprehensive analysis of initial DLT data, DLT in later cycles as well as PK dosing, the recommended phase 2 dose of cabozantinib in children with solid tumors was determined to be 40 mg/m^2/day (equivalent to an adult dose of 72 mg/day).

Adult NF1 Plexiform Neurofibroma Experience (NF105 Cohort A)

In cohort A of this trial, of 21 subjects evaluable for toxicity, the most common adverse events (any grade) on study were gastrointestinal (all 21 subjects), asymptomatic hypothyroidism (n=16), fatigue (n=13), headaches (n=11), palmar-plantar erythrodysethesia (PPE, n=10), and leukopenia (n=9). Eleven grade 3 adverse events occurred in 8 patients, including PPE (n=4), hypertension

(n=2), anorexia, vomiting, neutropenia, proteinuria, and skin infection. There were no grade 4 or 5 AEs.

Two patients discontinued cabozantinib due to dose limiting toxicity (DLT); both for PPE that did not resolve ≤ grade 1 within the protocol-mandated timeframe of 14 days to allow restarting of drug. There were a total of 10 dose reductions that occurred in seven subjects while on study for: PPE (n=7); skin infection (n=1); weight loss (n=2).

Of the eight subjects with a partial response, only four reached that response by cycle 8, and the maximal tumor reduction did not occur until cycle 18 in 4 subjects and cycle 24 in 2 subjects.

Because of the overall excellent safety profile of cabozantinib and the numerous late tumor responses, the requirement to stop study treatment in subjects who do not achieve at least a 15% reduction in tumor volume by 8 cycles will be eliminated in the pediatric cohort (Cohort B). Of note, the initial rationale for this criteria was the hypotheses that the likelihood of achieving a partial response (20% reduction in tumor volume) by 12 months would be minimal if there was not a 15% reduction by 8 cycles.

2.4 Clinical Safety Profile

Adverse Events
As of 28 February 2018, AE data are available for 3017 subjects who have been dosed with cabozantinib.

The most frequent AEs (≥ 5% incidence) reported at severity of Grade 3 and above include fatigue 14.3%), hypertension (13.9%), diarrhea (10.7%), anemia (75%), PPES (9.4%), asthenia (7.0%), pulmonary embolism (5.3%), and decreased appetite (5.6%).

The most frequently (≥ 20% incidence) observed AEs reported as related to cabozantinib, were diarrhea (52.9%), fatigue (50.1%), decreased appetite (43.0%), nausea (39.9%), PPES (37.0%), weight decreased (25.3%), vomiting (23.8%), dysgeusia (22.8%), hypertension (25.2%), and dysphonia (21.6%).

Table 5-2: Summary of Adverse Events Experienced by ≥ 10% of Subjects Treated with Single-Agent Cabozantinib, N = 3017

	All AEs		Related AEs	
MedDRA Preferred Term	Subjects with AE n (%)	Subjects with ≥ Grade 3 AE n (%)	Subjects with AE n (%)	Subjects with ≥ Grade 3 AE n (%)
Number of subjects with at least one event	3009 (99.7)	2498 (82.8)	2902 (96.2)	1913 (63.4)
Diarrhoea	1817 (60.2)	322 (10.7)	1596 (52.9)	293 (9.7)
Fatigue	1733 (57.4)	432 (14.3)	1513 (50.1)	361 (12.0)
Decreased appetite	1573 (52.1)	170 (5.6)	1297 (43.0)	132 (4.4)
Nausea	1478 (49.0)	132 (4.4)	1204 (39.9)	98 (3.2)

Palmar-plantar erythrodysaesthesia syndrome	1134 (37.6)	284 (9.4)	1117 (37.0)	282 (9.3)
Vomiting	1015 (33.6)	101 (3.3)	719 (23.8)	64 (2.1)
Weight decreased	988 (32.7)	108 (3.6)	764 (25.3)	85 (2.8)
Constipation	900 (29.8)	34 (1.1)	388 (12.9)	13 (0.4)
Hypertension	880 (29.2)	418 (13.9)	759 (25.2)	365 (12.1)
Dysgeusia	723 (24.0)	4 (0.1)	688 (22.8)	4 (0.1)
Dysphonia	718 (23.8)	9 (0.3)	604 (20.0)	7 (0.2)
Asthenia	700 (23.2)	210 (7.0)	537 (17.8)	153 (5.1)
Aspartate aminotransferase increased	596 (19.8)	132 (4.4)	483 (16.0)	85 (2.8)
Dyspnoea	574 (19.0)	95 (3.1)	204 (6.8)	24 (0.8)
Abdominal pain	568 (18.8)	110 (3.6)	282 (9.3)	27 (0.9)
Stomatitis	558 (18.5)	55 (1.8)	526 (17.4)	53 (1.8)
Mucosal inflammation	549 (18.2)	56 (1.9)	522 (17.3)	54 (1.8)
Anaemia	544 (18.0)	227 (7.5)	236 (7.8)	76 (2.5)
Alanine aminotransferase increased	511 (16.9)	102 (3.4)	432 (14.3)	78 (2.6)
Back pain	510 (16.9)	97 (3.2)	59 (2.0)	6 (0.2)
Headache	493 (16.3)	31 (1.0)	183 (6.1)	3 (0.1)
Pain in extremity	477 (15.8)	56 (1.9)	200 (6.6)	16 (0.5)
Rash	454 (15.0)	17 (0.6)	371 (12.3)	15 (0.5)
Cough	443 (14.7)	8 (0.3)	97 (3.2)	1 (< 0.1)
Oedema peripheral	416 (13.8)	20 (0.7)	114 (3.8)	4 (0.1)
Hypothyroidism	413 (13.7)	8 (0.3)	343 (11.4)	4 (0.1)
Dizziness	368 (12.2)	14 (0.5)	185 (6.1)	3 (0.1)
Dyspepsia	363 (12.0)	4 (0.1)	264 (8.8)	4 (0.1)
Hypokalaemia	361 (12.0)	109 (3.6)	161 (5.3)	50 (1.7)
Arthralgia	345 (11.4)	31 (1.0)	88 (2.9)	4 (0.1)
Pyrexia	329 (10.9)	15 (0.5)	59 (2.0)	2 (0.1)
Dry mouth	319 (10.6)	0	261 (8.7)	0
Hypomagnesaemia	313 (10.4)	37 (1.2)	205 (6.8)	28 (0.9)
Urinary tract infection	309 (10.2)	39 (1.3)	31 (1.0)	3 (0.1)
Insomnia	306 (10.1)	1 (< 0.1)	90 (3.0)	0
Dry skin	304 (10.1)	0	255 (8.5)	0
Muscle spasms	303 (10.0)	2 (0.1)	171 (5.7)	1 (< 0.1)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

At each level of subject summarization, a subject is counted once if the subject reported one or more events. Adverse events were coded based on MedDRA version 17.0.

Note: This table summarizes pooled data in the clinical database for single-agent cabozantinib studies (XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, XL184-301 cabozantinib arm, XL184-306 cabozantinib arm, XL184-307 cabozantinib arm, XL184-308 cabozantinib arm, XL184-309 cabozantinib arm, and XL184-401). The denominator for percentages is the number of treated subjects.

Events to Monitor

Adverse events of interest have been identified as categories of AEs that are known class effects of VEGF inhibitors, that may impact the risk/benefit of cabozantinib treatment, and that as a result of increased awareness should be diagnosed and appropriately clinically managed.

The AEs of interest and their observed frequencies are discussed in this section and include data only from open-label studies with single-agent cabozantinib in the clinical database as of 28 February 2018 (N = 3017).

Events to Monitor (ETMs) in the Pooled Single-Agent Studies

The definition a set of Events to Monitor (ETMs) in order to track events known to be associated with TKIs, VEGF pathway inhibition, and other events with potentially serious consequences. Each ETM comprises a set of AEs that are related to each other pathophysiologically.

The ETMs of diarrhea, PPES, and hypertension include AEs that were reported in high frequency in previous cabozantinib studies and have been commonly observed with VEGFR-TKIs. Less frequent but potentially life-threatening AEs that have been reported for subjects receiving cabozantinib and other VEGF pathway inhibitors are represented by the ETMs of GI perforations, fistulas, abscesses–all, intra-abdominal and pelvic abscesses, hemorrhages (≥ Grade 3), arterial thrombotic events, venous and mixed/unspecified thrombotic events, wound complications, osteonecrosis, proteinuria, and RPLS. In the interest of routine surveillance, QT prolongation is also tracked.

The AEs discussed in this section and summarized in Table 5-4 include data in the clinical database as of the AE cutoff dates for the Safety populations (ie, all subjects who received at least one dose of study treatment) from the pooled single-agent cabozantinib (N = 3017).

Table 5-4 Incidence of Events to Monitor

	Pooled Single-Agent Studies[b]		
	Cabozantinib (N = 3017)		
ETM[a]	All n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Diarrhea	1817 (60.2)	322 (10.7)	0
PPES	1134 (37.6)	284 (9.4)	0
Hypertension	911 (30.2)	427 (14.2)	0
Venous and mixed/unspecified thrombotic events	308 (10.2)	216 (7.2)	7 (0.2)
Proteinuria	212 (7.0)	37 (1.2)	0
Hemorrhage (≥ Grade 3)	147 (4.9)[c]	124 (4.1)	23 (0.8)
Abscess–all	135 (4.5)	50 (1.7)	1 (< 0.1)
Intra-abdominal and pelvic abscess	44 (1.5)	28 (0.9)	0

Arterial thrombotic events	68 (2.3)	42 (1.4)	3 (0.1)
Wound complications	60 (2.0)	19 (0.6)	0
Fistula	48 (1.6)	22 (0.7)	5 (0.2)
GI perforation	42 (1.4)	37 (1.2)	5 (0.2)
Osteonecrosis[d]	39 (1.3)	15 (0.5)	0
QT prolongation[e]	31 (1.0)	9 (0.3)	0
RPLS	1 (< 0.1)	1 (< 0.1)	0

ETM, event to monitor; GI, gastrointestinal; PPES, palmar-plantar erythrodysesthesia syndrome; RPLS, reversible posterior leukoencephalopathy syndrome.

Note: A subject is counted once per ETM for the most severe event if reporting one or more event.

[a] The complete lists of reported MedDRA preferred terms for each ETM are defined in Appendix J.

[b] Subjects included in the single-agent pool are those who received cabozantinib on XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, XL184-301, XL184-307, XL184-306, XL184-308, XL184-309, and XL184-401. The data cutoff dates for the pooled single-agent studies are presented in Appendix F. The denominator for percentages is the number of treated subjects.

[c] By definition, the ETM of hemorrhage includes only events of ≥ Grade 3. The data presented are for events of ≥ Grade 3.

[d] The reported ETMs for osteonecrosis comprised osteonecrosis of the jaw (1.2%; 28 of 36 subjects had CRPC [from Studies XL184-203, -306, & -307]), osteonecrosis (0.1%), and osteoradionecrosis (< 0.1%).

[e] The reported ETMs of QT prolongation were electrocardiogram QT prolonged (1.0%) and electrocardiogram QT interval abnormal (< 0.1%).

Discontinuation Due to Adverse Events

As of 28 February 2018, 933 (30.9%) subjects in pooled single-agent studies of cabozantinib permanently discontinued cabozantinib for the primary reason of AE or SAE. Adverse event data are available for all of these subjects. The most frequently reported AEs (≥1%) for subjects who discontinued for the primary reason of an AE or SAE were fatigue (3.8%), general physical health deterioration (2.7%), asthenia (1.9%), decreased appetite (1.9%), nausea (1.6%),diarrhea (1.0%), PPES (1.4%), and vomiting (1.0)%

Deaths

Through 28 February 2018, 275 of 743 subjects who received cabozantinib in ISTs conducted under separate US IND or ex-US equivalents held by the investigators; in these studies, reported in 551 SAEs in 310 cases. A total of 43 SAEs with fatal outcome were reported from ISTs through 28 February 2018. Twenty-five subjects died of progression of the underlying malignancy. Of the 17 subjects with fatal SAEs not related to underlying malignancy, 12 died of events that were assessed as not related to underlying malignancy, 12 died of events that were assessed as not related to study treatment. These comprised events of death (2 events), sudden death, sepsis, multi-organ failure, intracranial tumor hemorrhage, and myelodysplastic syndrome. One subject each died of fatal SAEs of hemorrhage and hypertensive heart disease that were considered possibly related to study treatment.

Through 28 February 2018, 253 of 912 subjects in NCI-CTEP studies reported 1084 SAEs in 456 cases. A total of 75 subjects experienced SAEs with fatal outcome in NCI-CTEP studies. Forty-six subjects died due to progression of the underlying malignancy. Of the 29 subjects with fatal SAEs not related to the underlying malignancy, 17 died of events assessed as not related to

study treatment. Twelve subjects died of a fatal SAE that were considered possibly related to the study treatment: sepsis (2 subjects), death, sudden death, intracranial hemorrhage, cardiac arrest, acute kidney injury, jejunal perforation, embolism, colon fistula, respiratory failure, and pneumonitis (1 subject each).

Volumetric Assessment of Plexiform Neurofibroma Size

PNs are complex-shaped and slow-growing peripheral nerve sheath tumors that are challenging to measure by simple linear measurements. Automated volumetric MRI analysis can sensitively and reproducibly detect small changes in PN size and it has become the measurement method of choice to determine tumor response and time to disease progression in recent clinical trials. There are two volume segmentation methods optimized for PN measurement, MEDx developed at the National Cancer Institute (NCI) and 3DQI used by the Tumor Imaging Metrics Core at Massachusetts General Hospital (MGH). The NF Clinical Trials Consortium has utilized MEDx in all of its PN trials. In a small, retrospective study volume measurements and volume changes over time were compared using these two different methods, and found good agreement. The goal is to prospectively evaluate a larger cohort of clinical trial participants to further define the level of agreement in volume measurements, disease status classifications, and objective response rates between MEDx and 3DQI.

Overview of Proposed Study

This phase II open label study will evaluate children and adults with neurofibromatosis type-1 (NF1) and plexiform neurofibromas treated with cabozantinib (XL184). This study will enroll subjects who either meet clinical diagnostic criteria or have an identified pathogenetic *NF1* mutation. Subjects on study must have clinically significant plexiform neurofibroma defined as potentially life-threatening, impinging on vital structures or significantly impairing the quality of life from pain or other symptoms. Patients must not have lesions suspicious for malignant tumors such as MPNSTs (malignant peripheral nerve sheath tumors) and suspicious tumors must be proven negative by histopathology prior to enrollment on study. This study will be open to patients ≥3 years of age that meet eligibility criteria. There will be two cohorts: A. Cohort of subjects ≥ 16years of age, B. Subjects ≥3 years to 15 years of age with progressive plexiform neurofibroma.

The study will be a Simon two-stage study design **for cohort A**. It will be a single-arm open-label study of cabozantinib and the primary endpoint is the ORR to cabozantinib at 1 year. In the first stage, 9 evaluable subjects per cohort will be accrued. If there is at least 1 response, accrual will continue to the second stage and an additional 8 evaluable subjects in that cohort will be enrolled. To allow for 25% unevaluable subjects, a maximum of 24 subjects per cohort will be enrolled. Radiographic response will be evaluated as the primary endpoint with 20% volumetric MRI response of the target lesion being the threshold criteria for tumor response. A target lesion will be selected at time of enrollment and tumor evaluations will occur serially while on study.

In Cohort A, all subjects will start cabozantinib at 40 mg. The published MTD for cabozantinib is 140 mg and the current recommended dose in Phase 3 clinical trials for subjects with medullary thyroid cancer is 100 mg. Doses of 40 mg and 60 mg continue to show efficacy in on-going phase 2 and phase 3 trials with reduced toxicity (personal communication John Frye, Exelixis). Subjects who tolerate 40 mg for 2 cycles will escalate to 60 mg. The rationale for this

is that the majority of subjects who develop toxicity do so after >2 weeks on drug as cabozantinib has a long half-life. Subjects who experience dose-limiting toxicity (see Section 7.0) at 40 mg will dose reduce to 20 mg when their toxicities resolve. Subjects without toxicity at 40mg will increase to 60mg. Subjects who experience toxicity at 60 mg will dose reduce to 40 mg. This dosing schema is designed to maximize safety and tolerability in this new population of patients.

In Cohort B, we will enroll a minimum of 17 evaluable subjects. To allow for up to 25% unevaluable subjects, a maximum of 24 subjects will be enrolled. Based on the preliminary response data (passed the threshold to move to stage 2) and minimal toxicity in Cohort A to date, a 2-stage design is not felt to be necessary for Cohort B.

Subjects in Cohort B will start at 30 mg/m^2/day dosing. Dose will be escalated at cycle 3 if tolerated to 40 mg/m^2. Subjects who experience DLT at 40 mg/m^2/day will dose reduce to 30 mg/m^2/day. Subjects who experience DLT at 30 mg/m^2/day will dose reduce to 23 mg/m^{2}day. Actual dosing will be based on the dosing nomogram in Appendix XI.

Subjects entered on the trial will be carefully monitored for the development of cabozantinib associated toxicities, and target modifications and interruptions will be performed as outlined in this protocol (see section 7.0).

In all consenting subjects entered on this trial a complete pharmacokinetic profile of cabozantinib after administration will be evaluated. In addition, cytokine and endothelial progenitor cell biomarkers will be drawn to assess treatment effect and to correlate with response.

In addition, since plexiform neurofibromas may significantly impact the lives of patients with NF1, this study will evaluate the effects of the disease and treatment with cabozantinib on the quality of life (QOL) of these subjects by assessing health related QOL, pain intensity, and pain interference.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

The NF Operations Center should be contacted to ensure availability of a treatment slot and PK slot.

3.1 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parent(s) or guardian if the patient is a child. When appropriate, pediatric patients will be included in all discussions. All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

- A study participant should sign the institution's HIPAA Consent.
- A study participant should sign the institution's Release of Medical Information Waiver.

3.2 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. Documentation of the informed consent for screening will be maintained in the subject's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. The completed eligibility checklist should be faxed or scanned and emailed to the NF Operations Center to confirm eligibility prior to subject enrollment.

3.3 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met, and a treatment number for subject has been confirmed by the NF Consortium Operations Center. All patients who give informed consent for the protocol in order to undergo screening for eligibility will be registered but are not considered enrolled until the screening is completed and they are determined to meet all eligibility criteria. Treatment must start within 14 days of enrollment. **Subjects must not receive any protocol therapy prior to enrollment.**

4.0 SUBJECT ELIGIBILITY

All studies to determine eligibility must be performed within 2 weeks prior to enrollment. The baseline MRI study documenting disease status is required within 4 weeks prior to study entry. All clinical and laboratory data required for determining eligibility of a subject enrolled on this trial must be available in the subject's medical or research record which will serve as the source document for verification at the time of audit/monitoring.

4.1 Inclusion Criteria for all subjects:

4.1.1 All subjects must have an identified pathogenetic constitutional *NF1* mutation OR the clinical diagnosis of NF1 using the NIH Consensus Conference criteria. In addition to a plexiform neurofibroma, one or more of the following diagnostic criteria for NF1 must be present:

4.1.1.1 Six or more café-au-lait spots (≥0.5 cm in prepubertal subjects or ≥1.5 cm in post pubertal subjects)

4.1.1.2 Freckling in the axilla or groin

4.1.1.3 Optic glioma

4.1.1.4 Two or more Lisch nodules

4.1.1.5 A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex)

4.1.1.6 A first-degree relative with NF1

4.1.2 Subjects must have plexiform neurofibroma(s) that are progressive (see section 4.1.2.1) **OR** are causing significant morbidity, such as (but not limited to) head and neck lesions that are compromising the airway or great vessels, brachial or lumbar plexus lesions that are causing nerve compression and loss of function, lesions causing major deformity (e.g., orbital lesions) or are significantly disfiguring (see section 4.1.2.2), lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Patients with paraspinal plexiform neurofibromas will be eligible for this trial. Histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a plexiform neurofibroma is clinically suspected.

4.1.2.1 For subjects enrolled for tumor progression, progression is defined as:

- Presence of new plexiform neurofibroma on MRI or CT (documented by comparison with prior MRI or CT), OR
- A measurable increase in plexiform neurofibroma size (≥ 20% increase in the volume, or a ≥ 13% increase in the product of the two longest perpendicular diameters, or a ≥ 6% increase in the longest diameter) documented by comparison of two scans (MRI or CT) in the time period of approximately one year or less prior to evaluation for this study.

4.1.2.2 For subjects enrolled for "major deformity" or a "significantly disfiguring" tumor, eligible tumors will be limited to tumors of the head & neck or those on other areas of the body that are unable to be concealed by standard garments. In order to enroll a plexiform neurofibroma for these indications, the Study Chair or Co-Chair must be contacted to review patient eligibility prior to enrollment.

4.1.3. <u>Disease status:</u>

Measurable disease: Subjects must have measurable plexiform neurofibroma(s) amenable to volumetric MRI analysis. For the purpose of this study, the target lesion must be seen on at least 3 consecutive MRI slices and the field of view must contain the entire tumor of interest. Tumors must be at least 3 mL in volume (most PNs 3 cm in longest diameter will meet this criteria). If the tumor is <3 cm in longest diameter, the patient may still be eligible. **Central review of the MRI of the target plexiform is required prior to enrollment to ensure that the tumor is measurable and amenable to volumetric analysis.** After consenting, please send the images on a CD along with the form in Appendix IX to Eva Dombi (see Appendix IX for address). Central review will take 3-7 days (please plan accordingly).

4.1.4. <u>Age</u>:

Subjects must be 3 years of age at the time of study entry. Subjects ≥16 years of age will be enrolled in Cohort A. Subjects 3-15 years of age will be enrolled in Cohort B.

4.1.5. <u>Subjects unable to consent to study:</u>

Adults (≥18 years of age) who are unable to provide informed consent will NOT be

enrolled on this study. Written informed consent must be obtained from all patients (≥18 years of age) or their legal guardians (if the patient is <18 years of age).

4.1.6. Performance Level:

Subjects must have Karnofsky or Lansky ≥ 50% (Appendix II). Note: Subjects who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

4.1.7. Prior Therapy

Patients who underwent surgery for a progressive plexiform neurofibroma will be eligible to enter the study after the surgery, provided the plexiform neurofibroma was incompletely resected and is measurable.

Patients are only eligible if complete resection of a plexiform neurofibroma with acceptable morbidity is not feasible, or if a patient with surgical option refuses surgery.

Patients may have been previously treated for a plexiform neurofibroma but must have fully recovered from the acute toxic effects of all prior chemotherapy or radiotherapy prior to entering this study.

a. Myelosuppressive chemotherapy: Must not have received within 4 weeks of entry onto this study.
b. Hematopoietic growth factors: At least 7 days since the completion of therapy with a growth factor that supports platelet, red or white cell number or function.
c. Biologic (anti-neoplastic agent): At least 14 days since the completion of therapy with a biologic agent. For agents that have known adverse events occurring beyond 14 days after administration (or 5 half-lives whichever is longer), this period must be extended beyond the time during which adverse events are known to occur. These patients must be discussed with the Study Chair on a case-by-case basis.
d. Investigational Drugs: Subjects must not have received an investigational drug within 4 weeks.
e. Steroids: Patients with endocrine deficiencies are allowed to receive physiologic or stress doses of steroids if necessary.
f. XRT: ≥ 6 months from involved field radiation to index plexiform neurofibroma(s); ≥ 6 weeks must have elapsed if patient has received radiation to areas outside index plexiform neurofibroma(s).
g. Surgery: At least 3 months since undergoing any major surgery. At least 1 month since undergoing any minor surgery. See section 4.2.1 for more details.

4.1.8. Organ Function Requirements

4.1.8.1. Adequate Bone Marrow Function Defined as:

- Peripheral absolute neutrophil count (ANC) ≥ 1500/μL
- Platelet count ≥ 100,000/μL (transfusion independent)
- Hemoglobin ≥ 10.0 gm/dL (may receive RBC transfusions)

4.1.8.2. Adequate Renal Function Defined as: maximum serum creatinine 1.5 mg/dL OR a creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2

Serum calcium, magnesium, and phosphorous with institutional normal limits (supplementation is permissible)

4.1.8.3. Adequate Liver Function Defined As:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGPT (ALT) ≤ 5 x upper limit of normal (ULN) for age, and
- Serum albumin ≥ 2 g/dL.

4.1.8.4. Blood pressure within upper limit of normal defined as:

- A blood pressure (BP) ≤ 95th percentile for age, height, and gender and not receiving medication for treatment of hypertension.

4.1.9. Major surgery: Only patients who are not anticipated to need major surgery within the next 3 months of enrollment are eligible.

4.2 Exclusion Criteria

4.2.1 Exclusion Criteria

- Evidence of an active optic glioma or other low-grade glioma, requiring treatment with chemotherapy or radiation therapy. Patients not requiring treatment are eligible for this protocol.
- Patients with malignant glioma, malignant peripheral nerve sheath tumor, or other malignancy requiring treatment in the last 12 months.
- Dental braces or prosthesis that interferes with volumetric analysis of the neurofibroma(s).
- The subject is unable to swallow tablets
- Women who are pregnant or breast-feeding.
- Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method during the period they are receiving the study drug and for 3 months thereafter. Abstinence is an acceptable method of birth control. Women of childbearing potential will be given a pregnancy test within **7 days** prior to administration of cabozantinib and must have a negative urine or serum pregnancy test.
- The subject has received prior treatment with a small molecule kinase inhibitor or a hormonal therapy (including investigational kinase inhibitors or hormones) within 14 days or 5 half-lives of the compound or active metabolites, whichever is longer, before the first dose of study treatment -OR- the subject has ever taken cabozantinib. Note: Subjects with prostate cancer currently receiving LHRH or GnRH agonist may be maintained on these agents.
- The subject has not recovered to baseline or CTCAE ≤ Grade 1 from toxicity due to all prior therapies except alopecia and other non-clinically significant AEs.

- The subject requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (e.g., clopidogrel). Low dose aspirin (≤ 81 mg/day), low-dose warfarin (≤ 1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.
- The subject requires chronic concomitant treatment of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort). The subject requires chronic concomitant treatment of strong CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, squinavir, telithromycin, aprepitant, erythromycin, fluconazole, grapefruit juice, verpamil, diltiazem, cimetidine, amiodarone, chloramphenicol, boceprevir, ciprofloxacin, delaviridine, diethyl-dithiocarbamate, fluvoxamine, gestodene, imatinib, mibefradil, mifepristone, norfloxacin, norfluoxetine, starfruit, telaprvir, voriconazole). Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. 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.
- History of noncompliance to medical regimens
- Patients unwilling to or unable to comply with the protocol, or who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study
- A known history of HIV seropositivity or known immunodeficiency. HIV testing will not be required as part of this trial, unless HIV is clinically suspected.
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of cabozantinib (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection). A nasogastric tube (NG tube) is allowed.
- Patients who have an uncontrolled infection.
- The subject has experienced any of the following:
    - clinically-significant gastrointestinal bleeding within 6 months before the first dose of study treatment
    - hemoptysis of ≥0.5 teaspoon (2.5 mL) of red blood within 3 months before the first dose of study treatment
    - any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment
    - The subject has radiographic evidence of cavitating pulmonary lesion(s). Chest x-ray will not be required as part of this trial, unless cavitating pulmonary lesion is clinically suspected.
- Other concurrent severe and/or uncontrolled medical disease which could compromise participation in the study (e.g. uncontrolled diabetes, uncontrolled hypertension, severe

infection, severe malnutrition, chronic liver or renal disease, active upper GI tract ulceration)

- Cardiovascular disorders including:
  - Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening
  - Any history of congenital long QT syndrome
  - Baseline QTc interval >470 msec in women and >450 msec in men
    - Concomitant treatment with medications that prolong the QT interval and have a known risk of Torsades de Pointes is not contraindicated, but should be avoided if possible and will require more frequent EKG monitoring (see Section 6.3).
- Any of the following within 6 months before the first dose of study treatment:
  - unstable angina pectoris
  - clinically-significant cardiac arrhythmias
  - stroke (including TIA, or other ischemic event)
  - myocardial infarction
  - thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (e.g. vena cava filter) are not eligible for this study)
- Any of the following within 28 days before the first dose of study treatment:
  - intra-abdominal tumor/metastases invading GI mucosa
  - active peptic ulcer disease,
  - inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis
  - malabsorption syndrome
- Any of the following within 6 months before the first dose of study treatment:
  - abdominal fistula
  - gastrointestinal perforation
  - bowel obstruction or gastric outlet obstruction
  - intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more than 6 months before the first dose of study treatment.
- Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of study therapy
- Other clinically significant disorders such as:
  - active infection requiring systemic treatment within 28 days before the first dose of study treatment
  - serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of study treatment
  - history of organ transplant
  - concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment
- History of major surgery as follows:

- Major surgery within 3 months of the first dose of cabozantinib if there were no wound healing complications or within 6 months of the first dose of cabozantinib if there were wound complications
- Minor surgery within 1 months of the first dose of cabozantinib if there were no wound healing complications or within 3 months of the first dose of cabozantinib if there were wound complications

- **In addition,** complete wound healing from prior surgery must be confirmed at least 28 days before the first dose of cabozantinib irrespective of the time from surgery

5.0 REQUIRED DATA

IRB Approvals
The PI from each participating institution will provide the NF Consortium Operations Center with a copy of the initial IRB protocol approval and the yearly IRB continuing reviews. The Study Coordinator will submit these to the USAMRMC ORP HRPO. Registration will be halted at a participating institution if a current continuing approval is not on file at the NF Consortium Operations Center.

Each participating institution is required to maintain a current MPA or FWA in order to participate in government-sponsored Group research. The files will be copied or made available for review by authorized persons as required for conduct of this trial.

Amendments and Consents
The PI from each participating institution will provide the NF Consortium Operations Center with a copy of IRB approval of all amendments to the protocol or consent. The NF Consortium Operations Center will provide these institutional reviews to the USAMRMC ORP HRPO. As this trial receives funding by the US Army, substantive amendments to the research protocol and any amendments that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation and site distribution. The USAMRMC ORP HRPO defines a substantive amendment as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

Data Collection and Toxicity Reporting
The trial is being conducted by the NF Consortium. Case report forms developed by the NF Consortium Operations Center will be used for submitting clinical data to the Operations Center. Data must be submitted to the Operations Center within two weeks of completing each required evaluation while the subject is on study.

The NCI POB will receive MRI studies electronically or on CD and completed worksheets for volumetric analysis. When sending the CD, the site must provide tracking # (FedEx or UPS) by email to Eva Dombi: dombie@mail.nih.gov.

Upon analysis of these studies results will be transmitted to the NF Consortium Operations Center.

Biological specimens for banking will be handled and stored in the biorepository located in the Colket Translational Research Building at the Children's Hospital of Philadelphia (CHOP), Philadelphia, PA. The specimens will be under the management of the Center for Data Driven Discovery in Biomedicine (D3b) and the Biorepository Core (BioRC), according to their standard operating procedures (SOPs). Samples will be stored at -80°C. Biological specimens will be coded with a randomly generated study number prior to shipping to the biorepository in order to prevent identification of subjects and protect confidentiality. The study number will not be derived from or related to information about the subject, and will not contain any elements of PHI. The specimen number will be entered into the NF Consortium Operations Center eDES, thus providing a link between the specimen and the study data. Specimens may be shared with outside investigators/laboratories, who may analyze (and store, if applicable) the samples. Shared specimens will be labeled only with a study number. Requests for samples will be reviewed by the NF105 Study Chairs and the NFCTC Biology Committee. If a subject withdraws consent to store samples after collection, existing samples in the biorepository will be destroyed; however, any samples already shared to an outside laboratory or other entity will not be destroyed and any data generated already from the samples will not be destroyed.

Representatives from the FDA, NF Consortium Quality Assurance Committee, and the U.S. Army Medical Research and Material Command will have access to the data and research records.

Alyssa Reddy, MD will serve as the medical monitor. She will serve as a patient advocate and is independent of the clinical study team. She will oversee the progress of the protocol, especially issues of individual subject/patient management and safety. The medical monitor is required to review all unanticipated problems involving risks to subjects or others, including all serious and unexpected adverse events associated with the protocol as defined in Section 10.0. The monitor provides an unbiased written report of the event.

Handling of Research Samples

This study is conducted at NF Consortium Sites and coordinated by the NF Consortium Operations Center. Sample labeling, collection and initial processing will be conducted as outlined in the study Appendix V and VI. Blood samples obtained for biomarker analysis will be sent to Riley Hospital for Children (CCRC, Indiana School of Medicine) for analysis. Blood samples for pharmacokinetic analysis will be sent to Alturas Analytics. Samples will be stored in designated monitored freezers. The protocol specific subject ID number will identify samples. Once analyzed for studies outlined in this protocol any remaining samples will be stored by Riley Hospital for Children until the study is complete, and the manuscript describing the study has been accepted for publication. Any use of samples not outlined in this protocol will require prospective IRB review and approval. The study will remain open and status reported to the IRB until all samples have been analyzed, reported or destroyed. Unintentional loss or destruction of any samples will be reported to the IRB as part of annual continuing reviews. MRI studies of PN will be obtained as described in Appendix IV and be sent on CD to the NCI POB. MRI studies will be loaded on one of three Sun Workstations, which are password protected and allow access only to Drs Dombi, Widemann, or associate investigators on the trial. CDs will be stored in locked filing cabinets.

Data and Center Audits

The trial will be audited by the NF Consortium Operations Center for compliance and safety. Independent monitors will visit participating sites and review case report forms and source documentation. Missing or spurious information and protocol deviations will be communicated in a report to the trial coordinating center. Protocol deviations, which may result in compromise to safely administer study drug, or to determine study endpoints will be included in the annual protocol review to the USAMRMC ORP HRPO.

All unexpected and serious adverse events will be forwarded to the Medical Monitor, the Study PI, the FDA, Exelixis, and the USAMRMC ORP HRPO by the NF Consortium Operations Center as defined in Section 8.0.

Volumetric MRI analysis will be used to determine disease progression, and subjects will not be removed from study based on 1-D or 2-D MRI measurements or based on clinical measurement of superficial lesions.

5.1 Tests and Observations

See Section 9.0 and Appendix I. Unless otherwise noted, all tests to determine eligibility must be completed within 14 days of study entry.

5.2 Records to be kept

Subject Registration and Case Report Forms

Subjects will be registered with the NF Consortium Operations Center via the electronic data entry system (eDES). Electronic and paper Case Report Forms (CRFs) will be developed by the Consortium Operations Center and PI. All data must be entered into the eDES. Sites have the option of maintaining a printed copy of completed forms in the subject's study binder that have been initialed and dated by the study team member entering the data into the paper case report form.

Subjects must not be identified by name on any study documents that are sent off site to any agency. The Subject Identification Number received upon data entry registration and placed on all case report forms and regulatory documents will identify subjects.

All data entered on a paper CRF must be legibly recorded in indelible ink or typed. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to it. The correction must be initialed and dated by the investigator or designated qualified individual. Any requested information that is not obtained as specified in the protocol should have an explanation noted on the CRF as to why the required information was not obtained. The electronic CRF provides audit trail showing when data is revised.

5.3 Role of Data Management

5.3.1 Instructions concerning the recording of study data on CRFs will be provided by the NF Operations Center.

5.3.2 It is the responsibility of the NF Operations Center to assure the quality of data for

their study. This role extends from protocol development to generation of the final study database.

6.0 TREATMENT PROGRAM

6.1 Treatment Overview

This is a Phase 2, single-arm, open-label study of cabozantinib in subjects with plexiform neurofibroma. The primary endpoint is the ORR to cabozantinib after 12 cycles (~12 months). In cohort A, subjects who did not achieve at least 15% reduction in index tumor after 8 cycles (~8 months) were considered treatment failures and taken off study. For cohort B (pediatric cohort), because of the overall excellent safety profile of cabozantinib and the numerous late tumor responses in cohort A (adult cohort) (see protocol section 2.3), the requirement to stop study treatment in subjects who do not achieve at least a 15% reduction in tumor volume by 8 cycles will be eliminated. Of note, subjects may begin cycle 9 and 13 while central review of tumor response is ongoing. For cohort A, a Simon 2-stage design will be used. In the first stage, 9 evaluable subjects will be accrued. If there is at least 1 response, accrual will continue to the second stage and an additional 8 evaluable subjects will be enrolled. In Cohort B, we will enroll a minimum of 17 evaluable subjects. To allow for up to 25% unevaluable subjects, a maximum of 24 subjects will be enrolled. Based on the preliminary response data (passed the threshold to move to stage 2) and minimal toxicity in Cohort A to date, a 2-stage design is not felt to be necessary for Cohort B. For each cohort, if there are a total of 3 responses among the total of 17 evaluable subjects, cabozantinib will be considered of clinical interest in NF1 plexiform neurofibromas.

6.2 Rationale for Cabozantinib Dose selection

Cohort A: The dosing for this study was developed based on review of existing efficacy and safety data from available cabozantinib therapeutic trials. A cabozantinib starting dose of 100 mg qDay has been studied in 171 CRPC (castration-resistant prostate cancer) subjects enrolled to the Phase 2 XL184-203 RDT. Despite relatively high rates of dose reductions to the next lowest dose of 60 mg qDay within the first 12 weeks of therapy (51%), this starting dose resulted in high rates of pain relief, bone scan improvement, and overall disease control.
In addition, preliminary data from a separate and ongoing dose-ranging study looking at lower doses of cabozantinib in CRPC coupled with results from a retrospective review of the Phase 2 XL184-203 RDT indicate that lower doses below 100 mg qd are likely to retain efficacy while improving upon tolerability:

Preliminary results from an ongoing dose-ranging study: To date, 9 subjects with metastatic CRPC enrolled to the first cohort (starting dose of 40 mg qd) are evaluable for bone scan response. All 9 subjects exhibit evidence of response on bone scan including two complete responses. Although most subjects did not have pain at baseline, one subject reported pain at baseline, which resolved by Week 6. No dose reductions or interruptions have been reported to date, although one subject discontinued study treatment for fatigue that was present at baseline and another subject discontinued because of a pathologic fracture. This provides preliminary evidence that lower doses are pharmacologically active in a patient population with advanced CRPC.

Retrospective review of Phase 2 XL184-203 RDT: While the overall rate of dose reduction from 100 mg to 60 mg was 51%, only 14% required an additional reduction in dose from 60 mg to the next lowest dose of 40 mg, which is consistent with an overall improvement in tolerability profile at the 60-mg dose level. The majority (69%) of subjects with pain at baseline who experienced early dose reduction (before Week 6) to 60 mg went on to report pain improvement at Week 6. Moreover, 80% of these subjects remained progression-free and continued to report pain relief at the Week 12 time point. Thus the dose of 60 mg qd appears to offer improved tolerability while maintaining efficacy in a patient population with advanced CRPC and cancer-related pain at baseline.

Further analysis of the timing of AEs that led to dose reductions or interruptions was conducted. The median time to first AE triggering a dose reduction or interruption at 100 mg qd was 29 days, with very few subjects experiencing significant toxicity in the first 2 weeks of study treatment.

As such, for Cohort A, this study will take a conservative approach to maximize safety and tolerability in our subject population. This study will adopt a starting cabozantinib dose of 40 mg qDay. Subjects will dose escalate after 2 cycles to 60 mg based on dose tolerability. Subjects who do not tolerate 40 mg will dose reduce to 20 mg (see section 7.0). Doses will be capped at 60 mg. The goal of this regimen is to improve the overall tolerability of cabozantinib while maintaining efficacy in this subject population. The rationale for delaying dose escalation until cycle 3 is based on previous experience of AE with cabozantinib. Because of the long half-life of cabozantinib, the median AE on previous trials was 29 days further justifying a later dose escalation schema.

Rationale for Dose selection for Cohort B:

The recommended Phase 2 dose in pediatric solid tumors was established by the recently completed COG Phase 1 trial to be 40 mg/m^2/day (see Section 2.3). Based on this experience, this study will take a conservative approach to maximize safety and tolerability in our subject population. This study will adopt a starting cabozantinib dose of 30 mg/m^2/day. Subjects will dose escalate after 2 cycles to 40 mg/m^2/day based on dose tolerability. Subjects who do not tolerate 30 mg/m^2/day will dose reduce to 23 mg/m^2/day (see section 7.0). Doses will be capped at 60 mg/day max daily dose. The goal of this regimen is to improve the overall tolerability of cabozantinib while maintaining efficacy in this subject population. The rationale for delaying dose escalation until cycle 3 is based on previous experience of AE with cabozantinib. Because of the long half-life of cabozantinib, the median AE on previous trials was 29 days further justifying a later dose escalation schema.

Cabozantinib pharmacokinetics will be collected at steady state to compare drug kinetics and metabolism in this subject population compared to existing data from non-NF oncology subjects. (See Appendix I, VI)

6.3 Administration, Dose, Schedule and Route

Treatment Program: Subjects will receive cabozantinib orally once daily in continuous administration. Cycles will be designated to last 28 days. There will be no planned dose

interruptions except holds for toxicity. The starting dose will be cabozantinib free base 40 mg daily with dose escalation after 2 cycles to 60 mg free base if no dose-limiting toxicity (see section 7.0) experienced in the previous cycle. Cabozantinib will be held for subjects who experience dose-limiting toxicity until the toxicity grade has decreased to grade 1. Cabozantinib will then be reduced by one dose level and not re-escalated in subsequent cycles. Subjects who experience dose-limiting toxicity at the 20 mg dose level will be off study. If 2 or more subjects experience dose-limiting toxicity at a particular dose level, study enrollment with be held while the DSMB reviews the toxicities. Subjects already at that dose level who do not experience dose-limiting toxicity may continue.

A cycle of therapy is considered to be 28 days, with the reporting period for each cycle being day 1 to day 28. In the absence of progressive disease or dose limiting toxicity (DLT), subjects may continue on therapy for a total of 12 total cycles. Subjects who have a radiographic response (20% or greater reduction in tumor volume) on therapy at the end of 12 cycles can continue on therapy for up to an additional year. The maximum duration for treatment under this study design is 24 cycles. In cohort A, subjects who did not achieve at least 15% reduction in index tumor volume after 8 cycles (~8 months) were considered treatment failures and taken off study. For cohort B (pediatric cohort), because of the overall excellent safety profile of cabozantinib and the numerous late tumor responses in cohort A (adult cohort) (see protocol section 2.3), the requirement to stop study treatment in subjects who do not achieve at least a 15% reduction in tumor volume by 8 cycles will be eliminated. Of note, subjects may begin cycle 9 and 13 while central review of tumor response is ongoing.

Cabozantinib must be taken on an empty stomach. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Subjects should be instructed to take their cabozantinib dose at approximately the same time every day. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should <u>not</u> be made up if it is within 12 hours of the <u>next</u> scheduled dose.

Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

Cabozantinib should NOT be re-taken if vomiting occurs after taking a scheduled dose. Dosing may continue the next day as scheduled.

Medications that <u>prolong the QT interval</u> and have a <u>known risk</u> of Torsades de Pointes should be avoided if possible, but are not explicitly excluded. Such medications include: amiodarone, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, escitalopram, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, quinidine, sevoflurane, sotalol, sparfloxacin, terfenadine, thioridazine, vandetanib. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated list

such as www.azcert.org/medical-pros/drug-lists/list-01.cfm?sort=Generic_name. If the subject starts such a medication, then EKG monitoring must be end of each cycle while on the medication.

Medications that may prolong the QT interval and have a possible risk of Torsades de Pointes (see http://www.azcert.org/medical-pros/drug-lists/list-02.cfm?sort=Generic_name) should be avoided if possible, but are not explicitly excluded. If the subject starts a medication with substantial evidence that the drug prolongs the QT interval, then EKG monitoring must be end of each cycle while on the medication.

Subjects or their parents/guardians will keep a diary to document the intake of each dose of cabozantinib and potential side effects. Subjects should be instructed to use the diary to record the date and time of each dose as well as observed side effects and supportive treatments used while on study. The subject may use the diary in Appendix III or a suitable alternative developed by the local institution. The subject diary should be reviewed by the treating physician with the subject or subject's family at each required clinical study evaluation. In addition, leftover study medication should be collected at each on study evaluation, and drug should be accounted for at this time.

All subjects will receive MRI measurements after 4, 8, and 12 cycles. Subjects who continue on drug beyond 12 cycles will undergo imaging after 18 and 24 cycles.

6.4 Criteria for starting subsequent cycles

A cycle may be repeated every 28 days if the subject does not have evidence of progressive disease and has again met laboratory parameters as defined in the eligibility criteria, with the exception of ANC, which must be >1000 to start each cycle.

6.5 Dose escalation Schema

Cohort A: The starting dose will be 40 mg with dose escalation after cycle 2 if no DLT (as defined in section 7.2) is experienced in the first 2 cycles. Cabozantinib will be held for subjects who experience DLT until the toxicity grade has decreased to grade 1. Cabozantinib will then be reduced by one dose level and not re-escalated in subsequent cycles. Subjects who experience toxicity at dose level -1 will be off study.

Dose Level	Dose (mg/dose)
-1	20 mg
1	40 mg
2	60 mg

Cohort B: The starting dose will be 30 mg/m^2 with dose escalation after cycle 2 if no DLT (as defined in section 7.2) is experienced in the first 2 cycles. Cabozantinib will be held for subjects who experience DLT until the toxicity grade has decreased to grade 1. Cabozantinib will then be reduced by one dose level and not re-escalated in subsequent cycles. Subjects who experience toxicity at dose level -1 will be off study.

Dose Level	Dose (mg/m^2/dose with max dose 60 mg/day)
-1	23 mg/m^2
1	30 mg/m^2
2	40 mg/m^2

Actual dosing will be based on the dosing nomogram in Appendix XI.

6.6 Agent Information

Composition, Formulation, and Storage

At study sites, all study medication will be stored as described in the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

Investigational Treatment

Chemical Name: Chemical Name: *N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

Cabozantinib Tablets and Storage

Exelixis internal number: XL184
Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. All tablet strengths are prepared from a common blend and are distinguished by shape. The 20 mg tablets are round and the 60 mg tablets are oval. The components of the tablets are listed in the table below.

Table Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib malate (25% drug load as cabozantinib)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide,	Glidant	0.3
Magnesium Stearate	Lubricant	0.75
Opadry Yellow Film Coating which includes: - HPMC 2910 / Hypromellose 6 cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00

Cabozantinib should be stored at controlled room temperature (20˚C to 25˚C, 68˚F to 77˚F)

7.0 MODIFICATIONS FOR ADVERSE EVENTS

7.1 General Guidelines for Treatment Delay, Dose Reduction, or Study Drug Discontinuation for Toxicity

Subjects will be monitored continuously for AEs throughout the study and for 30 days after the last dose of study treatment, and for any serious adverse event (SAE) assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the last dose of study treatment.

Subjects will be instructed to notify their physician immediately of any and all AEs. Subjects experiencing one or more AEs due to the study treatment may require a dosing delay or reduction(s) in their dose in order to continue with study treatment.

7.2 Definition of Dose-Limiting Toxicity (DLT)

Dose Limiting Toxicity Criteria

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (v4.0). Dose-limiting toxicity is defined as any of the following adverse events occurring during the DLT evaluation period that are at least possibly related to cabozantinib.

DLT evaluation period is cycles 1 and 2 on initial dose, and cycles 3 and 4 for subjects who increase dose.

For adverse events meeting the DLT definition at any time, dose limiting hematological and non-hematological toxicities are handled differently. For **hematologic toxicities**, there must be recovery to meet eligibility or baseline parameters within 14 days of drug discontinuation. For **general non-hematologic toxicities**, there must be recovery of the dose-limiting toxicity to (less than or equal) ≤ Grade 1 or to meet eligibility or baseline parameters within 14 days of drug discontinuation. *Dose modification parameters for **specific non-hematologic toxicities** including proteinuria, hypertension, deep vein thrombosis, liver toxicity, pancreatic toxicity and diarrhea are addressed in section 7.3.* If the required recovery for either hematologic or non-hematologic toxicity occurs within 14 days, then the subject may re-start Cabozantinib, but the dose will be reduced to the previous dose level. If the subject is at 20 mg dose and does not meet the parameters for recovery by 14 days, then the subject will be off study.

Dose limiting hematological and non-hematological toxicities are defined differently.

Non-Hematological Dose Limiting Toxicity

Any Grade 3 or Grade 4 non-hematological toxicity attributable to the investigational drug with the specific exclusion of:

- Grade 3 nausea and vomiting of < 3 days duration
- Grade 3 diarrhea ≤ 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT/bilirubin, that return to levels that meet initial eligibility criteria or baseline within 7 days of study drug interruption and that does not recur upon re-challenge with Cabozantinib. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.

- Grade 3 fever < 5 days duration.
- Grade 3 electrolyte abnormalities responsive to supplementation within one week.
- Grade 3 asymptomatic amylase or lipase elevation that resolves to ≤ Grade 1 within 7 days of study drug interruption and that does not recur upon re-challenge with cabozantinib.
- Grade 3 proteinuria, if confirmed by repeat P/C ratio obtained within 72 hours of first measurement.

- Dose-limiting hypertension
  a. Any Grade 4 hypertension
  b. A blood pressure >25 mmHg above the 95th percentile for age, height, and gender confirmed by repeated measurement is dose limiting.
  c. In subjects who begin antihypertensive therapy a blood pressure > 10 mmHg but ≤ 25 mmHg above the 95th percentile for age, height, and gender for > 14 days is dose limiting.

- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by subjects that it requires treatment interruption.

- Any toxicity requiring interruption of study drug for ≥ 7 days or which recurs upon drug challenge.

- Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

Hematological dose limiting toxicity

Hematological dose limiting toxicity is defined as:

- Grade 3 febrile neutropenia of ≥ 5 days duration
- Grade 4 neutropenia
- Grade 3 thrombocytopenia (platelets < 50,000)
- Grade 3 anemia (Hb < 8)

7.3 Dose Modifications For Adverse events

The Study Chair must be notified of any dosage modification or use of myeloid growth factor.

Dose Modifications for Hematological Toxicity

If a subject experiences dose-limiting Grade 4 neutropenia or grade 3 thrombocytopenia, the treatment will be withheld. Counts should be checked every 3 - 4 days for thrombocytopenia and every other day for

neutropenia during this time. If the toxicity resolves to meet eligibility parameters within 14 days of drug discontinuation, the subject may resume treatment at the next lower dose level. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

If dose-limiting toxicity does not resolve to meet eligibility or baseline parameters within 14 days of drug discontinuation, the subject must be removed from protocol therapy.

If dose-limiting toxicity recurs in a subject who has resumed treatment at the reduced dose, the subject must be removed from protocol therapy.

Dose Modifications for Non-Hematological Toxicity

If a subject experiences non-hematological dose-limiting toxicity, the treatment will be withheld. If the toxicity resolves to (less than or equal to) ≤ grade 1 or to meet eligibility or baseline parameters within 14 days of drug discontinuation, the subject may resume treatment at the next lower dose level. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

If dose-limiting toxicity does not resolve to (less than or equal to) ≤ grade 1 or to meet eligibility or baseline parameters within 14 days of drug discontinuation, the subject must be removed from protocol therapy.

If the same dose-limiting toxicity recurs in a subject who has resumed treatment at the reduced dose level, the subject must be removed from protocol therapy.

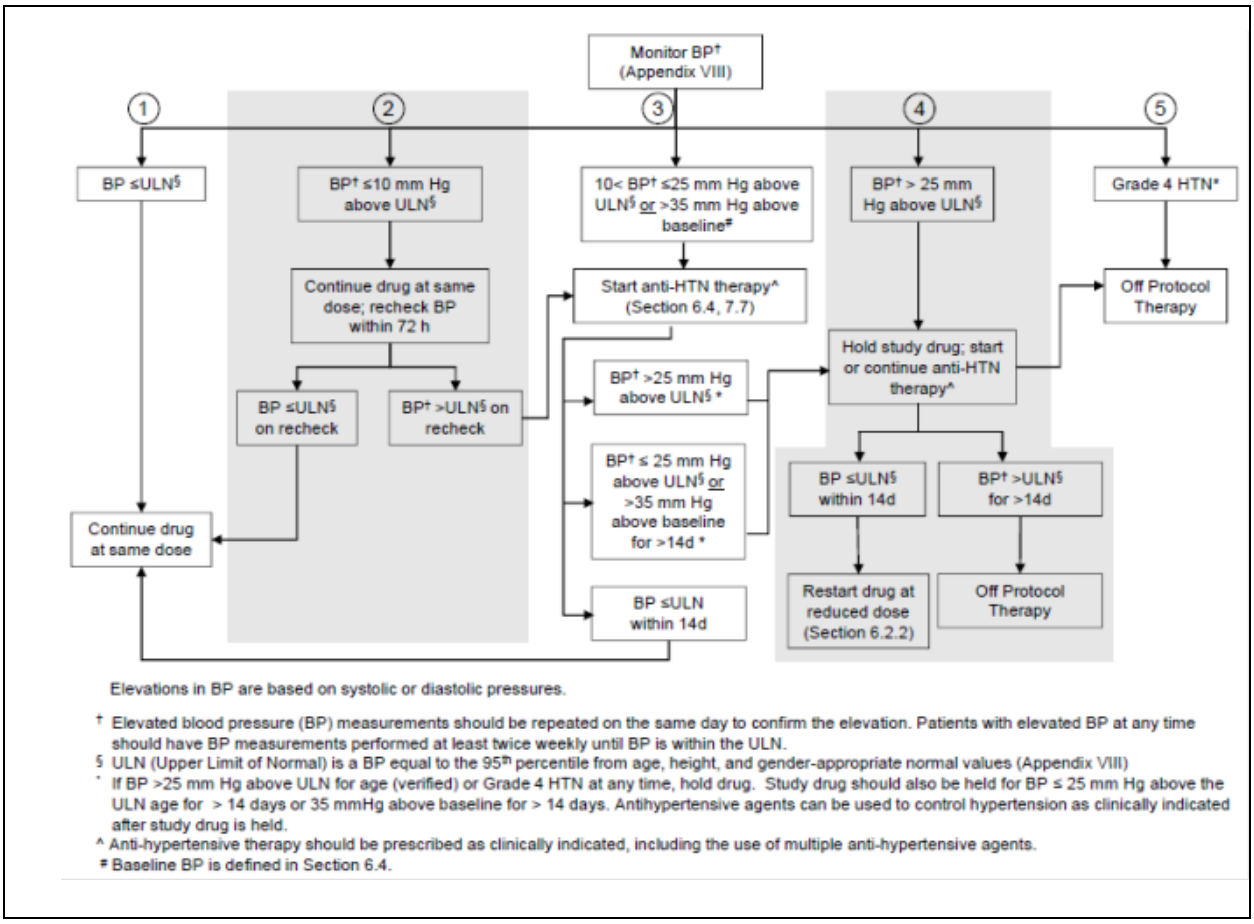
Dose Modifications for Proteinuria

- If urinalysis shows ≥ trace protein then obtain urine protein/creatinine (P/C) ratio.
- If the urine P/C ratio is >1, consider confirming with a 24 hour protein assessment within 7 days.
- If the urine P/C ratio ≤ 1.9 continue cabozantinib. If subject has Grade 3 proteinuria (urine P/C ratio >1.9), a second measurement should be obtained within 72 hours. A second confirmation of Grade 3 proteinuria will be considered a DLT.
- If the second measurement confirms Grade 3 proteinuria (urine P/C ratio >1.9), then interrupt cabozantinib treatment and re-assess weekly.
- If cabozantinib is held for ≥ 14 days then remove from protocol therapy. If the urine P/C ratio decreases to ≤ 1.9 in < 14 days then resume cabozantinib at a lower dose.
- Monitor the urine P/C ratio weekly for 2 consecutive weeks once protocol therapy resumes and obtain a 24-hour collection if ≥ 1 as above.
- Cabozantinib should be discontinued in subjects who develop nephrotic

syndrome (proteinuria > 3.5 grams per day in combination with low blood protein levels, high cholesterol levels, high triglyceride levels, and edema).

Dose Modifications for Hypertension

- **Baseline blood pressure** (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows: 1) Obtain 3 serial blood pressures from the same extremity with the subject in the same position at rest with an appropriately sized cuff that are separated by at least 5 minutes. Avoid using the lower extremity if possible. 2) Average the systolic blood pressure from the 2nd and 3rd measurements. 3) Average the diastolic blood pressure from the 2nd and 3rd measurements. 4) The baseline BP is the average of the systolic over the average of the diastolic measurements.
- **Elevation** in either the systolic or diastolic blood pressure should be considered when following the algorithm below.
- **The upper limit of normal (ULN)** is defined as a BP equal to the 95th percentile for age, height, and gender. .
- The NCI CTCAE will be utilized to determine the grade of hypertension for reporting purposes.
- Elevated BP measurements should be repeated on the same day to confirm the elevation. If confirmed, subjects with elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.
- The algorithm below will be used to manage cabozantinib - related hypertension.
- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.



Arm 1 of algorithm:

- If blood pressure (BP) ≤ 95% for age, height, and gender, continue cabozantinib at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN for age, height, and gender, continue cabozantinib at the same dose and recheck the BP within 72 hours.
  - If the BP is ≤ ULN on recheck, continue cabozantinib at the same dose.
  - If the BP remains above the ULN on recheck, then start antihypertensive therapy (Section 8) and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started.

Arm 3 of algorithm:

- If BP is 11 to 25 mm Hg above the 95% for age, height, and gender on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start anti-hypertensive therapy (see Section 8), continue cabozantinib at the same dose, and monitor BP at least twice weekly.

- If the BP returns to ≤ ULN within 14 days, continue cabozantinib at the same dose and continue anti-hypertensive therapy.
- If the BP remains elevated ≤ 25 mm Hg above the 95% or > 35 mm Hg above baseline for more than 14 days after the institution of anti-hypertensive therapy, **hold** cabozantinib, monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that cabozantinib is held. The antihypertensive therapy should be continued until the BP is less than the ULN.
  - If the BP returns to ≤ ULN within 14 days, restart cabozantinib at a reduced dose (Section 6.5).
  - If the BP remains > ULN for more than 14 days, subject is Off Protocol Therapy.
- If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, **hold** cabozantinib, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that cabozantinib is held.
  - If the BP is ≤ ULN within 14 days, cabozantinib may be restarted at a reduced dose (Section 6.5).
  - If the BP is > ULN for > 14 days, the subject is Off Protocol Therapy (Section 11.1).

Arm 4 of algorithm:

- If BP is > 25 mm Hg above the 95% for age, height, and gender **hold** cabozantinib, monitor BP and administer anti-hypertensive therapy as clinically indicated.
  - If the BP returns to ≤ ULN within 14 days, cabozantinib may be restarted at a reduced dose (Section 6.5).
  - If the BP is > ULN for >14 days, the subject is Off Protocol Therapy.

Arm 5 of algorithm:

- If the participant develops Grade 4 hypertension, **discontinue** cabozantinib, monitor BP and administer anti-hypertensive therapy as clinically indicated. The subject is Off Protocol Therapy.

Deep Venous Thrombosis

If a subject develops a DVT while on cabozantinib, they will be taken Off Protocol Therapy.

Dose Modifications for Liver Toxicity

Cabozantinib should be held for grade 3 elevation of ALT, AST or bilirubin. Note: For the purposes of this trial the ULN for ALT is defined as 45 U/L. Cabozantinib may be re-administered at the same dose if levels of ALT, AST and bilirubin meet eligibility criteria or baseline within 7 days of drug discontinuation. Elevated laboratory parameters should be checked at least twice weekly until eligibility criteria are met.

If lab values do not resolve to initial eligibility criteria or baseline within 7 days of interruption or if toxicity recurs with re-challenge, then this will be considered dose-limiting. Cabozantinib will then be dose-reduced when eligibility criteria are

met.

Dose Modifications for Pancreatic Toxicity

Cabozantinib should be held if subject experiences Grade 3 asymptomatic amylase or lipase elevation. Elevated laboratory parameters should be checked at least twice weekly until ≤ Grade 1.

If lab values do not resolve to ≤ 1 Grade within 7 days of interruption or if toxicity recurs with re-challenge, then this will be considered dose-limiting. Cabozantinib will then be dose-reduced when eligibility criteria are met.

Dose Modifications for Diarrhea

- If dose-limiting Grade 3 (> 3 days) or Grade 4 therapy-associated diarrhea is experienced by a subject despite maximal use of anti-diarrheal medications, the dose of Cabozantinib should be held and reduced to the next lower dose level once the diarrhea has resolved. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.
- If dose-limiting Grade 3 (> 3 days) or Grade 4 diarrhea recurs despite maximal use of anti-diarrheals and dose reduction, the subject should come off protocol therapy.
- Treatment of Diarrhea: Each subject will be instructed to have Loperamide available and begin treatment at the first episode of poorly formed or loose stools or at the earliest onset of bowel movements more frequent than normally expected for the subject. Subjects will also be instructed to contact their physician if any diarrhea occurs. Take 4 mg (4 teaspoonfuls of the 1 mg/5mL solution or 2 capsules/tablets) after the first loose bowel movement, followed by 2 mg (2 teaspoonfuls of the 1 mg/5mL oral solution or 1 capsule/tablet) every 2 hours. During the night, the subject may take 4 mg (4 teaspoonfuls of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours. Do not exceed 16 mg per day.

8.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to subjects receiving study drug. If these treatments are administered the subject will be removed from protocol therapy.

Investigational Agents

No other investigational agents may be given while the subject is on study.

Supportive Care

Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary. <u>See Section 4.1 for drugs that should not</u>

be used concomitantly due to potential interactions with cabozantinib.

Diarrhea is a common side effect of cabozantinib. Loperamide should be used at the first sign of significant diarrhea.

Palmar-plantar erythrodysesthesia syndrome (PPE; also known as hand-foot syndrome) is a common side effect of cabozantinib. Careful attention should be paid to skin exams and supportive care instituted early if any swelling or erythematous skin changes or symptoms of pain or burning/tingling are noted. Subjects should be instructed to apply moisturizing creams, avoid any trauma, harsh chemicals and limit hot water exposure. Topical steroid creams may be used and consider early dermatology referral (please see APPENDIX X for suggested prophylaxis and treatment for PPE).

Growth Factors

Growth factors that support platelet or white cell number or function can only be administered for culture proven bacteremia or invasive fungal infection. The Study Chair should be notified before growth factors are initiated.

Concomitant Medications

Medications that are strong inhibitors or inducers of CYP3A4 should be avoided

The use of enzyme inducing anticonvulsants is not permitted.

Medications that prolong the QT interval and have a known or possible risk of Torsades de Pointes should be avoided if possible, but are not explicitly excluded (see section 6/3)

Surgery

Subjects should not have elective surgical procedures while on therapy. For subjects who require emergent or urgent procedures (including dental surgery or invasive dental procedures), cabozantinib should be stopped at least 28 days prior to procedure, if feasible. Therapy may not be restarted until adequate wound healing (at least 2 weeks after major procedures, 7 days after minor procedures such as port-a-catheters, and 3 days for external lines [e.g. Hickman or Broviac].

Concurrent Anti-Hypertensive Therapy

The algorithm above will be used to grade and manage cabozantinib related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine, which are permissible without discussion with the study chair) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender.

Management of Hypothyroidism

Subjects with Grade 2 hypothyroidism adequately managed with thyroid hormone replacement may continue on protocol therapy. Subjects with Grade 3 or greater hypothyroidism will be considered to have had a dose-limiting toxicity. These subjects should be managed according to guidelines for non-hematologic toxicity and should also be evaluated by an endocrinologist for further management. Subjects who enter the study on thyroid replacement should have their medication adjusted to maintain TSH in the normal range.

9.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Pre and on study evaluations are described in Appendix I.

9.1 Required Clinical, Laboratory and Disease Evaluation

All entry/eligibility studies must be performed within 2 weeks prior to enrollment into the trial. The baseline MRI study documenting disease status is required within 4 weeks prior to study entry. Entry/eligibility studies (laboratory and MRI) may be counted as the baseline (pre-study) studies, as long as there has been no concerning change in clinical status prior to starting study drug (which must start within 14 days of enrollment).

9.2 History and physical examination and vital signs

Physical examination will be performed prior to entry, at Day 15 $\pm$3 days, at the end of cycle 1 $\pm$1 week, at cycle 2 Day 15 $\pm$1 week, at the end of cycle 2 $\pm$1 week, at cycle 3 Day 15 $\pm$1 week, at the end of cycle 3 $\pm$1 week, after cycles 4-12 $\pm$2weeks, and after cycles 14, 16, 18, 20, 22, 24 $\pm$2weeks. In addition, at the end of treatment $\pm$2 weeks if this is not encompassed in the times above. The exam must comprise a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system). Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded.

Vital sign assessment consists of height (first visit in Cohort A, and every visit in Cohort B), pulse, blood pressure, respiration rate, **oxygen saturation by pulse oximeter**, temperature and weight. Blood pressure, pulse and respiration rate should be measured on subjects after at least 3 minutes in the sitting position.

9.3 Phone Call

Subjects will be called to assess drug compliance and toxicity at the end of cycles 13, 15, 17, 19, 21, 23 $\pm$2weeks.

9.4 Laboratory Testing

CBC with differential and platelets, comprehensive metabolic panel with Ca, Mg, Phos, lipase, and amylase must be performed within two weeks prior to entry on trial, at Day 15 $\pm$3 days, at the end of cycle 1 $\pm$1 week, at cycle 2 Day 15 $\pm$1 week, at the end of cycle 2 $\pm$1 week, at cycle 3 Day 15 $\pm$1 week, at the end of cycle 3 $\pm$1 week, and after cycles 4-24 $\pm$2weeks. In addition, at the end of treatment $\pm$2 weeks if this is not encompassed in the times above.

PT, PTT, INR must be performed within two weeks prior to entry on trial, at the end of cycles 1-3 ±1 week, and after cycles 4-24 ±2weeks. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above.

Urinalysis must be performed within two weeks prior to entry on trial, at the end of cycles 1-3 ±1 week, and after cycles 4-24 ±2weeks. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above.

Urine protein:creatinine ratio must be performed within two weeks prior to entry on trial, at the end of cycles 1-3 ±1 week, and after cycles 4-24 ±2weeks. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above.

Thyroid stimulating hormone must be performed within two weeks prior to entry on trial, at the end of cycle 1 ±1 week, at the end of cycle 3 ±1 week, after cycles 6, 9, 12, 16, 20, 24 ±2 weeks. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above.

Urine or serum pregnancy test tests will be given to all females of childbearing age within 7 days prior to starting treatment medication. In addition, tests will be administered at the end of cycles 2 ±1 week, and after cycles 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 ±2weeks. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above.

9.5 EKG

12-lead EKG should be performed within two weeks prior to entry on trial, at the end of cycle 1 ±1 week, after cycle 2 ±1 week, and after cycles 4, 6, 9, 12, 16, 20, 24 ±2weeks. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above.

9.6 MRI for volumetric analysis of plexiform neurofibroma

Evaluate the plexiform neurofibromas(s) by MRI within 4 weeks prior to cycle 1 and after cycles 4 ±2 weeks, 8 ±2 weeks, 12 ±2 weeks, 18 ±2 weeks, and 24 ±2 weeks while on study and at end of study ±2 weeks. To evaluate the durability of response, subjects who responded while on treatment, will be recommended but not required to have a follow-up MRI scan at approximately 4 months and 12 months following completion of therapy. If a subject starts another tumor-directed therapy during the one year follow-up time, then they are off-study (and no further MRIs requested). See Appendix IV for imaging protocol.

9.7 Quality of Life and Pain Evaluations (Required)

This study will evaluate quality of life, pain intensity, and pain interference in patients during treatment with cabozantinib. The Pediatric Quality of Life Inventory (PedsQL) NF1 Module (Adult and Teen self-report forms) will be used to assess disease-specific QOL in subjects 16 years and older (see table below). The Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales will be used to assess general health related QOL in children 3-15.

Pain intensity in both cohorts will be assessed by self-report with the Numeric Rating Scale-11 (NRS-11) and pain interference will be measured by the Brief Pain Inventory (BPI) Interference Scale in subjects ≥ 16 and the Pain Interference Index in subjects 5-15 years. The following

table summarizes the quality of life and pain questionnaires to be completed by age of the subjects.

Quality of Life and Pain Questionnaires to be Completed by Age of Subject at Study Entry
Subjects >16 years

Questionnaire	Age of Subject (years) at Study Entry	
	16-20*	21+*
Disease Specific QOL		
***Subject**:* PedsQL NF1 Module-Teen or Peds QL NF1 Module-Adult	X	X
Pain		
	Age of Subject (years)	
	16+**	
***Subject**:* NRS-11 Pain Intensity	X	
and BPI-Pain Interference	X	

Background Information Forms to be Completed by the Subject

Questionnaire	Age of Subject (years)
	16+**
Background Information	
All subjects QOL Background Form	X

*If subjects are 21 years old at study entry, they should be administered the Adult PedsQL NF1 Module. If subjects are 16 to 20 years old at study entry, they should be administered the Teen PedsQL NF1 Module. However, if subjects turn 21 years old during the study, they should continue to be administered the Teen version of this scale that they started at study entry.

**All subjects should complete the same self-report pain intensity and pain interference measures and background form.

Patient Questionnaire	**Age of Patient (years)**		
	3 - 7	8 - 15	
Pain Intensity			
***Patient** self-report:* Numeric Rating Scale-11		√	
Pain Interference			
***Patient** self-report:* Pain Interference Index		√	
Global Impression of Change			
***Patient** self-report:* Global Impression of Change Scale		√ (follow-up evaluations only)	
General QOL			
***Patient** self-report:* PedsQL Acute form		√ 8 - 12 (Child)	√ 13 - 18 (Teen)

Subjects 3 – 15 years

Parent Questionnaires	**Age of Patient (years)**			
	3 - 7		8 - 15	
Background Information				
Parent *report:* Pediatric Background Form	√		√	
Pain Interference				
Parent *proxy report:* Pain Interference Index		√ (5 - 7)	√	
Global Impression of Change				
Parent *report*: Global Impression of Change Scale		√ (5 - 7; follow-ups evals only)	√ (follow-up evaluations only)	
General QOL				
Parent *proxy report:* PedsQL Acute form	√ 2 - 4 (Toddler)	√ 5 - 7 (Young Child)	√ 8 - 12 (Child)	√ 13 - 18 (Teen)

Clinician Questionnaire	**Age of Patient (years)**	
	3 - 7	8 - 15
Global Impression of Change		
Clinician *observer report:* Global Impression of Change Scale	√ (follow-up evaluations only)	√ (follow-up evaluations only)

√ Administer items with a check mark under the correct age range of the patient

To allow for more meaningful analysis of the QOL data, the subject (for those ≥16 years) and the parent/primary caregiver (for pediatric subjects 3 – 15 years) also will complete a background information form at study entry and each QOL assessment. This form will collect general information such as their level of education, work/school status, psychiatric diagnoses, and pain medications, as well as the visibility of NF1 tumors and severity of NF1 symptoms.

These forms should be completed pre-treatment, after cycle 4 ±2 weeks, 8 ±2 weeks, 12 ±2 weeks, 18 ±2 weeks, and 24 ±2 weeks. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above. When administering these forms, review the instructions with the subjects and check to make sure they answered all the items. If subjects have difficulty reading, it is permissible to read the items to them, but the subjects should answer the items themselves. Completed forms should be sent (fax or mail copies) to the NF Consortium Operations Center within 2 weeks of completion. For any questions regarding the QOL/pain assessment please contact: Pam Wolters at woltersp@mail.nih.gov. See **Appendix VII** for a description of the QOL and pain measures and forms.

The QOL documents will be reviewed centrally by Dr. Pam Wolters. If any responses are noted that suggest serious emotional distress, the PI at the subject's site will be notified. The site PI will be responsible for acknowledging to Dr. Wolters receipt of these concerns and for initiating appropriate action as deemed clinically necessary.

9.8 Biomarker studies

1. Plasma biomarker (cytokine) assays will be performed using multiplex simultaneous quantification of thirty soluble cytokines and growth factors including: VEGF, TGF-β, PDGF-AB/BB, MCP-1, MIP1α, MIP1β, TNFα, GM-CSF, EGF, IL-13, IL-1rα, IL-10, IL-4, IL6, FGF-2, and RANTES. The multiplex assay will be performed according to the manufacturer's protocol (Millipore Milliplex, Billerica, MA) and analyzed on a Luminex 200 cytometer with StarStation software (Luminex Corp, Austin, TX). Plasma samples for each subject and each treatment time point will be stored at -80C and thawed once for simultaneous assay. Samples will be collected within two weeks prior to cycle 1, at Day 15 $\pm$3 days, at the end of cycles 2 $\pm$1 week, and at the end of cycles 4 $\pm$1 week.

Rationale: It has been well recognized that cytokines mediate and regulate immunity and inflammation, which are an important component of the biological milieu associated with cancer progression. Cytokines have been used as biomarkers in research for prognosis and have been associated with symptoms and adverse outcomes in multiple conditions, including cancer. We have previously shown that multiple cytokines/growth factors are altered in subjects with plexiform neurofibromas as well as in tumor murine model of NF1. Our unpublished data suggest that the cytokine levels are associated with tumor progression and responsiveness to Gleevec therapy. The examination of cytokine patterns has been limited by traditional laboratory methods. Multiplex now permits the characterization of a broader array of cytokines in a single specimen. Because cytokines operate in integrated networks, a more complete understanding will be gained as multiple cytokines can be examined for patterns of response that may be associated with response to the treatment and the prognosis of NF1.

Please see Appendix V for details regarding obtaining sample and shipment.

2. Polychromatic Flow Cytometry (PFC) & Identification of Circulating Progenitor Cells (CPCs): PFC for the identification of CPCs will be performed at three time points. Whole blood will be drawn in EDTA tubes and sent for processing to the Indiana University Simon Cancer Center's Angiogenesis, Endothelial and Pro-Angiogenic Cell Core (AEPCC) Facility, which is directed by Dr. Karen Pollok. Using the PFC protocol developed by Dr. Case (Estes et al., Current Protocols in Cytometry), the phenotypic detection and enumeration of CPCs will be performed, and the ratio of pro-angiogenic (i.e. CD133+) vs. non-angiogenic CPCs will be calculated on all samples. Data obtained will then be correlated with tumor response. Samples will be collected within two weeks prior to cycle 1, at Day 15 $\pm$3 days, at the end of cycles 2 $\pm$1 week, and at the end of cycles 4 $\pm$1 week and sent immediately to the AEPCC Facility.

9.9 Biological Specimens for banking (Appendix XV)

Blood Samples will be drawn at baseline (pre-treatment), after course 4 (+2 weeks), after course 12 (+2 weeks), and at the end of treatment (+2 weeks) if this is not encompassed in the times

above. In addition, blood samples should be drawn around the time of tumor biopsy if tumor tissue is being submitted.

The following will be collected at each time point:

- Streck tube (for plasma): ~ 2 mL.
- EDTA tube (for DNA): ~ 5 mL.
- PAXGene tube (for RNA) ~ 2.5 mL.

Tubes should be inverted at least 10 times after being drawn.

The samples will only be obtained if the total blood volume does not exceed 5 mL/kg. If not enough blood can be drawn for all tubes, the priority order for obtaining the specimens is:
1) Streck tube, 2) EDTA tube, 3) PAXGene tube.

Label the specimens with the specimen labels provided with the specimen kit.

Blood specimens must be shipped (unprocessed) same day at ambient temperature to the biorepository by overnight delivery using shipping container provided by the biorepository (see Appendix XV).

Tumor Tissue (optional) will be collected from subjects undergoing a clinically indicated procedure and who consent:

- Fresh frozen tissue: 1-2 pea sized aliquots (~ 0.3 cm3, equivalent to 0.8 cm in diameter) of excess (left over) tumor tissue. Place each aliquot in a separate cryovial and label the specimen with subject's study number. Snap freeze the aliquots in liquid nitrogen (preferred) or dry ice and then store in a freezer at -80°C or below until they can be sent to the biorepository.
- 1 H&E stained slide cut from each submitted piece to confirm tumor is present.
- If fresh frozen tissue is unavailable, please submit processed DNA (at least 3 micrograms) and RNA (at least 400 nanograms with optimal RIN > 7) if available.

Fresh frozen tissue or DNA/RNA must be shipped on dry ice via overnight delivery using shipping materials provided by the biorepository (see Appendix XV). H&E slide should be shipped at ambient temperature.

10.0 ADVERSE REPORTING REQUIREMENTS

10.1 Definitions

- **Adverse Events**: An adverse event is any new, undesirable medical occurrence or change (worsening) of an existing condition in a subject that occurs during treatment, whether or not considered to be product related. Therefore, adverse events are treatment emergent signs or symptoms. Elective hospitalizations for pretreatment conditions (e.g., elective cosmetic procedures) are not adverse events. Non-clinically significant abnormal laboratory values should not be reported as adverse events; however, any clinical consequences of the

abnormality should be reported as adverse events. All adverse events must be noted on the case report forms and submitted to the operations center within 2 weeks of completion of every treatment cycle.

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 (within 24 hours) to the site PI and clinical coordinator, as well as the NF Operations Center. 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.

- **Serious Adverse Events**: A serious adverse event is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator's or sponsor's opinion on the relationship to investigational product.

  This includes, but may not be limited to, any event that (at any dose):
  is FATAL
  is LIFE THREATENING (places the subject at immediate risk of death);
  requires HOSPITALIZATION or prolongation of existing hospitalization;
  is a persistent or significant DISABILITY/INCAPACITY; or
  is a CONGENITAL ANOMALY/BIRTH DEFECT

Important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

10.2 Grading of Adverse Events using Common Terminology Criteria (CTCAE)

Adverse events (toxicities) will be graded according to the National Cancer Institute CTCAE version 4.0 for reporting of adverse events. A copy of the current version of the CTCAE version 4.0 can be downloaded from the CTEP home page:
http://ctep.cancer.gov/reporting/ctc.html

10.3 Attribution: Definitions of relationship to study medication are as follows:

- UNRELATED: bears no relation to timing of medication, similar to symptoms or signs expected in the disease process, does not recur on rechallenge.
- UNLIKELY: does not have temporal relationship to intervention, could readily have been produced by the subject's clinical state, environmental, or other interventions, does not reappear or worsen with reintroduction of intervention.
- POSSIBLY: bears relation to timing of medication, similar to symptoms or signs expected in the

disease process, does not recur on rechallenge.

- PROBABLY: bears clear relation to timing of medication, distinct from symptoms or signs expected in the disease process, does not recur on rechallenge.
- DEFINITELY: bears clear relation to timing of medication, distinct from symptoms or signs expected in the disease process, occurs on rechallenge.

The expected adverse events related to administration of cabozantinib are listed in Section 7.3. All other adverse events not attributed to cabozantinib will be considered unexpected. Adverse events attributable to cabozantinib will be reported if the adverse events are at an intensity that is more severe than previously documented or considered significant by the investigator.

10.4 Reporting Procedures for All Adverse Events

All observed or volunteered adverse events, regardless of suspected causal relationship to study drug, will be recorded as Adverse Events in the case report forms and submitted to the Operations Center within 2 weeks of completion of each treatment cycle. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbation of pre-existing illnesses should be recorded. Objective test findings (e.g. abnormal laboratory test results) should also be recorded.

It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require that the subject should be removed from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occurs, the subject will be given appropriate care under medical supervision until symptoms cease or until the condition becomes stable.

The severity of toxicities will be graded in accordance with the Common Terminology Criteria for Adverse Event (CTCAE) version 4.0 (http://ctep.cancer.gov/reporting/ctc.html).

The relationship of adverse events to the study medications will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the study medication?" Please answer Yes or No.

10.5 Expedited Reporting Guidelines

The following adverse events require expedited reporting:

- All adverse events that are both serious and unexpected
- Adverse events that might influence the benefit-risk assessment of administration of cabozantinib as outlined in the protocol
- All grade 5 adverse events
- Any adverse event that might require a target reduction
- A serious adverse event that occurs within 30 days of the last dose of the investigational agent
- Pregnancy

If a subject or a subject's partner becomes pregnant while receiving investigational therapy or within 30 days after the last dose of study drug, a report should be completed and expeditiously submitted as an SAE. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the cabozantinib should be reported as an SAE.

- Expedited AE reporting timelines defined:
  "24 hours; 3 business days" – The investigator must initially report the AE within 24 hours (or immediately if the event is fatal or life-threatening) of learning of the event to the Study Chair (fisherm@email.chop.edu) and NF Operations Center followed by a complete written report within 3 business days of the initial 24-hour report.

Adverse events requiring expedited reporting will be reported and documented on **Form FDA 3500A MedWatch Form** http://www.fda.gov/medwatch/getforms.htm) and forwarded to:

NF Consortium Operations Center
Clinical Nurse Manager: Lynn Merritt, RN 205-934-5376
Program Director: Karen Cole – Plourde, BS 205-934-5140
Research Compliance Manager: Juliette Southworth, BS 205-975-4075
Direct Email: nfcop@uab.edu

The clinical research manager from the NF Consortium Operations Center will forward all related adverse events that are both serious and unexpected to the FDA on **Form FDA 3500A MedWatch Form** http://www.fda.gov/medwatch/getforms.htm to:

MedWatch
Fax: 1-800-FDA-0178

The final MedWatch Form or CIOMS-1 form must be submitted by the study site to Exelixis within one to two business days of submission to the FDA or applicable regulatory agency (including confirmation of date that the report was submitted) to allow Exelixis time to cross-report to Exelixis' IND. E-mail: drugsafety@exelixis.com ; Fax 650-837-7392.

10.6 Reporting of Protocol Violations/Deviations and Unanticipated Problems

Site reporting to NF Operations Center
Sites will report unanticipated problems and/or protocol deviations that impact subject safety or the scientific integrity of the study to the Operations Center promptly to nfcop@uab.edu. Other protocol violations and deviations should be reported to the NF Operations Center annually.

NF Operations Center reporting requirements
The Operations Center will report unanticipated problems that impact subject safety or the scientific integrity of the study to the USAMRMC ORP HRPO promptly. Unanticipated problems

will also be reported to the protocol team, Medical Monitor, and DSMB.

All unanticipated problems involving risk to subjects or others must be promptly reported by the NF Operations Center via phone (301-619-2165), email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

Other protocol violations and deviations that do not impact subject safety or affect scientific integrity of the study will be provided annually to the Sponsor.

11.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

11.1 Criteria for Removal from Protocol Therapy

a. Progressive disease
b. < 15% reduction in index tumor volume after 8 cycles. (Of note, subjects may begin cycle 9 while central review of tumor response is ongoing) **(Cohort A only)**
c. < 20% reduction in index tumor volume after 12 cycles. (Of note, subjects may begin cycle 13 while central review of tumor response is ongoing)
d. Completion of cycle 24
e. Cabozantinib-related toxicity requiring removal (see Section 7)
f. Refusal of further protocol therapy by subject/parent/guardian
g. Other cancer develops
h. Non-compliance that in the opinion of the investigator does not allow for on-going participation.
i. Physician determines it is not in the subject's best interest.
j. Participant is prescribed a non-allowed concomitant medicine during study.
k. Subject must have surgery on a target PN.
l. Subject becomes pregnant
   - If a subject becomes pregnant while receiving investigational therapy or within 30 days after the last dose of study drug, the subject should be followed until the outcome of the pregnancy.

Subjects who are off protocol therapy are to be followed until they meet the criteria for OFF Study (see below).

11.2 Off Study Criteria

For subjects who did not have a response (<20% shrinkage of target tumor) or have tumor progression (≥ 20%) at any time:

a) Thirty days after the last dose of cabozantinib (but note that subjects with ongoing toxicity should be followed until the toxicity resolves or 30 days, whichever is longer)

For subjects who had a response (≥20% target tumor shrinkage by 12 cycles) and never experience tumor progression:
b) Completion of their one year follow-up MRI scan

For all subjects (supercedes "a" or "b"):
c) Death
d) Lost to follow-up
e) Withdrawal of consent for any further data submission.
f) Initiation of subsequent other medical treatment directed towards the plexiform neurofibroma
g) Initiation of medical treatment (e.g. chemotherapy, biologic therapy, radiation therapy) directed towards other NF1-related tumor, such as an optic pathway glioma.
h) Outcome of Pregnancy (for subjects who become pregnant while receiving investigational therapy or within 30 days after the last dose of study drug).

12.0 STATISTICAL AND ETHICAL CONSIDERATIONS

12.1 Subject Accrual

Subjects of both genders, from all racial and ethnic groups are eligible for this trial if they meet the criteria outlined in Section 4.0. To date, there is no information that suggests differences in drug metabolism or disease response among racial or ethnic groups or between the genders, indicating that results of the trial will be applicable to all groups. Most plexiform neurofibroma grow out of proportion to somatic growth for a period of time during childhood, but may reach a plateau by the end of puberty. Efforts will be made to extend the accrual to a representative population, but in a phase II study with limited accrual, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand, and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, age, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

12.2 Statistics and Feasibility

Sample Size
Cohort A: Minimum: 9 evaluable subjects Maximum: 19 evaluable subjects Target: 17 evaluable subjects. To allow for 25% unevaluable subjects, a maximum of up to 24 subjects will be enrolled. We anticipate enrollment to be completed in 24 months with primary outcome measure defined in 30 months.

The sample size for this trial is based on three primary factors: safety based on risk versus benefit; efficacy of 25% response rate and power of 80% to achieve feasibility if this rate were true. In order to balance these factors, we propose a two stage Simon Optimal Design (ref Controlled Clinical Trials 10:1-10 1989) for cohort A. Two stage designs are designed to provide an overall

Type I error that is based on the probability of stopping at the end of Stage 1 plus the conditional probability of rejecting the drug given one passed Stage 1 to get to Stage 2. Thus, the overall Type I error was set at 5% and power at 80%. We assume a null hypothesis success rate of 5% versus a treatment with a 25% response rate.

Stage 1 for cohort A will consist of 9 subjects to provide evidence of effectiveness and safety. If at least 1 of the 9 subjects achieves a radiographic response (≥20% reduction in tumor volume) the study will be allowed to recruit the total sample size of 17 evaluable subjects. The Stage I boundary is the same 0 of 9. The second stage of the design requires only 3 or more of the 17 subjects to have a positive response. If the null hypothesis is true, there is a 63% chance of terminating after Stage 1. If the probability of success is actually 0.25, there is a 92% chance that 1 or more subjects will exhibit a 20% reduction in tumor volume at Stage 1. Thus, it is expected that the trial will continue with continuous recruitment if the 25% success rate is correct.

For safety reasons, in cohort A, subjects who did not achieve at least a 15% reduction in tumor volume were not be continued beyond 8 cycles, as the likelihood of achieving a response (20% reduction in tumor volume) by 12 months is minimal. These subjects will be discontinued from the trial and counted in an "Intent to Treat" analysis as evaluable and as failures. If there are no subjects with a response (20% or more reduction in tumor volume) by the end of 8 cycles, but one or more with a 15% or more tumor volume reduction, recruitment will be suspended until the decision on futility (0 of 9 with at least 20% or more reduction in tumor volume after 12 cycles) or successful continuation can be definitively recommended. That is, if there are a number of subjects with 15% up to but not achieving a 20% reduction in tumor volume, the study will follow those subjects up to their post cycle 12 visit to determine if the recruitment can be restarted. If none of these 9 achieves a 20% tumor volume reduction by 1 year, the study will be terminated.

Cohort B: Enroll up to 24 evaluable subjects. Target: minimum of 17 evaluable subjects. To allow for up to 25% unevaluable subjects, a maximum of 24 subjects will be enrolled. We anticipate enrollment to be completed within 12 months with the primary outcome measure defined in 24 months.

The sample size for this trial is based on the safety and feasibility data needed: thus, safety based on risk versus benefit. For feasibility, we expect at least efficacy of a 25% response rate. We are only interested if cabozantinib is positive and thus, assume a 1 sided test using a Type I error of 5%. We assume a null hypothesis success rate of 5% versus a treatment with a 25% response rate. If all 20 patients are evaluable there is 80% power to detect differences between 25% and 5% with 80% power. The power in this strata is 64% when the minimal sample size is realized. Based on the preliminary response data (passed the threshold to move to stage 2) and minimal toxicity in Cohort A to date, a 2-stage design is not felt to be necessary for Cohort B.

For cohort B (pediatric cohort), because of the overall excellent safety profile of cabozantinib and the numerous late tumor responses in cohort A (adult cohort) (see protocol section 2.3), the requirement to stop study treatment in subjects who do not achieve at least a 15% reduction in tumor volume by 8 cycles will be eliminated.

12.3 Statistical Analysis Plan

The basic statistical analysis plan for this proof of concept study will describe the subject population by baseline characteristics: clinical, PK/PD, Quality of Life and pain scores at baseline. Following complete accrual, study logistics will be summarized as per a Consort Diagram with reasons for withdrawal or unable to complete the study tabulated for each cohort separately. Appropriate data analysis sets will be defined. The full-analysis set will include data from all subjects who receive ≥1 dose of therapy on this study; a safety analysis set will comprise data from subjects in the full-analysis set with any treatment doses. Other data sets (responding, evaluable, and pharmacodynamic/pharmacokinetic data sets) will be defined and will include data from subjects who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest.

Descriptive summaries will be prepared to show sample size, mean, standard deviation, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum for continuous variables and counts, percentages, and 95% CIs on the percentage for categorical variables. This will be done for each cohort separately. For endpoints relating to tumor control, subject well-being, and biomarkers, analyses will be done based on the full-analysis, responding, evaluable, or pharmacodynamic data sets, as appropriate. Time-to-event analyses will be performed with reference to the date of first treatment on this study. Analyses will focus on evaluation of outcomes within each treatment arm and will be largely descriptive in nature as per the sample size justification section within cohort. Changes in tumor volumes, etc. will be summarized by medians, ranges, and the corresponding 95% CI. Continuous and categorical variables will also be summarized as appropriate.

If both cohorts achieve the maximum number of participants, a pooled, but stratified analysis will be conducted to assess the estimates of success. Relationship of outcomes will be compared between cohort A and cohort B using stratified regression analyses and/or Cochran-mantel-Haenszel tests.

Based on the safety analysis set, information regarding study treatment administration, drug dosing and cycle compliance, safety variables, will be described and summarized. Using data from the pharmacokinetic analysis set plasma concentrations will also be described and summarized. Peak, Trough, Area under the curve and mean serum levels will be compared to tumor responsiveness. Safety will be assessed via tabulations of AEs and SAEs as well as Diary recordings following treatment dose/cycle of therapy.

All analyses for outcome results will be based on evaluable subjects, as defined in section 12.4.

At the end of the trial, we will report poor performance if the treatment is rejected at Stage 1, not meeting the criteria of at least 1 success in 9 cases. If there is no success at Stage II, we will report a failure to reject the null hypothesis using the conditional probability of the added subjects. If the null hypothesis is rejected, the probability of the estimated success rate will be reported and 95% confidence intervals as well as the distribution of changes in tumor size.

An early stopping rule will be invoked for both cohorts to potentially prevent accrual of subjects onto the study in the event that cabozantinib is associated with a higher than acceptable rate

of dose-limiting toxicity (DLT) requiring removal from study (set at 10% or higher) during the first 2 cycles. Toxicity will be continuously monitored. As per the 2nd table below, if at any time >2 of the first 10 subjects or 4 or more of the first 15 total subjects are removed for DLT, then accrual will be stopped until the DSMB reviews safety and efficacy data for the study and recommends termination or despite the DLT (because of the benefit:risk assessment or other reasoning) recommends reopening recruitment. Boundaries for DSMB for consideration of terminating each cohort (both cohort A and B) would be the same.

Table 1: Stopping Boundaries requiring DSMB to consider terminating trial

Number of subjects	Trial will be stopped if the number of subjects with severe toxicity is greater than or equal to the number below
10	3 (equivalent to a p-value of 0.07 that the rate of severe toxicity is 10% or less)
15	4 (equivalent to a p-value of 0.055 that the rate of severe toxicity is 10% or less)

Using these rules and the binomial distribution, the chance of putting the trial on hold and potentially stopping early within the first 10 subjects:

True probability of toxicity	Chance of stopping early
.10	7%
.20	32%
.25	47%
.30	62%
.35	74%
.40	83%

For the comparison of volumetric measures, 60 consecutive patients enrolled on Neurofibromatosis Clinical Trials Consortium PN studies will be included (including NF108). Two groups of independent volume measurements (NCI-MEDx and MGH-3DQI) will be

performed of the target lesions on up to 5 MRIs per subject (pre-study, baseline, pre-cycle 5, pre-cycle 9, pre-cycle 13). Interval change will be calculated to classify disease status as follows: progressive disease (PD) if volume increase is $\geq$ 20%, partial response (PR) if volume decrease is $\geq$ 20%, and stable disease (SD) if change is < 20% between time points. Of note, the results of the MEDx analysis at the NCI will be utilized in analyzing and making decisions on the clinical trial, as has been done on all previous Neurofibromatosis Clinical Trials Consortium PN trials. The results of the 3DQI analysis of each scan performed at the MGH will not be released to sites or the study team while the study is ongoing. Wilcoxon signed rank test will be used to statistically compare the numerical difference between PN volumes at each time-point, and the numerical difference between the percent changes in PN volumes over time. The Jonckheere-Terpstra trend test will be used to establish the degree of significance of the association in disease status classifications. After establishing the overall degree of agreement, the McNemar test for paired categorical data (for two categories) or an exact marginal homogeneity test (for 3 ordered categories) will be used to demonstrate the degree of balance in the discordant results. For the fraction of concordant disease status classifications and the overall response rate 95% confidence intervals will be calculated.

12.4 Definitions of Evaluable

12.4.1 Evaluable for Toxicity -
Subjects who receive at least 1 dose of the study drug and are removed from treatment for toxicity are evaluable. Any subject who completed one full cycle of therapy is evaluable for toxicity.

12.4.2 Evaluable for Response – Subjects who have completed at least two cycles of therapy and have had their first follow-up MRI evaluation. Subjects who did not respond and are later found to have a target tumor other than a plexiform neurofibroma (e.g. malignant peripheral nerve sheath tumor) are not evaluable for response.

13.0 RESPONSE CRITERIA

Tumor Assessment
Tumor response should be assessed by MRI at study entry and at after 4, 8, and 12 cycles. Subjects with at least a 20% reduction in tumor volume may continue on study and will be assessed by MRI after 18 and 24 cycles. Subjects with PD should have their treatment discontinued, and they should enter the post-treatment phase of the study. The same method for tumor assessment should be employed at every assessment.

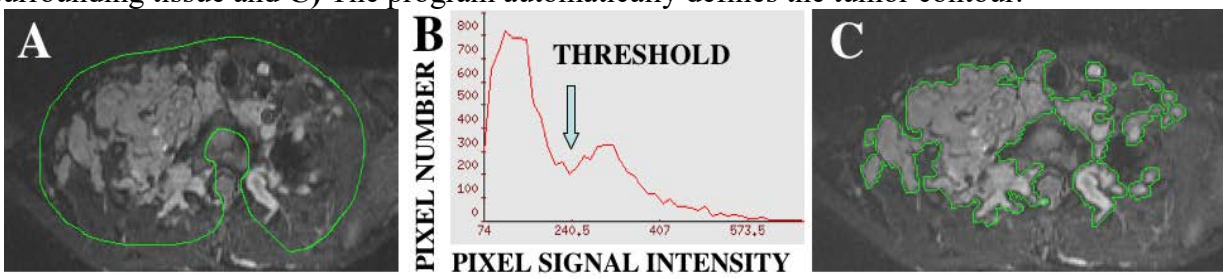
A. **Tumor Response Criteria for Plexiform Neurofibromas:** Tumor response is primary study variable and is the primary aim of this trial. Tumor response will be evaluated by volumetric MRI STIR imaging. Subjects who complete at least 2 cycles of therapy will be evaluable for disease response. Serial measurements of lesions are to be done with MRI. The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.

B. **Methodology to Determine Tumor Measurement**:

Volumetric MRI Method:
Tumor response criteria that are used for cancers are based on one-dimensional (1-D) and two-dimensional (2-D) tumor measurements. These methods have limited value in the assessment of treatment outcome for plexiform neurofibromas, which are frequently large, have a complex (non-spherical) shape, and have a slow growth pattern.

In order to reproducibly quantify the size of these complex lesions and detect small changes in the size over time, we used MR imaging characteristics of plexiform neurofibromas to develop an automated method of lesion detection and volume measurement. Axial and coronal short T1-inversion recovery (STIR) MR images are obtained to encompass the entire PN using a slice thickness of 5-10 mm with no skips between slices. PN volume is determined using a method developed on the MEDx software platform. This method is based on 1) contrast, defined by intensity in the tumor (high signal intensity) compared with the surrounding tissue (low signal intensity), 2) intensity gradient, defining the outside border (margin) of the lesion, and 3) size of the lesion. PN are substantial in size, and small isolated areas of high signal intensity can be ignored, because their contribution to the PN volume is insignificant. The steps of volumetric analysis are outlined in Figure 9.

Figure 9: Steps of automated volumetric MRI analysis of plexiform neurofibromas (PN): **A)** Original axial short T1 inversion recovery MRI of a neck PN. The PN appears bright vs. normal surrounding tissue. During the analysis a region of interest including the tumor and some low signal intensity surrounding tissue is manually outlined on each MRI slice. **B)** The program derives a histogram of pixel signal intensity and identifies a threshold that separates PN from surrounding tissue and **C)** The program automatically defines the tumor contour.



This automated method is sensitive (detects volume changes as small as 10%) and reproducible (coefficient of variation 0.6-5.6%), and yields similar results to manual tumor tracings (R=0.999).

This automated volumetric MRI analysis is applicable to most plexiform neurofibromas, and was used in a phase II trial of the farnesyltransferase inhibitor tipifarnib, in the phase I and II trials of pirfenidone, in the phase I trial of peg-interferon alfa-2b, and in the NF Consortium phase 2 trial of Sirolimus for children with NF1 and plexiform neurofibromas to assess changes in tumor size. Imaging studies on these multicenter trials are sent to the NCI, POB, where volumetric MRI analysis is performed. Tumor progression on these trials is defined as an increase in plexiform neurofibroma volume by ≥ 20%. This volume increase corresponds too much smaller changes in 1-D, or 2-D measurements as outlined in the Table below:

Table 4-2:
Equivalent percent change in diameter (RECIST), product of perpendicular diameters (WHO), and volume for spherical lesions (e.g., increasing the diameter of a sphere by 6% results in a 20% increase in the volume). Bold typeface highlight the definition of progression according to the standard RECIST and WHO criteria, and the definition for progression by volumetric measurements used on several currently ongoing clinical trials for NF1-related plexiform neurofibromas.

Percent Change in Tumor Size		
RECIST Diameter (1D)	WHO Product (2D)	Ongoing NF1 Studies Volume (3D)
6%	13%	**20%**
12%	**25%**	40%
20%	44%	73%

C. Overall Response Assessment:
Response Criteria for target lesions: For the purposes of this study, only the primary or target lesion will be assessed for response. Subjects will have volumetric MRI of target lesion done at 4 months, 8 months, and 12 months. Subjects who show objective response at 12 months can continue at the discretion of the investigator for up to 24 total cycles. For cohort A, subjects who did not show at least a 15% reduction in index tumor volume at 8 months were considered treatment failures and taken off study. For cohort B (pediatric cohort), because of the overall excellent safety profile of cabozantinib and the numerous late tumor responses in cohort A (adult cohort) (see protocol section 2.3), the requirement to stop study treatment in subjects who do not achieve at least a 15% reduction in tumor volume by 8 cycles will be eliminated.

If subject has lesions outside of target lesion, up to two non-target lesions may be selected and imaged at the same recommended intervals and submitted for analysis.

Partial Response (PR): ≥20% decrease in the volume of target lesion taking as reference the initial baseline measurements.

Stable Disease (SD): Neither sufficient decrease in the volume of target lesion to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

Progressive Disease (PD): 20% or more increase in the volume of ANY target or non-target lesion, taking as reference the smallest product observed since the start of treatment.

Correlative Response Variables

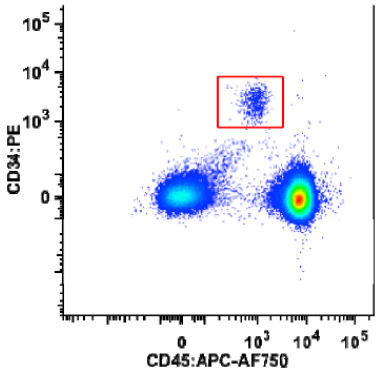
1. Serum bioactivity and cytokine measurements:

We have reported that mast cells, a cellular component in neurofibromas, play important role in the pathogenesis of neurofibromas and other skin malignancies in both human and murine systems (Coussens,1999; Galli SJ,1993; Hirota, 1993; Ryan, 1994; Galli,1993; Kerdel, 1987). Mast cells produce and release multiple mediators into the tumor microenvironment. These factors include histamine, serotonin, proteoglycans, and leukotrienes subsequent to activation of the c-kit receptor (Galli, 1993; Serve, 1995). Furthermore, mast cells release multiple growth factors such as vascular endothelial growth factor (VEGF) (Boesiger, 1998), an angiogenic factor, chemotactic factor for Schwann cells (Sondell, 1999), PDGF-B which promotes fibroblast proliferation and collagen synthesis. We have shown that kit-ligand is a key growth factor that is pivotal in all aspects of cellular functions of mast cells, such as proliferation, de novo synthesis of cytokines, degranulation, and migration to emerging tumors (Yang, 2003). Most importantly, targeting ckit pathway significantly reduced tumor size in a murine model of NF1 and a single case of NF1 patient with a plexiform neurofibroma. In the present study, we propose to evaluate cytokine levels in serum of NF1 subjects. The cytokine panel includes ~30 cytokines/chemokines/growth factors that have been reported altered in neurofibromas and other cancer types by us and others. Plasma biomarker assays will be performed using multiplex simultaneous quantification of about thirty soluble cytokines and growth factors including: VEGF, TGF-β, PDGF-AB/BB, MCP-1, MIP1α, MIP1β, TNFα, GM-CSF, EGF, IL-13, IL-1rα, IL-10, IL-4, IL6, FGF-2, and RANTES. The multiplex assay will be performed according to the manufacturer's protocol (Millipore Milliplex, Billerica, MA) and analyzed on a Luminex 200 cytometer with StarStation software (Luminex Corp, Austin, TX). Plasma samples of each subject at each treatment time point will be stored at -80C and thawed once for simultaneous assay.

2. Polychromatic Flow Cytometry & Identification of Circulating Progenitor Cells

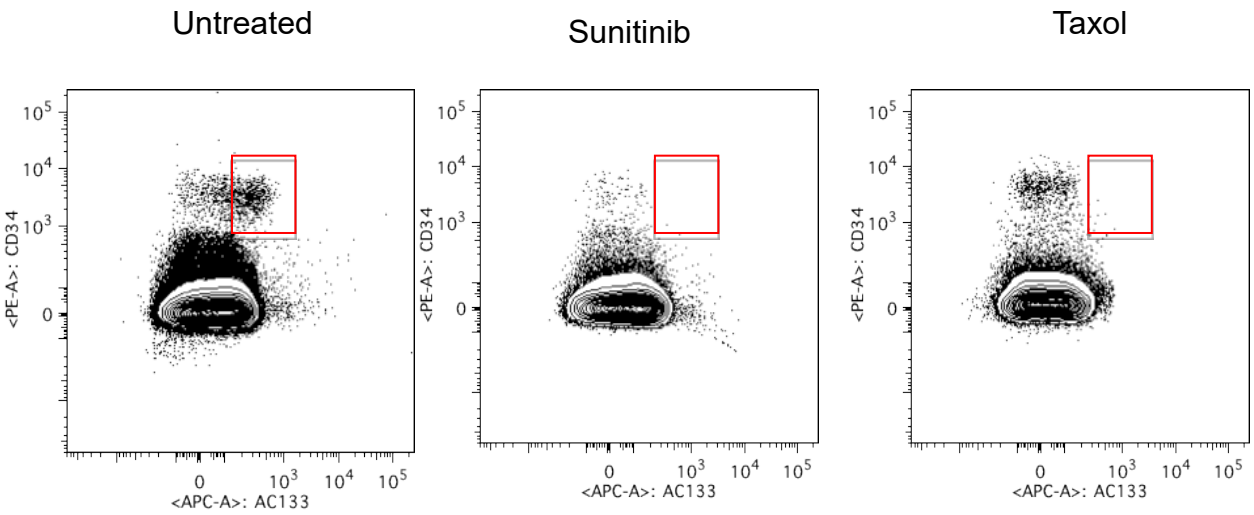
Endothelial progenitor cells (EPCs) and circulating progenitor cells (CPCs) are bone marrow-derived cells (BMDCs), which serve as important biomarkers of disease and for measuring the impact of anti-angiogenic treatments of cancer. Using conventional flow cytometry, Duda et al., recently standardized a method for enumerating specific EPC populations in blood that serve as biomarkers for vascular disease risk and response to anti-angiogenic therapies in human cancers [15]. Flow cytometry is a rapidly developing/expanding field, and recent improvements in technologies and various flow cytometry strategies have now been employed to measure circulating EPC and CPC concentrations in human peripheral blood. Utilizing a novel polychromatic flow cytometry (PFC) strategy to further characterize and purify CPCs, our group has shown that CPCs are phenotypically and functionally distinct from that of the well-studied EPCs [16]. This PFC technique is highly reproducible, allowing for use in longitudinal studies and eliminates any ambiguous data interpretation. In addition, the PFC protocol is cost and time effective, and can be completed in 2-2.5 hours utilizing existing commercially available technology.

In fact, subtle differences in phenotype separating the CPC population into pro-angiogenic and non-angiogenic populations turn out to be quite important, and is primarily based on the expression of the cell surface marker, CD133. By identifying the $CD133^{+}$ sub-population of the CPCs, which represent pro-angiogenic CPCs, the ratio of pro-CPCs versus non-CPCs are quite different in various disease states (Estes et al., *Cytometry A, 77A(9):115-121, 2011*). In normal patients, the ratio is 1.2-2. Cancer patients have a ratio >2.5, which has been shown to decrease to within the normal range following treatment with the anti-angiogenic compound Sutent. Furthermore, in patients with peripheral artery disease (PAD), the ratio is <1 (Estes et al., *Cytometry A, 77A(9):115-121, 2011*). Therefore, the ratio of pro-CPCs vs. non-CPCs may be utilized as a reliable marker for certain diseases, disease status and to monitor response to therapy/treatment.



- CPCs in a normal PB sample range from 0.05-0.15% of the total MNCs.
- In cancer patients the CPCs range from 1-2%.

For example, treatment of metastatic breast cancer patients with Sunitinib resulted in decreased numbers of pro-angiogenic CPCs as compared to untreated patients. Interestingly, when the treatment regime was coupled with Taxol, an increase in the non-angiogenic CPC fraction was observed. Therefore, it is extremely important to perform optimal PFC acquisition and analysis of these 2 phenotypically and functionally distinct cell sub-populations in order to obtain reproducible, reliable and accurate results.



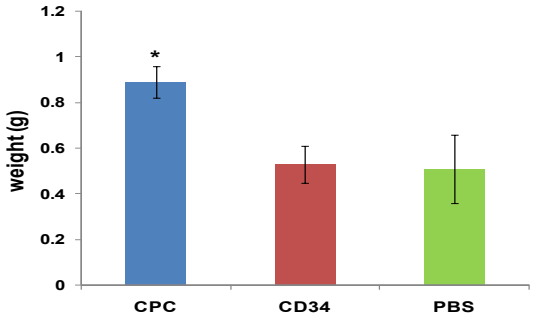


Figure 5. Comparison of Tumor Weights. At the end of the study, the mice were euthanized and the tumors from each cohort of mice were harvested and weighed. Tumor weights are from Expt II. *p<0.001, CPCs vs CD34 or PBS control. N=4 mice/cohort.

Furthermore, in a recent study by Pradhan et al., looking at CPCs in pediatric patients with various solid tumors as compared to age matched healthy controls, it was demonstrated that patients with cancer had a higher ratio of pro-CPCs versus non-CPCs. The median ratio of the pro-CPCs versus non-CPCs was 2.12 (0.34-5.95) at baseline for the patients, while the healthy controls had a median ration of 1.23 (0.24-1.54). Following treatment, the median ratio for the patients dropped to 1.59 (0.21-8.75) (Pradhan et al., *Cytometry Part B: Clinical Cytometry, 80B(5):335-338, 2011*). This was the first time that the two subsets had been reported in any human malignancy.

Additionally, injection of the purified pro-angiogenic CPC fraction was shown to enhance tumor growth in a murine xenograft model. In summary, NOD/SCID mice harboring pre-established melanoma xenografts (~100mm^3) were intravenously injected with purified human pro-CPCs, phosphate buffered saline (PBS), non-CPCs (Figure 4, Expt I) or CD34$^+$ cells (Figure 4, Expt II). Intravenous injection of pro-CPCs in mice harboring melanoma xenografts resulted in a statistically significant increase in tumor growth overtime when compared to controls (i.e. PBS, CD34$^+$ cells or non-CPCs) (Figure 4). In addition, at the completion of the study, excised tumors were weighed to further document changes in tumor growth. Tumors from mice injected with the pro-CPCs were significantly larger than tumors from the mice that received vehicle control (PBS) or CD34$^+$ cells (Figure 5) (Estes et al., *Cytometry A, 77A(9):115-121, 2011*). Histological analysis of tumors for the presence of human CPCs is in progress. In all future experiments, we will use CD34$^+$ cells as the negative control population. While we realize that pro-CPCs are certainly present in the CD34$^+$ cell population, our data suggest that the level of the pro-CPCs is not high enough in the bulk CD34$^+$ population to promote tumor progression unless the pro-CPCs are first purified from the CD34$^+$ population.

This evidence is compelling, and supports the role of pro-angiogenic CPCs in tumor progression, as well as the potential utility of the CPC ratio as a powerful biomarker in various disease states, including cancer. We will examine the role of CPCs as a biomarker in NF1 plexiform subjects treated with cabozantinib.

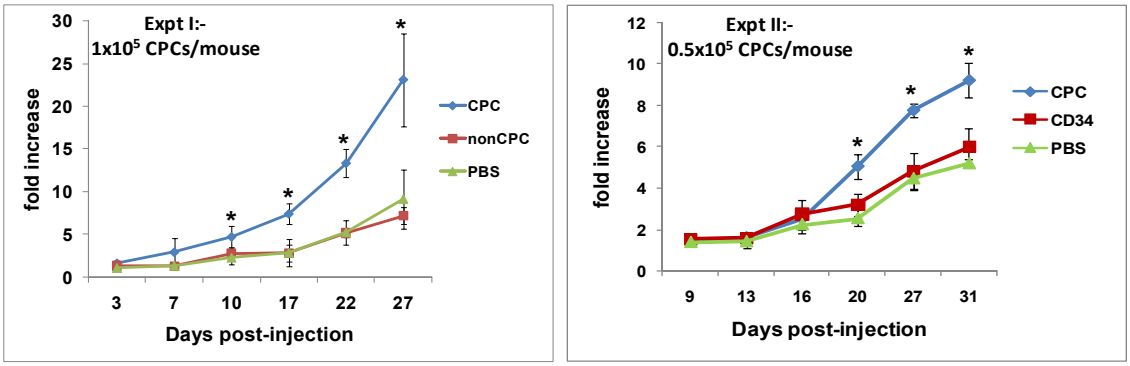


Figure 4. Intravenous Injection of CPCs Results in Significant Increases in Melanoma Xenograft Growth. NOD/SCID mice bearing human melanoma xenografts were intravenously injected with CPCs, control cells (Expt I=nonCPCs; Expt II= $CD34^+$ cells) or PBS. Tumor growth was monitored over time by caliper measurement. * p<0.001, CPCs vs. control cells or PBS. N=3-4 mice/cohort.

PFC and CPCs**:** PFC for the identification of CPCs will be performed at four time points as per protocol. Whole blood will be drawn in EDTA tubes and sent immediately for processing to the Indiana University Angio BioCore, which is directed by Dr. Karen Pollok. As samples are received, using the PFC protocol developed by Dr. Jamie Case (*Estes et al., Current Protocols in Cytometry, 52(9):9.33.1-9.33.11, 2010)*, the phenotypic detection and enumeration of CPCs will be performed, and the ratio of pro-angiogenic (i.e. $CD133^+$) vs. non-angiogenic CPCs will be calculated on all samples. Data obtained will then be correlated with tumor response.

3. Pharmacokinetics

Plasma samples will be collected for the purpose of determining XL184 concentrations for pharmacokinetic analysis of XL184 and/or metabolite concentrations.

For Cohort A: Blood samples will be obtained at the following time points: Cycle 1 Day 1 (pre, 4 hours after the first dose), Cycle 1 Day 15 (pre, and 4 hours after dose), Cycle 1 Day 28 (pre and 4 hours after dose) for subjects remaining on study, and if possible any time a subject experiences a DLT.

For Cohort B: Blood samples will be obtained at the following time points: Cycle 1 Day 1 (pre first dose), Cycle 2 Day 1 (pre-dose), Cycle 3 Day 1 (pre-dose) and Cycle 4 day 1 (pre-dose)

Blood samples (3 ml) will be collected in 3-mL K_2-EDTA Vacutainer tubes (lavender top) tubes for pharmacokinetic evaluation. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

Tubes should be chilled on wet ice or in a refrigerator prior to collection. Immediately after blood collection, blood tubes should be inverted several times and then kept on wet

ice until centrifuged. Within 30 minutes of blood collection, samples should be separated by centrifugation for 10 minutes (1000 - 1200 g) at approximately 4°C. The resultant plasma should be withdrawn in approximately equal volumes into two (2) appropriately labeled polypropylene tubes for PK assay and stored (within 1 hour of the blood sampling time) at -70°C or lower until shipment. The analyst should attempt to transfer the maximum amount of plasma without disturbing the barrier between the red blood cells (bottom layer) and the plasma (top layer). One tube is the primary sample; the other tube is the back-up sample. Samples should be shipped to the following address:

Alturas Analytics, Inc.
Attn: Jennifer Zimmer, PhD
Senior Scientist Executive Laboratory Manager
1324 Alturas Dr.
Moscow, ID 83843
Phone: (208) 883-3400
Fax: (208) 882-9246
Email: jzimmer@alturasanalytics.com

Refer to Appendix VI for additional sample processing and shipping instructions.
PK data will be analyzed and summarized by Exelixis Inc.

14.0 HUMAN SUBJECTS PROTECTION & DATA SAFETY MONITORING PLAN

Rationale for Subject Selection

Neurofibromatosis type 1 is a genetic disorder and the incidence of the disease in the various racial and ethnic groups may vary. This may impact on our ability to recruit sufficient numbers of patients within each group to this trial. Subject accrual in regards to gender, and racial and ethnic groups is described in Section 4.0. None of these groups are excluded from participation in the trial. Females who are pregnant or breast feeding will not be eligible for entry onto the trial because of the potential risks that cabozantinib could pose to the fetus or newborn. This trial is designed to determine the activity of cabozantinib in adolescents and adults with NF1 and inoperable PN. Individuals will be enrolled only at sites that participate in the NF consortium. Subjects may also be referred from outside centers but treatment will be directed at an NF consortium site.

Evaluation of benefits and risks/discomforts

The potential benefit from participation in this trial is the stabilization or reduction in the size of the PN, relief of symptoms caused by the PN, and prolongation of life. The primary risk to the subjects from participation in this trial is due to cabozantinib toxicities (Section 7.3), which have been reversible when they occur. Subjects enrolled on this trial will be carefully monitored for the development of toxicities, and guidelines for target modifications, discontinuation of drug, and a toxicity stopping rule are in place. Blood samples will be obtained on this trial for pharmacokinetic, pharmacodynamic, and pharmacogenetic studies; these are mandatory. Samples will be identified by a code number that can be traced to the subject only by contacting the trial coordinating center. However, as the blood samples are linked to the subject's name, a small risk persists that unauthorized persons could gain access to information. Some testing may eventually reveal information that could result in discrimination with health or life insurance or employment. We believe that these risks are minimal since it is already known that subjects enrolled on the study have neurofibromatosis. All research results will be kept confidential. Results from the pharmacodynamic and pharmacogenetic studies will be considered preliminary and will require further analysis for verification. Therefore, results will not be communicated with the research subjects. Subjects also have the right to withdraw the blood specimens obtained for research purposes at any time.

Risks to subjects from banking biological specimens include the risks of the blood draws for research purposes. Tumor specimens will be taken only from leftover specimens that were obtained for clinical purposes. The amount of blood to be obtained is minimal (approximately 10 ml) and no more than 5 mL/kg will be taken from any subject in a single day. Risks associated with blood draw are pain, bleeding or bruising at the spot where the needle is inserted, and rarely fainting or infection. Every attempt to draw the research blood samples in conjunction with other clinical blood draws will be made so that the risk of infection is not increased. Blood draws will be performed by trained personnel who are experienced in working with children and familiar with the challenges of drawing blood from this population. The risk of biological specimen banking is minimized by coding the specimens prior to shipping to the biorepository in order to prevent identification of subjects and protect confidentiality. In addition, the study subject ID number linked to the specimen will be maintained separately at the NF Consortium Operations Center at UAB.

Depending on the age of the subject MRI studies may require sedation or anesthesia, which is associated with additional risks. Separate informed consent will be obtained from research subjects for sedation or anesthesia for MRI scans.

Risk/benefit analysis

The primary objective of this phase II trial is to define the objective response rate of PN treated with cabozantinib, and thus subjects entered on the trial will be treated with therapeutic intent and response to the therapy will be closely monitored. Therefore, this protocol involves greater than minimal risk, but presents the potential for direct benefit to individual subjects. The potential benefit of this treatment with cabozantinib is that it may stop or slow down the growth of PN, or shrink PN. In addition cabozantinib may lessen the symptoms, such as pain, that are caused by the tumor. The MRI data in this study will be analyzed by a special approach called "volumetric MRI," in addition to being read in a standard manner by a radiologist. The volumetric MRI approach will provide more precise measurement of the size of PN, and therefore will give more complete and objective information on which to base any possible future treatment decisions. Volumetric MRI is currently not available on a routine clinical basis.

Consent and assent process and documentation

The investigational nature and 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 the patient's parents or guardian if he/she is a child, and a signed informed consent document will be obtained. Consent will be obtained by the site PI or an associate investigator on the trial according to state and institutional guidelines. When appropriate, pediatric patients will be included in all discussions and assent documented. All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

This is a multi-institutional trial, and the NF Operations Center will require evidence of local IRB approval and of USAMRMC ORP HRPO approval of the protocol prior to allowing for accrual of subjects at that institution. This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

Medical Monitor and Data Safety Monitoring Plan

The trial PI and clinical coordinator will review the study progress regularly. Subjects entered on the trial and adverse events will be reviewed to ensure that the study is implemented as outlined in the protocol. Monthly reports will be generated by the NF Consortium to assess completeness of data. There will be monthly phone conferences between the NF Consortium and the Principal Investigator to address QA issues. A Data Safety Monitoring Board has been established for the purpose of ensuring data compliance and regular monitoring of this trial.

Alyssa Reddy, MD will be the medical monitor for this study. She is a qualified physician and is not associated with this particular protocol. She will work closely with the Principal Investigator to monitor the participants' treatment while on this study.

For research determined to be greater than minimal risk, DODI 3216.02 requires **that the IRB approve, by name, an independent /medical monitor with expertise consonant with the nature of risk(s) identified within the research protocol**. The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities.

The medical monitor's duties should be based on specific risks or concerns about the research. The medical monitor may perform oversight functions and report their observations and findings to the IRB or a designated official. The medical monitor may be identified from within or outside the PI's institution.

Medical monitor functions may include:

- observing recruitment and enrollment procedures and the consent process for individuals, groups or units,
- overseeing study interventions and interactions,
- reviewing monitoring plans and UPIRTSO reports;
- overseeing data matching, data collection, and analysis

There may be more than one medical monitor (e.g., if different skills or experiences are necessary). The monitor may be an ombudsman or a member of the data safety monitoring board.
At a minimum, the medical monitor:

- may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research;
- shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report;
- shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

In addition, on this study, the medical monitor is specifically required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor should comment on the outcomes of the event or problem, and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor should also indicate whether he/she concurs with the details of the report provided by the study investigator.

15.0 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The Principal Investigator (Protocol Chair) holds the primary responsibility for publication of the study results; provided that the PI will provide any such publication to Exelixis, Inc. for review at least sixty (60) days prior to submission and also comply with any provisions regarding publication as are agreed to between the Neurofibromatosis Clinical Trials Consortium and Exelixis, Inc. in the Clinical Trial Agreement related to this study. The results will be made public within 24 months of the end of data collection. However, if a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International

Committee of Medical Journal Editors. In any event, a full report of the outcomes should be made public no later than three (3) years after the end of data collection. Authorship for abstracts and manuscripts resulting from this study will be determined according to guidelines established by the International Committee of Medical Journal Editors.

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APPENDIX I: SCHEDULE OF EVALUATIONS

STUDIES TO BE OBTAINED	Pre-Study[1]	Cycle 1	Cycle 2, 3	Cycle 4-12	Cycle 13-24	Completion of Rx
History	X	End	Day 15, End (each cycle)	End (each cycle)	Post cycle 14, 16, 18, 20, 22, 24	X
Physical exam with vital signs and pulse ox	X	Day 15, End	Day 15, End (each cycle)	End (each cycle)	Post cycle 14, 16, 18, 20, 22, 24	X
Height, weight, BSA[2]	X	End	Day 15, End (each cycle)	End (each cycle)	Post cycle 14, 16, 18, 20, 22, 24	X
Blood pressure	X	Day 15, End	Day 15, End (each cycle)	End (each cycle)	Post cycle 14, 16, 18, 20, 22, 24	X
Performance Status	X	End	Day 15, End (each cycle)	End (each cycle)	Post cycle 14, 16, 18, 20, 22, 24	X
Subject Diary	X	End	End (each cycle)	End (each cycle)	Post cycle 14, 16, 18, 20, 22, 24	X
Phone Call (to assess drug compliance and toxicity)					Post cycle 13, 15, 17, 19, 21, 23	
CBC, differential, platelets	X	Day 15, End	Day 15, End	End (each cycle)	End (each cycle)	X
CMP[3] with Ca, Mg, Phos, lipase, amylase	X	Day 15, End	Day 15, End	End (each cycle)	End (each cycle)	X
PT, PTT, INR	X	End	End (each cycle)	End (each cycle)	End (each cycle)	X
Urinalysis	X	End	End (each cycle)	End (each cycle)	End (each cycle)	X
Urine protein/creatinine	X	End	End (each cycle)	End (each cycle)	End (each cycle)	X
Pregnancy test[4]	X[5]		End cycle 2	Post cycle 4, 6, 8, 10, 12	Post cycle 14, 16, 18, 20, 22, 24	X
Thyroid stimulating hormone	X	End	End cycle 3	Post cycle 6, 9, 12	Post cycle 16, 20, 24	X
12- lead EKG[6]	X	End	End cycle 2	Post cycle 4, 6, 9, 12	Post cycle 16, 20, 24	X
MRI of target tumor	X			Post cycle 4, 8, 12	Post cycle 18, 24	X[7]
QOL	X			Post cycle 4, 8, 12	Post cycle 18, 24	X
Plexiform Neurofibroma Symptom Checklist	X			Post cycle 4, 8, 12	Post cycle 18, 24	X
Plexiform Neurofibroma Location & Associated Morbidities Form	X					
Plexiform Neurofibroma Clinician Morbidity Checklist	X			Post cycle 4, 8, 12	Post cycle 18, 24	X
Peripheral blood for cytokine assays	X	Day 15	End cycle 2	Post cycle 4		
CPC biological markers – flow	X	Day 15	End cycle 2	Post cycle 4		
Pharmacokinetics[8]	X	Cohort A:Day 15, End Cohort B: Day 1, Day 28	Cohort B: Cycle 3 Day 1	Cohort B: Cycle 4 Day 1		
Blood and Tissue collection[9]	X			Post cycle 4, 12		X

1. All studies to determine eligibility must be performed within 2 weeks prior to enrollment unless otherwise indicated (See section 9.0). Consent must be obtained prior to enrollment but does not expire at 2 weeks.
2. Height only required at baseline in Cohort A. Obtain at each study visit for Cohort B.
3. CMP should include: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase
4. For females of childbearing age
5. Within 7 days prior to starting treatment
6. If the subject starts a medication with substantial evidence that the drug prolongs the QT interval, then EKG monitoring must be end of each cycle while on the medication (see section 6.3)
7. For subjects with tumor response, MRI is recommended at 4 months and 12 months off therapy (except if they start other tumor-directed therapy).
8. PK for cohort A will be done Day 1, 15, 28: predose and 4 hours postdose. PK for Cohort B will be done Cycle 1 Day 1, Cycle 2 day 1, Cycle 3 day 1 and Cycle 4 Day 1
9. Blood samples should be drawn at the indicated time points as well as around the time of tumor biopsy if tumor tissue is being submitted (if the patient undergoes a clinically indicated tissue collection procedure). The following will be collected at each time point: Streck tube (for plasma): ~ 2 mL; EDTA tube (for DNA): ~ 5 mL; PAXGene tube (for RNA) ~ 2.5 mL.

APPENDIX II: PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX III: PARTICIPANT DOSE DIARY

PID 1: ______ PID 2: _______

Cycle Number:							
Cycle Start Date:							
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Dose Taken *place X in box*	☐ 1 = Taken ☐ 2 = Missed	☐ 1 = Taken ☐ 2 = Missed	☐ 1 = Taken ☐ 2 = Missed	☐ 1 = Taken ☐ 2 = Missed	☐ 1 = Taken ☐ 2 = Missed	☐ 1 = Taken ☐ 2 = Missed	☐ 1 = Taken ☐ 2 = Missed
Dose (*taken once per day*)	__ __ mg	__ __ mg	__ __ mg	__ __ mg	__ __ mg	__ __ mg	__ __ mg
Date Dose Taken	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
Time Dose Taken	___:___ AM PM	___:___ AM PM	___:___ AM PM	___:___ AM PM	___:___ AM PM	___:___ AM PM	___:___ AM PM
SIDE EFFECTS							
Nausea † *see scale below and place X in box*	☐ 0 = None ☐ 1 = Mild ☐ 2 = Moderate ☐ 3 = Severe	☐ 0 = None ☐ 1 = Mild ☐ 2 = Moderate ☐ 3 = Severe	☐ 0 = None ☐ 1 = Mild ☐ 2 = Moderate ☐ 3 = Severe	☐ 0 = None ☐ 1 = Mild ☐ 2 = Moderate ☐ 3 = Severe	☐ 0 = None ☐ 1 = Mild ☐ 2 = Moderate ☐ 3 = Severe	☐ 0 = None ☐ 1 = Mild ☐ 2 = Moderate ☐ 3 = Severe	☐ 0 = None ☐ 1 = Mild ☐ 2 = Moderate ☐ 3 = Severe
Vomiting *# of times in 24 hr*							
Diarrhea *# of times in 24 hr*							
Rash *Specify Location* →							
Other: *write in* →							

OTHER MEDICATIONS

Medication Name	Dose	Frequency	Start Date	Stop Date	Reason for Use of Medication
			___/___/_______	___/___/_______	
			___/___/_______	___/___/_______	
			___/___/_______	___/___/_______	

Reviewed by treating physician: ______________________________ **Date:** __ __ / __ __ / __ __ __ ______

Parent/Participant Signature: ______________________________ **Date:** __ __ / __ __ / __ __ __ ______

† Rate nausea **mild** if you are able to eat and drink a reasonable amount, **moderate** if you can eat and drink but the amount is substantially decreased, or **severe** if you are unable to eat and drink. Note: Cabozantinib should be taken daily at same time if possible. Cabozantinib should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose). Do NOT re-take if vomiting occurs after taking a scheduled dose.

APPENDIX IV: PROTOCOL FOR REQUIRED PRE-STUDY AND ON-STUDY MRI STUDIES

Prior to starting treatment on this study a target plexiform neurofibroma must be identified. In addition, up to two non-target plexiform neurofibromas may be identified as well.

The goal will be to use 3-D MRI only to follow the target and non-target plexiform neurofibroma(s) (a maximum of three lesions), which will be defined as index lesion(s).

Pre-study imaging evaluation:

1. Identify and select the index plexiform neurofibroma(s) (a maximum of three lesions) for 3-D MRI evaluation based on prior imaging studies. Should there be more than 3 progressing plexiform neurofibromas; the three most clinically relevant plexiform neurofibromas should be followed by 3-D MRI analysis.
2. Perform 3-D MRI sequences on the selected index lesions as outlined in the MRI acquisition protocols below.

On study imaging evaluation:

Unless clinically indicated otherwise obtain MRI of the index lesions only as outlined in the MRI acquisition protocol below at baseline and then after cycle 4, 8, 12, 18, 24 and end of study.

MRI protocols:

Images intended for volumetric analysis need to be performed without gaps between slices. Every attempt should be made to image the entire PN. The target tumor should be positioned close to the center of the imaging field and the outer edge of the tumor should be within the field of view. Peripheral nerve sheath tumors can be well visualized without the use of contrast agents on short TI inversion recovery (STIR) sequences because they have high signal intensity relative to normal tissues. The imaging protocol in the table below should be used for the imaging of the target and non target PN.

If necessary, participating institutions may modify the MRI sequences to optimize differentiation of tumor and surrounding tissue. Modifications should be noted, such that the same imaging protocol, and, if possible, the same MRI scanner, can be used for all subsequent MRI studies.
All MRI studies requested per protocol will be submitted to the NCI POB within 1 week of acquisition for volume analysis.

Volumetric sequence for PN**			
Axial STIR	**Recommended Range**	**Head-Neck or Small## Trunk-Extremity PN**	**Large## Trunk-Extremity PN**
Echo Train Length	5 - 15	7	15
TR	3000 - 6000	6000	4000
TE	30 - 50	34	30
TI	150-180	150	150
Slice Thickness	3 - 10 mm	3 mm	10 mm
Skip	0	0	0
Matrix	256x256 - 512x512	256x256	320 x256 - 512x512
FOV	18 - 50 cm	22 cm	45 cm
Phase FOV	0.8	0.8	0.8
NEX	2 - 4	3	2
Frequency Direction	A→P	A→P	A→P

**Spinal/paraspinal PN should be imaged with the appropriate protocol based on tumor size. Tumors that include the neck and trunk, for which the majority of the tumor is in the trunk, should be imaged with the Large Trunk-Extremity PN protocol.

##Tumors < 5 cm in longest diameter would be considered small. Tumors > 10 cm longest diameter would be considered large. Tumors between 5-10 cm in longest diameter should be imaged with the appropriate protocol based on best FOV coverage.

Please contact Dr. Dombi if there are questions regarding the appropriate coverage or imaging protocol.

Data Analysis:

- All MRI data will be analyzed at the Pediatric Oncology Branch of the NCI. The MRI data from each scan will be processed to assess the volume of the index plexiform neurofibroma(s). The tumor will be traced on subsequent contiguous MR slices, the numbers summed and then multiplied by the slice thickness to obtain a numerical volume measurement. The tumor will be identified by high signal on the STIR images not corresponding to known normal anatomic structures and corresponding with the cycle of known nerves. Each subject's volumetric measurement obtained from the initial MRI will serve as the baseline against which to assess incremental changes in volume that occur during the subsequent intervals. Volumetric measurements and 1-D, and 2-D data analysis will be done by 3 physicians trained in 1-D, 2-D, and 3-D MRI data analysis at the Pediatric Oncology Branch, NCI at an Image Review Workstation using MEDx software (Sensor Systems Inc.). Volumetric measurements will be used to determine disease progression as outlined in Section 13.0. Drs. Dombi and Widemann will inform Participating Investigators, the Principal Investigator, and the NF Consortium Operations Center about the results of the MRI study by written report.

Image and Data Acquisition:

- In order to perform quantitative analysis the Pediatric Oncology Branch must receive the imaging data from the investigator sites. All MRI studies requested per protocol will be submitted to the NCI POB within 1 week of acquisition for volume analysis. The Pediatric Oncology Branch will check all materials received for completeness and will notify the site if data, images, or information are missing or incomplete. Dr. Dombi will confirm for each patient in screening that the MRI imaging is adequate and that the target PN is measurable and amenable to volumetric MRI analysis.

- Address for shipment of imaging studies:
  Eva Dombi, MDNCI, POB
  10 Center Drive, Building 10, room 1-5750
  Bethesda, MD 20892-1101
  Phone: 301-451-7023
  E-mail: dombie@mail.nih.gov

APPENDIX V: BIOMARKER STUDIES

Biomarker Submission

A. Cytokines

Peripheral blood (6mL) will be collected via venous puncture into an 8 mL EDTA purple top tube (or divide between two 6 mL EDTA tubes). Spin at 2200 rpm (1200-1300g) for 15 minutes (break and acceleration 'on') at 4°C. Collect plasma and distribute/aliquot 1-1.5 mL into each 2mL cryovial (1-5 cyrovials). Fix a printed label on each tube with: site, patient ID number, sample time point, date, a # and amount/vial. Store samples at -80^{0}C until being shipped as a batch on dry ice.

Ship by FedEx Monday to Thursday on dry ice to:
CCRC, Indiana University School of Medicine
705 Riley Hospital Dr.
RI 2641
Indianapolis, IN 46202
Attn: Khadijeh (Sholeh) Bijangi-Vishehsaraei, MS, PhD

B. Endothelial Progenitor Cell (Contacts: Emily Sims, ecwillar@iu.edu and Matt Repass, mjrepass@iu.edu)

Once a subject has been identified and a baseline visit has been scheduled email: nfstudy@iu.edu to have CPT and balance CPT tubes sent to your site. CPT tubes have a 6 month shelf life. Store CPT tubes in an upright position out of direct sunlight and heat.

16 mL of peripheral blood (PB) will be collected via venous puncture into three 6mL EDTA purple top tube. For local processing, the PB sample will then be brought to the Angio BioCore at Indiana University with processing beginning within one hour of collection.

For off-site samples, 16 mL of PB will first be collected via venous puncture into three 6mL EDTA purple top tubes. The PB will then be transferred into two 8mL CPT tubes, gently invert eight times to mix blood with anticoagulant. The sample must be processed within **2 hours** of blood collection . Centrifuge for 30 minutes at 1500-1800g at room temperature. The centrifugation will separate the mononuclear cell (MNC) fraction and the plasma above the ficoll plug with the red blood cells passing through and going beneath the plug. Following centrifugation, the plasma/MNCs will then be poured into two clean/new 6mL EDTA tubes and shipped overnight (at room temperature) to the Angio BioCore. The MNCs are stable for 24 hours post collection after centrifugation and, therefore, must be shipped same day. All tubes should be labeled with site, patient ID number, sample time point, and date.

Please only ship samples by Federal Express priority overnight **Monday through Thursday**. Please inform the Angio BioCore of your incoming shipment

(ecwillar@iupui.edu, mjrepass@iupui.edu).

Ship by FedEx to:

Emily Sims & Matt Repass
Angio BioCore Lab
980 West Walnut Street, R3 Room C343
Indianapolis, IN, 46202
317-278-7232

APPENDIX VI: PHARMACOKINETIC STUDIES

Pharmacokinetic Worksheet

Subject Consortium ID number: _____
BSA (m^2): _____ Cabozantinib (mg) _____ mg given : _____

Cohort A (≥16 years of age)
Each study site will need:

1. Centrifuge with horizontal rotor capable of producing 1200 x g (set to 4ºC).
2. Non-defrosting freezer (-70°C or below)

Once sites have approval for enrollment and have possible candidate(s), contact Linh Nguyen, linguyen@exelixis.com & Clinical_Supplies@exelixis.com to request PK laboratory kits. Request should include completed PK request form. Provide correct contact person and shipping address for shipments and allow 5 days for shipment. Clinical sites will receive a Pharmacokinetic (PK) kit for each subject from Exelixis. Since PK kits are subject specific, do not interchange materials between the kits. Each kit contains several extra tubes and labels in addition to those required for the scheduled collections.

For Cohort A there will be a total of 6 samples drawn. Blood samples (3mL will be drawn for pharmacokinetic profile during cabozantinib (XL184) therapy at the following timepoints:

- Cycle 1, Day 1 (C1D1): Pre-cabozantinib dose (collected within 15 minutes prior to cabozantinib dosing) and 4 hours post cabozantinib dose
- Cycle 1, Day 15 (C1D15): Pre-cabozantinib dose (collected within 15 minutes prior to cabozantinib dosing), and 4 hours post cabozantinib dose
- Cycle 1, Day 28 (C1D28): Pre-cabozantinib dose (collected within 15 minutes prior to cabozantinib dosing), and 4 hours post cabozantinib dose

Procedure for Cohort A:
Samples will be drawn as 3 mL whole blood into K2EDTA (lavender top) tubes

1. Prior to obtaining blood from subjects at each timepoint, gather the following supplies together from the Study XL184-IST-014 PK Kit and your site supplies:
    - Obtain three barcoded plasma labels for PK sample. Confirm that the sample type, the date and collection time pre-printed on each label correspond with the sample type, date and time you will be collecting
    - One 3 mL K2-EDTA Vacutainer tube for each PK sample timepoint
    - Two Polypropylene tubes for PK plasma aliquot
    - Transfer pipettes
    - Dry ice (if –20 or -70°C freezer is not available)
2. Write the subject number, and site number (as applicable) in the spaces provided on the label. Record the last four digits from the barcode on the label onto the subject's

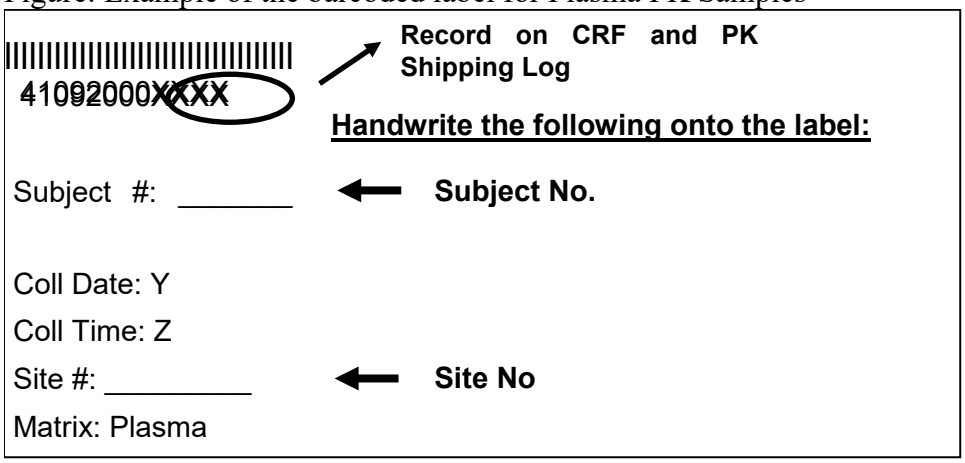
chart and PK shipping logs in the comment column. See Figure below for an example of the barcoded labels

3. Apply the barcoded labels to each of the three tubes for PK samples (1 for whole blood and 2 for plasma aliquots).
4. Secure each label with a strip of transparent cellophane tape.

(Note: it is important that the following steps are completed in sequence immediately within 30 minutes after collection of blood samples, unless otherwise noted):

5. Collect 3 mL of blood into a pre-labeled K2-EDTA Vacutainer tube (the tube with the Lavender Top)
6. Record the exact time (24-hour clock) that each sample was collected (be sure to use the same clock for recording both sampling and dosing times).
7. Invert the collection tube gently at least 5 times. (If separation of the plasma fraction cannot be immediately performed at this time, store the samples on ice, or refrigerate the sample, and re-mix the samples by gentle inversion prior to proceeding to step 8).
8. Separate the plasma fraction by centrifugation (1000-1200 × *g* for 10 minutes) using standard laboratory methods, materials, and equipment. A refrigerated centrifuge is preferred, and if available, should be set to 4ºC.
9. Aliquot the plasma (equal volume) into each of two pre-labeled 5-mL polypropylene tubes (primary and backup aliquots), being careful not to transfer blood cells.
10. Verify that each tube is tightly capped.
11. Store the plasma aliquots immediately in a non-defrosting freezer at -70°C (-20°C freezer can be used if -70°C freezer is not available). Samples must be stored on dry ice if a freezer is not immediately available.
12. For each subject, plasma samples should be shipped on dry ice to Alturas.

Figure: Example of the barcoded label for Plasma PK Samples



Cohort B (3-15 years of age)
Sites will use their own supplies to collect PK samples and apply a pre-printed label. The following supplies will be needed per timepoints:

1. Vacutainer Lavender Top Plastic, K2 EDTA, 3 mL tube
2. Transfer tube cryovial, 1.5 mL
3. Transfer pipettes
4. Labels
5. Dry ice
6. Centrifuge with horizontal rotor capable of producing 1200 x g (set to 4°C).
7. Non-defrosting freezer (-70°C or below)

For Cohort B there will be a total of 4 samples drawn. Blood samples (3ml will be drawn for pharmacokinetic profile during cabozantinib (XL184) therapy at the following timepoints:

- Cycle 1, Day 1 (C1D1): Pre-cabozantinib dose (collected within15 minutes prior to cabozantinib dosing)
- Cycle 2, Day 1 (C2D1) ±2 days: Pre-cabozantinib dose (collected within 15 minutes prior to Cabozantinib dosing),
- Cycle 3 Day 1 (C3D1) ±2 days: Pre-cabozantinib dose (collected within15 minutes prior to cabozantinib dosing)
- Cycle 4 Day 1 (C4D1) ±2 days: Pre-cabozantinib dose (collected within15 minutes prior to cabozantinib dosing)

Procedure for Cohort B:
Samples will be drawn as 3 mL whole blood into K2EDTA (lavender top) tubes

1. Prior to obtaining blood from subjects at each timepoint, gather the following supplies:
   - One 3 mL K2-EDTA Vacutainer tube for each PK sample timepoint
   - Transfer tube cryovial, 1.5 mL
   - Transfer pipettes
   - Labels
   - Dry ice (if –20 or -70°C freezer is not available)
2. Write the subject number, site number (as applicable) and Visit (C1D1, C2D1, C3D1 or C4D1) on the labels.
3. Apply the labels to each of the three tubes for PK samples (1 for whole blood and 2 for plasma aliquots).
4. Secure each label with a strip of transparent cellophane tape.

(Note: it is important that the following steps are completed in sequence immediately within 30 minutes after collection of blood samples, unless otherwise noted):

5. Collect 3 mL of blood into a pre-labeled K2-EDTA Vacutainer tube (the tube with the Lavender Top)
6. Record the exact time (24-hour clock) that each sample was collected (be sure to use the same clock for recording both sampling and dosing times).
7. Invert the collection tube gently at least 5 times. (If separation of the plasma fraction

cannot be immediately performed at this time, store the samples on ice, or refrigerate the sample, and re-mix the samples by gentle inversion prior to proceeding to step 8).

8. Separate the plasma fraction by centrifugation (1000-1200 × *g* for 10 minutes) using standard laboratory methods, materials, and equipment. A refrigerated centrifuge is preferred, and if available, should be set to 4ºC.
9. Aliquot the plasma (equal volume) into each of two pre-labeled 5-mL cryovial tubes (primary and backup aliquots), being careful not to transfer blood cells.
10. Verify that each tube is tightly capped.
11. Store the plasma aliquots immediately in a non-defrosting freezer at -70°C (-20°C freezer can be used if -70°C freezer is not available). Samples must be stored on dry ice if a freezer is not immediately available.
12. For each subject, plasma samples should be shipped on dry ice to Alturas.

Packaging Instructions:

1. The first aliquot of PK samples should be shipped to Alturas Inc. after each subject completed the C1D28 (for Cohort A) and C4D1 (for Cohort B).
2. The second aliquot of PK samples should be maintained at the sites as backup samples and be shipped along with the next available shipment.
3. Please pack all the samples for each subject in each sealable bag
4. Prior to shipment, verify that each tube is tightly sealed.
5. Place the tubes into a sealable plastic bag (one subject per bag) surrounded by absorbent material.
6. Complete the PK sample Shipping Log (noted below) based on the information on the site form recorded by the site staff. For each subject, place a copy of the shipping log into its own plastic bag, seal, and then add it to the bag containing that patient's samples. Retain a copy of each shipping log for your records. Seal the bag.
7. Place the plastic bags into a suitable Styrofoam shipping container (e.g., ThermoSafe) and fill with enough dry ice for 2 days in transit (e.g., 14 pounds).
8. Write the FedEx tracking number on each shipping log sheet and fax the log sheet to the attention of Dr. Zimmer at Alturas at (208) 882-9246.
9. Complete the Federal Express air bill and place it on the outside of the shipping container.

After each shipment, please notify Linh Nguyen, PhD (linguyen@exelixis.com), Jennifer Zimmer, PhD (jzimmer@alturasanalytics.com) at Alturas Ajalytics, and the NF Consortium Operations Center representative, Lynn Merritt, RN (nfcop@uab.edu).

Shipping Instructions: Samples will be shipped on dry ice **Monday thru Thursday by Federal Express.**

Ship samples to:
Alturas Analytics, Inc.
Attn: Jennifer Zimmer, PhD
Executive Laboratory Manager

1324 Alturas Dr.
Moscow, ID 83843
Phone: (208) 883-3400
Fax: (208) 882-9246
Email: jzimmer@alturasanalytics.com

** NOTE: Samples should be stored in -70°C freezer until the C1D28 (for Cohort A) and C4D1 (for Cohort B),and shipped as a batch per subject.

Cohort A: Protocol XL184-IST-014 PK Plasma Samples Shipping Log Relative to Dosing Time

Site Number:				**Site Name:**			
Subject ID:							**Comments : (Please note any discrepancies)**
Visit	**PK Sample Shipped**			**Not Done**	**Date Collected (dd mmm yyyy)**	**Time (24-h clock)**	
	Nominal Time Relative to Dosing Hour	**Plasma Sample**					
		Primary	**Back up**				
Cycle 1, Day 1 (C1D1)	0 (pre-dose) 4 hours post-dose	❑ ❑	❑ ❑	❑ ❑		_____:__ ___ _____:__ ___	
Cycle 1, Day 15 (C1D15)	0 (pre-dose) 4 hours post-dose	❑ ❑	❑ ❑	❑ ❑		_____:__ ___ _____:__ ___	
Cycle 1, Day 28 (C1D28)	0 (pre-dose) 4 hours post-dose	❑ ❑	❑ ❑	❑ ❑		_____:__ ___ _____:__ ___	

Shipping Prepared by: _____ Date Shipped: _____

Courier Used: _____ Tracking No. _____

Fax to the attention of Dr. Jennifer Zimmer at Alturas at Fax: (208) 882-9246.

Cohort B: Protocol XL184-IST-014 PK Plasma Samples Shipping Log Relative to Dosing Time

Site Number:				**Site Name:**			
Subject ID:							**Comments : (Please note any discrepancies)**
Visit	**PK Sample Shipped**			**Not Done**	**Date Collected (dd mmm yyyy)**	**Time (24-h clock)**	
	Nominal Time Relative to Dosing Hour	**Plasma Sample**					
		Primary	**Backup**				
Cycle 1, Day 1 (C1D1)	0 (pre-dose)	☐☐	☐☐	☐☐		_____: _____	
Cycle 2, Day 1 (C2D1)	0 (pre-dose)	☐☐	☐☐	☐☐		_____: _____	
Cycle 3, Day 1 (C3D1)	0 (pre-dose)	☐☐	☐☐	☐☐		_____: _____	
Cycle 4, Day 1 (C4D1)	0 (pre-dose)	☐☐	☐☐	☐☐		_____: _____	

Shipping Prepared by: _____ Date Shipped: _____

Courier Used: _____ Tracking No. _____

Fax to the attention of Dr. Jennifer Zimmer at Alturas at Fax: (208) 882-9246.

APPENDIX VII: CONSORTIUM QOL AND PAIN MEASURES

Below is a description of the QOL and pain measures to be administered in this protocol organized by the domain that the questionnaire assesses.

SUBJECTS ≥ 16 YEARS:

NF1 Disease Specific QOL Measure

The Adult PedsQL™ NF1 Module is a 74-item a self-report instrument to assesses NF1 disease-specific quality of life (QOL) in adults, ages 21 years and older. It is comprised of 16 scales: 1) Physical functioning (8 items), 2) Emotional functioning (5 items), 3) Social functioning (3 items), 4) Cognitive functioning (5 items), 5) Communication (3 items), 6) Worry (7 items), 7) Perceived physical appearance (3 items), 8) Pain and Hurt (3 items), 9) Paresthesias (2 items), 10) Skin irritation (5 items), 11) Sensation (4 items), 12) Movement and Balance (4 items), 13) Fatigue (3 items), 14) Daily activities (12 items), 15) Treatment anxiety (4 items) and 16) Sexual functioning (3 items) (Nutakki et al., submitted; N. Swigonski, personal communication, September 26, 2012).

The Teen PedsQL™ NF1 Module is a 75-item self-report for adolescents and young adults, ages 14 to 20 years of age, which includes 16 scales: 1) Physical functioning (8 items), 2) Emotional functioning (5 items), 3) Social functioning (3 items), 4) Cognitive functioning (7 items), 5) Communication (3 items), 6) Worry (6 items), 7) Perceived physical appearance (3 items), 8) Pain & Hurt (3 items), 9) Paresthesias (2 items), 10) Skin irritation (5 items), 11) Sensation (4 items), 12) Movement & Balance (4 items), 13) Fatigue (3 items), 14) Daily activities (12 items), 15) Treatment anxiety (4 items) and 16) School Activities (3 items).

The PedsQL™ NF1 Module format, instructions, and Likert response scale are similar to the PedsQL™ 4.0 Generic Core Scales and other PedsQL™ Disease-Specific Modules. The instructions ask how much of a problem each item has been during the past one month. A 5-point response scale is used for all items in the three versions of the instrument (0= never a problem, 1= almost never a problem, 2= sometimes a problem, 3= often a problem, 4= almost always a problem). Items are reverse scored and linearly transformed to a scale of 0-100 similar to PedsQL™ 4.0 Generic Core Scales (0= 100, 1= 75, 2= 50, 3=25, 4=0). Higher scores indicate better HRQOL and fewer symptoms or problems. The total scale score is computed as the sum of all items on the PedsQL™ NF1 Module divided by the number of items answered (this accounts for missing data). Subscale scores are computed as the sum of the items divided by the number of items that were answered in that scale. If more than 50% of the items in the scale are missing, the scale score is not computed.

Feasibility, measured by the percentage of missing responses, was 4.8 % for all scales on the adult version of the PedsQL™ NF1 Module. Internal consistency reliability for the Total Scale score (alpha =0.97) and Scale reliabilities ranging from 0.72 to 0.96 were acceptable for group comparisons. The PedsQL™ NF1 module distinguished between NF1 adults with excellent to very good, good, and fair to poor health status. Thus, preliminary data demonstrates the initial feasibility, reliability and validity of the PedsQL™ NF1

module in adult subjects (Nutakki et al., personal communication). The preliminary data in a small sample of adolescents also looks promising with good feasibility (percentage of missing responses was 8.9%) and a total scale reliability of 0.96 (N. Swigonski, personal communication, October 10, 2012).

Pain Measures

1. Pain Intensity

The Numerical Rating Scale-11 (NRS-11) is a self-report segmented 11-point numeric scale that assesses pain intensity[22]. It consists of a horizontal line with 0 representing "no pain" at the right end of the line and 10 representing "worst pain you can imagine" at the left end. Subjects are asked to circle the one number from 0 to 10 that best describes their "most important tumor pain" and 2) their "overall tumor pain" at its worst during the past week. It takes less than 1 minute to complete. The NRS-11 is recommended as a core outcome measure of pain intensity for clinical trials[21].

2. Pain Interference

The Brief Pain Inventory (BPI)—Pain Interference Scale is a 7-item self-report questionnaire that measures the extent to which pain interferes with daily functioning[20]. Subjects are asked to indicate how much pain interfered with various activities (general activity, mood, walking, normal work, relations with other people, sleep, and enjoyment of life) in the past week, with scores ranging from 0 (does not interfere) to 10 (completely interferes). A total score is obtained by taking the mean of the scores for all 7 items; thus, the total pain interference score can range from 0 to 7. This scale takes less than 2 minutes to complete. These items are recommended to assess pain interference in clinical trials[21].

Background Information

To allow for more meaningful analysis of the QOL data, the participant (for subjects $\geq$ 16 years) will complete a background information form at study entry and each subsequent QOL evaluation. This form will collect general information such as the subject's level of education, work status, psychiatric diagnoses, and pain medications, as well as the perceived visibility of NF1 tumors and severity of NF1 symptoms.

Administration Guidelines

These QOL and pain measures should be completed pre-treatment, after cycle 4 $\pm$2 weeks, 8 $\pm$2 weeks, 12 $\pm$2 weeks, 18 $\pm$2 weeks, and 24 $\pm$2 weeks. When administering these forms, review the instructions with the subjects and check to make sure they answered all the items. If subjects have difficulty reading, it is permissible to read the items to them, but the subjects should answer the items themselves. Completed forms should be sent (fax or mail copies) to the NF Consortium Operations Center within 2 weeks of completion. For any questions regarding the QOL/pain assessment please contact: Pam Wolters at woltersp@mail.nih.gov.

If subjects are 21 years old at study entry, they should be administered the Adult PedsQL NF1 Module. If subjects are 16 to 20 years old at study entry, they should be administered the Teen PedsQL NF1 Module. However, if subjects turn 21 years old during the study,

they should continue to be administered the Teen version of this scale that they started at study entry.
All subjects should complete the same self-report pain intensity and pain interference measures and background form.

Please see section 9 for a table listing the self-report QOL and pain measures to be completed by the subject.

NF1 QOL BACKGROUND INFORMATION SHEET

Participant's Study ID:_____
Course Number:_____

NF1 QOL Background Information Sheet
(For study participants to complete)

Today's Date:_____Date of Birth:_____Gender: M F Race:_____

Education: Highest grade level in school completed (1 – 12): _____
years of college completed (1 – 4): _____
years of graduate/professional school completed: _____

Your past school performance generally was: ☐above average ☐average ☐below average
Did you receive special education services (like resource room, extended time)? ☐yes ☐no ☐don't know

Currently, are you in school (enrolled in high school, college, vocational or graduate school, or taking classes)?
☐ yes ☐ no If yes, please specify what type of school:_____
Your current school performance generally is: ☐above average ☐average ☐below average
Do you currently receive special education services (like resource room, extended time)?
☐ yes ☐ no ☐ don't know

Work: Are you currently working? ☐yes ☐no If yes, the job is: ☐ part time ☐ full time
Please specify your job:_____

Learning/Psychiatric Diagnosis: Have you ever been diagnosed by a doctor or other health professional with any of the following? (Check an answer for *each* one).

Attention deficit/hyperactivity disorder..... ☐ yes ☐ no ☐ don't know
Learning disability (specify:_____) ☐ yes ☐ no ☐ don't know
Depression..... ☐ yes ☐ no ☐ don't know
Anxiety..... ☐ yes ☐ no ☐ don't know
Other (specify: _____) ☐ yes ☐ no ☐ don't know

Pain Medication: Are you taking any medication for pain on a regular basis? ☐ yes ☐ no
If yes, what kind of pain medication: ☐ over the counter (like Motrin or Tylenol) ☐ prescription ☐ both

Visibility of tumor(s): When dressed, are your plexiform neurofibroma tumor(s) visible?
(Please check *one*).

- ☐ mild: No visible tumor(s) outside of the normal clothing areas, and gait and posture appear normal when casually observed by others.
- ☐ moderate: Tumor(s) is visible on the neck, face, or hands, or other areas not typically covered by clothes, and/or gait or posture is somewhat affected.
- ☐ severe: Large tumor(s) is visible on the neck, face or hands, or other areas not typically covered by clothes and/or gait or posture is severely affected.

Severity of NF-1 symptoms: How would you rate the symptoms of NF-1 that you experience?
(Please check *one*)

- ☐ mild: Symptoms rarely affect physical well-being, daily functioning, or social life, such as neurofibroma(s) that are not visible and do not affect posture or gait noticeably, transient or mild pain that can be controlled, and/or mild learning disorders that generally do not affect activities of daily living.
- ☐ moderate: Symptoms moderately compromise daily functioning but are not severely disabling, such as external or internal neurofibroma(s), recurrent pain, problems with gait, posture, or vision, and/or learning disorders that may need intervention and somewhat affect activities of daily living.
- ☐ severe: Symptoms significantly impact daily functioning, such as large internal or external neurofibroma(s) or other serious NF-1 tumors, significant pain that is not controlled, severe problems with gait, posture, or vision, and/or severe learning disorders that require intervention and greatly affect activities of daily living.

PAIN QUESTIONNAIRE

Study ID:_____ 1
Protocol: NF105 Peds Cabo
Course Number:_____
Date:_____

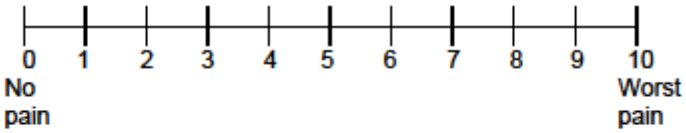
Child/Adolescent Pain Questionnaires
(Self-report form for ages 8 – 15 years)

Numeric Rating Scale – Pain Intensity

1. Please pick your most important tumor pain. We will ask you to tell us about that same tumor pain each time you fill out this form.

Where on your body is that tumor pain?_____.

Please circle the one number that best describes that tumor pain at its **worst** during the past 7 days.

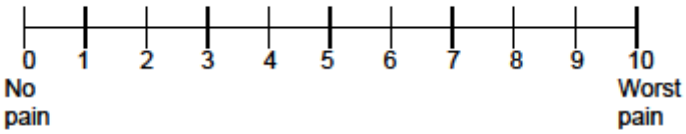


2. The doctors have picked the plexiform neurofibroma tumor in your _____ to measure for this study. We call this the "target tumor."

Is this the same tumor as the one you picked in the 1st question? ☐ Yes ☐ No

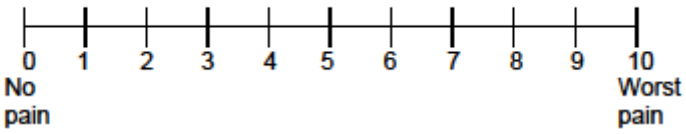
If yes, skip this question and continue to question #3.

If no, please circle the one number that best describes the pain from your target tumor at its **worst** during the past 7 days.



3. Do you have other kinds of pain besides tumor pain (for example, headaches or back pain)?
☐ Yes ☐ No

If yes, please circle the one number that best describes your other kinds of pain at their **worst** during the past 7 days.



QOL INSTRUMENT (TEEN REPORT)
For teens and young adults (16 to 20 years old) with NF-1

DIRECTIONS

Teens with neurofibromas sometimes have special problems. Please tell us how much of a problem each one has been for you during the **past ONE month** by choosing the appropriate options:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, take your best guess.
Thank you for your help!

Participant's Study ID: _____ Course Number:_____
Protocol:_____ Visit Date:_____

Please select which of the following describes you the best:

- ○ I am a teen or young adult (14 to 20 years old) with Neurofibromatosis Type 1 (NF-1)
- ○ Other, please specify _____

How old are you? (in years) _____

Do you have plexiform neurofibromas?

- ○ Yes
- ○ No
- ○ Don't know

If yes, on a scale of 0 to 10 (where 0 is plexiform neurofibromas have no impact to 10 where plexiform neurofibromas have a huge impact), please rate the impact of your plexiform neurofibromas on your day-to-day life. _____

In general, how would you rate your health?

- ○ Excellent
- ○ Very Good
- ○ Good
- ○ Fair
- ○ Poor

How many times did you visit the doctor for your NF-1 in the past ONE year? _____
On average, how many different medications do you take for your NF-1 in a day? _____

Participant's Study ID: _____ Course Number: _____
Protocol: _____ Visit Date: _____

*In the past **ONE month**, how much of a **problem** has this been for you...*

PHYSICAL FUNCTIONING *(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Having headaches	0	1	2	3	4
2. Feeling physically weak	0	1	2	3	4
3. Walking more than one block	0	1	2	3	4
4. Climbing stairs	0	1	2	3	4
5. Running	0	1	2	3	4
6. Doing a sports activity or exercise	0	1	2	3	4
7. Lifting something heavy	0	1	2	3	4
8. Doing chores around the house	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling anxious	0	1	2	3	4
2. Feeling sad	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Feeling frustrated	0	1	2	3	4
5. Feeling helpless or hopeless	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling isolated from others	0	1	2	3	4
2. Getting support from others	0	1	2	3	4
3. Having enough energy for social activities	0	1	2	3	4

COGNITIVE FUNCTIONING *(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Keeping attention on things	0	1	2	3	4
2. Remembering what people tell you	0	1	2	3	4
3. Remembering what you just heard or read	0	1	2	3	4
4. Thinking quickly	0	1	2	3	4
5. Solving math problems	0	1	2	3	4
6. Writing school papers or reports	0	1	2	3	4
7. Remembering what you were just thinking	0	1	2	3	4

Participant's Study ID: _____ Course Number: _____
Protocol: _____ Visit Date: _____

COMMUNICATION ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Telling the doctors and nurses how you feel	0	1	2	3	4
2. Asking the doctors and nurses questions	0	1	2	3	4
3. Talking with others about your disorder	0	1	2	3	4

WORRY ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Worrying about neurofibromas	0	1	2	3	4
2. Worrying about side effects from medical treatments	0	1	2	3	4
3. Worrying about whether or not medical treatments are working	0	1	2	3	4
4. Worrying that neurofibromas will grow bigger or reoccur	0	1	2	3	4
5. Worrying about my future or the risk of having children with Neurofibromatosis Type 1	0	1	2	3	4
6. Worrying about the risk of other health related issues associated with Neurofibromatosis Type 1	0	1	2	3	4

PERCEIVED PHYSICAL APPEARANCE ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling that I am not good looking	0	1	2	3	4
2. Not wanting other people to see my neurofibromas	0	1	2	3	4
3. Being embarrassed about others seeing my body	0	1	2	3	4

PAIN AND HURT ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Aching or hurting	0	1	2	3	4
2. Aching or hurting a lot	0	1	2	3	4
3. Not sleeping because of pain	0	1	2	3	4

PARESTHESIAS ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. A burning sensation in some part of my body	0	1	2	3	4
2. A tingling sensation in some part of my body	0	1	2	3	4

Participant's Study ID: _____ Course Number:_____
Protocol:_____ Visit Date:_____

SKIN IRRITATION *(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Itching	0	1	2	3	4
2. Itching a lot	0	1	2	3	4
3. Getting a skin rash when exposed to sun	0	1	2	3	4
4. Tolerating temperature changes	0	1	2	3	4
5. Rough skin	0	1	2	3	4

SENSATION *(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Vision in one or both eyes	0	1	2	3	4
2. Seeing well enough with glasses or contact lenses	0	1	2	3	4
3. Hearing in one or both ears	0	1	2	3	4
4. Speech	0	1	2	3	4

MOVEMENT AND BALANCE *(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Bending my body	0	1	2	3	4
2. Moving one or both legs	0	1	2	3	4
3. Using or moving one or both arms	0	1	2	3	4
4. Keeping balance when sitting/standing	0	1	2	3	4

SCHOOL ACTVITIES *(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Writing or drawing with a pen or pencil	0	1	2	3	4
2. Carrying school books	0	1	2	3	4
3. Using a mouse or keyboard on the computer	0	1	2	3	4

DAILY ACTVITIES *(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Putting on shoes	0	1	2	3	4
2. Buttoning my shirt	0	1	2	3	4
3. Combing my hair	0	1	2	3	4
4. Getting into the bathroom to use the toilet	0	1	2	3	4
5. Undressing to use the toilet	0	1	2	3	4
6. Getting in and out of bathtub or shower	0	1	2	3	4
7. Brushing my teeth	0	1	2	3	4
8. Eating with a fork and knife	0	1	2	3	4
9. Using a phone	0	1	2	3	4
10. Shopping	0	1	2	3	4
11. Managing money	0	1	2	3	4
12. Driving	0	1	2	3	4

QOL INSTRUMENT (TEEN REPORT): 16 to 20 years old

Participant's Study ID: _____ Course Number:_____
Protocol:_____ Visit Date:_____

FATIGUE *(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling tired	0	1	2	3	4
2. Resting a lot	0	1	2	3	4
3. Having enough energy to do things that I like to do	0	1	2	3	4

TREATMENT ANXIETY*(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting scared about going to the doctor	0	1	2	3	4
2. Getting scared about going to the hospital	0	1	2	3	4
3. Being responsible for my medicines or therapy	0	1	2	3	4
4. Managing my Neurofibromatosis Type 1	0	1	2	3	4

Please write any comments that you have about how NF-1 affects your health and well-being. Please write any comments about the survey and whether or not it captures how NF-1 affects people's health and well-being.

QOL INSTRUMENT (ADULT SURVEY)
For adults (≥ 21 years old) with NF-1

DIRECTIONS

This survey is for ADULTS with NF 1. Neurofibromatosis type 1 sometimes causes special problems. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not know an answer, take your best guess.
Thank you for your help!

Participant's Study ID: _____ Course Number:_____
Protocol:_____ Visit Date:_____

Please select which of the following describes you the best (you can choose more than one):

- ○ I am an adult with Neurofibromatosis Type 1 (NF-1)
- ○ I am a professional who treats people with NF-1
- ○ I am a friend or family member of a person with NF-1
- ○ Other, please specify _____

How old are you? (in years) _____

Do you have plexiform neurofibromas?

- ○ Yes
- ○ No
- ○ Don't know

If yes, on a scale of 0 to 10 (where 0 is plexiform neurofibromas have no impact to 10 where plexiform neurofibromas have a huge impact), please rate the impact of your plexiform neurofibromas on your day-to-day life. _____

In general, how would you rate your health?

- ○ Excellent
- ○ Very good
- ○ Good
- ○ Fair
- ○ Poor

How many times did you visit the doctor for your NF-1 in the past ONE year? _____

On average, how many different medications do you take for your NF-1 in a day? _____

Participant's Study ID: _____ Course Number:_____
Protocol:_____ Visit Date:_____

*In the past **ONE month**, how much of a **problem** has this been for you...*

PHYSICAL FUNCTIONING ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling physically weak	0	1	2	3	4
2. Walking more than one block	0	1	2	3	4
3. Climbing stairs	0	1	2	3	4
4. Running	0	1	2	3	4
5. Doing a sports activity or exercise	0	1	2	3	4
6. Lifting something heavy	0	1	2	3	4
7. Doing chores around the house	0	1	2	3	4

EMOTIONAL FUNCTIONING ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling anxious	0	1	2	3	4
2. Feeling sad	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Feeling frustrated	0	1	2	3	4
5. Feeling helpless or hopeless	0	1	2	3	4

SOCIAL FUNCTIONING ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting support from others	0	1	2	3	4
2. Having enough energy for social activities	0	1	2	3	4

COGNITIVE FUNCTIONING ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Keeping attention on things	0	1	2	3	4
2. Remembering what people tell you	0	1	2	3	4
3. Remembering what you just heard/read	0	1	2	3	4
4. Thinking quickly	0	1	2	3	4
5. Remembering what you were just thinking	0	1	2	3	4

COMMUNICATION ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Telling the doctors and nurses how you feel	0	1	2	3	4
2. Asking the doctors and nurses questions	0	1	2	3	4
3. Talking with others about your disorder	0	1	2	3	4

Participant's Study ID: _____ Course Number:_____

QOL INSTRUMENT (ADULT REPORT): ≥ 21 years old

Protocol:_____ Visit Date:_____

WORRY ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Worrying about my neurofibromas	0	1	2	3	4
2. Worrying about side effects from medical treatments	0	1	2	3	4
3. Worrying about whether or not medical treatments are working	0	1	2	3	4
4. Worrying that neurofibromas will grow bigger or reoccur	0	1	2	3	4
5. Worrying about my future or the risk of having children with Neurofibromatosis Type 1	0	1	2	3	4
6. Worrying about the risk of other health related issues associated with Neurofibromatosis Type 1	0	1	2	3	4

PERCEIVED PHYSICAL APPEARANCE ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling that I am not good looking	0	1	2	3	4
2. Not wanting other people to see my neurofibromas	0	1	2	3	4
3. Being embarrassed about others seeing my body	0	1	2	3	4

PAIN AND HURT ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Aching or hurting	0	1	2	3	4
2. Aching or hurting a lot	0	1	2	3	4
3. Not sleeping because of pain	0	1	2	3	4

PARESTHESIAS ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. A burning sensation in some part of my body	0	1	2	3	4
2. A tingling sensation in some part of my body	0	1	2	3	4

SKIN IRRITATION ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Itching	0	1	2	3	4
2. Itching a lot	0	1	2	3	4
3. Getting a skin rash when exposed to sun	0	1	2	3	4
4. Tolerating temperature changes	0	1	2	3	4
5. Rough skin	0	1	2	3	4

Participant's Study ID: _____ Course Number: _____
Protocol: _____ Visit Date: _____

SENSATION ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Vision in one or both eyes	0	1	2	3	4
2. Seeing well enough with glasses or contact lenses	0	1	2	3	4
3. Hearing in one or both ears	0	1	2	3	4
4. Speech	0	1	2	3	4

MOVEMENT AND BALANCE ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Bending my body	0	1	2	3	4
2. Moving one or both legs	0	1	2	3	4
3. Using or moving one or both arms	0	1	2	3	4
4. Keeping balance when sitting or standing	0	1	2	3	4

DAILY ACTVITIES ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Putting on shoes	0	1	2	3	4
2. Buttoning my shirt	0	1	2	3	4
3. Combing my hair	0	1	2	3	4
4. Getting into the bathroom to use the toilet	0	1	2	3	4
5. Undressing to use the toilet	0	1	2	3	4
6. Getting in and out of bathtub or shower	0	1	2	3	4
7. Brushing my teeth	0	1	2	3	4
8. Eating with a fork and knife	0	1	2	3	4
9. Using a phone	0	1	2	3	4
10. Shopping	0	1	2	3	4
11. Managing money	0	1	2	3	4
12. Driving	0	1	2	3	4

FATIGUE ***(problems with...)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Feeling tired	0	1	2	3	4
2. Resting a lot	0	1	2	3	4
3. Having enough energy to do things that I like to do	0	1	2	3	4

TREATMENT ANXIETY*(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Getting scared about going to the doctor	0	1	2	3	4

QOL INSTRUMENT (ADULT REPORT): ≥ 21 years old

2. Getting scared about going to the hospital	0	1	2	3	4
3. Being responsible for my medicines or therapy	0	1	2	3	4

Participant's Study ID: _____ Course Number:_____
Protocol:_____ Visit Date:_____

SEXUAL FUNCTIONING *(problems with...)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**	**Not Applicable**
1. Fatigue or lack of energy affecting your satisfaction with your sex life	0	1	2	3	4	5
2. Pain affecting your satisfaction with your sex life	0	1	2	3	4	5
3. Ability to have children with a fertile partner	0	1	2	3	4	5

Please write any comments that you have about how NF-1 affects your health and well-being. Please write any comments about the survey and whether or not it captures how NF-1 affects people's health and well-being.

SUBJECTS 3 - 15 YEARS:

I. QOL and Pain Measures for Subjects 3 – 15 years

In participants with plexiform neurofibromas (PN) in all locations, this study will assess general health-related qualify of life (QOL) and pain (pain intensity and pain interference) using patient-reported outcomes (PROs) as well as global impression of change as described below.

Description of QOL and Pain Measures

General Health-Related Quality of Life
Pediatric Quality of Life Inventory (PedsQL; Varni, 2001): The PedsQL 4.0 Generic Core Scales (Acute Form assessing the past 7 days) are multidimensional child *self-report* and *parent proxy report* scales to assess health-related quality of life (QOL) in children, adolescents, and young adults ages 2 – 25 years. It is a brief standardized pediatric QOL scale with good reliability and validity, which includes both generic and disease specific modules. It consists of a 23-item core measure of global QOL that has four subscales: physical functioning, emotional functioning, social functioning, and school functioning. The domain of physical functioning will be used as a specific secondary outcome measure for this study, especially the parent proxy for younger children as it assesses children under 6 years of age.
There are different forms for parents of patient's ages 2 – 18 years (toddler: 2 – 4; young child: 5 – 7; child: 8 – 12; adolescent: 13 – 18) and parallel self-report forms for patient's ages 5 – 25 years (young child: 5 – 7; child: 8 – 12; adolescent: 13 – 18; young adult: 18 – 25). It takes approximately 5 - 10 minutes to complete. For this study, children from 8 to 15 years of age will complete *self-report* measures of the PedsQL, and parents or legal guardians of children from 3 to 15 years of age will complete the *parent proxy report* measures of the PedsQL.

Pain Intensity
The Numerical Rating Scale-11 (NRS-11) is a *self-report* segmented 11-point numeric scale that assesses pain severity (Hawker et al., 2011). It consists of a horizontal line with 0 representing "no pain" at the right end of the line and 10 representing "worst pain you can imagine" at the left end. Patients are asked to circle the one number from 0 to 10 that best describes their worst pain over the past week for the following: 1) most important tumor pain chosen by the participant, 2) target tumor pain and 2) other pain. It takes less than 5 minute to complete. The NRS-11 is recommended as a core outcome *self-report* measure of pain intensity for clinical trials (Dworkin et al., 2005) in children with NF1 (Wolters, et al., 2013). Children, ages 8 to 15 years, will complete self-report measures of the NRS-11 for this study.

Pain Interference
The Pain Interference Index (PII) is a 6-item measure that assesses the degree to which pain has interfered with daily activities in the past week. This measure was developed in Sweden and validated in Swedish with a group of children and adolescents with longstanding idiopathic pain (Wicksell, Melin, Lekander, & Olsson, 2009). The author (R. Wicksell) translated the measure into English, and members of the Neurobehavioral Group (S. Peron and P. Wolters) worked with the Swedish group to modify the wording to make it more readable and to shorten the time frame to one week, and we adapted it to create a parallel parent version. Dr. Wicksell and the Swedish research group are supportive of our efforts to validate the self-report and parent versions of the PII in NF1. Results of our validation studies in children with NF1 and their parents indicate that the internal consistency and construct validity of the PII are good. These data support the use of the PII to assess pain interference in youth with NF1 and PNs (Martin et al., submitted).

For this study, children from 8 to 15 years of age will complete *self-report* PII, and parents or the legal guardian of children from 5 to 15 years of age will complete the *parent proxy report* PII.

Global Impression of Change
The patient Global Impression of Change (GIC) Scale evaluates the clinical significance of changes in pain intensity or other PN morbidities. We will administer an adapted version of the *self-report* GIC Scale at the **follow-up** PRO evaluations only (it should not be given pre-study because it assesses change from baseline). A parallel *parent proxy report* form also was developed. On the adapted GIC, patients (and their parents separately) will give their overall impression of change in level of the child's 1) tumor pain, 2) other pain, and 3) PN morbidity from before initiation of the study drug to the current evaluation point. This global measure of change will be administered to children ≥8 years and for parents of children ≥ 5 years of age at each PRO assessment. The GIC Scale has been used in several research studies on chronic pain in adults and more recently children (Arnold et al., 2011; Mohammad et al., 2014). It has been recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for clinical trials involving chronic pain (Dworkin et al., 2005; McGrath et al., 2008).

Global Impression of Change (in PN morbidities)
We also adapted the GIC for clinicians to rate change in PN morbidities for each participant from before the initiation of cabozantinib to the current evaluation point based on their history and physical examination. This global measure of change will be completed for participants of all ages by a clinician (familiar with the participant).

Pediatric Background Information
The Pediatric QOL Background Form should be completed by the parents/primary caregivers of all patients ages from 3-15 years **at each evaluation** to document information about demographics, use of pain medication, and NF1 disease severity. These data will be used to better interpret the PRO data.

Administration of QOL and Pain Measures
• Participants will complete the PRO measures at baseline (prior to starting treatment) and then after cycle 4 ±2 weeks, 8 ±2 weeks, 12 ±2 weeks, 18 ±2 weeks, and 24 ±2 weeks, except for the Global Impression of Change scale that will only be administered at the follow-up evaluations because it assesses change from baseline.

Self-report
• Children, 8 to 15 years of age, will complete the self-report measures of the PedsQL, NRS-11, and PII at baseline and all follow-up evaluations. The GIC scale will be done only at the follow-up evaluations after the other measures have been completed.

Parent Proxy Report
• Parents (or the legal guardian) of children, 3 to 15 years of age, will complete the parent proxy measures of the PedsQL and a background form.

• Parents (or the legal guardian) of children, 5 to 15 years of age, also will complete the parent proxy measures of the PII. At the follow-up evaluations only, they will be administered the GIC scale, which is to be completed after the other measures have been done.

Clinician Report

• Clinicians will complete the Global Impression of Change of the morbidities at the follow-up evaluations only for pediatric participants of all ages (3-15 years).

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Wicksell RK, Melin L, Lekander M, Olsson GL. (2009). Evaluating the effectiveness of exposure and acceptance strategies to improve functioning and quality of life in longstanding pediatric pain - A randomized controlled trial. Pain, 141:248-257.

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ID: _____
DATE: _____
CYCLE #: _____

NF CONSORTIUM PEDIATRIC CABO TRIAL IN CHILDREN WITH NF1

PRO CHECKLIST and COVERSHEET
(3-7 years at study entry)

PATIENT	Comments/Notes re: PRO assessment:
**** NO self-report PROs are administered to patients who are 3-7 years at baseline or subsequent visits (and they do not complete them even if they turn 8 since they were not done at baseline).**	

PARENT/GUARDIAN

**** PROs administered to all parents/ guardians:**

____ Pediatric Background Information Sheet (for all ages)

Pain Interference

____ Parent Proxy Report: Pain Interference Index (parents of ≥5 years only)

General QOL

____ Parent Proxy Report: PedsQL Acute Form (Toddler 2-4 years OR Young Child 5-7 years depending on age at baseline; move to the 8-12 parent form if the child turns 8 during the study)

****Administer after all other required PROs at f/up visits only (not baseline):**

Global Change Scale

____ Global Impression of Change Scale (parents of ≥5 years only)

- Select the correct PRO measures to administer and check off the PROs completed on the above list.
- The parent PRO measures should be administered to the same parent throughout the study.
- Administer the above measures at each of the required visits per protocol: Pre-treatment (baseline), after cycle 4 ±2 weeks, 8 ±2 weeks, 12 ±2 weeks, 18 ±2 weeks, and 24 ±2 weeks.

Post Assessment:	
__ Check all forms for completion __ PROs administered & checked by:_____(name) __ If PROs not completed, please circle reason code to the right→ __ Send PRO checklist/coversheet and forms to the NF Consortium Operations Center __Was an interpreter used to administer the forms to the participant and/or parent? __No __Yes If yes, which language:_____ __Which parent/primary caregiver completed the forms: __Mother __Father __Other, specify:_____	If the participant did not complete the PRO evaluation please circle reason(s) below: 1=Missed appointment 2=Left clinic early 3=Acute illness 4=Refused 5=Did not understand d/t cognitive impairments 6=Primary language not English 7=Research staff missed 8=Other (please specify:_____)

ID: _____
DATE: _____
CYCLE #: _____

NF CONSORTIUM PEDIATRIC CABO TRIAL IN CHILDREN WITH NF1

PRO CHECKLIST and COVERSHEET
(8-15 years at study entry)

PATIENT	**PARENT/GUARDIAN**
**** PROs administered to all patients:**	**** PROs administered to all parents/ guardians:**
Pain Intensity	
_____ Patient Self Report: Numeric Rating Scale-11 (ages ≥8 years)	____ Pediatric Background Information Sheet (all ages)
Pain Interference	***Pain Interference***
_____ Patient Self Report: Pain Interference Index (ages ≥8 years)	____ Parent Proxy Report: Pain Interference Index (≥8 years)
General QOL	***General QOL***
_____ Patient Self Report: PedsQL Acute Form (Child 8-12 OR Teen 13-18 years)	____ Parent Proxy Report: PedsQL Acute Form (Child 8-12 OR Teen 13-18 years)
*****Adminster after all other required PROs at f/up visits only (not baseline):**	*****Adminster after all other required PROs at f/up visits only (not baseline):**
Changes from baseline	***Changes from baseline***
____ Global Impression of Change Scale (ages ≥8 years)	____ Global Impression of Change Scale (parents of ≥8 years)

- Select the correct PRO measures to administer and check off the PROs completed on the above list.
- Write the physician-selected "target" tumor in the space provided on the NRS-11 at baseline and both the "target" tumor and self-selected tumor pain prior to administering it at the follow-up visits.
- The parent PRO measures should be administered to the same parent throughout the study, and the patient and parent should complete the measures separately
- Administer the above measures at each of the required visits per protocol: Pre-treatment (baseline), after cycle 4 ±2 weeks, 8 ±2 weeks, 12 ±2 weeks, 18 ±2 weeks, and 24 ±2 weeks.

Post Assessment:	
__ Check all forms for completion __ PROs administered & checked by:_____(name) __ If PROs not complete, please circle reason code to the right→ __ Send PRO checklist/coversheet and forms to the NF Consortium Operations Center __Was an interpreter used to administer the forms to the participant and/or parent? __No __Yes If yes, which language:_____ __Which parent/primary caregiver completed the forms: __Mother __Father __Other, specify:_____	If the participant did not complete the PRO evaluation please circle reason(s) below: 1=Missed appointment 2=Left clinic early 3=Acute illness 4=Refused 5=Did not understand d/t cognitive impairments 6=Primary language not English 7=Research staff missed 8=Other (please specify:_____)

Participant's study ID:_____ Course number:_____
Protocol: NF105 Peds Cabo Visit Date:_____

Pediatric NF1 PRO Background Information Sheet
(For parents or primary caregivers to complete)

Today's date:_____ Child's age:_____ Child's sex: M F

The same parent/primary caregiver needs to complete the parent questionnaires at each study visit, except for the demographic section (shaded), which only needs to be done once at the first visit. Please provide the initials of the parent/primary caregiver completing the form_____ and relationship to the child ☐ mother ☐ father ☐ other, please specify:_____

Demographics: What is the total number of years of education completed by the parents/primary caregivers?

	Parent 1	Parent 2
Write in the highest grade in school completed (from 1 – 12):	_____	_____
Write in the number of years of college completed (from 1 – 4):	_____	_____
Write in the number of years of graduate/professional school completed:	_____	_____

Relationship of child to primary caregiver: ☐biological ☐adopted ☐foster ☐extended family

Special Education or Psychiatric Diagnosis: Has your child ever been diagnosed by a doctor or other health professional with any of the following special education or psychiatric diagnoses?
(Please check *each* of the following yes or no).

Attention deficit/hyperactivity disorder	☐ yes ☐ no	Anxiety	☐ yes ☐ no
Learning disability (specify:_____)	☐ yes ☐ no	Other (specify: _____)	☐ yes ☐ no
Depression	☐ yes ☐ no		

Current Alternative or Special Educational Services: Do you home school your child (by choice)? ☐ yes ☐ no
Does your child receive any of the following services? (Please check *each* of the following yes or no).

Self-contained special education class	☐ yes ☐ no	Speech therapy	☐ yes ☐ no
Pull-out services/resource room	☐ yes ☐ no	Physical therapy	☐ yes ☐ no
Mainstream class with aide	☐ yes ☐ no	Occupational therapy	☐ yes ☐ no
Homebound schooling (e.g., due to medical reasons)	☐ yes ☐ no	Other: (specify:_____)	☐ yes ☐ no

School Performance: Your child's current overall school performance is:
☐Above average ☐Average ☐Below Average

If your child is too young for school, your child's overall development is:
☐Above average ☐Average ☐Below Average

Pain Medication: Is your child taking any medication for pain on a regular basis? ☐ yes ☐ no
If yes, what kind of pain medication: ☐ over the counter (like Motrin or Tylenol) ☐ prescription ☐ both

Visibility of tumor(s): When dressed, is your child's plexiform neurofibroma tumor(s) visible? (Please check *one*).

- ☐ mild: No visible tumor(s) outside of the normal clothing areas, and gait and posture appear normal when casually observed by others.
- ☐ moderate: Tumor(s) is visible on the neck, face, or hands, or other areas not typically covered by clothes, and/or gait or posture is somewhat affected.
- ☐ severe: Large tumor(s) is visible on the neck, face or hands, or other areas not typically covered by clothes and/or gait or posture is severely affected.

Severity of NF-1 symptoms: How would you rate the symptoms of NF-1 that your child experiences? (Please check *one*).

- ☐ mild: **Symptoms rarely affect physical daily functioning**, such as neurofibroma(s) that are not visible and do not affect posture or gait noticeably, transient or mild pain that can be controlled, and/or mild learning disorders that generally do not affect activities of daily living.
- ☐ moderate: **Symptoms moderately affect daily functioning** but are not severely disabling, such as external or internal neurofibroma(s), recurrent pain, problems with gait, posture, or vision, and/or learning disorders that may need intervention and somewhat affect activities of daily living.
- ☐ severe **Symptoms significantly impact daily functioning**, such as large internal or external neurofibroma(s) or other serious NF-1 tumors that affect function, significant pain that is not controlled, severe problems with gait, posture, or vision, and/or severe learning disorders that require intervention and greatly affect activities of daily living.

Study ID:_____ 1
Protocol: NF105 Peds Cabo
Course Number:_____
Date:_____

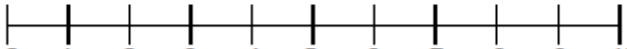
Child/Adolescent Pain Questionnaires
(Self-report form for ages 8 – 15 years)

Numeric Rating Scale – Pain Intensity

1. Please pick your most important tumor pain. We will ask you to tell us about that same tumor pain each time you fill out this form.

Where on your body is that tumor pain?_____.

Please circle the one number that best describes that tumor pain at its **worst** during the past 7 days.



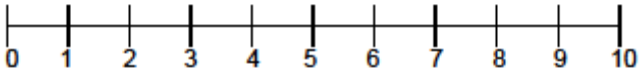
No pain — Worst pain

2. The doctors have picked the plexiform neurofibroma tumor in your _____ to measure for this study. We call this the "target tumor."

Is this the same tumor as the one you picked in the 1st question? ☐ Yes ☐ No

If yes, skip this question and continue to question #3.

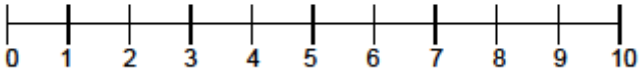
If no, please circle the one number that best describes the pain from your target tumor at its **worst** during the past 7 days.



No pain — Worst pain

3. Do you have other kinds of pain besides tumor pain (for example, headaches or back pain)?
☐ Yes ☐ No

If yes, please circle the one number that best describes your other kinds of pain at their **worst** during the past 7 days.



No pain — Worst pain

Study ID:_____
Protocol: NF105 Peds Cabo
Course Number:_____
Date:_____

Child/Adolescent Pain Questionnaires

(Self-report form for ages 8 – 15 years)

Pain Interference Index

Below you will find a list of questions about you and your tumor pain. Please answer each question by circling one number between 0 and 6.

We are asking about your **tumor pain** during the **past 7 days**.

In the past 7 days:

		Not at all			Some			Completely
1.	Has your tumor pain made it hard for you to pay attention (for example, do classwork, homework, read)?	0	1	2	3	4	5	6
2.	Has your tumor pain made it hard for you to do things outside of school (play/ free time activities)?	0	1	2	3	4	5	6
3.	Has your tumor pain made it hard for you to spend time with friends?	0	1	2	3	4	5	6
4.	Has your tumor pain affected your mood?	0	1	2	3	4	5	6
5.	Has your tumor pain made it hard for you to do physical activities (like run, walk up stairs, play sports, do chores)?	0	1	2	3	4	5	6
6.	Has your tumor pain made it hard for you to sleep?	0	1	2	3	4	5	6

Adapted by the Health Psychology and Neurobehavioral Research Group, NCI (06/30/17)

Study ID:_____
Protocol: NF105 Peds Cabo
Course Number:_____
Date:_____

Parent Pain Questionnaire

(Parent proxy report form for children ages 5 – 15 years)

Pain Interference Index

Below you will find a list of questions about your child. Please answer each question by circling one number between 0 and 6.

We are asking about your child's **tumor pain** during the **past 7 days**.

In the past 7 days:

		Not at all						Completely
1.	Has your child's tumor pain made it difficult for your child to pay attention (for example, do classwork, homework, read)?	0	1	2	3	4	5	6
2.	Has your child's tumor pain made it difficult for your child to do things outside of school (play/free time activities)?	0	1	2	3	4	5	6
3.	Has your child's tumor pain made it difficult for your child to spend time with friends?	0	1	2	3	4	5	6
4.	Has your child's tumor pain affected your child's mood?	0	1	2	3	4	5	6
5.	Has your child's tumor pain affected your child's ability to do physical activities (like run, walk up stairs, play sports, do chores)?	0	1	2	3	4	5	6
6.	Has your child's tumor pain affected your child's sleep?	0	1	2	3	4	5	6

Adapted by the Health Psychology and Neurobehavioral Research Group, NCI (06/30/17)

C3D Study ID:_____
Protocol: NF105 Peds Cabo
Course Number:_____
Date:_____

Child Global Impression of Change Scale
(For children ages ≥ 8 years)

1. Think about your tumor pain. Compared to before you started taking the medicine for this study, would you say your tumor pain is:

- ☐ 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. Now think about all the other kinds of pain you may have (not tumor pain). Compared to before you started taking the medicine for this study, would you say your other pain is:

- ☐ 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)

C3D Study ID:_____
Protocol: NF105 Peds Cabo
Course Number:_____
Date:_____

3. Think about your tumor-related problems other than pain (such as moving, vision, hearing, appearance, etc.). Compared to before the you started taking the medicine for this study, would you say your tumor-related problems 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 (related to these three questions):_____
_____
_____
_____
_____

C3D Study ID:_____
Protocol: NF105 Peds Cabo
Course Number:_____
Date:_____

Parent Proxy GIC Scale
(For parents of children ≥ 5 years)

1. Think about your child's tumor pain. Compared to before your child started taking the medicine for this study, would you say your child's tumor pain is:

- ☐ 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. Now think about all the other kinds of pain your child may have (not tumor pain). Compared to before your child started taking the medicine for this study, would you say your child's other pain is:

- ☐ 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)

Study ID:_____
Protocol: NF105 Peds Cabo
Course Number:_____
Date:_____

Clinician Observer Global Impression of Change Scale
(Completed at follow-up evaluations for all patients)

1. Think about the participant's PN-related morbidities specified at baseline. Compared to before the participant started taking the drug for this study, would you say the participant's morbidities 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 the changes you have noticed:_____
_____
_____
_____
_____

Initials of clinician completing form:_____

Study ID#: _____
Date: _____
Protocol: _____
Cycle: _____

PedsQL™

Pediatric Quality of Life Inventory
Acute Version

Version 4.0

PARENT REPORT for **TODDLERS** (ages **2-4**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

Study ID#: _____
Date: _____
Protocol/Cycle: _____

PedsQL 2

*In the past **7 days**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in active play or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Bathing	0	1	2	3	4
6. Helping to pick up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Playing with other children	0	1	2	3	4
2. Other kids not wanting to play with him or her	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

Please complete this section if your child attends school or daycare

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Doing the same school activities as peers	0	1	2	3	4
2. Missing school/daycare because of not feeling well	0	1	2	3	4
3. Missing school/daycare to go to the doctor or hospital	0	1	2	3	4

Study ID#: _____
Date: _____
Protocol: _____
Cycle: _____

PedsQL™

Pediatric Quality of Life Inventory
Acute Version

Version 4.0

PARENT REPORT for **YOUNG CHILDREN** (ages **5-7**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

Study ID#: _____
Date: _____
Protocol/Cycle: _____

PedsQL 2

*In the past **7 days**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores, like picking up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school activities	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

PedsQL 4.0 - Parent (5-7) Acute
03/00

Study ID#: _____
Date: _____
Protocol: _____
Cycle: _____

PedsQL™

Pediatric Quality of Life Inventory
Acute Version

Version 4.0

CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

Study ID#: _____
Date: _____
Protocol/Cycle: _____

PedsQL 2

*In the past **7 days**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

PedsQL 4.0 - (8-12) Acute
03/00

Study ID#: _____
Date: _____
Protocol: _____
Cycle: _____

PedsQL™
Pediatric Quality of Life Inventory
Acute Version

Version 4.0

PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

Study ID#: _____
Date: _____
Protocol/Cycle: _____

PedsQL 2

*In the past **7 days**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

PedsQL 4.0 - Parent (8-12) Acute
03/00

Study ID#: _____
Date: _____
Protocol: _____
Cycle: _____

PedsQL™

Pediatric Quality of Life Inventory

Acute Version

Version 4.0

TEEN REPORT (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

Study ID#: _____
Date: _____
Protocol/Cycle: _____

PedsQL 2

*In the past **7 days**, how much of a **problem** has this been for you …*

About My Health and Activities *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

About My Feelings *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

How I Get Along with Others *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

About School *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

Study ID#: _____
Date: _____
Protocol: _____
Cycle: _____

PedsQL™
Pediatric Quality of Life Inventory
Acute Version

Version 4.0

PARENT REPORT for **TEENS** (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your teen**. Please tell us **how much of a problem** each one has been for **your teen** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

Study ID#: _____
Date: _____
Protocol/Cycle: _____

PedsQL 2

*In the past **7 days**, how much of a **problem** has your teen had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other teens	0	1	2	3	4
2. Other teens not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teens	0	1	2	3	4
4. Not able to do things that other teens his or her age can do	0	1	2	3	4
5. Keeping up with other teens	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

PedsQL 4.0 - Parent (13-18) Acute 03/00

APPENDIX VIII: BLOOD PRESSURE NORMS

Blood pressure (BP) levels for MALES

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
≥17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Blood pressure (BP) levels for FEMALES

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
≥17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Blood pressure (BP) levels for <u>BOYS</u>

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
≥17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Blood pressure (BP) levels for GIRLS

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10t	25th	50th	75th	90th	95th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
≥17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

APPENDIX IX: MRI ELIGIBILITY FORM

This form must accompany all MRI studies sent to the NCI POB for review of target plexiform neurofibroma eligibility (i.e. whether it is measurable and amenable to volumetric analysis). Please mail the MRI on a CD along with this form to:

Eva Dombi, MD
NCI, POB
10 Center Drive
Building 10 CRC, Room 1-5750
Bethesda, MD 20892
Phone: 301-451-7023
E-mail: dombie@mail.nih.gov

PID#1: _____ Date of MRI: _____

Location of target plexiform: _____

From:
Name of Investigator: _____

Study Center: _____

Phone #: _____

Email Address: _____

From Eva Dombi, MD:

The target PN is measurable and amenable to volumetric analysis:

Yes:_____ No: _____

Comments: _____

APPENDIX X: SUGGESTED PROPHYLAXIS AND TREATMENT FOR PALMAR-PLANTAR ERYTHODYSESTHESIA SYNDROME (PPE)

These guidelines were developed by the company (Exelixis) based on their experience treating over 1000 patients. These guidelines are helpful in prevention and treatment.

Prophylaxis:

Ammonium lactate 12% cream BID to palms of hands and soles of feet.

Treatment: (to begin as soon as mild symptoms begin)

1. Urea 20% cream twice daily and
2. Clobetasol 0.05% cream once to twice daily

Management of Treatment-Emergent Hand-Foot Syndrome (PPES)

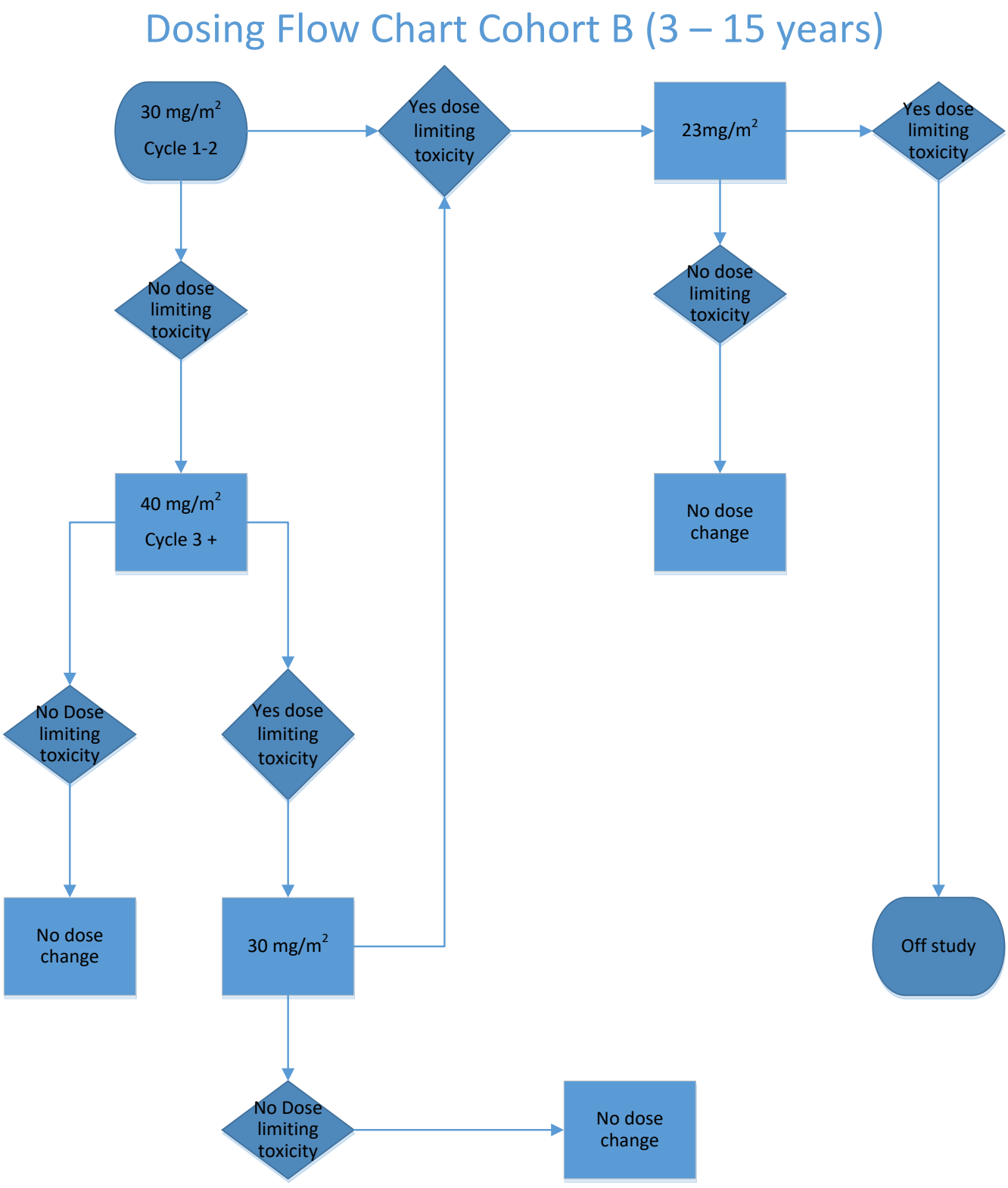
CTCAE v.4.0 Grade	Action To Be Taken
Grade 1	Study treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, study treatment should be reduced to the next lower dose level.[a] Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Study treatment may be continued if PPES is tolerated. Study treatment should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with clobetasol 0.05% cream twice daily AND analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. Discontinue subject from study treatment if PPES does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drug; PPES, palmar plantar erythrodysesthesia syndrome.

[a] Permitted dose levels are defined by individual protocols.

APPENDIX XI: CABOZANTINIB DOSING NOMOGRAM

23 mg/m2, Level -1	30 mg/m2, Level 1	40 mg/m2, Level 2	Dose/Schedule	Weekly Dose
0.34 – 0.43			20 mg M, W, F	60 mg
0.44 – 0.55	0.35 – 0.42		20 mg M, W, F, Sun	80 mg
0.56 – 0.68	0.43 – 0.52	0.33 – 0.39	20 mg M, W, H, Sat, Sun	100 mg
0.69 – 0.79	0.53 – 0.60	0.40 – 0.45	20 mg M, T, W, F, Sat, Sun	120 mg
0.80 - 0.96	0.61 – 0.73	0.46 – 0.55	20 mg Daily	140 mg
0.97 – 1.11	0.74 – 0.85	0.56 – 0.64	40 mg M, W, F, Sun	160 mg
1.12 – 1.36	0.86 – 1.04	0.65 – 0.78	40 mg M, W, H, Sat, Sun	200 mg
≥ 1.37	1.05 – 1.21	0.79 – 0.90	40 mg M, T, W, F, Sat, Sun	240 mg
	≥ 1.20	0.91 – 1.09	40 mg Daily	280 mg
		1.10 – 1.17	60 mg M, W, H, Sat, Sun	300 mg
		1.18 – 1.36	60 mg M, T, W, F, Sat, Sun	360 mg
		≥ 1.37	60 mg Daily	420 mg


Dosing Flow Chart Cohort B (3 – 15 years)
30 mg/m2
Cycle 1-2
Yes dose limiting toxicity
23mg/m2
Yes dose limiting toxicity
No dose limiting toxicity
No dose limiting toxicity
40 mg/m2
Cycle 3 +
No dose change
No Dose limiting toxicity
Yes dose limiting toxicity
No dose change
30 mg/m2
Off study
No Dose limiting toxicity
No dose change

APPENDIX XII: PLEXIFORM NEUROFIBROMA SYMPTOM CHECKLIST

To be completed by Patient if able, otherwise completed by the Parent/Guardian. To be completed by the same individual at each timepoint.

Testing should be performed pre-treatment, and then post cycles 4, 8, 12, 18, 24.

Select one:

Pre-treatment ☐ Post cycle 4 ☐ Post cycle 8 ☐ Post cycle 12 ☐

Post cycle 18 ☐ Post cycle 24 ☐ Other (Please specify): _____

For each item below, please check one box (unless otherwise indicated) to describe how much each of these has been a problem for you in the past two weeks:

1) Fatigue/feeling tired	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
2) Sleep problems	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
3) Less appetite (eating less)	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
4) More appetite (eating more)	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot

5) Headaches	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
6) Vision changes	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
7) Decreased hearing	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
8) Mouth Sores	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
9) Trouble swallowing	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
10) Choking	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
11) Snoring	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
12)Frequent awakenings at night	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot

13) Cough	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot

14) Wheezing	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
15) Difficulty breathing	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot

16) Chest pain	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
17) Palpitations/fluttering	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
18) Shortness of breath with activity	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
19) Shortness of breath at rest	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
20) Swelling in hands/feet	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot

21) Abdominal pain	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
22) Heartburn	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
23) Nausea	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
24) Vomiting	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
25) Diarrhea	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
26) Constipation	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
27) Stool incontinence	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot

28) Pain with urination	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
29) Increased urinary frequency/urgency	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
30)Difficulty beginning urination	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
31)Urinary incontinence	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot

32) Weakness	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot

If yes, where?					
33) Muscle pain	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
If yes, where?					

34) Dizziness	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
35) Numbness	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot
36) Tingling	❑ Not at all	❑ A little	❑ Some	❑ Pretty much	❑ A lot

COMPLETED BY: _____ DATE _____

APPENDIX XIII: PN LOCATION AND ASSOCIATED MORBIDITIES

INSTRUCTIONS:

To be completed by the Site PI prior to starting treatment

- Assess PN location(s) by clinical exam and imaging studies (target PN and up to 2 non target PN; fill out a separate form for each PN)
- List morbidities present using numbers below (see list)
- If no morbidity present, list potential morbidities based on PN site(s)

PN Location				**PN Associated Morbidities**		
	R	L	B/L	Pain (Y/N)	Present PN Morbidities (using numbers listed below)/ Comments	Potential Morbidities
Orbit						
Face						
Ear canal						
Tongue						
Anterior neck/upper airway						
Posterior neck (cervical paraspinal)						
Mediastinum						
Intra-thoracic						
Thoracic/paraspinal/chest wall						
Liver						
Abdominal						
Mesentery						
Posterior abdomen/pelvis (Lumbo-sacral plexus)						
Perineum/peri-rectal/bladder						

Upper arm (Brachial plexus)						
Forearm						
Hand						
Thigh/upper leg						
Lower leg						
Foot						
Other (please specify):						

Morbidities:			
1- Vision loss 2- Facial motor dysfunction 3- Auditory loss	4- Difficulty swallowing 5- Abnormal speech 6- Airway obstruction 7- Respiratory compromise	8- Bladder dysfunction 9- Bowel dysfunction 10- Motor weakness 11- Decreased range of motion	12- Sensory deficit 13- PN related Disfigurement/ appearance
14- Other (please describe):			

*****Instruction to site PI: Please place asterisk next to target lesion morbidity.**

APPENDIX XIV: PLEXIFORM NEUROFIBROMA CLINICIAN MORBIDITY ASSESSMENT

Instructions

- To be completed by the treating physician.
- At baseline, please identify morbidities.
- Please fill out a separate form for each PN identified in Appendix XIII)
- At follow-up, for each morbidity identified at baseline, please document whether the noted morbidity is:
    - worse
    - stable
    - improved but still present
    - resolved
- Please include comments (ex. previously was using 2 pain medications and now using one; previously on Bipap setting of 8, now on Bipap setting of 4). If available, please provide any objective applicable testing results related to morbidities (in the comments box).

Please document the Baseline Morbidities.

Baseline Morbidity 1:

Baseline Morbidity 2:

Baseline Morbidity 3:

Baseline Morbidity 4:

COMPLETED BY: _____ DATE: _____

Follow-up assessments should be performed post cycles 4, 8, 12, 18, 24.

Select one:
Post cycle 4 ☐ Post cycle 8 ☐ Post cycle 12 ☐

Post cycle 18 ☐ Post cycle 24 ☐ Other (Please specify): _____

Evaluation Date:

For each baseline morbidity, please document whether the morbidity is:
1) worse; 2) stable; 3) improved but still present; or 4) resolved

	Select One	Comments
Baseline Morbidity #1	- Worse - Stable - Improved but still present - Resolved	
Baseline Morbidity #2	- Worse - Stable - Improved but still present - Resolved	
Baseline Morbidity #3	- Worse - Stable - Improved but still present - Resolved	
Baseline Morbidity #4	- Worse - Stable - Improved but still present - Resolved	

COMPLETED BY: _____ DATE: _____

APPENDIX XV: BIOLOGICAL SPECIMEN FOR BANKING – COLLECTION AND SHIPPING

1) Blood

Prior to the day of blood draw, the site will have arranged for a sample collection kit supplied by the biorepository to be shipped to the site. The Center for Data Driven Discovery in Biomedicine (D3b) at CHOP will be providing kits and labels. The kit will contain tubes and bar-coded labels (which include a specimen number) for blood collection. It will also contain shipping materials and instructions for sending collected blood samples to the biorepository, as well as a pre-paid shipping label.

Samples

- Streck tube (for plasma): ~ 2 mL.
- EDTA tube (for DNA): ~ 5 mL.
- PAXGene tube (for RNA) ~ 2.5 mL.

Tubes should be inverted at least 10 times after being drawn.

The samples will only be obtained if the total blood volume does not exceed 5 mL/kg. If not enough blood can be drawn for all tubes, the priority order for obtaining the specimens is: 1) Streck tube, 2) EDTA tube, 3) PAXGene tube.

Label the specimens with the specimen labels provided with the specimen kit.

Blood samples must be shipped (unprocessed) same day at ambient temperature to the biorepository by overnight delivery using shipping container provided by the biorepository. Samples must be shipped Monday through Thursday.

Enter the specimen numbers into the NF Consortium Operations Center eDES.

For questions about shipping, kits, tubes, etc., and to confirm the shipping address prior to sending samples, please contact: Elizabeth Appert (apperte@email.chop.edu) and BioRc (biorc@email.chop.edu).

2) Tumor Tissue

Prior to the day of surgery, the site will have arranged for a tissue sample collection kit supplied by the biorepository to be shipped to the site. The Center for Data Driven Discovery in Biomedicine (D3b) at CHOP will be providing kits and labels. The kit will contain bar-coded cryovials (which include a specimen number) for tissue collection. It will also contain shipping materials and instructions for sending collected tissue samples to the biorepository, as well as a pre-paid shipping label.

Samples

- Fresh frozen tissue: 1-2 pea sized aliquots (~ 0.3 cm^3, equivalent to 0.8 cm in diameter) of excess (left over) tumor tissue. Place each aliquot in a separate cryovial and label the specimen with subject's study number. Snap freeze the aliquots in liquid nitrogen (preferred) or dry ice and then store in a freezer at -80°C or below until they can be sent to the biorepository.
- 1 H&E stained slide cut from each submitted piece to confirm tumor is present.
- If fresh frozen tissue is unavailable, please submit processed DNA (at least 3 micrograms) and RNA (at least 400 nanograms with optimal RIN > 7) if available.

Label the specimen manifest with the subject's study number.
Fresh frozen tissue or DNA/RNA must be shipped on dry ice via overnight delivery using shipping

materials provided by the biorepository. The H&E slide should be shipped at ambient temperature. Samples must be shipped Monday through Thursday.

Enter the specimen numbers into the NF Consortium Operations Center eDES.

For questions about shipping, kits, tubes, etc., and to confirm the shipping address prior to sending samples, please contact: Elizabeth Appert (apperte@email.chop.edu) and BioRc (biorc@email.chop.edu).