

PROTOCOL SUBMISSION FORM Amendment Form	PROTOCOL NO. 01C0222-I	PRINCIPAL INVESTIGATOR (NIH Employee Name, Inst/Br, Telephone and e-mail): Brigitte Widemann NCI POB 301.496.7387 widemanb@mail.nih.gov
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PROTOCOL TITLE: "A Phase II Randomized, Cross-Over, Double-Blinded, Placebo-Controlled Trial of the Farnesyltransferase Inhibitor R115777 in Pediatric Patients with Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas"

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The Following revisions were incorporated into this protocol and approved by:

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☐ New Principal Investigator
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☐ Non-NIH Personnel Change
☐ Converting to multi-institutional trial
DEC clearance required? ☐ Yes ☒ No

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PROTOCOL CONTENT CHANGES

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| <input type="checkbox"/> Precis | <input type="checkbox"/> Data Collection/Evaluation |
| <input type="checkbox"/> Study Objectives | <input type="checkbox"/> Human Subject Protections |
| <input type="checkbox"/> Background and Rationale | <input type="checkbox"/> Data Reporting |
| <input type="checkbox"/> Eligibility Assessment and Enrollment | <input type="checkbox"/> IND/IDE Information |
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Does the amendment impact the risk/benefit assessment?

- ☐ Yes ☒ No

INFORMED CONSENT DOCUMENTATION

- ☒ Text Revisions to Consent(s)
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☐ No Changes to Consent Form

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IRB Meeting Date:

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**A Phase II Randomized, Cross-Over, Double-Blinded, Placebo-Controlled
Trial of the Farnesyltransferase Inhibitor R115777 in Pediatric Patients with
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PROPRIETARY and CONFIDENTIAL

This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organization of the trial and on condition that all such persons agree not to further disseminate it.

PRECIS

R115777 is a farnesyltransferase inhibitor that blocks the post-translational isoprenylation of *ras* and other farnesylated proteins. The *ras* proteins are integral in cell signaling pathways, and farnesylation is essential for the function of both mutant and non-mutant *ras* proteins. Patients with neurofibromatosis type 1 (NF1) have an increased risk of developing tumors of the central and peripheral nervous system, and there are no standard treatment options, other than surgery, available for these tumors. Neurofibromin, which is the product of the NF1 gene, contains a domain with significant homology to *ras* GTPase-activating proteins (GAP). Although NF1 patients lack germline *ras* mutations, the decreased levels of neurofibromin have been shown to be associated with a constitutively activated *ras*-GTP status. Thus, upstream inhibition of *ras* farnesylation may inhibit growth of tumors in NF1 patients. A randomized, cross-over, double-blinded, placebo-controlled pediatric phase II trial of oral R115777 will be performed in children and young adults with NF1, who have progressive, plexiform neurofibroma(s) to determine the effect of this novel anticancer drug on the rate of growth of neurofibromas. The endpoint of the trial is time to progression. R115777 will be administered orally at a dose of 200 mg/m² twice daily for cycles of 21 days followed by a 7 day rest period based on the results of our prior pediatric phase I trial.

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1.0 INTRODUCTION

1.1 OBJECTIVES

PRIMARY STUDY OBJECTIVES:

- 1.1.1 To assess the effect of R115777, administered on a chronic oral schedule (21 days on followed by 7 days rest), on the time to disease progression in children and young adults with neurofibromatosis type 1 (NF1) and progressive plexiform neurofibromas.
- 1.1.2 To define the objective response rate of progressive plexiform neurofibromas to R115777.
- 1.1.3 To describe and define the toxicities of R115777, administered on a chronic oral schedule (21 days on followed by 7 days rest), in pediatric patients and young adults.

SECONDARY STUDY OBJECTIVES:

- 1.1.4 To measure the level of farnesylprotein transferase (FPTase) activity in tumor specimens and peripheral blood mononuclear cells obtained from patients treated on this trial, and to assess the value of FPTase activity as a surrogate marker for the antiproliferative effect of R115777.
- 1.1.5 To assess the value of three-dimensional MRI (3D-MRI) and uni-dimensional MRI (1D-MRI) data analysis in the evaluation of plexiform neurofibromas, and to compare both to conventional two-dimensional MRI (2D-MRI) data analysis.
- 1.1.6 To analyze tumor specimens from patients with NF1 treated with R115777 for the level of expression of *N-ras*, *K-ras*, and *H-ras*, and to correlate the level of expression and the *ras* mutation status with the efficacy of R115777.
- 1.1.7 To analyze tumor specimens from patients treated on this trial, for NF1 gene mutations in the GAP related domain, and to correlate these findings with the antiproliferative effect of R115777.
- 1.1.8 To establish tumor cell lines from tumor specimens (plexiform neurofibromas and discrete neurofibromas) obtained from patients treated on this trial.
- 1.1.9 To contribute tumor specimens obtained on this trial to an already existing tissue bank. Tumor samples from plexiform neurofibromas will undergo a central pathology review including a detailed morphologic, ultrastructural and immunohistochemical analysis. Tumor cell lines and tumor samples will be made available to the scientific community, after obtaining IRB approval in order to collect more information on the

pathology, genetics, and cell biology of plexiform and discrete neurofibromas.

1.1.10 To determine circulating levels of nerve growth factor from blood samples at various time points during treatment with R115777/placebo, and to correlate levels of NGF with the development of clinical neurotoxicity from R115777.

1.1.11 To assess the quality of life of patients treated with R115777 or placebo using the newly developed National Institutes of Health (NIH) Impact of Pediatric Illness (IPI) Scale, which assesses the impact of disease and treatment on children's behavior, and to evaluate the ability of this new assessment tool to measure changes in a child's quality of life.

1.2 BACKGROUND AND RATIONALE

1.2.1 INTRODUCTION

Neurofibromatosis 1 (NF1) is a common autosomal dominant, progressive genetic disorder with an incidence of 1:3000 (>80,000 persons affected in The United States). NF1 is characterized by diverse, progressive cutaneous, neurological, skeletal and neoplastic manifestations with no standard drug treatment options available. Patients with NF1 have an increased risk of developing tumors of the central and peripheral nervous system including plexiform neurofibromas (27%)[10] optic gliomas gliomas (15-20%), pheochromocytomas (1%),[1] malignant peripheral nerve sheath tumors (5%), and neurofibrosarcomas (6%).[5, 17] Plexiform neurofibromas are nerve sheath tumors that grow along the length of nerves and involve multiple branches of a nerve. They are a major source of morbidity, causing disfigurement, impairment of nerve function, and in some cases development of malignant peripheral nerve sheath tumors.

Neurofibromin, the NF1 gene product, contains a domain with significant homology to *ras* GTPase-activating proteins (GAP).[1, 8, 14] The *ras* proteins are integral in cell signaling pathways, and activation of *ras* leads to cell proliferation. GAPs catalyze the hydrolysis of *ras*-GTP (the active form of *ras*) to *ras*-GDP and lead to *ras* inactivation. Patients with NF1 have decreased levels of neurofibromin, which is associated with an activated *ras*-GTP status. Agents directed at inhibiting *ras*, therefore, are a rational choice for trials of potential therapeutic agents in patients with NF1 and progressive plexiform neurofibromas.

1.2.2 INHIBITION OF POST-TRANSLATIONAL FARNESYLATION

Farnesylation is a post-translational modification in which a farnesyl isoprene group is added to a number of cellular proteins by the enzyme, farnesyl-protein transferase (FPTase). The *ras* family of G proteins is one of the classes of proteins that are modified by FPTase. H-, K-, and N-*ras* are 21 kDa guanine nucleotide-binding proteins that control a multitude of cell signaling events.[2, 22] Mutant *ras* genes have the ability to transform cells into a malignant phenotype, and *ras* mutations have been observed in approximately 30% of all human cancers.[21] Patients with NF1 do not

have germline *ras* mutations. However, tumor cell lines established from malignant schwannomas of NF1 patients have been shown to have a constitutively activated *ras*-GTP status. Neurofibromin, which is the product of the NF1 gene, contains a domain that shows significant homology to *ras* GTPase-activating proteins (GAP).[8] In these cell lines, there are normal levels of GAP, but decreased levels of neurofibromin, supporting the role of the NF1 gene as a tumor suppressor gene. Advances in the understanding of *ras* oncoprotein function suggest novel points for anti-tumor intervention. *Ras* is synthesized as a cytosolic precursor that ultimately localizes to the cytoplasmic face of the plasma membrane after a series of post-translational modifications. The first obligatory step in this series of post-translational modifications is the addition of a farnesyl moiety. This modification is essential for *ras* function.[13] FPTase appears to be an appropriate biochemical target for the development of inhibitors of post-translational processing of *ras* resulting in prevention of *ras*-mediated cellular transformation[4, 7, 16, 19].

1.2.3 PRECLINICAL ANTITUMOR ACTIVITY OF R115777

R115777 is a potent and selective non-peptidomimetic inhibitor of FPTase both *in vitro* and *in vivo*. In several preclinical studies, R115777 was shown to inhibit the growth of H-*ras*, K-*ras* and N-*ras* transformed tumors.[6]

In intact tumor cells in culture, R115777 produced antiproliferative effects at nanomolar concentrations. The proliferation of NIH 3T3 stably transfected with the activated T24 H-*ras* oncogene (T24 cells) was inhibited by R115777 with an IC₅₀ of 1.7 nM. Inhibition of p21 *ras* farnesylation was observed in T24 cells in the same concentration range which inhibited cell proliferation. In LoVo cells and HCT116 cells, two human colon cancer cell lines transformed by an activated K-*rasB* oncogene, R115777 inhibited cell proliferation with IC₅₀'s of 16 and 22 nM, respectively. In intact CAPAN-2 human pancreatic cancer cells, which bear a K-*rasB* mutation, R115777 inhibited cell proliferation with an IC₅₀ of 16 nM.

Although FPTase inhibitors were developed to treat tumors with *ras* mutations, it has been shown in established cell lines that FPTase inhibitors also inhibit tumors without *ras* mutations, including breast, colon, prostate, epidermoid, Ewing's sarcoma and rhabdomyosarcoma. Peptidomimetic FPTase inhibitors inhibit the growth of the Ewing's sarcoma cell line RD-ES, which does not contain a *ras* mutation.[24]

Patients with neurofibromatosis type 1 (NF1) do not have germline *ras* mutations. However, tumor cell lines established from malignant schwannomas of NF1 patients have been shown to have a constitutively activated *ras* GTP status. The growth of the malignant schwannoma cell line, ST88-14, derived from a patient with NF1 was inhibited by a bisubstrate analog FPTase inhibitor in a concentration-dependent manner.[27]

In nude mice bearing subcutaneous T24 cell tumors, R115777 administered orally (BID) at doses of 6.25, 12.5 and 25 mg/kg inhibited the growth of tumors by 56%, 84% and 86%, respectively after 15 days of treatment. In nude mice bearing the K-*rasB*

transformed LoVo human colon tumors, R115777 administered orally (BID) at doses of 25, 50 and 100 mg/kg inhibited tumor growth by 11%, 68% and 81%, respectively after 32 days of treatment. In nude mice bearing subcutaneous CAPAN-2 tumors, R115777 administered orally (BID) significantly inhibited tumor growth at doses of 50 and 100 mg/kg. A 56% reduction of final tumor weight was observed at the 50 mg/kg dose level and a 76% reduction of final tumor volume was observed at the 100 mg/kg dose level.

1.2.4 TOXICOLOGY OF R115777

The toxicity profile of R115777 has been well characterized in animals. In a one-month repeat-dose pilot toxicity study in rats, five males and five females per dosage group were dosed orally by gavage with R115777 at doses 0, 5, 20 and 80 mg/kg/day. Rats dosed at 5 mg/kg showed no adverse effects. At 20 mg/kg, a minimal decrease in body weight gain and slight atrophic and degenerative histological changes in the nasal epithelium were the only effects observed. Dosing at 80 mg/kg resulted in sedation, ptosis, salivation and in a decrease in body weight. Hematological examination revealed slight decreases in the number of white blood cells (decrease in lymphocytes and eosinophils).

A one-month pilot study was conducted in Beagle dogs. Doses of 0, 2.5, 10 and 40 mg/kg were given orally to two males and two females per dosage group. Dosing at 2.5 mg/kg resulted in a slightly decreased weight of the testes, histologically confirmed by slight atrophy. At 10 mg/kg, changes consisted of a decrease in platelets in one dog and a decreased weight of the testes. Dosing at 40 mg/kg resulted in the death of all four dogs within 15 days. Vomiting, diarrhea and decreased food consumption and body weight were noted. Hematological changes were characterized by marked leucopenia, thrombocytopenia, an increase in activated partial thromboplastin time, and a slight decrease in hematocrit and hemoglobin. Biochemistry revealed decreases in sodium, potassium, chloride, inorganic phosphate and gamma glutamyltransferase while increases in total protein, cholesterol, phospholipids, blood urea nitrogen, total bilirubin and alkaline phosphatase were observed. Histological examination in most dogs given 10 mg/kg and in all dogs given 40 mg/kg revealed atrophy of the hematopoietic tissue with signs of mitotic arrest (e.g., bone marrow, thymus, lymph nodes, mucosa-associated lymphoid tissue and spleen). As a consequence of the severe thrombocytopenia, systemic hemorrhage was seen in the intestine, mesentery, hematopoietic system, lung, brain, adrenals, skeletal muscle, vagina and subcutaneous tissue. In a toxicity study with recovery in Beagle dogs, oral doses of 10 mg/kg and 40 mg/kg were administered daily until hematological changes occurred. Two dogs per group were tested. Leukopenia and thrombocytopenia were noted after four and seven days in both dogs, after which dosing was stopped. Within 14 days after dosing was stopped, complete hematological recovery was observed. Histological examination of the testes indicated moderate atrophy. Slight lymphoid depletion in the mesenteric lymph node and the gut associated lymphoid tissue were also seen in the male. Examination of three bone marrow biopsies, taken at different times during the study,

revealed distinct regeneration of the hematopoietic tissue. The degree of atrophy ranged from severe atrophy with marked loss of early precursors at the end of dosing to slight atrophy and increase in blast cells at the end of recovery.

Dose dependent lens opacities have been observed after 1 month of dosing of 60 mg/kg in male Wistar rats (2 out of 30 rats), in 10 mg/kg dosed females (1 out of 20 rats), in 40 mg/kg dosed females (13 out of 19 rats) and in 60 mg/kg dosed females (26 out of 28 rats). Changes consisted of localized or diffuse (sub)capsular opacification at the posterior pole of the lens. The degree of opacification and the area involved was never so extended as to make visualization of the fundus difficult. This effect was not observed in dogs receiving chronic administration of R115777

1.2.5 PHASE I CLINICAL TRIALS OF R115777 IN ADULTS

Solid tumor trials: In the first adult phase I trial (R115777-USA-1), oral R115777 was administered initially as a solution, then as capsules every 12 hours for 5 days, and repeated every 2 weeks.[28] Doses were escalated from 25 mg q12h to 1300 mg q12h. An MTD was not reached in this trial. One of six patients on the 1300 mg dose level developed dose-limiting grade 3 peripheral neuropathy, described as severe burning in the lower extremities, oral cavity and vaginal area. The pain resolved within 24 hours of stopping R115777. This patient had a history of prior mild peripheral neuropathy attributed to paclitaxel therapy. Non-dose-limiting toxicities (non-DLT) observed at the 800 and 1300 mg dose levels were fatigue and an increase in serum creatinine. Nausea and vomiting were observed more frequently with the oral solution than with the capsules, but were observed with the capsule formulation at the 800 and 1300 mg dose levels. Myelosuppression was mild.

A phase I trial of oral R115777 on a q12h for 21 day schedule followed by a 7 day rest period was performed at the Fox Chase Cancer Center (R115777-USA-3). At doses >300 mg q12h, dose-limiting myelosuppression was observed. In addition, some patients experienced fatigue and weakness.

Two additional adult phase I trials were performed in Europe (R115777-BEL-7, R115777-BEL-2) to evaluate the safety, pharmacokinetics and define and MTD of R115777, when administered for 4 weeks and continuously for 3 months or more, respectively. Reversible grade III diarrhea was reported in a single patient from the Netherlands treated at a dose 300 mg bid. Grade II hypokalemia and grade II renal insufficiency was observed in one patient. After stopping study medication hypokalemia and renal insufficiency decreased to grade I.

On the continuous dosing phase I trial R115777 was administered at doses from 50 mg to 500 mg BID.[23] Dose limiting toxicities (DLT) toxicities were grade 4 neutropenia (1 pt each at 400 and 500 mg), grade 3 thrombocytopenia (1 patient at 500 mg), and sensory and motor peripheral neuropathy grade 3 (at 500 mg). The neuropathy was not completely reversible in all patients. One patient developed grade 3 skin hypersensitivity at 150 mg BID. The MTD was 300 mg BID. One partial remission was seen in a patient with non-small cell lung cancer.

A phase II study of R115777 in patients with advanced breast cancer was recently completed.[12] R115777 was administered continuously at a dose of 400 mg BID to six patients, and because of dose-limiting neutropenia on this schedule, at a reduced dose of 300 mg BID to the subsequent 21 patients. Sixteen patients had received prior chemotherapy. Toxicities in the 21 patients included grade 3 to 4 neutropenia (29%), grade 3 thrombocytopenia (11%), grade 2 to 3 paresthesias/numbness (26%) after a median of 10 weeks on therapy, grade 2 to 3 diarrhea (11%), skin rash (11%), and fatigue (28%). Confirmed partial responses (PR) were seen in 3 patients (12%). The abstract did not describe the time frame for recovery from R115777 associated toxicities or if patients fully recovered from neurotoxicity.

A phase I trial of the combination of oral R115777 with gemcitabine,[20] in which gemcitabine was administered at a fixed dose of 1000 mg/ m² i.v. on days 1, 8, and 15 every 4 weeks, and R115777 was administered continuously at doses ranging from 100 to 300 mg q12h was also performed. The MTD of R115777 on this trial is 200 mg q12h, and neutropenia was the DLT.

A sensory peripheral neuropathy manifesting with pain, tingling, numbness and dysesthesias was observed in more than 50% of 19 adult patients who were treated in Europe on a trial of continuous administration of R115777 at a dose of 350 mg twice daily. The neuropathy was only observed in patients who received doses of R115777 >200 mg q12h, and who had received the drug for >12 weeks duration. Peripheral neuropathy had not previously been observed on the intermittent schedule, but there were not as many patients on the intermittent schedule who had prolonged therapy. The neuropathy was reversible in all patients after discontinuation of R115777.

Leukemia trial: A phase I trial of R115777 in adult patients with refractory leukemias was conducted at the University of Maryland.¹⁷ Patients received oral R115777 q12h for up to 21 days at doses ranging from 100 to 1200 mg for 21 days followed by a 1-2 week rest period. Thirty patients with refractory leukemias (22 AML, 5ALL, 3 CML in blast crisis) were enrolled. Reversible myelosuppression was observed at doses \geq 600 mg q12h. Reversible polydipsia and paresthesias were observed at the 900 mg dose level. Dose-limiting neurotoxicity manifesting with confusion, ataxia and vision changes was observed in 3/3 patients entered at the 1200 mg dose level within 48 hours of starting R115777. These toxicities resolved completely within 72 hours of stopping R115777. Responses (2 CR, 7 PR) were observed at all dose levels. Inhibition of FPTase was > 80% at dose levels \geq 300 mg q12h. Inhibition of farnesylation of lamin A and heat shock protein HDJ2 was observed in 4/4 and 6/6 patients at the 600 mg dose level, respectively. The MTD was 900 mg q12h, which is 3-fold higher than the MTD in adults with solid tumors.

1.2.6 PHASE I CLINICAL TRIALS OF R115777 IN CHILDREN

Solid Tumor Phase I: The Pediatric Oncology Branch, Texas Children's Cancer Center, and the Children Hospital of Cincinnati are currently completing a collaborative pediatric phase I trial of R115777 in patients with refractory solid tumors or patients

with neurofibromatosis type 1 (NF1) and progressive neurofibromas (R115777-USA-6). The MTD was initially determined on a q12h for 21 days schedule followed by a 7-day rest. The MTD determined on the 21 day schedule was then administered on a continuous dosing schedule (28 day cycles with no rest period). No dose escalation on the continuous dosing schedule was planned. Thirty-six patients (23 with refractory solid tumors, 13 with NF1) were entered on the 21 day dosing schedule, and six patients (2 with refractory solid tumors, 4 with NF1) on the continuous dosing schedule. Four dose levels were studied: 150 mg/m²/dose (n=4), 200 mg/m²/dose (21-day schedule, n=13; continuous dosing, n=6), 275 mg/m²/dose (n=12), and 375 mg/m²/dose (n=7). Non dose-limiting toxicities included myelosuppression, rash, nausea, diarrhea, abdominal pain, and fatigue. Observed dose limiting toxicities are shown in the table below:

Dosel Level (mg/m²/dose)	Pts (n)	Pts DLT (n)	Dose-limiting toxicities (grade)
21 day schedule followed by 7 days rest			
150	4		
200	13	2	1 Seizure (3), 1 Platelets (4)
275	12	3	2 Platelets (3)+ANC (4), 1 diarrhea (3)
375	7	4	2 Rash (3), 1 ANC (4) + hypofibrinogenemia (3), 1 Nausea, Vomiting, Diarrhea (3)
Continuous dosing schedule with no rest			
200	6	1	Rash (3)

The seizure was observed on day 21 of treatment in one patient with adrenocortical carcinoma and no prior history of seizures. MRI of the head showed diffuse white matter changes, which improved on a follow-up scan. All dose-limiting toxicities resolved after discontinuation of R115777. The MTD determined for patients with NF1 and refractory solid tumors combined was 200 mg/ m²/dose q12h on both schedules

Four patients with NF1 continue to receive R115777 on the 21 day schedule after a median of 19 (range 18-23) cycles, and 3 patients with NF1 continue to receive R115777 on the continuous dosing schedule after a median of 11 cycles (range 4-13). Peripheral neuropathy has not been observed in this trial. However, because of the development of peripheral neuropathy in adults, who were treated on the continuous dosing schedule, the 21 day schedule followed by a 7 day rest period will be used in future trials with R115777.

Leukemia Phase I: A phase I trial of R115777 for children with refractory leukemias is ongoing. Twenty children with refractory ALL (n=11), AML (n=8), or JMML (n=1) were treated. Overall, R115777 has been well tolerated. At the starting dose (300 mg/m² q12h po x 21 d, repeated q28 d), 3 of 6 evaluable patients had grade 3 adverse events (AE), which included rash (n=1), hyperbilirubinemia (n=1), hyperbilirubinemia and AST (n=1). The dose was de-escalated to 200 mg/m², and 2 of 6 evaluable patients developed grade 3 AE, which included mucositis (n=1), hyperbilirubinemia (n=1). Two of the three patients who developed grade 3 hyperbilirubinemia, had a history of hyperbilirubinemia during the days preceding treatment with R115777, but normal or grade 1 bilirubin immediately prior to R115777. After discontinuation of R115777, bilirubin remained elevated in one patient, continued to increase in one patient, and decreased to grade 1 toxicity in one patient. The relationship of the study drug to this AE, and of the dose of study drug to this AE are thus unclear.

The protocol was amended to only allow entry of patients with normal liver function tests at trial entry (normal bilirubin, AST, and ALT). Currently, the 300 mg/m² dose level is expanded to enroll up to 12 evaluable patients.

1.2.7 CLINICAL PHARMACOKINETICS OF R115777 IN ADULTS AND CHILDREN

Pharmacokinetic analysis of plasma samples from 19 patients treated on an adult phase I trial with R115777 revealed:

- R115777 is rapidly absorbed after oral administration (time to peak was approximately 2-4 hours). The bioavailability of the capsules increased when given after a meal.
- The concentrations of R115777 decline biphasically with an initial, dominant half-life of about 2-3 hours and with a median terminal T_{1/2} of about 6 hours;
- Over the dosage range studied to date the pharmacokinetics of R115777 appear to be linear;
- The average accumulation ratio of R115777 was calculated at 1.1, and therefore minimal accumulation is expected on the q12 hr dosing regimen.
- In healthy human adults plasma protein binding of R115777 was very high, with a free fraction of 0.66-0.77%.
- In human hepatocytes glucuronidation of R115777 at the imidazole nitrogen was the major metabolic pathway.

Pharmacokinetic analysis of oral R115777 has also been performed on plasma samples from 30 children (median age 13 years, age range 5 to 17 years) treated on our pediatric phase I trial. In general the pharmacokinetics of R115777 are similar in adults and children. Preliminary observations regarding the plasma pharmacokinetics of R115777 in pediatric patients are:

- R115777 is rapidly absorbed after oral administration: The average time to peak concentration was 2.7 hours (range 1.0 -8.0 hours);
- The Average terminal half-life was 6.8 hours (range 2.8-16.7 hours) The determination of $T_{1/2}$ was limited by the 36-hr sampling and highly dependent on the ability to quantify low concentrations of R115777 in the terminal phase;
- Over the dosage range studied to date the pharmacokinetics of R115777 appear to be linear: The average AUC increased from 4318 ng•h/ml (\pm 1763) at the 150 mg/ m² dose level to 13536 ng•h/ml (\pm 7831) at the 375 mg/ m² dose level. The C_{max} increased from 1034 ng/ml (\pm 566) at the 150 mg/ m² dose level to 2433 ng/ml (\pm 730) at the 375 mg/ m² dose level.
- Minimal accumulation is expected on the q12 hr dosing regimen.

1.2.8 PROPOSED PEDIATRIC PHASE II TRIAL OF R115777

Patients with NF1 are at increased risk of developing a variety of benign and malignant tumors of the central and peripheral nervous system. Plexiform neurofibromas occur with the highest frequency, and are associated with considerable morbidity. Management of plexiform neurofibromas is generally surgical. However, up to 44% of tumors progress after the first surgery, most commonly in patients younger than ten years of age with head and neck tumors that could not be completely resected.[18] There is no other standard treatment modality for patients with progressive plexiform neurofibromas.

Neurofibromas do not follow a classical oncology model, in which tumor growth occurs unchecked unless therapy is provided. Rather, neurofibroma growth can be unpredictable, including periods of rapid growth and others of quiescence. Some neurofibromas remain static indefinitely after a period of active growth. This erratic behavior can make it difficult to document the effectiveness of a potential treatment.

A "Natural History Protocol" (Principal Investigator Dr. Bruce Korf) is currently open to patients with NF1 with the main goal to provide data on the growth rate of neurofibromas. Patients entered on this study do not receive treatment for their disease, but are followed closely clinically and by serial MRI's. Volumetric MRI analysis is evaluated for it's value in determining the growth rate of plexiform neurofibromas. Results from this study will prove very valuable for the design of treatment protocols, but are not available to this time point.

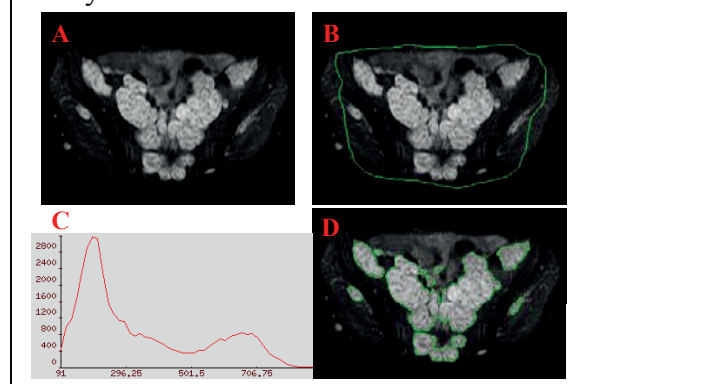
This trial will be a randomized, cross-over, double-blinded, placebo-controlled pediatric phase II trial of oral R115777 in children and young adults with NF1 who have progressive plexiform neurofibroma(s). Each patient will serve as his/her own control for the primary endpoint of time to progression. After documentation of progressive disease on the first treatment, patients will be crossed over to receive R115777 (if placebo was first given) or placebo (if R115777 was first given). The first treatment that a patient is randomized to receive (either placebo or R115777) is defined as "phase A",

and the second treatment (either placebo or R115777), is defined as “phase B”. This trial design is ethical, because alternative designs without placebo control could bias observation, and there is no standard treatment to which R115777 may be compared. In addition, each patient will receive study medication provided there is disease progression, and therefore may derive benefit from the trial.

R115777 or placebo will be administered twice daily for 21 days followed by a 7 day rest period between cycles. The dose of R115777 for this trial will be 200 mg/m²/dose every 12 hours, the MTD on the intermittent dosing schedule on the pediatric phase I trial.

Imaging and measurement of plexiform neurofibromas: Tumor response criteria that are used for cancers are based on one-dimensional (1-D) and two-dimensional (2-D) tumor measurements (Therasse et al., 2000; Estey et al, 1986). 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

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



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. 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, plexiform neurofibroma volume was also determined by manually tracing the tumor borders on each MR image. The results of application of the automated method are shown in the table below.

	Observer 1	Observer 2
Mean tumor volume ml, median (range)	291 (80.9-1581)	290 (75.7-1603)
Inter-day CV %, median (range)	3.6 (0.7-6.0)	1.6 (0.6-5.6)
Median (range) % difference in volume between observers	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 is used in the currently ongoing phase II trial of the farnesyltransferase inhibitor R115777 and in the phase I trial of pirfenidone for children with NF1 and plexiform neurofibromas to assess changes in tumor size, and in both clinical trials tumor progression is defined as an increase in tumor volume by $\geq 20\%$.

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	Phase II R117555 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 R115777 NF1 phase II trial

3D-MRI analysis will be evaluated against conventional 2D-MRI and 1D-MRI analysis for its reproducibility in the assessment of disease status of plexiform neurofibromas. Tumor response will therefore also be assessed using 1D-MRI data analysis. Each patient will undergo MRI imaging of all known disease prior to entry on each phase of the study. At the time of study entry the extent of the progressive plexiform neurofibroma(s) will be determined, and followed for response using 1D-, 2D-, and 3D-MRI (appendix 1).

In order to enhance the knowledge about the molecular basis of NF1, and to develop surrogate markers for tumor response, this study will attempt to obtain biopsies from easily accessible discrete neurofibromas or superficial plexiform neurofibromas from all eligible patients prior to entry to treatment, and if feasible at a later time point during treatment on each arm of the study. Discrete neurofibromas undergo a natural history, beginning as small growing lesions, and maturing into static lesions. It is possible that the biology of these lesions differ, and hence might yield different results in studies of *ras* expression, *ras* mutations and FPTase activity.

However, they may still prove valuable as surrogates. Furthermore, it is anticipated that some patients may require surgery during their treatment on this trial, either for complications of NF1 or for other unrelated medical reasons, and attempts will be made to obtain tumor biopsies at this time. Tumor biopsies are invasive procedures, and patients may refuse to undergo biopsies and still be eligible for the study.

Tumor samples obtained on this study will be contributed to an already existing tumor tissue bank, and samples obtained from plexiform neurofibromas will undergo a central pathology review including a detailed morphologic, ultrastructural and immunohistochemical analysis (Appendix 2, 3, 4). All tumor samples will be used to establish tumor cell lines (Appendix 3, 4). Tumor samples obtained prior to study entry, and once at steady state on treatment during each study phase ("A", "B"), will be used for molecular biological studies (FPTase activity), expression of *N-ras*, *K-ras*, and *H-ras*, *ras* mutations, and NF1 gene mutations in the GAP related domain.

Peripheral blood mononuclear cells and tumor specimens obtained at various time points during the trial will also be used to measure the level of farnesyl-protein transferase (FPTase) activity in order to determine the value of FPTase activity as a surrogate marker of tumor response (Appendix 5).

The contribution of tumor specimens to a central tissue repository will provide valuable resources for ongoing as well as future studies aimed at investigating the molecular pathogenesis of NF1 tumors, and may allow for the development of predictive markers (clinical or molecular) to identify individuals at risk for cancer development. The identification of at risk individuals will have significant impact on our management and evaluation of individuals with this common inherited predisposition to cancer syndrome.

Recently the development of chemotherapy induced peripheral neuropathy has been correlated with circulating levels of nerve growth factor [3]. Patients who received neurotoxic agents experienced a decrease in circulating levels of NGF, which correlated with the development and severity of peripheral neuropathy. Peripheral neuropathy has been observed in adult patients after ≥ 12 weeks of chronic dosing. This trial will therefore attempt to measure NGF at various time points during treatment with R115777 and placebo, and to correlate levels with the development of neuropathy (Appendix 6).

The quality of life of patients treated with R115777 or placebo on this study will be assessed using the National Institutes of Health (NIH) Impact of Pediatric Illness (IPI) Scale. This questionnaire was developed to assess the effects of chronic illness and treatment on the everyday behavior of children. It assesses adaptive behavior, emotional functioning, physical status and central nervous system symptoms. This questionnaire has not been completely validated, and means and standard deviations for different subgroups of patients on the scale and subscales are not available yet. Without normative data on this scale for patients with NF1, and having a relatively small sample size in the protocol, it may be difficult to analyze the data as an outcome

measure for this particular study. Attempts will be made to compare the quality of life of patients while they receive treatment with placebo or R115777. The IPI scale should be administered to all patients ≥ 6 years and ≤ 18 years of age and their primary caregiver prior to the start of therapy. This questionnaire will not be administered to patients > 18 years. This assessment consists of an age-appropriate questionnaire and generally takes less than 30 minutes to complete. Patients between the ages of 6 and 10 years of age should be administered the IPI-Young Child form; patients between 11 and 18 years of age should be administered the IPI-Older Child/Adolescent form; the patient's primary caregiver should receive the IPI-Parent Form.

2.0 ENROLLMENT PROCEDURES

2.1 ELIGIBILITY CRITERIA

2.1.1 INCLUSION CRITERIA

2.1.1.1 Age: ≥ 3 years and ≤ 25 years of age

2.1.1.2 Diagnosis: Patients with NF1 and progressive plexiform neurofibromas that have the potential to cause significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions), lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. 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. In addition to plexiform neurofibroma(s), all study subjects must have at least one other diagnostic criteria for NF1 listed below (NIH Consensus Conference[9]):

1. Six or more café-au-lait spots (≥ 0.5 cm in prepubertal subjects or ≥ 1.5 cm in postpubertal subjects)
2. Freckling in the axilla or groin
3. Optic glioma
4. Two or more Lisch nodules
5. A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex)
6. A first degree relative with NF1

In this study a plexiform neurofibroma is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal plexiform neurofibroma involves two or more levels with connection between the levels or extending laterally along the nerve.

2.1.1.3 Measurable disease: Patients must have measurable plexiform neurofibroma(s). For the purpose of this study a measurable lesion will be defined as a

lesion of at least 3 cm measured in one dimension. There must be evidence of recurrent or progressive disease as documented by an increase in size or the presence of new plexiform neurofibromas on MRI. Progression at the time of study entry is defined as:

- A measurable increase of the plexiform neurofibroma ($\geq 20\%$ increase in the volume, or a $\geq 13\%$ increase in the product of the two longest perpendicular diameters, or a $\geq 6\%$ increase in the longest diameter) over the last two consecutive scans (MRI or CT), or over the time period of approximately one year prior to evaluation for this study.
- 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.

2.1.1.4 Prior therapy: Patients with NF1 are eligible at the time of recurrence or progression of inoperable plexiform neurofibroma.

A surgical consultation should be obtained prior to enrollment on the study to evaluate if tumor resection is a feasible option. Patients will only be eligible if complete tumor resection is not feasible, or if a patient with a surgical option refuses surgery.

Since there is no standard effective chemotherapy for patients with NF1 and progressive plexiform neurofibromas, patients may be treated on this trial without having received prior therapy.

Patients must have recovered from the toxic effects of all prior therapy before entering this study. The Cancer Therapy Evaluation Program Common Toxicity Criteria (CTC) Version 2.0 will be used for toxicity assessment. A copy of the CTC version 2.0 can be downloaded from the CTEP home page at <http://ctep.cancer.gov>. Recovery is defined as a toxicity grade <2 , unless otherwise specified in the Inclusion and Exclusion Criteria.

Patients must have had their last dose of radiation therapy at least six weeks prior to study entry, and their last dose of chemotherapy at least four weeks prior to study entry. Patients who received G-CSF after the prior cycle of chemotherapy must be off G-CSF for at least one week prior to entering this study.

2.1.1.5 Performance Status: Patients should have a life expectancy of at least 12 months and an ECOG performance score of 0, 1, or 2 (see below). Patients who are wheelchair bound because of paralysis should be considered “ambulatory” when they are up in their wheel chair.

ECOG Performance Status

Score	Clinical Status
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed < 50% of the day
3	Symptomatic, in bed > 50% of the day but not bedridden
4	Bedridden

2.1.1.6 Hematologic Function: Patients must have an absolute granulocyte count $\geq 1,500/\mu\text{L}$, a hemoglobin ≥ 9.0 gm/dl, and a platelet count $\geq 150,000/\mu\text{L}$ at study entry, and a normal fibrinogen.

2.1.1.7 Hepatic Function: Patients must have a bilirubin within normal limits and SGPT $\leq 2\times$ upper limit of normal. Patients with Gilbert syndrome are excluded from the requirement of a normal bilirubin. (Gilbert syndrome is found in 3-10% of the general population, and is characterized by mild, chronic unconjugated hyperbilirubinemia in the absence of liver disease or overt hemolysis).

2.1.1.8 Renal Function: Patients must have an age-adjusted normal serum creatinine (see table below) OR a creatinine clearance $\geq (70 \text{ mL/min/1.73 m}^2)$.

Age (Years)	Maximum Serum Creatinine (mg/dl)
≤ 5	0.8
$5 < \text{age} \leq 10$	1.0
$10 < \text{age} \leq 15$	1.2
> 15	1.5

2.1.1.9 Informed Consent: All patients or their legal guardians (if the patients is <18 years old) must sign an IRB approved document of informed consent (screening protocol) prior to performing studies obtained exclusively to determine patient eligibility. After confirmation of patient eligibility all patients or their legal guardians must sign the protocol specific informed consent to document their understanding of the investigational nature and the risks of this study before any protocol related studies are performed (other than the studies which were performed to determine patient eligibility). When appropriate pediatric patients will be included in all discussion. Per institutional guidelines, age appropriate assent forms for children from 7 through 12 years, and for children may be developed and, when appropriate, will be signed by the pediatric patients in order to obtain written assent.

2.1.1.10 Durable Power of Attorney (DPA): All patients ≥ 18 years of age will be offered the opportunity to assign DPA so that another person can make decisions about their medical care if they become incapacitated or cognitively impaired.

2.1.1.11 Ability to undergo MRI examinations.

2.1.2 EXCLUSION CRITERIA

2.1.2.1 Pregnant or breast feeding females are excluded, because the toxic effects and pharmacology of R115777 in the fetus and newborn are unknown.

2.1.2.2 Clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction) which in the judgment of the Principal or Associate Investigator would compromise the patient's ability to tolerate R115777 or are likely to interfere with the study procedures or results.

2.1.2.3 Prior treatment with >1 prior myelosuppressive chemotherapy regimen.

2.1.2.4 An investigational agent within the past 30 days.

2.1.2.5 Evidence of an optic glioma, malignant glioma, malignant peripheral nerve sheath tumor or other cancer requiring treatment with chemotherapy or radiation therapy.

2.1.2.6 Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumor, or immunotherapy.

2.1.2.7 Inability to return for follow-up visits or obtain follow-up studies required to assess toxicity and response to therapy.

2.1.2.8 Prior treatment with R115777.

2.2 PRE-TREATMENT EVALUATION (SEE APPENDIX 7)

Pre-treatment blood tests should be performed within 2 weeks prior to enrollment on the trial unless otherwise stated. The evaluation required prior to starting treatment phase "A" and "B" is listed in table form in Appendix 7.

2.2.1 History and Physical Examination: Complete history (including prior and concurrent therapy), physical examination including documentation of measurable disease, performance status, and signs and symptoms. A complete neurologic examination should be performed and focus on signs of sensory peripheral neuropathy. Height, weight and body surface area must be recorded. History and physical examination will be documented in case report forms as outlined Section 5.1.1. The BSA should be calculated from the average of 3 repeated measurements of weight and height on the same day using the formula below or a formula used at a participating institution:

$$BSA = \frac{Weight (kg)^{0.425} \bullet Height (cm)^{0.725}}{139.315}$$

2.2.2 PHOTOGRAPHY: When possible, plexiform neurofibromas that are visible on the body surface should be photographed prior to treatment with R115777 and placebo. A size marker should be taped to the skin in the field of view when appropriate, and

the plexiform neurofibroma should be photographed so that it fills the frame. Frontal and side images will be taken, as appropriate. Copies of photographs should be sent to the study coordinator, identified by the subject ID number, date, and treatment phase ("A" or "B") and treatment cycle number.

2.2.3 HEMATOLOGY: Complete blood counts, differential, platelet count, PT, PTT and fibrinogen.

2.2.4 CHEMISTRIES: Electrolytes (including calcium, phosphorus and magnesium), creatinine, SGPT, and bilirubin.

2.2.5 URINALYSIS

2.2.6 URINE PREGNANCY TEST: For all females of child-bearing potential.

2.2.7 RADIOGRAPHIC EVALUATION (APPENDIX 1): MRI scan of the progressing plexiform neurofibroma(s) within 2 weeks prior to enrollment on study. In addition, if possible, MRI scan of all known additional, measurable plexiform neurofibroma(s) within 2 weeks of enrollment on study. The progressing plexiform neurofibroma(s) will be identified as index lesion(s), and will be studied by 3-D MRI. Should there be more than 3 progressing plexiform neurofibromas, the three most clinically relevant plexiform neurofibromas will be followed by 3-D MRI analysis. The imaging protocol outlined in Appendix 1 will be used each time MRI examinations are performed to assess the effect to R115777.

2.2.8 OPHTHALMOLOGIC EVALUATION: Ophthalmologic examination prior to or within the first three days of starting treatment with R115777 or placebo, including visual fields if the patient is able to cooperate with the exam and examination of the lens for opacifications.

2.2.9 TISSUE PROCUREMENT: In patients with easily accessible discrete neurofibromas or superficial plexiform neurofibromas, who consent to the procedure, biopsies will be performed prior to the first dose of treatment at study entry. In addition, attempts will be made to obtain tumor specimens from any patients requiring surgery for complications of their tumors or for unrelated medical problems. Peripheral blood mononuclear cells for FPTase assay (Section 2.2.10, Appendix 5) should be obtained at the same time as biopsy whenever possible. As this is an invasive procedure, patients may refuse biopsy and still be eligible for the study.

Kits will be supplied for handling and shipping of tumor specimens. To obtain a kit, please call Ms. Andy Gillespie at (301) 402-1848 seven days prior to the planned surgery (Appendix 3, Appendix 4). Two kits will be sent by FedEx to arrive several days prior to the surgical procedure. Included in the kits will be all media and tubes needed for shipment. Procedures for tissue handling and shipment are provided in Appendices 3 and 4, respectively.

2.2.10 FARNESYL-PROTEIN TRANSFERASE (FPTase) ACTIVITY IN PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMC): Peripheral blood mononuclear cells (PBMC) will be

collected pretreatment. The activity of FPTase will be measured in these samples as a surrogate for tumor FPTase inhibition. If the patient has consented to a tumor biopsy, PBMCs should be obtained at the same time as the biopsy (Section 2.2.9). PBMC should be separated from 20 ml of heparinized blood (10 ml in children ≤ 10 kg) as described in Appendix 5.

2.2.11 NERVE GROWTH FACTOR (NGF): A blood sample will be collected pretreatment. NGF levels will be correlated with the development of clinical neurotoxicity (Appendix 6).

2.2.12 QUALITY OF LIFE (QOL) ASSESSMENT: The National Institutes of Health (NIH) Impact of Pediatric Illness (IPI) Scale, which assesses the impact of disease and treatment on children's behavior, should be administered to all patients $\geq 6 \leq 18$ years of age and their primary caregiver prior to the start of therapy. This assessment consists of an age-appropriate questionnaire and generally takes less than 30 minutes to complete. Patients between the ages of 6 and 10 years of age should be administered the IPI-Young Child form; patients between 11 and 18 years of age should be administered the IPI-Older Child/Adolescent form; the patient's primary caregiver should receive the IPI-Parent Form. This questionnaire will not be administered to patients > 18 years.

3.0 IMPLEMENTATION OF STUDY

3.1 STUDY DESIGN

3.1.1 RANDOMIZED DESIGN

This is a randomized, cross-over, double-blinded, placebo-controlled pediatric phase II trial of oral R115777 in children and young adults with NF1 who have progressive plexiform neurofibroma(s). Patients will be randomized to either receive R115777 or placebo first. After documentation of progressive disease on the first treatment, patients will be crossed over to receive R115777 (if placebo was first given) or placebo (if R115777 was first given). The first treatment that a patient is randomized to receive (either placebo or R115777) is defined as "phase A", and the second treatment (either placebo or R115777), is defined as "phase B". There should be a 2 week washout period, during which no drug is administered, when crossing over from the first (phase A) to the second (phase B) treatment. The treatment cycle number will reset to "1" when the patient crosses over from "phase A" to "phase B". For study purposes "arm 1" is defined as treatment with R115777 first followed by placebo, and "arm 2" is defined as treatment with placebo first followed by R115777.

3.1.2 PATIENT REGISTRATION AND RANDOMIZATION

Patients must be registered by contacting Ms. Andy Gillespie at the Pediatric Oncology Branch (POB) (phone number, 301-402-1848, e-mail: gillesan@mail.nih.gov). When registering a patient, information about all entry criteria (e.g., laboratory results) must be available to allow for verification of eligibility. Dr. Brigitte Widemann (phone number: 301-496-7387, e-mail: bw42y@nih.gov) or Dr. Frank Balis (phone number 301-

496-0085, e-mail balisf@mail.nih.gov) must also be contacted to discuss the patient prior to entry on study. The completed Eligibility Checklist (Appendix 8A) and the Blinded Patient On Study Form (Appendix 8B) must be faxed to the (POB) c/o Ms. Andy Gillespie (Fax: 301-480-8871). All patients will be registered with Orkand (phone: 301-402-1732, fax: 301-480-0757) by the POB research nurse. Orkand will notify the POB research nurse and the Pharmaceutical Management Branch (PMB), CTEP, NCI of the patient's ID number using the completed Blinded Patient On Study Form (Appendix 8B). The POB research nurse will notify the registering site of the patient's ID number and, based on notification by Orkand, the PMB will ship drug for that specific patient ID number to the registering site (see section 8.0). After patient registration the POB research nurse will also ship a module with the necessary materials to administer the quality of life assessment, and the required tests outlined in Appendix 5, 6, and 7 to the participating institution. The POB research nurse must also be notified when the patient progresses after "phase A" (i.e., crossover notification to the PMB) and when the patient progresses after "phase B" (i.e., off-study notification to Orkand and PMB) by faxing the completed Progression Checklist (Appendix 9A) and the Blinded Patient Crossover/Off Study Form (Appendix 9B) to the Pediatric Oncology Branch (c/o Andy Gillespie) at (301) 480-8871. The POB research nurse will notify the PMB when a patient progresses on treatment "phase A", and Orkand and the PMB when a patient progresses on treatment "phase B" using the completed Blinded Patient Crossover/Off Study Form (Appendix 9B). A "roadmap" for the patient registration process is shown in Appendix 10.

3.1.3 DOSING SCHEDULE AND PRESCRIBING

R115777 or placebo will be administered orally q12h for 21 days followed by a 7 day rest period between cycles (28-day treatment cycle). The patient's prescriptions must include the **patient ID number** (e.g., 01C0222-01), the **patient initials** (e.g. ABC = first three letters of patient's last name), the **phase** (i.e., "Phase A" or "Phase B"), the **body surface area** (in m²), and the dose (i.e. ___ mg po q12h). "Phase A" will be defined as the treatment after initial randomization until documentation of progressive disease. "Phase B" will be defined as the treatment after the patient is crossed over to receive R115777 (if placebo was first given) or placebo (if R115777 was first given). The dosage of R115777 will be 200 mg/m²/dose (see dosing table in section 3.2). Patients will continue on therapy until they meet one of the off-study criteria (Section 3.6). There should be a 2 week washout period, during which no drug is administered, when crossing over from "Phase A" to "Phase B". Patients or their guardians will keep a diary to document the intake of each dose of R115777 and potential side effects (Appendix 11A). Each institutional pharmacy will ensure quality control procedures for R115777 and placebo allocation, and will use the Pill Count Case Report Form (Appendix 11B) for dispensing the boxes, and for counting the dispensed and returned tablets. The tearoff labels from boxes will also be attached on this form. The patient diary and the Pill Count Case Report Form should be reviewed with the patient's family after completion of every three treatment cycles, and drug should be accounted for at this

time (Appendix 11A/B). These diaries and copies of the Pill Count Case Report Form will be forwarded to Ms. Andy Gillespie (Pediatric Oncology Branch, NCI, FAX: 301-480-8871, Phone: 301-402-1848) after completion of every 3 treatment cycles.

3.1.4 MONITORING TIME TO PROGRESSION AND RESPONSE

This phase II trial is designed to determine the time to tumor progression and response rate with R115777 in patients with NF1 and progressive plexiform neurofibromas. The primary endpoint will be time to progression. Each patient will undergo MRI imaging of all known disease prior to entry on study. At the time of study entry one to three progressing plexiform neurofibroma(s) will be identified as index lesion(s), and followed for progression and response using 1D-, 2D-, and 3D-MRI. Results obtained with 1D-MRI and 3D-MRI analysis will be compared to conventional 2D-MRI analysis for their ease and reproducibility. The imaging protocol outlined in Appendix 1 will be used each time MRI scans are performed to assess response to R115777. MRI scans are performed prior to cycles 1, 4, 7, 10, and then after every 6 cycles on each study phase. If a patient is removed from a study phase because of clinical evidence of disease progression, the MRI scans should be repeated if they had not been performed within the past 4 weeks.

3.1.5 DEFINITION OF TUMOR PROGRESSION

- A $\geq 20\%$ increase in the volume (by 3D-MRI) of at least one of the index plexiform neurofibromas compared to the pretreatment volume measured prior to the start of the current treatment phase.
- Appearance of new discrete dermal neurofibroma(s) does not qualify for disease progression.
- Worsening of existing symptoms or the appearance of new symptoms that persist for more than 7 days and that are felt to be definitely related to plexiform neurofibroma should be evaluated by repeating the MRI. Patients should not be classified as having progressive disease solely on the basis of new or increased symptoms without discussing the case with the protocol Principal Investigator.
- Patients with other evidence of disease progression than outlined above should also be discussed with the Principal Investigator.

3.1.6 TISSUE PROCUREMENT

This study will attempt to obtain biopsies from easily accessible discrete neurofibromas or superficial plexiform neurofibromas from all eligible patients prior to the start of treatment, and if feasible at a later time point during treatment (at steady state, between day 15-21 on cycle 1) on each treatment phase. In addition, attempts will be made to obtain tumor specimens from any patients requiring surgery for complications of their tumors or for unrelated medical problems (Appendices 3 and 4). Peripheral blood mononuclear cells for FPTase activity (Section 3.1.8, Appendix 5) should be collected at the same time as the biopsy.

The following studies will be performed with tumor specimens (Appendices 2, 3, 4): (1) FPTase activity, (2) expression of *N-ras*, *H-ras*, and *K-ras*, and (3) *ras* mutations, and (4) NF1 mutations in the GAP related domain, (5) establishment of tumor cell lines, and (6) detailed immunohistochemical analysis (plexiform neurofibromas only). Findings will be correlated with response to treatment with R115777. It is hypothesized that *ras* mutations will be rare, germline NF1 mutations will be found in all tumors, and additional NF1 mutations will be found in many cases.

3.1.7 ESTABLISHMENT OF TUMOR CELL LINES AND TISSUE BANK

Attempts will be made to establish tumor cell lines from tumor specimens from patients treated on this trial. The tissue bank and pathology review will be open to use by the scientific community, provided IRB approval for research questions not addressed by this protocol is obtained, in order to collect more information on the pathology, genetics, and cell biology of plexiform neurofibromas.

3.1.8 FPTASE ACTIVITY IN PBMC

FPTase activity will be assessed in PBMCs pretreatment and once between days 15 and 21 of treatment (steady state) on cycle #1 of each treatment phase ("A" and "B") as a surrogate marker for the effect of R115777 (Appendix 5). PBMCs should be obtained at the same time as tumor biopsies in patients who consent to a biopsy.

3.1.9 NERVE GROWTH FACTOR (NGF)

A blood sample will be collected pretreatment, and then prior to cycles 4, 7, 10, and then after every six cycles on treatment phase ("A" and "B"). NGF levels will be correlated with the development of clinical neurotoxicity (Appendix 6).

3.1.10 MONITORING TOXICITY

The hematologic and non-hematologic toxicities of R115777 will be monitored and recorded throughout treatment with R115777 or placebo. (Appendix 1 and Sections 3.4 and 3.7). The Cancer Therapy Evaluation Program Common Toxicity Criteria (CTC) Version 2.0 will be used for toxicity assessment. A copy of the CTC version 2.0 can be downloaded from the CTEP home page at <http://ctep.cancer.gov> (Section 5.3).

3.2 DRUG ADMINISTRATION

R115777 or placebo in 50 mg tablets will be manufactured by Janssen Pharmaceuticals and supplied by CTEP, NCI under IND #58359. Tablets will be administered orally immediately after a meal every 12 hours for 21 days followed by a 7 day rest period (28 day cycles). The dose of R115777 or placebo will be 200 mg/m² every 12 hours, and is based on the maximum tolerated dose on the intermittent dosing schedule from the pediatric phase I trial. See Section 2.2.1 for calculation of BSA. Each patient's dose will be rounded to the nearest 50 mg according to the following dosing table:

BSA (m ²)	R115777 / Placebo (mg po q12h)	R115777 / Placebo (# of 50 mg tablets po q12h)
0.00 - 0.37	50	1
0.38 - 0.62	100	2
0.63 - 0.87	150	3
0.88 - 1.12	200	4
1.13 - 1.37	250	5
1.38 +	300	6

Tablets may be crushed for easier consumption in young children.

R115777/placebo should be re-taken if vomiting occurs within 30 minutes of taking the dose.

Patients who have to undergo an elective major surgical procedure (not to include the biopsy of discrete neurofibromas requested on this protocol) should stop taking study drug one week before the surgery, and are allowed to resume study drug 2 weeks after surgery, provided they have recovered from the procedure.

3.3 MODIFICATIONS FOR TOXICITY

Patients who experience **grade 2 toxicity** (CTC v. 2) related to R115777 or placebo should have R115777/placebo withheld until the toxicity resolves (grade ≤ 1) and then restarted at the same dose level. If the grade 2 toxicity recurs, the R115777/placebo dose should be withheld again until the toxicity resolves (grade ≤ 1) and then reduced by 50 mg per dose. For patients with a BSA ≤ 0.37 the dose will be reduced to 50 mg once daily. If the grade 2 toxicity recurs the patient should be taken off protocol. If a grade 2 toxicity persists for >10 days off therapy, the patient should be discussed with the PI.

Patients who experience **grade 3 or 4 toxicity** related to R115777 or placebo should have their dose withheld. If the toxicity returns to grade ≤ 1 within 10 days, patients may resume R115777/placebo at a dose reduced by 50 mg per dose. For patients with a BSA ≤ 0.37 the dose will be reduced to 50 mg once daily. If the toxicity persists at grade ≥ 2 for >10 days without administration of R115777/placebo or the grade 3 or 4 toxicity recurs at the lower dose level, the patient should be removed from the study (see Section 3.6.2).

If the toxicity warrants, the physician can determine whether the patient is receiving R115777 or placebo (unblind the study) by calling Dr. Brigitte Widemann (301) 496-7387 or Dr. Frank Balis (301) 496-0085. These physicians can also be reached through (301) 496-7704 or the NIH page operator (301) 496-1211 (see section 8.2.5). Pediatric Oncology Branch staff will require the protocol number (i.e., 'T99-0090'), the patient's ID number (e.g., '00-C0222-01'), the phase (i.e., 'A' or 'B'), and the patient's

initials (first three letters of last name, eg., 'ABC') to unblind the patient. The unblinded patient must be removed from the study.

3.4 ON STUDY EVALUATION (SEE APPENDIX 7)

3.4.1 HISTORY & PHYSICAL EXAMINATION: Every 2 weeks during the first 3 cycles on each treatment phase ("A", "B"). Physical exam should include assessment of performance status (documentation if changed from baseline), measurement of visible or palpable neurofibroma, height, weight and body surface area prior to every treatment cycle. A complete neurologic examination should be performed and focus on signs of sensory peripheral neuropathy. After cycle 3 perform prior to each cycle. History and physical examination will be documented in case report forms as outlined Section 5.1.1.

3.4.2 PHOTOGRAPHY: When possible, plexiform neurofibromas that are visible on the body surface should be photographed prior to treatment cycle 1, 4, 7, 10, and then after every 6 cycles on each treatment phase ("A", "B"). A size marker should be taped to the skin in the field of view when appropriate, and the plexiform neurofibroma will be photographed so that it fills the frame. Frontal and side images will be taken, as appropriate. Copies of photographs identified by the patient ID number, date, treatment phase ("A" or "B"), and treatment cycle should be sent to:

Andy Gillespie, R.N.
Pediatric Oncology Branch, NCI
10 Center Drive, MSC 1928
Bldg. 10/Rm. 13N240
Bethesda, MD 20892-1928

3.4.3 LABORATORY ASSESSMENT (see Appendix 7). Laboratory studies will be documented in case report forms as outlined Section 5.1.1.

Hematology: During the first 3 cycles of treatment on each treatment phase ("A", "B"), obtain complete blood count, differential and platelet count every other week (more frequent monitoring may be performed if the ANC $<1,000/\text{mm}^3$ or platelet count $<50,000/\text{mm}^3$). During subsequent cycles complete blood count, differential, and platelet count will be obtained prior to each cycle. PT, PTT and fibrinogen will be obtained prior to each treatment cycle on each treatment phase.

Chemistries: During the first 3 cycles of treatment on each treatment phase ("A", "B"), obtain electrolytes, creatinine, calcium, magnesium, phosphorus, SGPT, and bilirubin every other week. During subsequent cycles these tests should be performed prior to each treatment cycle.

Urinalysis: Prior to treatment cycle 1, 4, 7, 10, and then q 6 cycles on each treatment phase ("A", "B").

3.4.4 RADIOGRAPHIC EVALUATION: Evaluate the index lesions by MRI prior to cycle 1 on treatment phase "A", and prior to cycle 4, 7, 10, and then after every 6 cycles on each treatment phase ("A", "B"). The protocol outlined in Appendix 1 will be used each

time MRI examinations are performed to assess progression or response to R115777 or placebo. In patients with clinical suspicion of disease progression MRI analysis should be performed earlier using the protocol outlined in Appendix 1. At the time of disease progression on treatment phase "A", if possible, a MRI scan of all known measurable plexiform neurofibromas in addition to the index lesions should be performed, in order to have a new baseline prior to treatment phase "B" (Appendix 1).

3.4.5 OPTHALMOLOGIC EVALUATION: Prior to or within the first three days of starting treatment phase "A", and prior to or within the first 3 weeks of starting treatment phase "B". Exam should include visual fields if the patient is able to cooperate with the exam and examination of the lens for opacifications.

3.4.6 TISSUE PROCUREMENT: In patients with easily accessible discrete neurofibromas or superficial plexiform neurofibromas, who consent to the procedure, biopsies will be performed prior to the first dose of treatment on phase "A", and if feasible at one steady state time point on each treatment phase ("A", "B") (between day 15-21 on cycle #1) of treatment. In addition, attempts will be made to obtain tumor specimens from any patients requiring surgery for complications of their tumors or for unrelated medical problems. Peripheral blood mononuclear cells for FPTase assay (Section 3.4.7, appendix 5) should be obtained at the same time as biopsy whenever possible. As this is an invasive procedure, patients may refuse biopsy and still be eligible for the study.

Two kits will be supplied for handling and shipping of tumor specimens. To obtain the kits, please call Ms Andy Gillespie (301)-402-1848. Kits will be sent by FedEx to arrive several days prior to the surgical procedure. Included in the kits will be all media and tubes needed for shipment. Procedures for tissue handling and shipment are provided in Appendices 3 and 4, respectively.

3.4.7 FPTase ACTIVITY IN PBMC: PBMC should be collected pretreatment, and once between days 15 and 21 of treatment (steady state) on cycle #1 of each treatment phase ("A" and "B"). If the patient has consented to a tumor biopsy, PBMCs should be obtained at the same time as the biopsy (Section 3.4.6). PBMC should be separated from 20 ml of blood (10 ml in children ≤ 10 kg) as described in Appendix 5.

3.4.8 NERVE GROWTH FACTOR: A blood sample will be collected pretreatment, and prior to cycles 4, 7, 10, and then after every six cycles on each treatment phase ("A", "B"). Nerve growth factor levels will be correlated with the development of clinical neurotoxicity (Appendix 6).

3.4.9 QUALITY OF LIFE (QOL) ASSESSMENT: The National Institutes of Health (NIH) Impact of Pediatric Illness (IPI) Scale, which assesses the impact of disease and treatment on children's behavior, should be administered to all patients ≥ 6 years to 18 years of age and their primary caregiver prior to the start of therapy, and then prior to cycles 4, 7, 10, and then after every 6 cycles on each treatment phase. This questionnaire has not been completely validated, and means and standard deviations for different subgroups of patients on the scale and subscales are not available yet. This assessment

consists of an age-appropriate questionnaire and generally takes less than 30 minutes to complete. Patients between the ages of 6 and 10 years of age should be administered the IPI-Young Child form; patients between 11 and 18 years of age should be administered the IPI-Older Child/Adolescent form; the patient's primary caregiver should receive the IPI-Parent Form. This questionnaire will not be administered to patients > 18 years. Patient and parent response forms should be photocopied after completion and copies sent to Ms. Andy Gillespie, Pediatric Oncology Branch, NCI, FAX: (301)-480-8871, Building 10, Room 13N240, 10 Center Drive, Bethesda, MD 20892-1928 within 2 weeks of completion of the cycle of therapy. Any questions regarding the administration of the IPI Scale should be addressed to Pam Wolters, Ph.D. at phone: 301-496-0561, e-mail: pw34m@nih.gov.

3.5 CONCURRENT THERAPY

Other cancer chemotherapy, radiation therapy, immunotherapy, or investigational agents can not be administered to patients receiving R115777 or placebo.

Alternative Therapy: Oral vitamin or nutritional supplements may be used if approved by the patient's primary physician, and should be recorded in the patient's history and diary.

Pharmacokinetic data suggest that H₂ antagonists and proton pump inhibitors do not alter the exposure to R115777 to a clinically significant extent. Patients may use proton pump inhibitors or H₂ antagonists during the treatment portion of this study. However, patients should be instructed to use antacids (Mg- or Al-containing formulations) AT LEAST 2 hours before or after intake of the oral study drug.

3.6 OFF STUDY CRITERIA

3.6.1 ADMINISTRATIVE: A patient may be taken off the study for the following non-medical or administrative reasons:

- Patient refusal of further treatments (reasons must be noted on the patient's CRF).
- It is deemed in the best interest of the patient. In this instance the Principal Investigator should be notified and the reasons for withdrawal should be noted in the CRF.
- Serious protocol violation as determined by the PI or representative from CTEP.

3.6.2 TOXICITY: Recurrent grade 3 or 4 toxicity after dose reduction or persistent toxicity grade ≥ 2 for >10 days without administration of drug that is considered primarily related to study drug (Section 3.3). Persistent (>10 days) grade 2 toxicity should be discussed with the PI prior to removing the patient from the study. The protocol Principal Investigator and CTEP should be notified immediately in the event of severe or life-threatening toxicity (Dr. Brigitte Widemann, 301-496-7387, 301-496-1211).

page operator, and CTEP, Investigational Drug Branch (301) 230-2330 (recorder after hours).

If toxicity necessitates unblinding the study drug for a patient, the patient should be removed from the study.

3.6.3 TUMOR PROGRESSION: Any patient with clinical or radiographic evidence of progressive disease (see Section 3.1.5) on treatment “phase A”, as documented by 3D-MRI, following any treatment cycle will be switched to treatment “phase B” (from R115777 to placebo or vice versa). After disease progression on both treatment phases, patients will be removed from study (see Sections 3.1.5 and 5.2). The POB research nurse must be notified when the patient progresses after “phase A” (crossover notification to PMB) and when the patient progresses after “phase B” (i.e., off-study notification to Orkand and PMB) by faxing the completed Tumor Progression Checklist and the Crossover / Off-Study Form (Appendix 9A/B) to the Pediatric Oncology Branch (c/o Andy Gillespie) at (301) 480-8871.

3.6.4 The development of a concurrent serious medical condition that might preclude or contraindicate the further administration of R115777.

3.7 POST-STUDY EVALUATION

The following tests and procedures should be performed, if possible, at the time a patient comes off study regardless of the reason for coming off study, unless the test or procedure has been performed in the past 6 weeks (2 weeks for physical examination and laboratory assessment).

3.7.1 HISTORY & PHYSICAL EXAMINATION (including a neurologic exam, performance status, and measurement of visible or palpable tumor lesions).

3.7.2 PHOTOGRAPHS of visible lesions (See Section 3.4.2)

3.7.3 LABORATORY ASSESSMENT

Complete blood count, differential and platelet count, PT, and PTT.

Electrolytes, creatinine, calcium, magnesium, phosphorus, SGPT, bilirubin.

Urinalysis.

3.7.4 MRI Scan of the index lesions and any other progressing lesions using the protocol outlined in Appendix 1.

4.0 SUPPORTIVE CARE

GENERAL: Appropriate antibiotics, blood product support, antiemetics and general supportive care will be used as indicated.

HEMATOPOIETIC GROWTH FACTORS: Hematopoietic growth factors (e.g., EPO, G-CSF, GM-CSF) should **not** be administered except to those patients with either grade 4 neutropenia and blood culture positive septicemia, or grade 4 neutropenia of ≥ 7 days duration.

5.0 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

The POB, NCI will coordinate data collection and supply the data to the trial sponsor (CTEP) via the CDUS online system. Data will also be entered into the NCI Center for Cancer Research (CCR) C3D database. Documentation and date of IRB approval must be provided to CTEP and the POB, NCI prior to initial patient entry from each institution. The completed Eligibility Checklist and On-Study Form (Appendix 8 A/B) must be faxed to Ms. Andy Gillespie at (301) 480-8871 prior to patient entry onto the trial. The completed Tumor Progression Checklist and Crossover / Off-Study Form (Appendix 9A/B) must be faxed to Ms. Andy Gillespie at the time a patient has documented tumor progression on treatment phase "A" and on treatment phase "B".

5.1.1 CASE REPORT FORMS

Case Report Forms have been developed by the POB. CRFs should be completed after each patient evaluation and submitted within 2 weeks of completion of each evaluation to:

Pediatric Oncology Branch, NCI
c/o Ms. Andy Gillespie
FAX: (301) 480-8871
Bldg. 10/Rm. 13N240
10 Center Drive, MSC 1928
Bethesda, MD 20892-1928

The following forms should be submitted to the POB:

ELIGIBILITY CHECKLIST AND BLINDED PATIENT ON STUDY FORM (APPENDIX 8 A/B): To be completed at study entry and forwarded to Ms. Andy Gillespie (301) 480-8871 (Phone, 301-402-1848)

PROGRESSION CHECKLIST AND BLINDED PATIENT CROSSOVER / OFF-STUDY FORM (Appendix 9A/B): To be completed and forwarded to Ms. Andy Gillespie (301) 480-8871 (Phone, 301-402-1848) when a patient progresses on treatment phase "A" and "B".

PATIENT DIARIES AND PILL COUNT CASE REPORT FORM (APPENDIX 11A/B): Patients or their guardians will keep a diary to document the intake of each dose of R115777 or placebo and potential side effects (Appendix 11A). Each pharmacy will use the Pill Count Case Report Form (Appendix 11B). The completed diaries and Pill Count Case Report Forms will be forwarded to Ms. Andy Gillespie after every three treatment cycles at (301) 480-8871 (Phone, 301-402-1848).

MRI STUDIES (Appendix 1): A copy of the MRI protocol used to obtain the baseline MRI study should be Faxed to Ms. Andy Gillespie within 1 week of obtaining the MRI study. MRI studies should be submitted electronically or on CD or optical disk to the

NCI POB within 1 week of obtaining the study. The institutional radiology report for each study should be faxed to Ms. Andy Gillespie within 1 week.

QOL ASSESSMENT (NIH IPI SCALE) FORMS: Patient and parent response forms should be photocopied after completion and copies sent to Ms. Andy Gillespie, Pediatric Oncology Branch, NCI, FAX: (301)-480-8871, Building 10, Room 13N240, 10 Center Drive, Bethesda, MD 20892-1928 within 2 weeks of completion of the cycle of therapy. Any questions regarding the administration of the IPI Scale should be addressed to Pam Wolters, Ph.D. at phone: 301-496-0561, e-mail: pw34m@nih.gov.

LABORATORY STUDIES: Results of laboratory studies requested per protocol should be faxed to Ms. Andy Gillespie within 1 week of performing the study.

Protocol violations should be directly reported to Dr. Brigitte Widemann (phone: 301-496-7387, fax: 301-480-8871, e-mail: bw42y@nih.gov).

Patients will be identified in all data collection forms and on photographs only by their initials and study number in an effort to maintain patient confidentiality. All patient documents, including informed consent and case report forms, will be kept in designated offices, in locked file cabinets with access only to personnel involved in the clinical trial. The NCI Center for Cancer Research (CCR) C3D electronic database is password protected and allow access only to persons directly involved in the clinical trial. All documents will be stored for at least 2 years after the drug has received marketing approval, or after the decision has been made not to market the drug.

5.2 RESPONSE CRITERIA

Response is assessed at the time that follow-up 3D-MRI scans are performed (prior to cycles 4, 7, 10, then q6 cycles). For the purpose of determining the level of response (complete, partial, minor, etc.) measurements from the follow-up scans are compared to the tumor size in the pretreatment MRI scan using 3D data analysis. Response determined using 3D-MRI volumetric analysis will be compared with 2D- and 1D-MRI measurements.

COMPLETE RESPONSE (CR): A complete resolution of all measurable or palpable soft tissue tumors for ≥ 4 weeks and no appearance of new lesions.

PARTIAL RESPONSE (PR): A $\geq 50\%$ reduction in the sum of the volume of all index lesions for ≥ 4 weeks.

MINOR RESPONSE (MR): A $\geq 25\%$ but $< 50\%$ reduction in the sum of the volume of all index lesions for ≥ 4 weeks.

STABLE DISEASE (SD): A $< 20\%$ increase, and $< 25\%$ decrease in the sum of the volume of all index lesions for ≥ 4 weeks.

PROGRESSIVE DISEASE (PD):

- A $\geq 20\%$ increase in the volume (by 3D-MRI) of at least one of the index plexiform neurofibromas compared to the pretreatment volume measured prior to the start of the current treatment phase.
- The appearance of new discrete subcutaneous neurofibromas does not qualify for disease progression.
- Worsening of existing symptoms or the appearance of new symptoms that persist for more than 7 days and that are felt to be definitely related to the plexiform neurofibroma should be evaluated by repeating the MRI. Patients should not be classified as having progressive disease solely on the basis of new or increased symptoms without discussing the case with the protocol Principal Investigator.
- Patients with other evidence of disease progression than outlined above should also be discussed with the Principal Investigator.

5.3 TOXICITY CRITERIA

Toxicity will be graded according to the CTEP Expanded Common Toxicity Criteria, version 2. The Cancer Therapy Evaluation Program Common Toxicity Criteria (CTC) Version 2.0 will be used for toxicity assessment. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>).

5.4 STATISTICAL CONSIDERATIONS

5.4.1 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 2.1. 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 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.

5.4.2 STATISTICS AND FEASIBILITY

The primary objective of the study is to determine whether R115777 ("drug") is able to increase the time to progression of patients who have NF1 with progressive plexiform neurofibromas. The study will be conducted as a crossover, two-arm randomized, double-blind, placebo controlled trial. After being randomized to drug or placebo, patients will be followed until progression. Once patients have progressed (documented by MRI), they will be crossed over to receive the placebo if they originally

received drug, and drug if they originally received placebo. Because the time until crossover is dependent on time until progression, this differs from a classic crossover study, in which patients are followed on both treatment arms for a predetermined fixed period of time, evaluated, given a wash-out period, and then followed identically on the other agent. As such, results from the first placebo vs. drug period will be used to determine sample size, and will constitute the primary endpoint of time to disease progression. The natural history of the growth rate and range of plexiform neurofibromas is not well known. In addition to the analysis of time to disease progression on the first treatment phase, a paired comparison of the first and second treatment phase (each patient will serve as his/her own control) will be performed using appropriate non parametric methods. This analysis will also help provide additional information on the differences in the natural history of NF1, and also address the effect of other variables, for example age differences, which may impact on the growth rate of plexiform neurofibromas.

Because the estimate of time to progression for patients eligible for this trial is approximately 6 months, it would be desirable to increase this time to 12 months. A one-tailed hypothesis will be used since it would only be considered interesting to see the improvement of drug compared to placebo. With 80% power and a one-tailed $\alpha=0.05$, in order to detect a difference in median time to progression (during the first part of the trial) between the two arms of 6 vs. 12 months, 30 patients per arm are required (60 total) assuming 36 months of accrual and 12 months of additional follow-up following entry of the last patient. Kaplan-Meier analysis using log-rank statistics will be used to perform the required evaluation. We plan to replace patients who were diagnosed with a malignant peripheral nerve sheath tumor (MPNST) after enrolling on study, as these patients will not be evaluable for the primary outcome measure, which is time to progression of progressive plexiform neurofibromas. For this reason we will increase the accrual ceiling to 63 patients

Randomization of patients between the two study arms will be performed centrally by Orkand (See Section 3.1.1, 3.1.2). With more than one institution participating, it is expected that 20 patients per year can be entered onto the trial, with an expected accrual period of 3 years.

This trial will be monitored by the NCI/DCS Data Safety and Monitoring Board. Due to the projected accrual rate, it is expected that 3 interim evaluations and a final evaluation will take place at each of 4 consecutive annual meetings of the DSMB. Using the O'Brien-Fleming approach, if the p-values at the following evaluations are less than or equal to those tabled below, then the trial would be declared to have a statistically significant result; no further accrual would be required once such a determination has been made.

Evaluation #	Threshold p-Value (one-tailed)
1	0.00005

2	0.0039
3	0.0184
4 (FINAL)	0.0412

In addition, if, at any annual evaluation, a conditional power analysis indicates that there is a minimal chance of declaring a significant advantage to drug with the addition of the remaining planned patients based on results to date and the hypothesized results, then the DSMB may choose to close the study to further accrual.

Time to progression between the two study arms will be compared separately for the two periods of the cross-over study; initial treatment and second (crossover) treatment. Both comparisons will be reported in order to describe the effect of drug on this endpoint. In addition, because each patient will have received both placebo and drug, comparisons of time to progression can be undertaken between both treatment conditions, employing methodology for paired subject data in order to further interpret the findings.

The quality of life of patients treated with R115777 and placebo on this study will be assessed using the National Institutes of Health (NIH) Impact of Pediatric Illness (IPI) Scale (Section 1.2.8), and scores of patients will be compared using the paired t-test.

5.5 MULTI-INSTITUTIONAL GUIDELINES

5.5.1 IRB APPROVALS

The PI from each participating institution will provide the Study Coordinator with a copy of the initial IRB protocol approval and the yearly IRB continuing reviews, and the Study Coordinator will submit these to the NCI IRB. Registration will be halted at a participating institution if a current continuing approval is not on file at the NCI IRB.

5.5.2 AMENDMENTS AND CONSENTS

The PI from each participating institution will provide the Study Coordinator with a copy of IRB approval of all amendments to the protocol or consent, and the Study Coordinator will submit these institutional reviews to the NCI IRB.

5.5.3 PATIENT REGISTRATION

All patients entered at the POB, NCI will be registered with the DCS Central Office (ORKAND). The completed eligibility checklist and On-Study Form (Appendix 8 A/B) must be FAXed to the POB prior to enrollment on the trial.

5.5.4 DATA COLLECTION AND TOXICITY REPORTING

The trial is being sponsored by CTEP and monitored through the CDUS system. Case report forms developed by the Pediatric Oncology Branch will be used for submitting clinical data to the coordinating center and this data will be entered into the NCI CCR C3D database. Data must be

submitted to the Coordinating Center within 2 weeks of completing each treatment cycle while the patient is on treatment. All adverse events from participating institutions will be submitted to the NCI IRB by the Study Coordinator.

5.5.5 DATA AND CENTER AUDITS

The trial will be audited by the trial sponsor CTEP for compliance and safety. In addition, the NCI CCR will audit this trial via contract for compliance and safety. Volumetric MRI analysis will be used to determine the primary study endpoint, which is disease progression. The volumetric analysis for all measurements will be performed centrally at the NCI, POB with Dr. N. Patronas serving as the responsible neuroradiologist for this trial.

6.0 HUMAN SUBJECTS PROTECTIONS

6.1 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 5.4.1. None of these groups are being 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 and unknown risks that R115777 could pose to the fetus or newborn. This trial is designed to determine the activity of R115777 in childhood with NF1 and plexiform neurofibromas and, therefore, children will be entered onto this research trial. Patients who are ≥ 18 years will be offered the opportunity to assign DPA prior to study entry.

6.2 PARTICIPATION OF CHILDREN

This trial is designed to study the effect of R115777 on time to disease progression in children and young adults with progressive plexiform neurofibromas. Therefore children who meet eligibility criteria for this trial will be entered in the study. Children will be evaluated and cared for by physicians trained in pediatrics and pediatric oncology, and will be followed in the Pediatric Oncology Branch clinic.

6.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

This trial will be a randomized, cross-over, double-blinded, placebo-controlled pediatric phase II trial of oral R115777 in children and young adults with NF1 who have progressive plexiform neurofibroma(s). Each patient will serve as his/her own control for the primary endpoint of time to progression. Because of the unpredictable nature of tumor growth in NF1, alternative designs without placebo control could bias observation, and there is no standard treatment to which R115777 may be compared. In addition, each patient will receive study medication provided there is disease progression, and therefore may derive benefit from the trial. R115777 is a farnesyltransferase inhibitor. It was designed to inhibit the farnesylation of *ras* and

therefore inhibit the activity of mutated *ras* proteins. However, it may also be useful for other mutations upstream from the farnesylation of *ras*, such as is found in patients with NF1. Since neurofibromin, the product of the NF1 gene, is decreased in tumors from patients with NF1, and since this is associated with a constitutively activated *ras* protein, R115777 is a rational therapeutic approach for patients with plexiform neurofibromas. The potential benefit from participation in this trial is the stabilization or reduction in the size of the tumor(s), relief of symptoms caused by the tumor(s), and prolongation of life. The primary risk to the subjects from participation in this trial is from R115777 toxicity (primarily myelosuppression). Toxicities from R115777 are outlined in Section 1.2.5, 1.2.6, and 8.1.9 and have been reversible when they occur. The attempt will be made to obtain tumor biopsies from easily accessible tumor nodules at several time points during the study to answer study related research questions. Tumor samples will be contributed to a central tissue repository, and will be made available to researchers who obtain IRB approval to study additional research questions. Samples will be identified by a code number that can be traced to the patient only by contacting the trial coordinating center. However, as the tumor sample is linked to the patient'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 patients enrolled on the study have neurofibromatosis. All research results will be kept confidential. Patients who do not give permission for tumor biopsies will still be eligible for the treatment part of this study. Patients also have the right to withdraw the tumor specimen from the tissue repository at any time.

6.4 RISK/BENEFIT ANALYSIS

The primary objective of this phase II trial is to define the time to progression of plexiform neurofibromas treated with R115777 or placebo, and thus patients 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 to children, but presents the potential for direct benefit to individual subjects. Although patients will be treated with placebo, the risk of placebo is minimal and no other standard therapy is available. In addition, all patients will receive R115777, provided there is disease progression on the first treatment phase.

6.5 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 or the patient's parents or guardian if he/she is a child, and a signed informed consent document will be obtained. The investigators have received a waiver from the IRB to allow only one parent to sign the informed consent to enter a child on the protocol. Because many patients must travel to the clinical site from long distances at substantial expense, requiring both parents to be present for the consent process could be a financial

hardship for many families. Consent will be obtained by the PI or an associate investigator on the trial. Where deemed appropriate by the clinician and the child's parents or guardian, the child will also be included in all discussions about the trial. Age appropriate assent forms for children from 7 through 12 years, and for children from 13 through 17 years have been developed and will be signed by the pediatric patients in order to obtain written assent. This is a multi-institutional trial, and the NCI as coordinating center will require evidence of local IRB approval of the protocol prior to allowing for accrual of patients at that institution. This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

6.6 HANDLING OF RESEARCH SAMPLES

This study is conducted at and coordinated by the Pediatric Oncology Branch, NCI. Sample labeling, collection and initial processing will be conducted as outlined in the study Section 3.4.6, 3.4.7, and 3.4.8, as well as in Appendices 2 to 6. Tumor samples sent to the central tissue procurement facility at Washington University will be handled as described in Section 3.4.6 and in Appendix 2. Should tumor sample be left after completion of research studies described in the protocol, prospective approval from the IRB with oversight of the tissue bank will be obtained prior to performing additional studies. This is also described in the informed consent. Blood samples sent to the NCI for analysis of farnesyltransferase activity (Section 3.4.7, Appendix 5), or for nerve growth factor analysis (Section 3.4.8, Appendix 6) will be stored in designated monitored freezers at -70°C or -20°C as indicated in the protocol in the Pharmacology & Experimental Therapeutics Section (PETS) Laboratory, POB, NCI on 1 West. Samples will be identified by protocol specific patient ID number, and will be tracked using the PETS pharmacokinetics filemaker database. Samples will be analyzed for farnesyltransferase activity and nerve growth factor at the NCI, POB and be considered the responsibility of Brigitte Widemann, MD. Once analyzed for studies outlined in this protocol any remaining samples will be stored by the POB, NCI until the study is complete, and the manuscript describing the study has been accepted for publication. At this point remaining samples will be destroyed. The study will remain open and status reported to the NCI IRB until all samples have been analyzed, reported or destroyed. Unintentional loss or destruction of any samples will be reported to the NCI IRB as part of annual continuing reviews. Any use of samples not outlined in Sections 3.4.7 and 3.4.8 or in Appendices 5 and 6 will require prospective NCI IRB review and approval.

7.0 DATA REPORTING

Unless otherwise stated, all forms should be submitted to:

Andy Gillespie, R.N.
Pediatric Oncology Branch, National Cancer Institute
Building 10/Room 13N240, 10 Center Drive
Bethesda, MD 20892

Phone (301) 402-1848

FAX (301) 480-8871

7.1 PATIENT REGISTRATION AND RANDOMIZATION

See Section 3.1.2 and Appendix 10. The eligibility checklist is in Appendix 8 A/B.

7.2 CASE REPORT FORMS

The POB will provide Case Report Forms for recording relevant clinical data for each patient entered on the trial (Section 5.1). The Progression Checklist (Appendix 9A/B) must be submitted before patients can be crossed over from phase A to phase B (see Appendix 10). Patient diaries and Pill Count Case Report Forms (Appendix 11A/B) should be provided to patients and their families and submitted after completion with the label from the patient's prescription attached after completion of every 3 treatment cycles.

7.3 SAFETY REPORTING

7.3.1 ADVERSE EVENTS

Adverse events are any unfavorable and unintended sign (including an abnormal laboratory finding) symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable or definite).

Life-threatening adverse events are any adverse event that places the patient or subject, in view of the investigator at an immediate risk of death from the reaction.

Serious adverse events are any adverse event occurring at any dose that result in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, and other medically significant events.

Unexpected adverse events are any adverse events, which are not listed in the Agent Specific Adverse Event List (ASAEL) which is a subset of the Comprehensive Adverse Events and Potential Risks List (CAEPR).

Expected adverse events are those events listed in the Agent Specific Adverse Event List (ASAEL) which is a subset of the Comprehensive Adverse Events and Potential Risks List (CAEPR) (Section).

All observed or volunteered adverse events, regardless of treatment group or suspected causal relationship to study drug, will be recorded on the Adverse Event page(s) of the case report form. 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., electrocardiogram changes, abnormal laboratory test results) that result in a change in study drug dosage should also be recorded.

Adverse events should be graded according to the CTEP Common Toxicity Criteria version 2, which can be downloaded from <http://ctep.cancer.gov>. Next it will be determined if the adverse event is related to the medical treatment (attribution). If so, it will be determined whether the adverse event is expected or unexpected. Using the guidelines outlined in Section 7.3.2 adverse events will then be reported to the NCI using a routine report (CDUS), and if required, the Adverse Event Expedited Reporting System (AdEERS), an electronic system for expedited submission of adverse event reports, in addition to the CDUS.

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

7.3.2 ADVERSE EVENT REPORTING

The NCI/DCTD requirements for reporting Adverse Events (AE) will be followed. All serious adverse events, and the adverse events outlined in the table below regardless of attribution require expedited reporting.

Expedited AE reporting for this study must use AdEERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (<http://ctep.cancer.gov>). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (<http://ctep.cancer.gov>).

In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at <http://ctep.cancer.gov>) and faxed to 301-230-0159. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site.

Phase 2 and 3 Trials utilizing an Agent under a CTEP IND: AdEERS Reporting Requirements for Adverse Events That Occur Within 30 Days¹ of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days
¹ Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows: AdEERS 24-hour notification followed by complete report within 5 calendar days for: <ul style="list-style-type: none"> • Grade 4 and Grade 5 unexpected events AdEERS 10 calendar day report: <ul style="list-style-type: none"> • Grade 3 unexpected events with hospitalization or prolongation of hospitalization • Grade 5 expected events ² Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.									
December 15, 2004									

Note: All deaths on study must be reported using expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
 - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
 - “10 calendar days” – A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
- The Comprehensive Adverse Events and Potential Risks List (CAEPR), the Agent Specific Adverse Event List (ASAEEL), and a list of toxicities with yet undetermined relationship to R115777 can be found in the protocol in Section 8.1.11.

A list of all known toxicities can be found in the protocol document (Section 8) or consent form.

Reactions judged definitely not treatment related should not be reported. However, a report should be submitted if there is reasonable suspicion of drug effect. Hospitalizations for procedures judged definitely not treatment related do not require expedited reporting.

All reportable adverse events (as defined above), regardless of treatment group or suspected relationship to study drug, must be reported to:

Brigitte Widemann, M.D.
Pediatric Oncology Branch
10 Center Drive, 10-CRC, Room 1-5750
Bethesda, MD 20892
Phone: (301) 496-7387
FAX: (301) 402-0575
E-mail: bw42Y@nih.gov

All serious adverse events (as defined in Section 7.3) for NCI patients must be reported to the Institutional Principal Investigator, Dr. Brigitte Widemann, M.D., within 7 days (see contact information above).

The NCI Protocol PI will report to the NCI-IRB:

- All serious adverse events (SAEs) that are **not** in the consent form, but are possibly, probably or definitely related to the research. A SAE is defined as an untoward medical occurrence that
 - resulted in a death;
 - was life-threatening;
 - required or prolonged hospitalization;
 - caused persistent or significant disability/incapacity;
 - resulted in congenital anomalies or birth defects; or
 - required intervention to prevent permanent impairment or death.
- All other deaths that occur within 30 days of receiving R115777/placebo.
- All grade 3 and 4 (CTC v3) events that are not in the consent and that are possibly, probably or definitely related to the research.

Reports must be received by the NCI-IRB within 7 days of notification of the event.

Forms for submission of an AE to CTEP/NCI/DCTD and the POB/NCI can be obtained from the CTEP website at <http://ctep.cancer.gov>.

The NCI POB will distribute Adverse Event Expedited Reports distributed by CTEP to responsible Investigators at participating sites.

7.4 ASSURANCES

Each participating institution is required to maintain a current Multiple Project Assurance 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.

7.5 IRB APPROVALS

As the coordinating center for this clinical trial, the POB will be responsible for verifying Institutional Review Board (IRB) approval of the protocol. Each participating institution must provide a copy of their IRB approval to the POB before that center can enter and register a patient on study. The participating institutions must also provide the POB with a copy of documentation that the protocol has undergone yearly IRB review and a copy of IRB approvals for any protocol amendments.

7.6 PATIENT DATA REPORTING AND AUDITS

Clinical data from patients treated on this trial will be submitted to the POB on the provided case report forms and will be entered into the CCR C3D database by POB data managers/research nurses. The study will be monitored by Clinical Data Update Systems (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due to CTEP Jan 31, April 30, July 31, and October 31. 3-D MRI analysis for assessing the volume of plexiform neurofibromas will be performed centrally. The NCI Clinical Trials Monitoring Service (CTMS) may independently audit selected charts on patients who are treated on this trial. Selected patient charts to be audited must be sent to the POB from participating institutions. In addition, the NCI CCR will audit this trial via contract for compliance and safety.

8.0 PHARMACEUTICAL INFORMATION

8.1 R115777 AND PLACEBO

R115777 with matching placebo will be provided to study participants free-of-charge by the Janssen Research Foundation and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Note that this study involves a crossover from R115777 to placebo (Arm 1) or from placebo to R115777 (Arm 2). The medication for the first phase (initial randomization) will be labeled as "Phase A", and the medication for the second phase (crossover randomization) will be labeled as "Phase B", regardless of which arm the patient is randomized to. When dispensing the medication, please be certain that the physician has specified on the prescription (1) the patient ID number [e.g., '01C0222-01']; (2) the patient initials [e.g., 'ABC' = first three letters of the patient's last name]; (3) the phase [i.e., "Phase A" or "Phase B"]; (4) the body surface area [in m²]; and (5) the dose [i.e., "___mg po q12h"]. Check to be certain that the patient ID number and phase specified on the patient's box(es) of medication correspond to the patient ID number and phase specified on the patient's prescription. If the patient ID number or phase is missing from the patient's prescription, you must contact the physician!

R115777 (NSC 702818 / IND #58359) and matching placebo will be supplied in blister packages in a cardboard box. Each box will contain 70 - 50mg tablets and will be sealed with a tamper-evident seal. Each box will be labeled with:

- the protocol number (i.e., 'T99-0090')
- the patient ID number (e.g., '01C0222-01' where '01C0222' represents the NIH Clinical Center protocol number and '01' represents a patient sequence number assigned at registration)
- the patient initials (e.g., 'ABC' = first three letters of the patient's last name)
- a blank line for the patient's name
- the phase (i.e., 'Phase A' or 'Phase B')
- the agent identification (i.e., 'R115777 50mg or Placebo')
- the number of tablets (i.e., '70 tablets')
- administration instructions (i.e., 'Take ___ tablets every 12 hours after meals.')
- storage instructions (i.e., 'Store at controlled room temperature [59° to 77° F]. Protect from moisture.')
- emergency contact instructions
- a Julian date

At the time the box is dispensed to the patient, the pharmacist should enter the patient's name and the number of tablets (based on the patient's BSA / prescribed dose) in the spaces provided.

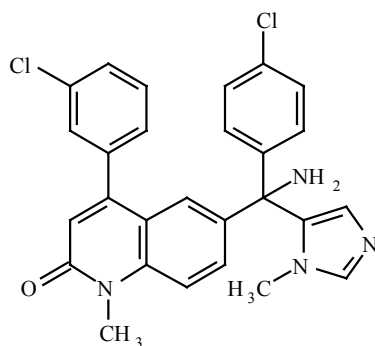
BSA (m ²)	R115777 / Placebo (mg po q12h)	R115777 / Placebo (# of 50 mg tablets po q12h)	3-cycle supply (# of boxes of 70 tablets provided)
0.00 - 0.37	50	1	2

0.38 - 0.62	100	2	4
0.63 - 0.87	150	3	6
0.88 - 1.12	200	4	8
1.13 - 1.37	250	5	9
1.38 +	300	6	11

The Julian date indicates the day the box was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2001 = 01, 2002 = 02) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a box labeled and shipped on January 1, 2001 would have a Julian date of '01001' and a box labeled and shipped on December 31, 2002 would have a Julian date of '02365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all boxes (i.e., both R115777 and placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

8.1.1 CHEMICAL NAME: R115777 is a methyl-quinolone. The full chemical name is (R)-6-[amino(4-chlorophenyl) (1-methyl -1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone.

8.1.2 CHEMICAL STRUCTURE:



8.1.3 MOLECULAR FORMULA: C₂₇H₂₂Cl₂N₄O

8.1.4 MOLECULAR WEIGHT: 489.4

8.1.5 FORMULATION: Supplied as a film-coated compressed tablet containing either 50mg of R115777 (active) or 0 mg of R115777 (placebo) with lactose, unmodified maize starch, hypromellose, microcrystalline cellulose, croscopvidone, colloidal silicon dioxide, and magnesium stearate. The coating contains hypromellose, propylene glycol, titanium dioxide, and talc.

8.1.6 STORAGE: Store at room temperature (59° to 77° F) and protect from moisture.

8.1.7 STABILITY: Shelf life surveillance studies are ongoing.

8.1.8 ROUTE OF ADMINISTRATION: Oral. The bioavailability of the tablet increases under the influence of a meal. Based on these findings, it is advised to administer the tablets of R115777 immediately after a meal. The tablets may be

crushed if a patient is unable to swallow the intact tablet; however, the entire tablet must be administered.

8.1.9 Dose: For this protocol, the dose of R115777 is 200mg/m² (rounded to the nearest 50mg) orally after meals every 12 hours for 21 days followed by a 7 day rest period for a cycle length of 28 days. Cycles are repeated until the patient progresses.

8.1.10 Drug Interactions: Pharmacokinetic data suggest that H₂ antagonists and proton pump inhibitors do not alter the exposure to R115777 to a clinically significant extent. Patients may use proton pump inhibitors or H₂ antagonists during the treatment portion of this study. However, patients should be instructed to use antacids (Mg- or Al-containing formulations), e.g., Maalox or Mylanta AT LEAST 2 hours before or after intake of the oral study drug.

8.1.11 KNOWN TOXICITIES:

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" <http://ctep.cancer.gov/reporting/adeers.html> for further clarification. Frequency is provided based on 2702 patients. Below is the CAEPR for R115777.

Version 2.0, March 2, 2009

Adverse Events with Possible Relationship to Tipifarnib (R115777) (CTCAE 3.0 Term) [n= 2702]			Agent Specific Adverse Event List (ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD/BONE MARROW			
Hemoglobin			<i>Hemoglobin</i>
	Leukocytes (total WBC)		<i>Leukocytes (total WBC)</i>
	Lymphopenia		
Neutrophils/granulocytes (ANC/AGC)			<i>Neutrophils/granulocytes (ANC/AGC)</i>
Platelets			<i>Platelets</i>
CARDIAC GENERAL			
	Hypotension		
CONSTITUTIONAL SYMPTOMS			
Fatigue (asthenia, lethargy, malaise)			<i>Fatigue (asthenia, lethargy, malaise)</i>
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)		<i>Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)</i>
	Insomnia		
DERMATOLOGY/SKIN			

	Photosensitivity		Photosensitivity
	Rash/desquamation		Rash/desquamation
GASTROINTESTINAL			
Anorexia			Anorexia
	Constipation		Constipation
	Dehydration		
Diarrhea			Diarrhea
	Heartburn/dyspepsia		Heartburn/dyspepsia
	Mucositis/stomatitis (functional/symptomatic) - Select		Mucositis/stomatitis (functional/symptomatic) - Select
Nausea			Nausea
Vomiting			Vomiting
HEMORRHAGE/BLEEDING			
		Hemorrhage, CNS	
	Hemorrhage, pulmonary/upper respiratory - Nose		
	Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)		
INFECTION			
	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10 ⁹ /L, fever ≥38.5 degrees C)		
	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10 ⁹ /L) - Select		Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10⁹/L) - Select
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select		Infection with normal ANC or Grade 1 or 2 neutrophils - Select
	Infection with unknown ANC - Select		Infection with unknown ANC - Select
LYMPHATICS			
	Edema: limb		
METABOLIC/LABORATORY			
	Bilirubin (hyperbilirubinemia)		Bilirubin (hyperbilirubinemia)
	Creatinine		Creatinine
	Lipase		Lipase
	Potassium, serum-low (hypokalemia)		Potassium, serum-low (hypokalemia)
NEUROLOGY			
	Confusion		Confusion
	Dizziness		Dizziness
	Neuropathy: sensory		Neuropathy: sensory
	Somnolence/depressed level of consciousness		
PAIN			
	Pain - Abdomen NOS		Pain - Abdomen NOS
	Pain - Chest/thorax NOS		
	Pain - Head/headache		Pain - Head/headache
	Pain - Pain NOS		
PULMONARY/UPPER RESPIRATORY			
	Cough		
	Dyspnea (shortness of breath)		Dyspnea (shortness of breath)

RENAL/GENITOURINARY			
	Renal/Genitourinary - Other (Renal insufficiency)		<i>Renal/Genitourinary - Other (Renal insufficiency)</i>

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

Also reported on tipifarnib (R115777) trials but with the relationship to tipifarnib (R115777) still undetermined:

ALLERGY/IMMUNOLOGY – Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)

BLOOD/BONE MARROW – Blood/Bone Marrow – Other (leukocytosis)

CARDIAC ARRHYTHMIA – Palpitations; Supraventricular and nodal arrhythmia - Atrial fibrillation; Supraventricular and nodal arrhythmia - Sinus tachycardia; Supraventricular and nodal arrhythmia - Supraventricular tachycardia; Ventricular arrhythmia - Ventricular tachycardia

CARDIAC GENERAL – Cardiopulmonary arrest, cause unknown (non-fatal); Left ventricular systolic dysfunction

COAGULATION – PTT (Partial Thromboplastin Time)

CONSTITUTIONAL SYMPTOMS – Rigors/chills; Sweating (diaphoresis); Weight loss

DERMATOLOGY/SKIN – Dry skin; Hair loss/alopecia (scalp or body); Pruritus/itching

ENDOCRINE – Hot flashes/flushes

GASTROINTESTINAL – Dry mouth/salivary gland (xerostomia); Flatulence; Gastrointestinal – Other (polydipsia); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI - Small bowel NOS; Taste alteration (dysgeusia)

HEMORRHAGE/BLEEDING – Hematoma; Hemorrhage, GI - Oral cavity; Hemorrhage, GI – Upper GI NOS

HEPATOBIILIARY/PANCREAS – Liver dysfunction/failure (clinical)

INFECTION – Opportunistic infection associated with \geq Grade 2 Lymphopenia

LYMPHATICS – Lymphatics - Other (localized lymphadenopathy)

METABOLIC/LABORATORY – Alkaline phosphatase; ALT, SGPT (serum glutamic pyruvic transaminase); AST,SGOT (serum glutamic oxaloacetic transaminase); Amylase; Calcium, serum-high (hypercalcemia); Glucose, serum-high (hyperglycemia); Magnesium, serum-low (hypomagnesemia); Potassium, serum-high (hyperkalemia); Sodium, serum-low (hyponatremia); Triglyceride, serum-high (hypertriglyceridemia)

MUSCULOSKELETAL/SOFT TISSUE – Muscle weakness, generalized or specific area (not due to neuropathy)

NEUROLOGY – Ataxia (incoordination); Extrapyrarnidal/involuntary movement/restlessness; Memory impairment; Mood alteration – Agitation; Mood alteration - Anxiety; Mood alteration - Depression; Neuropathy: motor; Psychosis (hallucinations/delusions); Seizure; Syncope (fainting); Tremor

OCULAR/VISUAL– Dry eye syndrome; Ocular/Visual - Other (abnormal vision)

PAIN – Pain - Back; Pain - Bladder; Pain - Bone; Pain - Joint; Pain - Muscle

PULMONARY/UPPER RESPIRATORY – Hiccoughs (hiccups, singulitus); Hypoxia; Pneumonitis/pulmonary infiltrates; Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)

RENAL/GENITOURINARY – Urine color change

VASCULAR – Phlebitis (including superficial thrombosis); Thrombosis/thrombus/embolism

Note: Tipifarnib (R115777) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

8.2 DRUG ORDERS, TRANSFERS, RETURNS, ACCOUNTABILITY / EMERGENCY UNBLINDING

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (301) 496-5725 Monday through Friday between 8:30am and 4:30pm Eastern Time.

8.2.1 DRUG ORDERS: No starter supplies will be available for this study. Orkand will notify the PMB (see Section 3.1.2 and Appendix 8A/B) when a patient is registered by the Pediatric Oncology Branch research nurse. Using the “On-Study Form” in Appendix 8B, Orkand will provide the protocol number (i.e., T99-0090), the patient ID / sequence number (e.g., ‘01C0222-01’), the patient initials (e.g., ‘ABC’ = first three letters of the patient’s last name), and the patient’s BSA (in m²). Based on the patient’s BSA, the PMB will ship an initial three month patient-specific supply (see table in Section 8.1) for “Phase A” to the registering site.

Two months after the initial request (i.e., one month before needed), clinical sites may reorder an additional three month supply by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (<http://ctep.cancer.gov>) or by calling the PMB at 301-496-5725. The patient ID number (e.g., ‘01C0222-01’) and patient initials (e.g., ‘ABC’) should be entered in the “Patient or Special Code” field. In addition, the patient’s BSA must be provided. All drug orders should be shipped directly to the physician responsible for treating the patient.

When the patient progresses on Phase A, the Pediatric Oncology Branch research nurse will notify the PMB (see Section 3.1.2 and Appendix 9A/B). Based on the patient’s BSA, the PMB will again ship an initial three month patient-specific supply (see table in Section 8.1) for Phase B to the registering site. Any remaining supplies for Phase A should be returned immediately on receipt of supplies for “Phase B” (see Section 8.2.3).

8.2.2 DRUG TRANSFERS: Boxes **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating center to another participating center, the principal investigator at a participating center changes, etc) must be approved **in advance** by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-480-4612) a Transfer Investigational Agent Form available on the CTEP home page <http://ctep.cancer.gov>, or by calling the PMB at 301-496-5725. The patient ID number (e.g., ‘01C0222-01’) and patient initials (e.g., ‘ABC’) should be entered in the “Received on NCI Protocol No.” and the “Transferred to NCI Protocol No.” fields in addition to the protocol number (i.e., T99-0090).

8.2.3 DRUG RETURNS: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed boxes remaining when a patient completes the first blinded treatment phase, sealed boxes remaining when a patient completes the second blinded treatment phase, expired boxes recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the CTEP home page <http://ctep.cancer.gov>, or by calling the PMB at 301-496-5725. The patient ID number (e.g., '01C0222-01') and patient initials (e.g., 'ABC') should be entered in the "Lot No. and Sample No." field.

8.2.4 DRUG ACCOUNTABILITY: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page <http://ctep.cancer.gov>, or by calling the PMB at 301-496-5725. A separate NCI Investigational Agent Accountability Record must be maintained for each patient on this protocol. The patient ID number (e.g., '01C0222-01') and the **phase** (i.e., "Phase A" or "Phase B") should be entered in the "Patient's ID No." field.

8.2.5 EMERGENCY UNBLINDING: In the event of an emergency, call Dr. Brigitte Widemann (301-496-7387) or Dr. Frank Balis (301-496-0085). These physicians can also be reached through 301-496-7704 or through the NIH Page Operator at 301-496-1211. Pediatric Oncology Branch staff will require the protocol number (i.e., T99-0090), the patient ID number (e.g., '01C0222-01'), the patient initials (e.g., 'ABC'), and the phase (i.e., 'Phase A' or 'Phase B') to unblind the patient.

9.0 CLINICAL TRIALS AGREEMENT (CTA)

The agent(s) (hereinafter referred to as "Agent", R115777, used in this protocol is/are provided to the NCI under a Clinical Trials Agreement (CTA) between Company: Janssen Pharmaceuticals (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment, Diagnosis. Therefore the following obligations/guidelines apply to the Agent(s) in this study:

- 1) The Agent(s) may not be used outside the scope of this protocol, nor can the Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to the Collaborator(s) and should be maintained as such by the investigators.
- 2) For a clinical protocol where there is an investigational Agent used in combination with other investigational Agent(s), each the subject of different CTAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data").
 - a) NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

- b) Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
 - c) Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
- 3) The NCI encourages investigators to make data from these clinical trials fully available to Collaborators for review at the appropriate time. Clinical trial data developed under the CTA will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate.
 - 4) When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.
 - 5) Any data provided to Collaborator(s) must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
 - 6) Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission of publication. Collaborator(s) will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator(s) intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator(s) for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:
Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Room 718
Bethesda, MD 20892
Fax: 301-402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator(s).

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11.0 APPENDICES

APPENDIX 1: PROTOCOL FOR REQUIRED PRE STUDY AND ON STUDY MRI STUDIES

Prior to starting treatment on this study all known measurable tumors should be imaged with MRI to obtain a baseline. Tumor spread in patients with NF1 can be very extensive, and may not allow for all lesions to be followed using 3D-MRI.

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

Pre-study radiographic evaluation:

- Identify and select the progressive 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 will be followed by 3-D MRI analysis.
- Perform 3-D MRI sequences on the selected index lesions as outlined in the MRI acquisition protocols below.
- In addition, if possible, perform MRI of all additional measurable plexiform neurofibroma(s).

On study radiographic evaluation:

Unless clinically indicated otherwise obtain MRI of the index lesions only as outlined in the MRI acquisition protocol below prior to cycles 4, 7, 10, and then after every 6 cycles on each treatment phase ("A", "B").

At the time of disease progression on treatment phase "A", if possible, a MRI scan of all known measurable plexiform neurofibromas in addition to the index lesions should be performed, in order to have a new baseline prior to treatment phase "B".

MRI protocols:

Depending on the location of the index lesions the Spine, Head/Neck or Trunk/Extremities protocols outlined on the following pages will be used.

The measurement of very irregular or infiltrative neurofibromas will present major challenges, and in some cases, it may be difficult to precisely define tumor margins. If necessary, participating institutions may modify the MRI sequences to optimize differentiation of tumor and surrounding tissue. Modifications should be documented in the MRI protocols, and the same imaging protocol, and, if possible, the same MRI scanner, should be used for all subsequent MRI studies.

Every attempt should be made to image the entire progressive plexiform neurofibroma(s).

A written protocol for scanning each patient has to be established at the time of study entry to allow for reproducibility of follow-up studies.

If possible, Ms. Andy Gillespie should be notified at least 24 hours prior to performing a MRI (Fax: 301-480-8871, phone: 301-402-1848, e-mail: gillesan@mail.nih.gov).

A copy of the MRI protocol used to acquire the baseline MRI study will be faxed to Ms. Andy Gillespie (301-480-8871) within 24 hours of obtaining the MRI study.

MRI studies should be submitted electronically or on CD or optical disk to the NCI POB within 1 week of obtaining the study. The institutional radiology report for each study should be faxed to Ms. Andy Gillespie within 1 week.

MRI PROTOCOL- SPINE

Patient ID number: _____

Note: All series except for #4 and #5 should be performed as a normal clinical scan as specified by the radiologist. The additional Series #4 and #5 may or may not be part of the normal clinical scan sequence, however these series are required for the NF1 study protocol and must be performed within protocol specifications as indicated below.

- | | | |
|-------------------|----------------------|--------------------------|
| 1. SAGITTAL T1 | LOCALIZER—SPINE COIL | Per normal clinical scan |
| 2. SAGITTAL T1 | | Per normal clinical scan |
| 3. SAGITTAL FSEIR | | Per normal clinical scan |
| 4. AXIAL FSEIR | | |

Axial FSEIR	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	5		
TR	6000		
TE	34		
TI	150		
Slice Thickness	5 mm		
Skip	0		
Matrix	256x256		
FOV	22 cm		
NEX	1		
Frequency Direction	R→L		
Options	Tailored RF, FC, PC, 0.75 FOV		

5. CORONAL FSEIR

Coronal FSEIR	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	5		
TR	6000		
TE	34		
TI	150		
Slice Thickness	5 mm		
Skip	0		
Matrix	256x256		
FOV	22 cm		
NEX	1		
Frequency Direction	S→I		
Options	Tailored RF, FC, PC		

- | | |
|----------------------------|--------------------------|
| 6. AXIAL T1 | Per normal clinical scan |
| 7. AXIAL T1- POST CONTRAST | Per normal clinical scan |

Date:_____ Signature (responsible MRI technician):_____

4/21/2009

T-99-0090, 01-C-0222

Baseline study only, fax completed form to: Ms. Andy Gillespie at: 301-480-8871 (phone: 301-402-1848)

MRI Protocol- Head/Neck

PATIENT ID NUMBER: _____

Note: All series except for #2 and #3 should be performed as a normal clinical scan as specified by the radiologist. The additional Series #2 and #3 may or may not be part of the normal clinical scan sequence, however these series are required for the NF1 study protocol and must be performed within protocol specifications as indicated below.

1. SAGITTAL T1

Per normal clinical scan

2. AXIAL FSEIR

Axial FSEIR	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	5		
TR	6000		
TE	34		
TI	150		
Slice Thickness	4 mm		
Skip	0		
Matrix	256x256		
FOV	22 cm		
NEX	1		
Frequency Direction	A→P		
Options	Tailored RF, FC, 0.75 FOV		

3. CORONAL FSEIR

Coronal FSEIR	Protocol Specifications	Actual Specifications	Reason For Change
Echo Train Length	5		
TR	6000		
TE	34		
TI	150		
Slice Thickness	5 mm		
Skip	0 mm		
Matrix	256x192		
FOV	22 cm		
NEX	1		
Frequency Direction	S→I		
Options	Tailored RF, PC		

4. AXIAL T1

Per normal clinical scan

5. AXIAL T1- POST CONTRAST

Per normal clinical scan

Date: _____ Signature (responsible MRI technician): _____

Baseline study only, fax completed form to: Ms. Andy Gillespie at: 301-480-8871 (phone: 301-402-1848)

MRI Protocol-Trunk/Extremities

PATIENT ID NUMBER: _____

Note: All series except for #1 and # 2 should be performed as a normal clinical scan as specified by the radiologist. The additional Series #1 and # 2 may or may not be part of the normal clinical scan sequence, however these series are required for the NF1 study protocol and must be performed within protocol specifications as indicated below.

1. AXIAL PLANE-STIR

Axial Plane STIR	Protocol Specifications	Actual Specifications	Reason For Change
Coil: Body			
Sequence: Fast Spin Echo (Turbo) FSEIR			
Echo Train Length	5		
TR	6000		
TE	15		
TI	150		
Slice Thickness	10 mm		
Skip	0		
Matrix	512x160		
FOV	40x30		
No. of Excitations/ Sequence	0.5		
No. of Acquisitions	1		
Saturation	None		

2. CORONAL PLANE STIR

Coronal Plane STIR	Protocol Specifications	Actual Specifications	Reason For Change
Coil: Body			
Sequence: Fast Spin Echo (Turbo) FSEIR			
Echo Train Length	5		
TR	3400		
TE	15		
TI	150		
Slice Thickness	5 mm		
Skip	0		
Matrix	512x160		
FOV	48x48		
No. of Excitations/ Sequence	1		
No. of Acquisitions	1		
Saturation	None		

Date: _____

Signature (responsible MRI technician): _____

4/21/2009

T-99-0090, 01-C-0222

Baseline study only, fax completed form to: Ms. Andy Gillespie at: 301-480-8871 (phone: 301-402-1848)

Data Analysis:

- All MRI data will be analyzed at the Pediatric Oncology Branch of the NCI under guidance of Dr. N. Patronas (head neuroradiologist). 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 T2 images not corresponding to known normal anatomic structures and corresponding with the course of known nerves. Each patient'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 1D-, and 2D-data analysis will be done by 2 physicians trained in 1D-, 2D-, and 3D-MRI data analysis at the Pediatric Oncology Branch, NCI at an Image Review Workstation using MEDx software (Sensor Systems Inc.). Dr. Nicholas Patronas, NCI, will review and confirm 1D-, 2D-, and volumetric measurements for all images obtained on the study. Volumetric measurements will be used to determine disease progression as outlined in Section 5.2. After review by Dr. Patronas, the Principal Investigator will inform the Participating Investigators about the results of the MRI study by written report.
- The results of volumetric MRI measurements will be compared with 1D- and 2D-MRI measurements, with results of the photographic evaluation, the physical examination and the study subject's subjective impression following clinical variables.

Image And Data Acquisition:

In order to perform quantitative analysis the Pediatric Oncology Branch must receive the imaging data from the investigator sites.

Distribution of images from all participating institutions to the NCI POB will be performed by a contractor.

The contractor will:

- Contact participating institutions to determine the best mode of electronic data transfer
- Prepare each site for electronic data transfer via network access device, File Transfer Protocol (ftp), optical disk or modem depending on the investigator site.
- Provide training and technical support for each site
- Ensure complete, secure and timely data transfer to the POB, NCI within 24-72 hours of obtaining the MRI study.

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.

APPENDIX 2: PATHOLOGY ANALYSIS OF PLEXIFORM NEUROFIBROMAS**PATHOLOGICAL ANALYSIS OF PLEXIFORM NEUROFIBROMAS:**

The ability to design rational therapies for plexiform neurofibromas in NF1 is heavily dependent upon an improved understanding of the composition, biological properties, and growth characteristics of these tumors. The cellular constituency of plexiform neurofibromas is often complex and mixed, including Schwann cells, fibroblasts, perineurial and dendritic/monocytic cells. The patterns are further complicated due to the intrinsic intra-neural growth pattern as well as entrapment of native neural elements. This complex intermingling of cellular elements has impeded our most basic understanding of these tumors. It has also rendered molecular studies, which require relatively pure cellular populations difficult to interpret. Therefore, combined morphologic, immunohistochemical, and molecular studies are needed to elucidate the histogenesis, growth patterns, and malignant evolution of these tumors.

The Plexiform Neurofibroma Analysis component consists of two parts: (1) the central diagnostic neuropathology review with accompanying light- and electron-microscopic effort to identify the actual cell populations comprising the tumor and (2) immunohistochemical and FISH analysis of tumor specimens. All tissues received from surgical biopsies and/or resections will be reviewed by Dr. Arie Perry.

With this combined approach, the range of cellular constituents and their neoplastic properties will be carefully documented in plexiform neurofibromas. Along with related assays being developed (see below), we will provide a better understanding of histogenesis, growth potential, and malignant transformation of these tumors, thus facilitating a rational approach for guiding patient management.

The detailed pathological analysis outlined below will only be performed on biopsies of plexiform neurofibromas, from patients enrolled in the Phase II FTI study. We expect 5-10 such samples per year.

Standard Pathological Analysis: The paraffin blocks will be sectioned and the resulting slides will be stained with hematoxylin-and-eosin (overview). Selected blocks with the greatest degree of tumor purity and/or foci of malignant degeneration will be additionally stained with Masson's trichrome (collagen and myelin), alcian blue (acid proteoglycan), reticulin (basement membrane) and peroxidase-linked antibodies against neurofilament protein (axons), S-100 protein (Schwann cells), vimentin (mesenchymal elements including fibroblasts), chromogranin (entrapped or neoplastic ganglion cells), GFAP (some Schwann cells), Leu-7 (some Schwann cells), epithelial membrane antigen (perineurial cells), cytokeratin (epithelial differentiation), HMB-45 (melanin-containing cells), desmin (skeletal muscle differentiation), MIB-1 (Ki-67) antigen (growth fraction = proliferation index), collagen type IV (basement membrane), CD34 (endothelial cells and endoneurial dendritic/monocytic cells), muscle specific actin (some perineurial cells), and CD68 (macrophages).

Glutaraldehyde-fixed tissue will be processed into epoxy resin for high-resolution light microscopy, and electron microscopy; ultrastructural criteria exist for the differential identification of Schwann cells, perineurial-like cells, and endoneurial

fibroblasts and macrophages. All the attendant microscopy will be done, and the findings entered in the project's database, by Dr Perry.

Investigational Neuropathology Studies: Although initial studies will focus on routine morphologic, immunohistochemical, and ultrastructural characterization of submitted tumors, a number of additional novel studies are currently being developed. In this section, we propose to critically evaluate the following questions:

- (1) What are the cell types present in plexiform neurofibromas?
- (2) Are cell types different for plexiform neurofibromas obtained from different sites (e.g., cranial nerve, spinal nerve, peripheral nerve)?
- (3) Does proliferation index correlate with growth or molecular/cellular characteristics?
- (4) What is the range of neoplastic properties commonly seen in plexiform neurofibromas and how do these differ in benign and malignant lesions?
- (5) Are there any immunohistochemical or DNA FISH markers (e.g. p53 protein expression or gene copy number) which may predict a high risk of subsequent tumor progression or malignant transformation in plexiform neurofibromas?
- (6) Is there any correlation between tumor vascularity, which may correlate with tumor progression in plexiform neurofibromas?
- (7) Is there a correlation between MAPK activity in the tumor and FTI treatment?

Immunohistochemical analysis of tumors will include p53 protein (overexpression due to mutation or protein stabilization common in MPNST components), Factor VIII and vascular endothelial growth factor (highly vascular tumors) and neurofibromin protein (antibody provided by Dr. David Gutmann, Director of the Neurofibromatosis Clinic, Washington Univ. School of Medicine). Recently, Drs. Perry and Gutmann have successfully applied a neurofibromin antibody to archival paraffin-embedded astrocytomas resected from patients with NF1. A similar approach will be utilized in our study of plexiform neurofibromas, enabling morphologic correlation and the determination of what proportion of cells have lost expression. This will be followed by the development of several dual-color immunohistochemical assays such as Neurofibromin/MIB-1, Neurofibromin/p53, S-100/MIB-1, S-100/Neurofibromin, etc. Results will determine for the first time, which cell types are actively proliferating, lack expression of neurofibromin, and/or overexpressing p53 protein. Tumor vascularity will be determined based on the VEGF and Factor VIII expression.

Dr. Perry has extensive experience with fluorescence *in situ* hybridization (FISH) studies in paraffin embedded tumor. FISH and combined FISH/Immunohistochemistry assays will be utilized to identify specifically which cell types have deleted the *NF1* gene.

Snap-frozen specimens when available will be homogenized for Western immunoblot analysis of ras pathway effector protein activities using activation-specific antibodies. In these experiments, equal amounts of total protein will be analyzed by Western blotting with phospho-MAPK and phospho-akt/PKB antibodies and normalized to the total MAPK and akt/PKB protein levels in each tumor. Densitometry

will be performed to quantitate the levels of MAPK and akt/PKB activation in these tumors.

The Neuropathological Review Facility is intended to provide a resource for consistent pathological analysis of plexiform neurofibromas. This will, in the long run, facilitate better pathological classification of plexiform neurofibromas and permit correlations of pathological characteristics with clinical and cellular/molecular features.

CONTRIBUTION OF TUMOR SPECIMENS TO A CENTRAL TUMOR REPOSITORY:

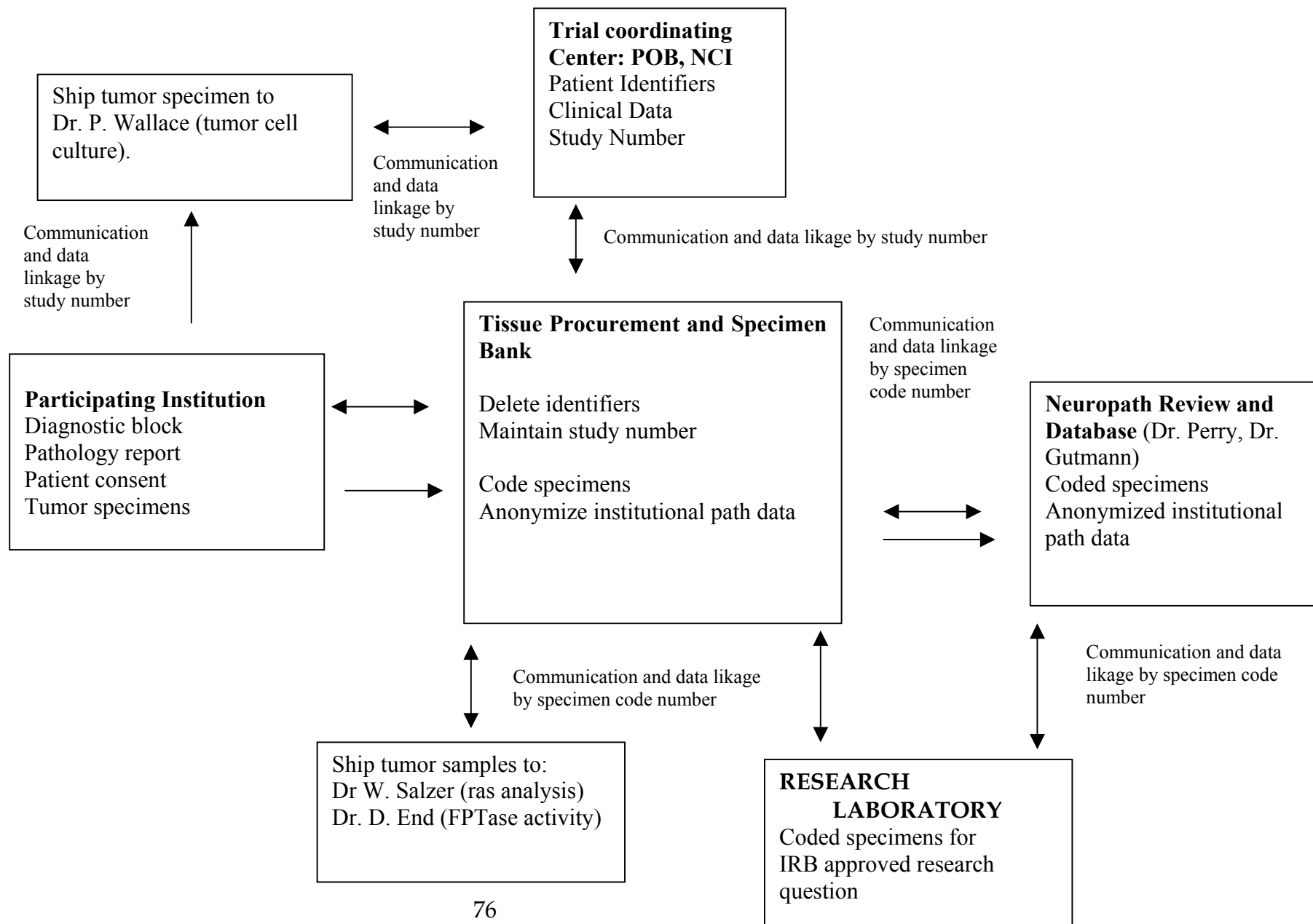
All tumor samples obtained on this study (obtained from biopsies of discrete neurofibromas and plexiform neurofibromas), with the exception of the tumor sample obtained for establishment of tumor cell lines, will be sent to the tissue procurement facility.

Tissue Acquisition (Appendix 3): To assist in the collection of tissue specimens, the project's Tissue Procurement Facility will provide submitting centers with a complete specimen shipping kit after notification by the Pediatric Oncology Branch. This kit will be sent to the submitting institution several days before the planned tissue resection. The kit will contain all materials and instructions for the proper collection and shipping of specimens to the Tissue Procurement Facility. A second specimen shipment kit for shipment of a tumor sample dedicated to the establishment of tumor cell lines will be sent to the participating institution by the Pediatric Oncology Branch, and also contain all materials and instructions for the proper collection and shipping of specimens .

Tissue shipment (Appendix 4): All patient specimens (with exception of the specimen obtained for tissue culture), and a copy of the patient consent will be sent by overnight express courier to Dr. Mark Watson at the Tissue Procurement Facility. After performing the local institutional evaluation and issuing a pathology report, a copy of the pathology report, and all paraffin blocks should be sent to the tissue procurement facility. If submission of all paraffin blocks is not possible or prohibited by participating pathology departments, 5 unstained slides from each block will be sent instead. These slides will then be stained and reviewed by Dr. Perry, who will then select 1 or 2 appropriate blocks to be sent for further study. Blocks will be returned to the submitting institutions upon completion of studies or within 24 hours of written request by the submitting institution.

Upon entry to the Tissue Procurement Facility, all specimens will be coded and recorded in the facility database. The Tissue Procurement Facility will forward appropriate coded specimens to Dr. Perry for centralized pathology review and other studies described above, and to Dr. Wanda Salzer (analysis of ras expression, and NF1 mutation) and Janssen Pharmaceuticals (FPTase activity) for investigations related to the protocol. The remainder of the specimens (including paraffin blocks) will be stored by the Tissue Procurement Facility until needed for future research studies or recall by the submitting institution. **Figure 1** diagrams the proposed flow of information and specimens, the coding scheme, and the residence of each data set. This is a coded, double-broker model designed to maintain patient confidentiality while making meaningful research studies possible. All tumor samples remain linked to the patient

data by the study number. Only the coordinating Center (POB) will have access to the clinical data. Communication between the central tissue repository and the POB will use the patient study number. Communication between research laboratories and the tissue bank will use the specimen code number. The tumor sample obtained for establishment of tumor cell lines will be sent directly from the participating institution to Dr. Wallace and will be identified by the patient study number.

Figure 1: Proposed Scheme for Specimen and data exchange, and specimen and data encoding

APPENDIX 3: INSTRUCTIONS FOR TISSUE ACQUISITION OF DISCRETE AND PLEXIFORM NEUROFIBROMAS

Five to seven days prior to the planned tumor biopsy please notify Ms Andy Gillespie at the POB, NCI, about the planned biopsy: Phone: 301-402-1848, Fax: 301-480-8871, e-mail: gillesan@mail.nih.gov. To assist in the collection of tissue specimens, two specimen shipment kits will be sent to participating institutions:

- The project's Tissue Procurement Facility will provide submitting centers with a specimen shipping kit for shipment of tumor samples. The kit will contain all materials and instructions for the proper collection and shipping of specimens to the Tissue Procurement Facility.
- The NCI, Pediatric Oncology Branch will provide submitting institutions with a second specimen shipment kit (to ship the tumor sample for the culture of tumor cells), which will contain all materials and instructions for proper collection.

STEPS FOR TISSUE COLLECTION ARE AS FOLLOWS:

1. To enable future molecular and biochemical analyses with the specimen, the participating institutional pathologist must receive the tumor tissue fresh, rather than "fixed in formalin". After resection, the tissue should be transported from the O.R. to the pathologist within 30 minutes. The specimen must not be placed in formalin, but may be placed in normal saline, Ringer's solution, or any other physiologic buffer solution.
2. A representative and sufficiently large piece of the specimen should be fixed in formalin for paraffin processing as per the institution's standard policies and procedure. Pathologists will be instructed to thoroughly sample the surgical specimen (at least one block per centimeter in greatest dimension). This material will be used to make the clinical diagnosis and, later, sent for central pathology review.
3. If tissue remains, an additional piece of tissue 0.5-1 cm³ in size will be snap frozen in liquid nitrogen or a -50°C histological bath. This material will be shipped to the Tissue Procurement Facility on dry ice for future molecular and genetic research studies.
4. If tissue remains, aseptically remove any capsular material and slice at least 0.5 cm³ of the tumor tissue to increase the exposed surface area. Half fill a 50 ml screw top, conical centrifuge tube with Transport Medium (Leibovitz's L-15 Medium with 1.0% penicillin/streptomycin, 100U/ml) and shake vigorously to oxygenate. Label the tube with patient's study number. Place the slices into the medium, secure the top and wrap with parafilm. Insulate the tube by encasing with several wraps of fine bubble wrap. Place the package on top of a small reusable cold ice pack in a size-matching styrofoam shipping box with cardboard outer. Tape the box lid shut. Ship by

overnight express courier, priority delivery to Dr. Peggy Wallace, University of Florida for culture of tumor cells.

5. If tissue still remains, 2-4 2 mm fragments, preferably from various sites representing a spectrum of gross appearances, will be placed in the provided gluteraldehyde container. These specimens will be used for electron microscopy studies.
6. If tissue still remains, another representative specimen will be placed in the provided formaldehyde container. This specimen will be embedded at the Tissue Procurement Facility and used in the event that the submitting institution's specimen block is not available.
7. If tissue still remains, the remainder of the specimen will be divided into 1 cm³ segments and snap frozen as described in (3).

APPENDIX 4: INSTRUCTIONS FOR SHIPMENT OF TUMOR BIOPSIES

Shipments should not be sent on Fridays or on the day preceeding a holiday.

Five to seven days prior to tumor resection, please call Ms Andy Gillespie at the Pediatric Oncology Branch, NCI (phone: 301-402-1848, fax: 301-480-8871, e-mail: gillesan@mail.nih.gov). Provide the name, phone number and shipping address of the physician responsible for tissue acquisition.

Two shipping modules will be mailed via overnight express to the physician indicated:

At the time of resection, tissue should be IMMEDIATELY transported from the operating room to the attending surgical pathologist. Material should be handled as outlined in Appendix 3.

After collection the tumor sample, which will be used for establishment of a tumor cell line, should be placed in L-15 (a tissue culture medium), identified with the patient's study number, and be sent on top of a small reusable cold ice pack in the specimen kit provide by the POB, NCI immediately via FedEx to:

Margaret Wallace, Ph.D.
Professor, Molecular Genetics & Micro., and Pediatric Genetics
University of Florida
Box 100266, 1600 SW Archer Road, ARB Room R2-220
Gainesville, FL 32610-0266
Phone: (352)-392-3055
Fax: (352) 392-2042
E-mail: peggyw@ufl.edu

Please notify Dr. Wallace prior to shipment, and contact her with any questions you may have regarding this sample.

All other tumor specimens (snap frozen tissue, tissue in glutaraldehyde, and formaldehyde container) should be placed in the specimen kit provided by the Tissue Procurement Facility, and shipped on dry ice to:

M. Watson, M.D., Ph.D.
Division of Laboratory Medicine / Box 8118
Alvin J. Siteman Cancer Center / Box 8100
Washington University School of Medicine
660 S. Euclid Avenue, St. Louis, MO 63110
Phone: (314)-454-7919, Fax: (314)-454-5525

Snap frozen tissue has to be maintained in the cryobath or a -70 degree freezer until it is ready for shipment. It is very important that: (1) Tissue be frozen as soon as possible after resection; (2) Tissue be frozen rapidly; and (3) Tissue be maintained at or below -50 degrees until shipment.

Please notify Dr. Watson prior to shipment, and contact him with any questions you may have regarding these samples.

APPENDIX 5: PROCEDURE PBMC SEPARATION FOR FARNESYLTRANSFERASE ACTIVITY**PBMC Collection Steps:**

- Collect peripheral blood (20 ml in children >10 kg weight, 10 ml in children ≤10 kg weight) in preservative free heparin (10-20 units heparin/1ml of blood).
- Place peripheral blood in polypropylene screw top tube(s).
- Label tube with: Patient initials, Patient ID number, date, treatment phase ("A", "B"), and day of treatment (pre, day 15-21).

Shipment Of Peripheral Blood:

- Place tube(s) in container.
- Place the container with the polypropylene tube(s) in Styrofoam box. Add a package of wet ice in Styrofoam box, if it is expected that the ambient temperature cannot be maintained between below 90 ° Fahrenheit.
- Package sample as appropriate for biologic material.

Required PBMC samples	Date of sample collection
Pretreatment (prior to phase "A")	
Steady state on treatment phase "A" (day 15-21, cycle#1)	
Steady state on treatment phase "B" (day 15-21, cycle#1)	

- **Ship the sample and the information requested above on the same day it was obtained with Federal express overnight priority delivery to:**

Dr. Brigitte Widemann
 Pediatric Oncology Branch, NCI
 10 Center Drive
 1 – CRC, Rm 1-5750,
 Bethesda, MD 20892-1101

- Notify Dr. Widemann prior to shipment of the sample (Phone:301-496-7387, e-mail: bw42y@nih.gov).
- Do not ship samples for delivery on a weekend or Holiday.
- Samples must be received by Dr. Widemann within 24 hours of obtaining the sample.

PROCESSING OF SAMPLES

- After arrival at the Pediatric Oncology Branch, NCI:
- Mononuclear cells will be separated using the ficoll technique.
- The number of mononuclear cells in the specimen will be determined.

- The samples will be processed for FPTase activity

APPENDIX 6: DETERMINATION OF NERVE GROWTH FACTOR

All materials necessary will be provided by the POB, NCI.

Obtain exactly 3 cc of whole blood in a red top tube (pretreated with a protease inhibitor, provided by the POB, NCI). After obtaining the sample:

- Storage for 1 hour at room temperature (15-25 °C),
- Overnight storage in the refrigerator at 2-8 °C.
- Centrifugation for 20 minutes at 2-8 °C at 2000 x g.
- Remove supernatant, and place supernatant in tube (provided by POB).
- Label tube (labels provided by POB) with patient initials, ID#, date, cycle and treatment phase.
- Storage of samples until shipment: -20 °C.

Ship frozen samples and completed collection sheet on dry ice to:

Ms. Nalini Jayaprakash
Pediatric Oncology Branch, NCI
10 Center Drive, 10-CRC, Rm 1-3872
Bethesda, Maryland 20892-1101

Please notify Ms. Jayaprakash prior to shipping at (301) 402-6642, e-mail: jayapran@mail.nih.gov. No shipments to arrive on Holidays or on Saturdays.

Samples can be batched for each treatment phase.

Patient initials:		Patient ID number:	
-------------------	--	--------------------	--

Treatment Phase	Sample	Date obtained
A	Prior to phase A	
A	Pre cycle # 4	
A	Pre cycle # 7	
A	Pre cycle # 10	
A	Pre cycle # 16*	
B	Pre cycle #4	
B	Pre cycle # 7	
B	Pre cycle # 10	
B	Pre cycle # 16*	

* And then after completion of every 6 treatment cycles.

APPENDIX 7: REQUIRED STUDY EVALUATIONS

Prior To Starting Treatment, During, And Post Treatment for Each Study Phase ("A" and "B"):

Observation	Pretreatment (Phase A&B)	During Cycle (Phase A&B)	Prior to Each Cycle (Phase A&B)	Post Study
History & physical exam	X	q 2 weeks, Cycles 1-3	X	X
Performance status	X		X (document if changed)	X
Body surface area	X		X	
Photography of lesions, if possible	X		Cycles 4, 7, 10, then q 6 cycles	X
CBC, platelets, differential	X	q 2 weeks, Cycles 1-3	X	X
PT, PTT, Fibrinogen	X		X	X
Electrolytes and creatinine	X	q 2 weeks, Cycles 1-3	X	X
Ca ²⁺ , Mg ²⁺ , PO ₄	X	q 2 weeks, Cycles 1-3	X	X
SGPT, bilirubin	X	q 2 weeks, Cycles 1-3	X	X
Urinalysis	X		Cycles 4, 7, 10, then q 6 cycles	X
Urine pregnancy test	Females			
3D-MRI of index lesions	Phase A only		Cycles 4, 7, 10, then q 6 cycles	X
Ophthalmologic examination	X			X
QOL assessment	Phase A only		Cycles 4, 7, 10, then q 6 cycles	
Tumor Biopsy	Phase A only	Between days 15-21, Cycle 1 Phase A and B		
PBMC for FPTase	Phase A only	Between days 15-21, Cycle 1		

Nerve growth factor Phase A only

Cycles 4, 7, 10, then q 6 cycles

APPENDIX 8 A: ELIGIBILITY CHECKLIST FOR PROTOCOL

Patient initials:	First three letters of last name: _____		
Date of birth:	_____	Race:	_____
		Gender:	_____
Patient measurements:	Weight (kg): _____	Height (cm): _____	BSA (m ²): _____
(please average 3 heights and weights)	_____	_____	_____
Institution:	_____		
Physician:	_____		
NF1 diagnostic criteria:	Plexiform neurofibroma: _____	≥6 Café-au-lait spots: _____	
	Freckling: _____	Optic glioma: _____	
	≥ 2 Lisch nodules: _____	Bony dysplasia: _____	
	1 st degree relative with NF1: _____		
Progressive plexiform Neurofibroma over prior two scans:	≥20% increase in tumor volume: _____	%: _____	
	≥ 13% increase in product of two longest perpendicular diameters: _____	%: _____	
	≥6% increase in longest diameter: _____	%: _____	
	Date of scans: _____	1. _____	2. _____
	Tumor measurements: _____	cm: _____	cm: _____
	Inoperable: _____	Yes: _____	No: _____
	Measurable: _____	Yes: _____	No: _____
	Potential for morbidity: _____	Yes: _____	No: _____
	Location: _____		
Recovered from tox. of prior Rx:	Yes: _____	No: _____	
Date of last dose of (NA if none):	Radiation Rx: _____	ChemoRx: _____	
ECOG performance score:	_____	Life expectancy ≥12 mo:	Yes: _____ No: _____
	Date CBC/Diff and coags drawn: _____		
Hematologic parameters:	ANC: _____	Hgb: _____	Plt: _____
	Fibrinogen: _____	Normal range: _____	
	Date chemistries drawn: _____		
Liver function tests:	SGPT: _____	ULN: _____	Bili: _____ ULN: _____
Renal function:	Creat: _____	Normal range: _____ or Creat clear: _____	
Signed informed consent:	Yes: _____	Date: _____	No: _____
Pregnant or breast feeding:	Yes: _____	No: _____	Date of pregnancy test: _____
Other significant illnesses:	Yes: _____	No: _____	DPA offered: Yes: _____ No: _____ NA: _____
>1 myelosuppressive chemoRX:	Yes: _____	No: _____	Prior R115777: Yes: _____ No: _____
	_____	_____	: _____
Investigational agent last 30 days:	Yes: _____	No: _____	
Active MPNST or other cancer	Yes: _____	No: _____	
Ongoing XRT, chemoRX, GCSF, hormonal or immunoRx	Yes: _____	No: _____	
Able to return for follow-up	Yes: _____	No: _____	

Name of person completing form: _____ **Signature/Date:** _____

APPENDIX 8 B: BLINDED PATIENT ON-STUDY FORM

PROTOCOL T99-0090 / 01-C-0222

A Phase II Randomized, Crossover, Double-Blind, Placebo-Controlled Trial of the
Farnesyltransferase Inhibitor R115777 in Pediatric Patients with Neurofibromatosis Type I
and Progressive Plexiform Neurofibromas

Patient ID: 01C0222- ____**Patient Initials:** ____

(provided by Orkand)

(CC protocol number - patient sequence number)

(first three letters of last name)

☐ **On-Study Form:**

Date of Registration / On-Study Date (MM/DD/YYYY): ____ / ____ / ____

Drug Order:

NSC Number: 702818

Drug Name, Strength, Unit, Form: **Phase A** R115777 50mg / Placebo tablets

Quantity Ordered:

Check One	BSA (m ²)	R115777 / Placebo (mg po q12h)	# of Boxes (70 tablets per box)
<input type="radio"/>	0.00 - 0.37	50	2
<input type="radio"/>	0.38 - 0.62	100	4
<input type="radio"/>	0.63 - 0.87	150	6
<input type="radio"/>	0.88 - 1.12	200	8
<input type="radio"/>	1.13 - 1.37	250	9
<input type="radio"/>	1.38 +	300	11

Registering Physician:

Name (print): Dr. _____

Institution: _____

Address (city / state): _____, _____

NCI Investigator Number: _____

Phone Number: _____ - _____ - _____

Date Faxed to PMB by Orkand (MM/DD/YYYY): ____ / ____ / ____

Name of person faxing to PMB (print): _____

Signature of person faxing to PMB: _____

Phone number of person faxing to PMB: _____ - _____ - _____

Fax to: Donna Shriner / Melizza Ford

Pharmaceutical Management Branch, Cancer Therapy Evaluation
Program, DCTD, NCI: 301-402-4870

Questions: Contact Donna Shriner or Melizza Ford of the Pharmaceutical Management
Branch at 301-496-5725.

APPENDIX 9A: PROGRESSION CHECKLIST FOR PROTOCOL

To be completed when patient progresses on Phase A and Phase B

Patient initials:	First three letters of last name:	_____
Patient ID number:	_____	
Patient measurements:	Weight (kg): _____	Height (cm): _____ BSA (m ²): _____
Institution:	_____	
Registering physician:	Name: _____	
Contact RN:	Name: _____	Phone: _____
Treatment phase completed:	A: _____ B: _____	Date: _____
Cycle number completed:	_____	
Last R115777/Placebo dose:	Date: _____	
Location of progressive plexiform neurofibroma(s):	_____	
Evidence for progression:	$\geq 20\%$ increase in tumor volume: _____ Clinical progression: _____	
Name of person completing form:	_____	
Signature/Date:	_____	
<hr/>		
POB RN:	_____	
Date PMB notified:	_____	
Date Orkand notified:	_____	

Fax completed form to Ms Andy Gillespie at 301-480-8871, call with questions: 301-402-1848

APPENDIX 9 B: BLINDED PATIENT CROSSOVER / OFF-STUDY FORM

PROTOCOL T99-0090 / 01-C-0222

A Phase II Randomized, Crossover, Double-Blind, Placebo-Controlled Trial of the
Farnesyltransferase Inhibitor R115777 in Pediatric Patients with Neurofibromatosis Type I
and Progressive Plexiform Neurofibromas

Patient ID: 01C0222-__ __**Patient Initials:** __ __ __

(CC protocol number - patient sequence number)

(first three letters of last name)

☐ **Crossover Form:**

Date of Progression on Phase A / Crossover Date (MM/DD/YYYY): __ / __ / __

Drug Order:

NSC Number: 702818

Drug Name, Strength, Unit, Form: **Phase B** R115777 50 mg / Placebo tablets

Quantity Ordered:

Check One	BSA (m ²)	R115777 / Placebo (mg po q12h)	# of Boxes (70 tablets per box)
<input type="radio"/>	0.00 - 0.37	50	2
<input type="radio"/>	0.38 - 0.62	100	4
<input type="radio"/>	0.63 - 0.87	150	6
<input type="radio"/>	0.88 - 1.12	200	8
<input type="radio"/>	1.13 - 1.37	250	9
<input type="radio"/>	1.38 +	300	11

☐ **Off-Study Form:**

Date of Progression on Phase B / Off-Study Date (MM/DD/YYYY): __ / __ / __

Registering Physician:

Name (print): Dr. _____

Institution: _____

Address (city / state): _____, _____

NCI Investigator Number: _____

Phone Number: _____ - _____ - _____

Date faxed to PMB by Pediatric Oncology Branch (MM/DD/YYYY): __ / __ / __

Name of person faxing to PMB (print): _____

Signature of person faxing to PMB: _____

Phone number of person faxing to PMB: _____ - _____ - _____

Fax to: Donna Shriner / Melizza Ford

Pharmaceutical Management Branch Cancer Therapy Evaluation
Program, DCTD, NCI: 301-402-4870

Questions: Contact Donna Shriner or Melizza Ford of the Pharmaceutical Management
Branch at 301-496-5725.

APPENDIX 10: ROADMAP FOR PATIENT REGISTRATION AND CROSSOVER**PATIENT REGISTRATION**

- 1) Contact Dr. Brigitte Widemann (301) 496-7387 or Dr. Frank Balis (301) 496-0085, to discuss the patient prior to entry on study. Call Ms. Andy Gillespie, RN to register patient at (301-402-1848). FAX the completed Eligibility Checklist (Appendix 8A) and Blinded Patient On Study Form (Appendix 8B) to the Pediatric Oncology Branch c/o Andy Gillespie, RN at (301) 480-8871.
- 2) POB RN registers patient with Orkand (phone: 301-402-1732, fax: 301-480-0757) using the completed Eligibility Checklist (Appendix 8A) and Blinded Patient On Study Form (Appendix 8B).
- 3) Orkand notifies the POB RN and the Pharmaceutical Management Branch (PMB), NCI, (phone; 301-496-5725, fax: 301-402-4870) of the patient's ID number using the Blinded Patient On Study Form (Appendix 8B).
- 4) The POB RN notifies the registering site of the patient's ID number using the Blinded Patient On Study Form (Appendix 8B).
- 5) The PMB ships drug for that ID number for "phase A" to registering site.
- 6) POB ships module with necessary materials to administer quality of life assessment and tests outlined in appendix 5, 6, and 7 to participating institution.

DISEASE PROGRESSION ON "PHASE A"

- 1) FAX the completed Progression Checklist (Appendix 9A) and Blinded Patient Crossover/Off Study Form (Appendix 9B) to the Pediatric Oncology Branch c/o Andy Gillespie, RN at (301) 480-8871.
- 2) Return unused drug to the PMB (Section 8.2.3)
- 3) POB RN notifies the PMB (phone: 301-496-5725, fax: 301-402-4870) using the completed Blinded Patient Crossover/Off Study Form (Appendix 9B).
- 4) PMB ships drug for that ID number for "phase B" to registering site.

DISEASE PROGRESSION ON "PHASE B"

- 1) FAX the completed Progression Checklist (Appendix 9A) and the Blinded Patient Crossover/Off Study Form (Appendix 9B) to the Pediatric Oncology Branch: Andy Gillespie, RN at (301) 480-8871.
- 2) Return unused drug to the Pharmaceutical Management Branch (Section 8.2.3)
- 3) POB RN notifies Orkand (phone: 301-402-1732, fax: 301-480-0757) and the PMB (phone: 301-496-5725, fax: 301-402-4870) using the completed Progression Checklist (Appendix 9A) and Blinded Patient Crossover/Off Study Form (Appendix 9B).
- 4) POB RN will take Patient off protocol.

EMERGENCY UNBLINDING

In the event of an emergency, call the Dr. Brigitte Widemann (301) 496-7387 or Dr. Frank Balis (301) 496-0085. These physicians can also be reached through the NIH page operator (301) 496-7704 or (301) 496-1211. Pediatric Oncology Branch staff will require the protocol number (i.e., 'T99-0090'), the patient's ID number (e.g., '00-C0222-01'), the phase (i.e., 'A' or 'B'), and the patient's initials (first three letters of last name, eg., 'ABC') to unblind the patient.

APPENDIX 11A: PATIENT DIARY FOR R115777/PLACEBO

Patient initials/ID number: _____ Dose: _____ Treatment Phase: _____ Cycle Number: _____ Cycle Start Date: _____

Date →														
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Time R115777 /Placebo dose taken* →														
Indicate reason for missed doses →														
SIDE EFFECTS														
Nausea (see scale below)† →														
Vomiting (# of times in 24 hr) →														
Diarrhea (# of times in 24 hr) →														
Pain, or numbness in hands/feet →														
OTHER SIDE EFFECTS (list below)														
→														
→														
→														

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

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

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

Physicians should fax completed form to Ms Andy Gillespie at 301-480-8871, call with questions: 301-402-1848 Parent/patient initials _____

4/21/2009

T-99-0090, 01-C-0222

APPENDIX 11 B: PILL COUNT CASE REPORT FORM

PROTOCOL T99-0090 / 01-C-0222

A Phase II Randomized, Crossover, Double-Blind, Placebo-Controlled Trial of the
Farnesyltransferase Inhibitor R115777 in Pediatric Patients with Neurofibromatosis Type I
and Progressive Plexiform Neurofibromas

Patient's Institution ID#: _____ **Patient's Name:** _____
Patient ID: 01C0222-____ **Patient Initials:** ____
(CC protocol number - patient sequence number) (first three letters of last name)

Phase: ____ Phase A ____ Phase B **Cycle:** ____

Strength: ____ 50mg (28 day cycle - 21 days on / 7 days off)

Start Date (MM/DD/YYYY): ____ / ____ / ____

Number of boxes dispensed (place additional labels on page 2 - make copies if necessary) ____

Total number of tablets dispensed to patient (number of boxes * 70 tablets per box) ____

End Date (MM/DD/YYYY): ____ / ____ / ____

Total number of tablets returned by patient: ____

Number of tablets taken by patient (total dispensed minus total returned) ____

Date Pill Count Form Completed (MM/DD/YYYY): ____ / ____ / ____

Name of person Completing Pill Count Form (Print): _____

Name of Principal Investigator (print): Dr. _____

Institution: _____

Please fax completed forms to Ms. Andy Gillespie (301 480-8871) after completion of every 3 treatment cycles.

PLACE BOX ONE LABEL HERE

PLACE BOX TWO LABEL HERE

PLACE BOX THREE LABEL HERE
(if applicable)

PLACE BOX FOUR LABEL HERE
(if applicable)

PLACE ADDITIONAL BOX LABEL
HERE

(if applicable)

PLACE ADDITIONAL BOX LABEL
HERE

(IF APPLICABLE)

PLACE ADDITIONAL BOX LABEL
HERE

(if applicable)

PLACE ADDITIONAL BOX LABEL
HERE

(if applicable)

PLACE ADDITIONAL BOX LABEL
HERE

(if applicable)

PLACE ADDITIONAL BOX LABEL
HERE

(if applicable)

PLACE ADDITIONAL BOX LABEL
HERE

(if applicable)

PLACE ADDITIONAL BOX LABEL
HERE

(if applicable)

PLACE ADDITIONAL BOX LABEL
HERE

(if applicable)

PLACE ADDITIONAL BOX LABEL
HERE

(if applicable)

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient
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INSTITUTE: National Cancer Institute

STUDY NUMBER: 01-C-0222 PRINCIPAL INVESTIGATOR: Brigitte Widemann, M.D.

STUDY TITLE: A Phase II Randomized, Cross-Over, Double-Blinded, Placebo-Controlled Trial of the Farnesyltransferase Inhibitor R115777 in Pediatric Patients with Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas

Continuing Review Approved by IRB on 1/12/09

Amendment Approved by IRB on 6/5/09 (J)

Date Posted to Web: 6/27/09

Standard

INTRODUCTION

We invite you/your child to take part in a research study at the National Institutes of Health (NIH).

First, we want you/your child to know that:

Taking part in NIH research is entirely voluntary.

You/your child may choose not to take part, or you/your child may withdraw from the study at any time. In either case, you/your child will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you/your child must be taking part in a study or be under evaluation for study participation.

You/your child may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you/your child have such beliefs, please discuss them with your NIH doctors or research team before you/your child agree to the study.

Now we will describe this research study. Before you/your child decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your/your child's personal physician or other health professional.

You/your child have neurofibromatosis type I (also called NF1), and one or more tumors called plexiform neurofibroma(s) that appear to be increasing in size over the past year and have the potential to cause serious medical problems. Plexiform neurofibromas, which are tumors that arise from nerves, occur commonly in patients with NF1. The only known effective treatment for plexiform neurofibromas is surgery, but many times complete surgical removal of all of the plexiform neurofibromas is not possible, because of the number or location of the tumors.

The underlying cause of NF1 is a defective gene. Genes carry the information for the body composition and characteristics. For example, genes determine the color of the eyes. The function of the gene, which is defective in NF1, is to produce a protein called neurofibromin. In patients with NF1, neurofibromin is decreased, and the decrease in neurofibromin is felt to contribute directly to tumor formation. Neurofibromin helps control the activity of another protein called *ras*. *Ras* can be thought of as an "on/off" switch for cell growth. When *ras* is "on", cells grow. When *ras* is "off",

PATIENT IDENTIFICATION	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient NIH-2514-1 (4-97) P.A.: 09-25-0099 File in Section 4: Protocol Consent (1)
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MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate in A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study
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STUDY NUMBER: 01-C-0222

CONTINUATION: page 2 of 7 pages

the cells do not grow. Neurofibromin helps to keep *ras* "off". Decreased levels of neurofibromin therefore may allow for uncontrolled cell growth and tumor formation.

Drugs that inactivate *ras* are being studied as a new way to treat cancer. These drugs may also provide a logical means of controlling the tumors in patients with NF1. R115777 is a new experimental drug that interferes with the function of the *ras* protein and other proteins in cells by blocking a step in the formation of these proteins. R115777 can block the growth of cancer cells in test tubes and in animals, but we do not know yet whether it will be effective for the treatment of plexiform neurofibromas in patients with NF1. This experimental drug has only been administered to a small number of adult and pediatric patients with a variety of different types of cancer and NF1. We do not know if this drug will be effective in your/your child's plexiform neurofibromas. R115777 is not approved by the Food and Drug Administration (FDA) for commercial use, but the FDA has permitted its use in this research study.

DESCRIPTION OF RESEARCH STUDY

The main purposes of this research study are (1) to determine if R115777 can slow down the growth rate of plexiform neurofibromas in patients with NF1, (2) to determine if R115777 can result in shrinkage of progressive plexiform neurofibromas, (3) to determine the types of side effects that can be produced by R115777 in children and young adults with NF1 and (4) to study the biology of the tumors from patients with NF1.

The growth of plexiform neurofibromas can be unpredictable, including periods of rapid growth and other periods of no measurable tumor growth. This unpredictable behavior can make it difficult to measure the effectiveness of R115777 as a treatment for plexiform neurofibromas. In order to find out if R115777 will be helpful for patients with plexiform neurofibromas, we will compare the effects of the drug to a placebo (a similar tablet that does not contain R115777) in each patient who is treated on the study. Before starting any treatment we will randomly determine (determined by coin flip) whether you/your child will initially receive either R115777 or placebo. Neither you/your child nor anyone involved in the care of you/your child, such as the nurses and physicians at the NCI and your/your child's doctor at home, will know if you/your child are is receiving R115777 or the placebo.

We will follow you/your child closely throughout the study for signs of increase of the plexiform neurofibroma by regular clinical examinations, if possible photography of visible tumors (with your permission, please see below), and MRI scans. You/your child will be identified on photographs only by the study ID number, and photographs will be located in a separate locked folder at the Pediatric Oncology Branch, NCI. If we find that the plexiform neurofibromas are increasing in size, you/your child will be switched to the other treatment. For example, if you/your child were getting the placebo first, then you/your child will be switched to R115777. As long as we find tumor growth during the initial part of the study, at some point you/your child will receive R115777. Should the tumor be stable or decrease in size, you/your child will continue to receive the same treatment for as long as it is well tolerated and appears to be of benefit. The treatment will only be switched or stopped if it is not controlling the growth of the plexiform neurofibromas. You/your child will be removed from the study when growth of the plexiform neurofibroma is noted on the second treatment phase. At that time we will perform a thorough clinical evaluation, in addition to a MRI study, and arrange for necessary follow-up care by your/your child's physician. Other reasons for removal from the protocol could be if you/your child did not tolerate R115777/placebo because of side effects of the drug, if you/your child developed another serious medical condition, which would not allow the administration of R115777/placebo, or if you/your child were unable to comply with the protocol. Although the design of this study is complicated, we think that it offers the best chance of determining if R115777 is of benefit for progressive plexiform neurofibromas. A total of approximately 60 patients will be entered on this study.

R115777 or placebo will be given by mouth in the form of tablets taken every 12 hours for 21 days followed by a 7 day rest period (1 cycle = 28 days, 21 days drug, 7 days rest period). R115777 will be given at the highest dose, which was

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84) NIH-2514-2 (10-84) P.A.: 09-25-0099
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MEDICAL RECORD**CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 01-C-0222

CONTINUATION: page 3 of 7 pages

found to be well tolerated by most patients in a prior clinical trial. Each dose will be 200 mg/m² body surface area, which is calculated from your/your child's height and weight. Tablets can be crushed for easier consumption, if necessary. R115777 or placebo should be taken after a meal. This treatment will be continued, unless unacceptable side effects or increase in the size of the plexiform neurofibromas are observed. You/your child will be examined by a doctor initially every other week during this treatment, and will have routine blood tests performed initially every other week. The frequency of these studies will be spread out after three cycles of treatment. MRI scans to measure the size of your/your child's plexiform neurofibromas will be performed periodically throughout the course of treatment. In addition to measuring the plexiform neurofibroma in the longest dimensions, we will also determine the volume of the plexiform neurofibroma to test if changes in the tumor volume may better reflect changes in the tumor size than standard measurements.

We will provide you with a form on which you will record the time each dose is administered, any side effects that you/your child experience, and any other medicines that you/your child are taking. This diary is an important part of our monitoring of this experimental drug.

Blood samples of 2 to 4 teaspoons each will also be taken prior to the first dose of treatment, and at one time point after at least 14 days of treatment on each study phase (R115777 or placebo) to measure the effect of R115777 on proteins in blood cells. A blood sample of less than one teaspoon will be obtained prior to starting treatment and prior to cycles 4, 7, 10, and then after every 6 cycles on each study phase to measure the level of a substance called nerve growth factor. The analysis of nerve growth factor will be used to determine if it can predict which patients may be at risk to develop side effects from R115777.

Should you/your child have superficial (just under the skin) tumor nodules, we would also like to ask you/your child to provide a piece of tumor from one of these nodules prior to the first dose of any treatment, and if feasible at one time point after at least 14 days of treatment on each study phase (R115777 or placebo) to learn more about changes in tumors of patients with NF1. In addition, should you/your child have to undergo surgery for a complication of your/your child's tumor, we would like to obtain a sample of the tumor. In this case we would only obtain the tumor sample after the pathologist and surgeon have determined that any material necessary for clinical care has been obtained. We will perform a detailed analysis of the tumor samples to better understand the cell components of plexiform neurofibromas, and will attempt to grow tumor cells in culture. In addition we will analyze the tumor samples for changes in the NF1 gene and in the *ras* gene and *ras* protein. These studies may help us to better understand which patients may benefit from the treatment with R115777. Any results from these studies will be preliminary and will require further analysis for verification. Therefore, neither you/your child nor anyone else will be informed about results of the studies performed on your/your child's neurofibroma tissue.

Should any tumor sample be left over after performing the above studies, we would like to retain these samples in a central tumor repository (storage site) at Washington University in St. Louis, Missouri. The tissue will be identified with a code number, and will only be possible to connect with your/your child's name through the trial coordinating center "Pediatric Oncology Branch of the NCI" in Bethesda, MD. The tissue may be distributed to investigators to help with their research on neurofibromatosis. There is a chance that the tumor sample you/your child are providing for this study, may have some commercial applicability. There are no plans to provide financial compensation to you/your child, should this occur. Any future research done with these samples will be conducted under a protocol approved by the Institutional Review Board with oversight of the tissue bank. You/your child will not receive further notice of future uses of your/your child's sample, unless a future use could involve more than minimal risk to you/your child. Any results from these studies will be preliminary and will require further analysis for verification. Therefore, neither you/your child nor anyone else will be informed about results of the studies performed on your/your child's neurofibroma tissue. All research results will be kept confidential. You can decide not to allow storage of your/your child's tumor sample at the tissue repository (please

PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (10-84)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

MEDICAL RECORD**CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 01-C-0222

CONTINUATION: page 4 of 7 pages

see below), or withdraw your/your child's specimen from the tissue repository at any time. Please contact Dr. Brigitte Widemann, Principal Investigator of this study, if you wish to do so.

If you decide not to have a tumor sample taken, you/your child can still participate in the treatment part of this study (please see below). We will give you/your child a separate consent form, for the tumor biopsy that explains the procedure and its risks more fully. If you decide not to give permission for storage of the tumor sample in the central tumor repository, you/your child can still participate in the treatment part of the study (please see below).

In addition we would like to assess your/your child's quality of life by giving you/your child a questionnaire, which you/your child would complete periodically throughout the treatment course.

Should significant new findings regarding the treatment of NF1 become available during the course of this study, which may influence your decision to continue on this study, we will provide you/your child with that information.

R115777 and placebo will be provided without charge, as will all examinations and studies performed at the NIH. The NIH will usually not pay for physical examinations or laboratory tests required for the study, which are performed outside of the NIH.

Please indicate below if you/your child agree or disagree to the following study procedures:

- | | | | |
|--|---------------------------------|------------------------------------|-----------|
| 1) Regular photographs of visible tumors: | Agree: <input type="checkbox"/> | Disagree: <input type="checkbox"/> | Initials: |
| 2) Obtain tumor sample(s) of superficial tumor nodules: | Agree: <input type="checkbox"/> | Disagree: <input type="checkbox"/> | Initials: |
| 3) Storage of the tumor sample(s) in a central tumor repository: | Agree: <input type="checkbox"/> | Disagree: <input type="checkbox"/> | Initials: |

ALTERNATIVE APPROACHES OR TREATMENTS

You/your child will only be eligible for this trial if complete surgical removal of the progressive plexiform neurofibroma(s) is not feasible. Alternatives to this treatment may include partial surgical removal of the plexiform neurofibroma, other experimental therapies, or you/your child may decide not to receive any treatment at this point in time.

RISKS OR DISCOMFORTS OF PARTICIPATION

The side effects of R115777 have been studied in animals, in adult patients with cancer, and in children with cancer and NF1. R115777 may affect several organs or tissues of your/your child's body. The side effects most commonly observed in adults were decrease in the bone marrow function leading to a drop in the white blood cell count (neutropenia, granulocytopenia), platelet count, or red blood cell count, and nausea and vomiting. A decrease in white blood cells leads to an increased risk for infections and fever including sepsis. A decrease in the platelet count can result in bleeding or bruising and may require platelet transfusions to correct it. A decreased red blood cell count leads to anemia causing tiredness, and may require red blood cell transfusions to correct it. Other likely side effects include loss of appetite, diarrhea, nausea or vomiting. When R115777 was given continuously to adult patients with breast cancer (every day without a rest period) for a time period exceeding 12 weeks, more than half of the patients developed signs of nerve damage with pain, tingling and numbness or weakness in the hands or feet. Less frequently, R115777 caused headaches, dehydration, skin rash, sensitivity to sunlight (photosensitivity) and peeling skin, a decrease in kidney function (increase in serum creatinine), a decrease in the potassium level (an important chemical), reversible liver damage, heartburn, decrease in blood pressure, irritation or sores in the lining of your mouth or esophagus or intestines, constipation, nosebleed, fever or infection, tiny broken blood vessels under the skin and changes in a chemical called lipase, which is required to digest food. One adult developed headaches and a defect in vision, which were reversible. The same patient later developed a stroke, which was felt not to be related to the R115777. In adult patients with

PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (10-84)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

MEDICAL RECORD**CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 01-C-0222

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leukemia who received high doses of R115777 (900 to 1200 mg twice daily) increased thirst, confusion, changes in vision, and difficulties to coordinate body movements were observed. These side effects subsided completely within a few days after stopping R115777. Other less-frequently observed side effects include swelling of the arms and legs, dizziness, sleepiness, pain in the belly, chest or in general, or cough or shortness of breath. One rare but serious side effect observed was bleeding into the brain or spinal cord.

The side effects observed to date in the children and adolescents treated with R115777 are similar to those observed in adults and include: 1) A decrease in the bone marrow function, with a drop in the white blood cell, platelet count and red blood cell count, 2) the development of a rash which may be more pronounced in skin areas exposed to sun, and 3) the development of nausea, vomiting, diarrhea and abdominal pain. One patient had a seizure while receiving R115777, and one patient experienced a reversible decrease in fibrinogen (a substance important for blood clotting). Few children with leukemia developed an increase in blood tests, which measure liver function (bilirubin, AST), with an unclear relationship to R115777. In addition, 1 patient with leukemia developed mouth sores (mucositis). Signs of nerve damage have not been reported in any of the children treated to date. However, this does not guarantee that children will not develop neurologic toxicity, particularly after administration of R115777 for a long time period. All of these side effects have been reversible.

The dose of R115777 that you/your child get was determined in a prior clinical study in pediatric patients with cancer and NF1. This dose of R115777 was well tolerated by most patients. However, since this is a new experimental treatment, other presently unknown side effects may occur. These side effects could potentially be serious and even fatal. You/your child will be watched closely and the drug will be discontinued if serious side effects develop.

The risks from the blood drawing to assess the affect of R115777 in the body include the discomfort from having needle sticks if required and a small risk of infection.

Participation in the present study may render you/your child ineligible to participate in other research studies that limit the number or type of treatments that patients may have received, and in some cases, the types of side effects that patients may have experienced.

Tumor Studies: You/your child will receive a separate consent form for the tumor biopsy that explains the procedure and risks more fully. Tumor material will be obtained for research purposes on this study. With your permission, left over tumor will be sent to a central tissue repository. Although there is no immediate plan to perform studies from any tumor samples obtained, tumor material will be stored for possible future testing. It is expected that the tissue samples will be stored indefinitely in the repository. The sample will be identified by a code number that can be traced to you/your child only by contact with the trial coordinating center "Pediatric Oncology Branch, NCI" in Bethesda, MD. Neither you nor anybody else will be informed about results of testing performed on your/your child's blood sample or tumor tissue. Every effort will be made to keep test results confidential. However, as the tumor and sample can be linked to your/your child's name, a small risk persists that unauthorized persons could gain access to the information. Some testing may eventually reveal information that, in some cases, may result in discrimination with health or life insurance or employment. We believe that these risks are minimal since it is already known that you/your child have neurofibromatosis.

MRI: Magnetic resonance imaging (MRI) is a standard procedure used for imaging plexiform neurofibromas. When having a MRI, you/your child will lie motionless on a table that slides into a tunnel slightly wider than your/your child's body for about one hour. There is very little room in the MRI, however you/your child will easily be able to hear and speak to research staff. As images are taken, the MRI makes loud banging noises as though it was being pounded on the outside with a hammer. Earplugs will be offered to help reduce the noise. MRIs use powerful magnets. There are no known or foreseeable risks associated with exposures to MRI provided no metal implanted prostheses (*e.g.*, vascular clamps or pacemakers; braces are not a problem) are present. Should you/your child have a metal prosthesis you/your child may be excluded from participating in the study for your/your child's own safety. All potential subjects will be

PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (10-84)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

MEDICAL RECORD**CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 01-C-0222

CONTINUATION: page 6 of 7 pages

screened for the presence of such prior to the examination. Some participants in the study may require sedation or anesthesia to perform MRI. Consent for this will be obtained prior to the MRI. There are risks associated with sedation and anesthesia, including the risk of death in rare instances.

If you/your child are a female and old enough to get pregnant, you/your child will be given a pregnancy test before you/your child begin the treatment, in order to make sure that you/your child are not pregnant. If there is a chance that you/your child could become pregnant during this study, you/your child should not participate in the study. If you/your child are sexually active, you/your child must use an appropriate and effective method of birth control while you/your child are taking part in this study. If you/your child become or are found to be pregnant while taking part in this study, you/your child must notify one of the doctors listed on this form right away so the treatment can be discussed.

If you/your child are a male, you/your child should also use a means of birth control while taking part in this study (if sexually active), because we do not know what effect the experimental drug may have on your/your child's sex cells and what effect this would have upon the development of an unborn child.

POTENTIAL BENEFITS OF PARTICIPATION

The potential benefit of this treatment with R115777 is that it may cause your/your child's neurofibroma to stop growing or shrink for a period of time or it may lessen the symptoms, such as pain, that are caused by the tumor. It is our intent to benefit each subject in the trial. However, because there is not much information about the drug's effect on plexiform neurofibromas in humans, we do not know if you/your child will benefit from taking part in this study, although the knowledge gained from this study may benefit others. 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 plexiform neurofibromas, 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.

RESEARCH SUBJECT'S RIGHTS

Joining this research study is voluntary. You/your child may ask the doctors and nurses any questions about this treatment. If you/your child decide at any time that you/your child do not want to receive this treatment any more, then tell us (Dr. Brigitte Widemann, phone 301-496-7387, Dr. Frank Balis phone 301-496-0085, or Ms. Andy Gillespie, RN, phone 301-402-1848) and we will discontinue it. You/your child may be eligible to receive experimental therapy other than the drug described here, or can receive therapy consisting of symptomatic treatment only.

Your/your child's medical record may be reviewed by qualified representatives from the National Cancer Institute, or by representatives from the Food and Drug Administration (FDA).

PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (10-84)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient
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STUDY NUMBER: 01-C-0222

CONTINUATION: page 7 of 7 pages

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your/your child's research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your/your child's medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your/your child's NIH medical records. However, you/your child should know that the Act allows release of some information from your/your child's medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your/your child's participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you/your child have the right to pursue legal remedy if you believe that your/your child's injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you/your child have any problems or questions about this study, or about your/your child's rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Brigitte Widemann; Building 10, Room 13C103, Telephone: 301-496-7387. Other researchers you/your child may call are: Dr. Frank Balis, Telephone 301-496-0085; and Andy Gillespie, R.N., Telephone 301-402-1848.

You/your child may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you/your child want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:			
A. Adult Patient's Consent I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study. _____ Signature of Adult Patient/Legal Representative Date		B. Parent's Permission for Minor Patient. I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable.) _____ Signature of Parent(s)/Guardian Date	
C. Child's Verbal Assent (If Applicable) The information in the above consent was described to my child and my child agrees to participate in the study. _____ Signature of Parent(s)/Guardian Date			
THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JANUARY 12, 2009 THROUGH JANUARY 11, 2010.			
_____ Signature of Investigator Date		_____ Signature of Witness Date	

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY (Continuation Sheet)

• Adult Patient or • Parent, for Minor Patient

NIH-2514-1 (12-08)

P.A.: 09-25-0099

FAX TO: (301) 480-3126

File in Section 4: Protocol Consent

MEDICAL RECORD	MINOR PATIENT'S ASSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Attach to NIH-2514-2, Consent to Participate in a Clinical Research Study
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INSTITUTE: National Cancer Institute

STUDY NUMBER: 01-C-0222 PRINCIPAL INVESTIGATOR: Brigitte Widemann, M.D.

STUDY TITLE: A Phase II Randomized, Cross-Over, Double-Blinded, Placebo-Controlled Trial of the Farnesyltransferase Inhibitor R115777 in Pediatric Patients with Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas

Continuing Review Approved by IRB on 1/12/09

Amendment Approved by IRB on 6/5/09 (J)

Date Posted to Web: 6/27/09

Minor 7 thorough 12 years of age

You have an illness called neurofibromatosis type 1. We will call it NF1 for short. NF1 can cause lumps that are called tumors to grow inside of your body and these tumors can cause pain or other problems. Sometimes the tumors can be taken out with an operation, but if they can't then doctors don't have other ways to make them stop growing or make them go away.

We are trying to find new medicines that can slow down or stop NF1 tumors from growing, and we are asking you to help us test one of these new medicines that is called R115777. We don't know yet whether this new medicine will work.

We can measure the size of your tumor and check to see if your tumor is growing by doing scans that can take a picture of the inside your body without hurting you. This is called an MRI scan. You will lie down on a bed, and the bed is pushed into a machine. This can be scary because you are in a small space and the machine makes a lot of noise. The scan usually takes about 1 hour, and you have to lie still during the scan. Some kids need medicines to make them sleep during the scan because it is too scary or they can't lie still that long.

NF1 tumors don't grow all of the time. They can grow for a while and then stop growing for a while without any treatment. This makes it hard for us to tell if a new medicine is really working.

To find out if a new medicine works we will measure the change in the size of your tumor while you are taking pills that have the new medicine in them, and we will also measure the change in tumor size while you are taking pills with no medicine in them. You, your parents, and your doctors will not know whether the pills that you are taking have the medicine or not. You may start with the pills that have the medicine first or you may start with the empty pills first. If your tumor grows, then we will switch you to the other type of pills. If your tumor stays the same size then you will keep taking the same pills.

You will take pills twice a day for 21 days and then you will have a break for 7 days before you start taking the pills again. We will do the MRI scans to check the size of your tumor after every 3 months for the first year and then after every 6 months.

The new medicine that we are testing can cause side effects, which can make you feel bad. Side effects can happen when the new medicine effects other parts of your body than the tumor. These side effects do not happen to everyone who takes the new medicine. In some people the medicine can make them feel sick to their stomach or throw up. It can also cause diarrhea (watery poop), skin rash, which is red itchy bumps, make your nose bleed, or have tingling, numbness or pain in your hands and feet. Let us know if you feel dizzy, confused, have a sore mouth, have trouble catching your breath, have trouble going to the bathroom (poop), or have trouble going to sleep. The new medicine can

PATIENT IDENTIFICATION

MINOR PATIENT'S ASSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

NIH-2514-2 (4-97)

P.A.: 09-25-0099

File in Section 4: Protocol Consent (3)

STUDY NUMBER: 01-C-0222

CONTINUATION: page 2 of 2 pages

also lower your blood cells that carry oxygen to your body, fight infections, and make your blood clot when you get a cut. It can also change how your kidneys or liver work, so we will check for all of these by doing blood tests every 2 weeks after you start the new medicine and then every 4 weeks after you have been on the medicine for a while. We get this blood by putting a small needle into a vein in your arm. This feels like a prick or bee sting. If the side effects happen to you, they will go away after you stop taking the medicine. Tell your parents or your doctors if you think that you have any of these side effects.

If this new medicine works, it may slow down or stop the growth of your tumor.

Ask your parents or your doctors or nurses if you have questions about this new medicine or the way that we are testing it. We are asking for your permission and your parents permission before we test this new medicine on you. You can decide not to take part in this study if you don't want to and you can stop taking the medicine at any time, if you change your mind.

Revision Copy

I have had this study explained to me in a way that I understand, and I have had the chance to ask questions. I agree to take part in this study.

Signature of Minor Patient: _____ Date: _____

Signature of Investigator: _____ Date: _____

MEDICAL RECORD	MINOR PATIENT'S ASSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Attach to NIH-2514-2, Consent to Participate in a Clinical Research Study
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INSTITUTE: National Cancer Institute

STUDY NUMBER: 01-C-0222 PRINCIPAL INVESTIGATOR: Brigitte Widemann, M.D.

STUDY TITLE: A Phase II Randomized, Cross-Over, Double-Blinded, Placebo-Controlled Trial of the Farnesyltransferase Inhibitor R115777 in Pediatric Patients with Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas

Continuing Review Approved by IRB on 1/12/09
 Amendment Approved by IRB on 6/5/09 (J)
 Minor 13 through 17 years of age

Date Posted to Web: 6/27/09

Introduction: We would like to invite you to take part in a research study at the National Institutes of Health (NIH). Before you decide about taking part in the study, we want you to know why we are doing the study and if it will help you. We also want you to know about any risks (what might go wrong) and what you will have to do. You can only be in the study if you and your parent(s) agree.

This form gives you information about the study. Your doctor will talk to you about the study and answer questions you have. If you would like to take part in this study, we will ask you to sign this form to show that you understand this study. We will give you a copy of this form to keep. It is important that you know:

You do not have to join the study

You may change your mind and drop out of the study at any time

If we make important changes to the study we will tell you about it and make sure you still want to be in the study.

Purpose of the study

You have an illness called neurofibromatosis type 1 or NF1, which has caused a tumor (called plexiform neurofibroma) to grow inside your body. This tumor may cause you pain, discomfort, or other problems as it gets larger. There are no effective treatments other than surgery to make these tumors go away. Because your tumor cannot be taken out completely, we want to see if a new drug with the name R115777 will help to stop your tumor from growing, or shrink your tumor. This drug has been given in the past to adults with other diseases than NF1, and to some children with cancer or NF1.

Because we do not know whether this new drug will work, we are doing a study where we are giving R115777 to just a few children and adults with NF1 and a tumor called a plexiform neurofibroma, which has shown recent growth and cannot be completely removed by surgery.

We want to answer four questions about this new drug R115777 and NF1 tumors:

Will this new drug, R115777, slow down how fast your NF1 tumor(s) grow(s)?

Will R115777 make your NF1 tumor(s) smaller?

Does R115777 make you feel different or cause anything new to happen to you (for example, does the drug make you feel tired or does it make your stomach upset)?

What more can we learn about NF1 tumors?

PATIENT IDENTIFICATION	MINOR PATIENT'S ASSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY NIH-2514-2 (4-97) P.A.: 09-25-0099 File in Section 4: Protocol Consent (4)
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MEDICAL RECORD**CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 01-C-0222

CONTINUATION: page 2 of 3 pages

Study plan

These are difficult questions to answer but we have written a plan or study, which we think, will help us find the answers. We want to watch you and look at your tumors when you are taking the R115777 pills for a period of time and when you are taking pills that don't have the drug. The pill that does not contain R115777 looks just like the R115777 pill. This way you, your parents, and your doctors will not know which type of pill you are taking and we will be able to find out if the R115777 is really working. Before you take any drug, a coin will be flipped to decide if you will take the R115777 pills or the empty pills first. You will continue to take that pill until your tumor(s) grow(s) and then you will be switched over to the other pill and take it until your tumor(s) grow(s) once again. We will not know when you are taking the R115777 or the empty pills.

The plan or protocol we have written explains the rules about this study. It tells us how you take the drug, when you take the drug and how we will keep a very close eye on you while you are on our study. You will take the R115777 or empty pills two times a day for 21 straight days and then you will stop taking the pills for 7 days in a row. You will continue taking the R115777 or empty pills this way until your tumors grow or you do not feel well enough to swallow the pills. We will know when your tumors grow because after every 3 months during the first year, and then after every 6 months, you will have a MRI scan, which takes a picture of the inside of your body. To take the picture you lay down on a bed, which slides into a large machine. It may be scary if you don't like small places. You will need to lie still for approximately 1 hour. The scanner is also very noisy while it is working. You may have to receive a medicine to make you sleep while you get the scans. The medicine will be put into a vein in your arm through a small needle. It will feel like a prick or bee sting when the needle is placed in your arm. In addition to the pictures we take, we will also look at your blood, in the beginning every 2 weeks, and then every 4 weeks. We draw the blood from your arm by placing a small needle into the vein in your arm, which will feel like a prick or a bee sting. Once the blood is drawn the needle is taken out and you will be given a band-aid.

Risks or side effects:

Drugs can make you feel different or cause something new to happen to you. These are called side effects of a drug. At the dose of R115777 you will receive, the drug has been well tolerated by a small number of children with NF1. However, the following side effects may happen to you. Your stomach may be upset, causing some nausea or vomiting. The drug may cause you to have diarrhea or watery bowel movements. A bumpy redness called a skin rash may appear on your skin that can itch or your skin may become more sensitive to sunlight. R115777 may also affect your blood, which is made up of many different parts or cells. One of them is your white blood cells, which helps your body fight germs or infections. R115777 may lower the number of white blood cells in your body, which may cause you to have a fever or get sick. Few adult patients who took the drug continuously without a break for more than 3 months developed pain and tingling in the tips of the fingers and toes. All reported side effects from R115777 went away after the drug was stopped. Less likely side effects may include difficulty having a bowel movement, heartburn, nosebleed, mouth sores, swelling of the arms or legs, confusion or dizziness, sleepiness, pain in the chest or belly, headache, cough or having difficulty breathing. This drug may change how your kidneys or liver work so we will check for this by doing blood tests. Should you develop a side effect we may decide to stop the drug until the side effects go away, and then restart the drug at a lower dose. One rare but serious side effect observed was bleeding into the brain or spinal cord.

Taking R115777 might be harmful to an unborn child. Birth control measures must be used by all females of child-bearing age or who can become pregnant and are sexually active or by their sexual partners while in this study, such as: Contraceptive pill or use of condom and spermicide cream. As effects of R115777 on a newborn child are unknown, breast-feeding mothers must stop breast-feeding their child. Males who are sexually active, must also use means of birth control while participating in the study.

PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (10-84)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

STUDY NUMBER: 01-C-0222

CONTINUATION: page 3 of 3 pages

Potential Benefits:

R115777 might slow down or stop the growth of your tumor or even might decrease its size. Taking part in this study will help us to find out if R115777 works.

Alternatives to Participation

The only known effective treatment for plexiform neurofibromas is surgery. In many cases the tumor cannot be removed completely, and in some cases surgery cannot be safely done. Participation in this study will only be offered to you if your tumor cannot be safely removed, or if you or your parents don't want you to have surgery.

Confidentiality

We will keep the records of this study confidential. Only people working on the study will know your name.

Please ask your doctor or research nurse any questions you might have about this study. Keep asking until you understand. You can decide not to take part in this study if you don't want to. Your doctors and nurses will understand if you don't want to participate. If you agree to go on this study, know that you can stop whenever you choose.

We are asking for your permission and your parent's permission before we give this new medicine to you. A copy of this form will be given to you and your parents.

By signing this form, you agree that you have talked to your doctor about the study and understand it, and want to be in the study. You also agree that we have talked to you about the risks and benefits of the study, and about other choices. You may drop out of the study at any time and no one will mind. Please call the Principal Investigator Dr. Brigitte Widemann, M.D., at 301-496-7387 if you have any questions.

I have had this study explained to me in a way that I understand, and I have had the chance to ask questions.
I agree to take part in this study.

Signature of Minor Patient: _____ Date: _____

Signature of Investigator: _____ Date: _____