

PROTOCOL SUBMISSION FORM Amendment Form	PROTOCOL NO. 04C0080-C	PRINCIPAL INVESTIGATOR (NIH Employee Name, Inst/Br, Telephone and e-mail): Brigitte Widemann NCI POB 301.496.4256 widemanb@mail.nih.gov
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PROTOCOL TITLE: "Phase II Trial of Pirfenidone in Children, Adolescents, and Young Adults with Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas"

ABBREVIATED TITLE: 04C0080

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Phase II Trial of Pirfenidone in Children, Adolescents, and Young Adults with Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas

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PRECIS

Background:

- Neurofibromatosis Type 1 (NF1) is an autosomal dominant, progressive genetic disorder characterized by diverse clinical manifestations. Patients with NF1 have an increased risk of developing tumors of the central and peripheral nervous system including plexiform neurofibromas, which are benign nerve sheath tumors that may cause severe morbidity and possible mortality. The histopathology of these tumors suggests that events connected with formation of fibroblasts might constitute a point of molecular vulnerability. Gene profile analysis demonstrates overexpression of fibroblast growth factor, epidermal growth factor, and platelet-derived growth factor in plexiform neurofibromas in patients with NF1. Pirfenidone is a novel anti-fibrotic agent that inhibits these and other growth factors. Clinical experience in adults has demonstrated that pirfenidone is effective in a variety of fibrosing conditions and pirfenidone is presently under study in a phase II trial for adults with progressive plexiform neurofibromas. A phase I trial of pirfenidone in children and young adults with NF1 and plexiform neurofibromas was completed, and has established the phase II dose (the dose resulting in a mean drug exposure [AUC] not more than 1 standard deviation below the mean drug exposure [AUC] in adults who received pirfenidone at the dose level demonstrating activity in fibrosing conditions). Pirfenidone has been well tolerated.

Objectives:

- To determine whether pirfenidone increases the time to disease progression based on volumetric measurements in children and young adults with NF1 and growing plexiform neurofibromas
- To define the objective response rate to pirfenidone in NF1-related plexiform neurofibromas.
- To describe and define the toxicities of pirfenidone.

Eligibility:

- Individuals (≥ 3 years to ≤ 21 years of age) with a clinical diagnosis of NF1 and inoperable, measurable, and progressive plexiform neurofibromas that have the potential to cause substantial morbidity.

Design:

- The phase II dose will be used in a single stage, single arm phase II trial. The natural history of the growth of plexiform neurofibromas is unknown. For this reason, time to disease progression on the placebo arm of an ongoing NCI POB placebo-controlled, double-blind, cross-over phase II trial of the farnesyltransferase inhibitor R115777 for children and young adults with NF1 and progressive plexiform neurofibromas will be used as historical control to determine if pirfenidone increases time to disease progression. Eligibility criteria and method of tumor measurements are identical for both trials.
- Pirfenidone will be administered orally as capsules at a dose of 500 mg/m² three times a day (q8h) for cycles of 28 days with no rest period between cycles based on the results of our pediatric phase I trial.

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1.0 INTRODUCTION

1.1 OBJECTIVES

PRIMARY STUDY OBJECTIVES:

- 1.1.1 To determine whether pirfenidone, administered on a chronic oral schedule (28 day cycles with no rest period between cycles), increases the time to disease progression based on volumetric measurements in children and young adults with neurofibromatosis type 1 (NF1) and growing plexiform neurofibromas.
- 1.1.2 To define the objective response rate to pirfenidone in NF1-related plexiform neurofibromas.
- 1.1.3 To describe and define the toxicities of pirfenidone, administered on a chronic oral schedule (28 day cycles with no rest period between cycles), in children and young adults with NF1.

SECONDARY STUDY OBJECTIVES

- 1.1.4 To assess the quality of life of patients treated with pirfenidone using the 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.
- 1.1.5 To assess the value of three-dimensional MRI (3-D MRI) in the evaluation of plexiform neurofibromas, and to compare 3-D MRI to conventional two-dimensional MRI (2-D MRI) and one-dimensional MRI (1-D MRI) data analysis.
- 1.1.6 To contribute tumor specimens from patients who undergo tumor surgery or biopsies for clinical reasons to an already-existing tissue bank at Washington University, St. Louis, MO. Tumor specimens of plexiform neurofibromas will undergo central pathology review, including detailed morphological, ultrastructural immunohistochemical, and mRNA gene expression profile analysis
- 1.1.7 To make tumor specimens that are obtained on this trial available to the scientific community, after obtaining IRB approval, in order to collect more information on the pathology, genetics, and cell biology of plexiform neurofibromas.

1.2 BACKGROUND AND RATIONALE

1.2.1 NEUROFIBROMATOSIS TYPE I AND PLEXIFORM NEUROFIBROMAS

Neurofibromatosis type 1 (NF1) is a common autosomal dominant, progressive 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%), optic gliomas (15-20%),

pheochromocytomas (1%), malignant peripheral nerve sheath tumors, (5%), and neurofibrosarcomas (6%) (Korf, 1999; Korf, 2000).

The two main peripheral nerve tumors in patients with NF1 are neurofibroma, a benign tumor, and malignant peripheral nerve sheath tumor (MPNST). These tumors are related in that most MPNST arise by malignant transformation of neurofibroma. Such an event occurs in about 5% of NF1 patients (Korf, 2000). However, based on a recent study, the life time risk of MPNST in NF1 is much higher with 8-13% (Evans, 2002). There are multiple types of neurofibromas including localized cutaneous neurofibroma, localized intraneuronal neurofibroma, diffuse neurofibroma, massive soft tissue neurofibroma and plexiform neurofibroma. Plexiform neurofibromas are benign nerve sheath tumors that grow along the length of nerves and involve multiple branches of a nerve. These tumors are usually diagnosed early in life, may be multiple and might develop throughout life. Early childhood, puberty and childbearing age in females are considered to be the periods of greatest risk for disease progression (Needle et al., 1997). Approximately 20-44% of individuals with NF1 develop plexiform neurofibromas (Huson et al., 1988). These tumors may cause significant disfigurement, as well as compression of vital structures. As examples, plexiform neurofibromas may infiltrate the orbit and displace the globe and compromise vision; paraspinal tumors (also referred to as dumbbell lesions) can compress the spinal cord and cause paralysis; tumors in mediastinum may compress the trachea or great vessels; and tumors of the extremities can cause local nerve infiltration, progressive neurologic deficit and often unremitting pain (Needle et al., 1997).

Plexiform neurofibromas and paraspinal neurofibromas cause major morbidity and mortality in NF1 (Rasmussen et al., 2001; Korf, 1999). There is no currently accepted effective drug therapy for plexiform neurofibromas. The rate of growth of this histologically benign neoplasm is commonly unpredictable and often episodic (Korf, 2000). Plexiform neurofibromas rarely regress spontaneously, and in many patients their growth is relentless. The management of plexiform neurofibromas is especially difficult due to the infiltrating nature of tumors.

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. (Needle et al., 1997). There is no other standard treatment modality for patients with progressive plexiform neurofibromas.

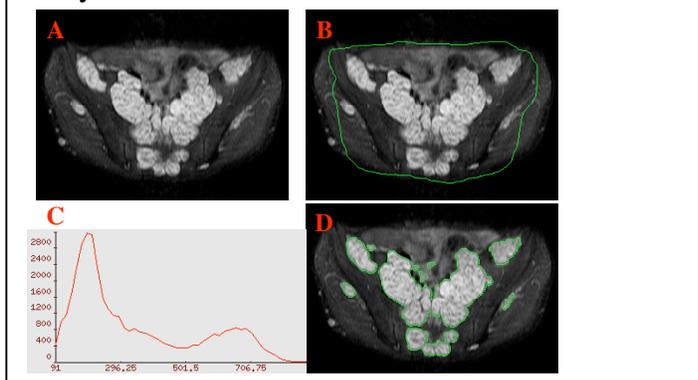
The unknown natural history of plexiform neurofibromas in NF1 and difficulties in measuring changes in size of these complex, large, and slow growing lesions have made it difficult to define the benefit of medical treatments for plexiform neurofibromas. However, a number of medical treatments including thalidomide (Gupta et al., 2003), cis retinoic acid, interferon alfa 2b, methotrexate and vinblastine, PEG interferon alfa-2b, and the farnesyltransferase inhibitor R115777 have been evaluated or are undergoing evaluation in early clinical trials for patients with NF1 and plexiform neurofibromas with the goal to reduce the growth rate or shrink these tumors. Published results are available only for the phase I thalidomide trial. In this trial thalidomide was administered to 20 patients with NF1 and plexiform neurofibromas at doses up to 200 mg/day. Response was assessed by clinical measurements and 2-D radiographic measurements. Of 12 patients who completed 1 year of treatment, four

showed a <25% reduction in tumor size, and seven showed symptomatic improvement with predominantly a decrease in pain. To date no medical treatment has demonstrated clear benefit for patients with NF1 and plexiform neurofibromas.

1.2.2 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 within MEDx (v3.41) software (Sensor Systems, Inc. Sterling, VA). Reproducibility and inter-observer variability of this automated method were

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



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

1.2.3 MOLECULAR VULNERABILITY OF NEUROFIBROMAS

The histopathology of cutaneous neurofibromas is characterized by slender spindle cells with abundant extracellular matrix of dense, wavy collagen fibers and extracellular mucoid material. Up to 70% of the tumor dry weight of a neurofibroma is collagen [Peltonen et al., 1985; Uitto et al., 1986]. Type I collagen is most abundant, and collagens type III and V are represented in lesser amount [Uitto et al., 1986; Konomi et al., 1989]. In comparison with normal skin fibroblasts, early passage fibroblasts from neurofibromas synthesize and secrete higher amounts of collagen [Peltonen et al., 1985; Uitto et al., 1986]. Several studies imply that fibroblasts might have an important role in the pathogenesis of these tumors [Kadano et al., 1994; Sasaki et al., 1992]. The role of growth-promoting cytokines, such as transforming-growth factor-beta 1 (TGF-beta1), fibroblast growth factor (FGF), epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) in proliferation of fibroblasts, is well established [Kaneko et al., 1998]. There is evidence that neurofibroma-derived fibroblasts are stimulated by basic fibroblast growth factor (bFGF), EGF, TGF-beta1 and PDGF in lower concentration than control fibroblasts [Kitano et al., 1992; Atit et al. 1999] In addition, Nf1+/- mouse skin wounds have abnormal granulation tissue, composed mostly of collagen. They also showed increase in collagen deposited by Nf1-/- fibroblasts, which are activated by a RAS-independent pathway. More recently, De Clue et al. [2000] demonstrated epidermal growth factor receptor (EGF-R) expression in Schwann cell-derived tumors similar to NF1, and suggested that EGF-R expression plays a significant role in NF1 tumorigenesis and Schwann cell transformation. De Clue et al. also showed that growth of NF1 MPNST lines and the transformed NF1-/- mouse embryo Schwann cells was greatly stimulated by EGF in vitro and could be blocked by agents that antagonize EGF-R function. These findings suggest that events connected with fibrogenesis might constitute a point of molecular vulnerability of NF1-related tumors.

1.2.4 GENE PROFILE ANALYSIS OF PLEXIFORM NEUROFIBROMAS

Gene expression profiling was performed on 5 individual snap frozen plexiform neurofibromas using the Affymetrix G110 microarray (1,992 human transcripts) at the

Children's National Medical Center. Genes that are potential targets of the novel anti-fibrotic agent, pirfenidone, were specifically analyzed for their level of mRNA expression. These include FGF, FGFR1, PDGF, PDGFR, EGF, EGFR, and fibronectin.

The following preliminary data were obtained:

Gene	%NF-1 Tumors Positive	% Transcripts Positive	NF-1 Mean Expression Level	Medulloblastoma Mean Expression Level
FGF	100% (5/5)	100% (15/15)	706	196
FGFR1	100% (5/5)	100% (10/10)	532	125
PDGF	20% (1/5)	20% (1/5)	885	303
PDGFR	100% (5/5)	100% (5/5)	586	392
EGF	20% (1/5)	20% (1/5)	223	156
EGFR	60% (3/5)	60% (3/5)	566	179
Fibronectin	60% (3/5)	60% (3/5)	2,461	936

These preliminary data confirm that most gene targets (except for PDGF and EGF) for pirfenidone are overexpressed by neurofibromas at relatively high levels (compared to a cohort of 30 medulloblastomas profiled at this institution). These data provide justification for the study of novel agents targeting these molecules in this group of tumors.

1.2.5 PIRFENIDONE

Pirfenidone, 5-methyl-1-phenyl-2-(1H)-pyridone, is a novel anti-fibrotic drug that has been shown to inhibit fibroblast growth and collagen synthesis. It modulates the action of cytokines, including platelet derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), intercellular adhesion molecule-1 (ICAM-1) (Kaneko et al., 1998), and TGF-alpha-1-induced fibronectin synthesis (Zhang et al., 1998). These effects result in inhibition of proliferation and collagen matrix synthesis by human fibroblasts. Antifibrotic effects are well-documented *in vitro*, *in vivo* and animal experiments, indicating therapeutic potential in many fibrosing conditions (Shimizu et al., 1997, 1998; Iyer et al., 1998; Al-Took et al., 1998; Dosanjh et al., 1998; Suga et al., 1995). Although the understanding of molecular events that lead to the development of neurofibromas in NF1 is still primitive, comparison of the effects of pirfenidone with the observed alterations in NF1 lead to a hypothesis that pirfenidone may exert a therapeutic effect in NF, perhaps leading to shrinkage or decreased growth rate of existing neurofibromas, or prevention of new lesions.

1.2.6 PRECLINICAL STUDIES PIRFENIDONE

In vitro studies: *In vitro* cell culture studies demonstrated a dose dependent inhibition of human (WI38) lung fibroblasts and collagen formation by pirfenidone. Effects are present at concentration 10 to 20 times lower than those impairing cell viability (1200 mcg/ml). (Lefkoviwitz and Margolin 1993). Pirfenidone blocked the proliferation of WI38 fibroblasts after exposure to TGF- β -1, PDGF, FGF and EGF. Collagen output by these cells was also inhibited by pirfenidone. Similar effects were observed in serum-

stimulated myometrial and leiomyoma cells (Lee et al., 1998). Pirfenidone efficiently decreased cellular proliferation in both myometrial and leiomyoma cells. Densitometric analysis of Northern blot showed decreased expression of collagen type I and type III mRNA. Pirfenidone moderates fibronectin synthesis by cultured human retinal pigment epithelial cells when stimulated with TGF- β -1, but does not have an effect on fibronectin synthesis in non-stimulated cells. It has been shown that the excessive cell proliferation induced by cytokine growth factors such as TGF- β -1, can be completely arrested by pirfenidone in the culture media at concentrations that are 1/10 to 1/20 of the toxic dose. Transfer of such pirfenidone-exposed cells to culture media, which contain no pirfenidone, results in recovery of normal proliferation capacity (Margolin 2001). Therefore, the anti-fibrotic effect of pirfenidone may be partly mediated through inhibition of TGF- β -1-induced fibronectin synthesis (Zhang et al, 1998).

Kaneko et al (1998) investigated the effect of pirfenidone on the expression of intercellular cell adhesion molecules (ICAM-1). The synovial fibroblasts were treated with interleukin 1- α in the presence and absence of Pirfenidone, and assayed for the expression of cell adhesion molecules. Pirfenidone significantly down-regulated the expression of ICAM-1 on cultured synovial fibroblasts in a dose-dependent manner. In contrast, expression of endothelial-leukocyte adhesion molecule-1 was not affected. Pirfenidone also significantly suppressed cellular binding between cultured lymphocytes and IL-1- α -stimulated synovial fibroblasts. Therefore, down-regulation of ICAM-1 might be another mechanism of action of pirfenidone. The results from another study suggest that pirfenidone may have antitumor effects on malignant gliomas, whose biological properties resemble those of NF-1-derived tumors, and that these effects may be mediated, in part, through EGFR phosphorylation inhibition (Krishnan et al, 2007).

In vivo studies: The effects of pirfenidone on survival and growth of neurofibroma xenografts were evaluated (Babovic-Vuksanovic et al., 2000; 2004). Sixteen SCID mice with implanted tumors (7 schwannoma and 9 neurofibroma) were treated with oral pirfenidone (in a dose of 500 mg/kg per day, equivalent to 1500 mg/m²/day)). Sixteen untreated mice with implants from the same tumors were used as controls. Tumor implants were monitored over a period of six weeks. Tumor survival and progression were evaluated at autopsy examination. The survival of subcutaneously implanted tumors was slightly higher than the survival of tumors implanted into the epineurium of the sciatic nerve ($p > 0.5$). Survival of implanted schwannomas and neurofibromas in animals that received pirfenidone was significantly lower than in control animals (see table below).

Effect of treatment with pirfenidone on survival rate of human xenotransplants in SCID mice

Survival of human xenotransplant	Pirfenidone therapy		p
	Treated	Not treated	
Neurofibroma	21/32 (65.6%)	31/32 (96.8%)	<0.001
Schwannoma	17/21 (80.9%)	20/21 (95.2%)	<0.01

No mortality or signs of drug toxicity were noted in animals treated with pirfenidone. The data suggest that pirfenidone interferes with neural tumor survival and that this agent might be a good candidate for clinical trials in patients with neurofibromatosis.

Experiments on hamsters showed that pirfenidone abolishes the fibrosing effects of bleomycin on the lung (Schelegle et al., 1997), blocking polyhydroxylase activity and the rise of hydroxyproline level. Histopathologic studies of these animals revealed that there were fewer lesions of alveolar consolidation and fibrosis in the lungs of the hamsters that received bleomycin and pirfenidone (Iyer 1995, 1998). Similar effects against cyclophosphamide-induced pulmonary fibrosis in rats were reported (Kehrer and Margolin, 1997). Further experiments provided evidence that the antifibrotic effect of pirfenidone was partly due to suppression of the bleomycin-induced inflammation and partly due to down-regulation of bleomycin-induced over-expression of lung procollagen I and III genes (Iyer et al., 1998). Gurujealakshmi (1999) postulated that the protective effect of pirfenidone against bleomycin-induced lung fibrosis might be mediated by a reduced PDGF isoforms production by lung macrophages.

In other studies oral pirfenidone given to nude mice caused degradation and absorption of human keloid xenografts (Shetlar et al, 1995; 1998) and benign prostate hypertrophy tissues transplanted into such mice (Shetlar et al., 1992). Shimizu et al. (1998 and 1997) reported favorable effects of pirfenidone on the experimentally induced renal disease in rats, demonstrating that it can attenuate both renal fibrosis and renal damage in the animal model. The authors suggested that this drug might be useful for preventing progressive, irreversible renal failure.

In vivo laboratory data also show that pirfenidone is effective against experimentally induced glomerulosclerosis in rats (Shimizu et al., 1996) and liver cirrhosis in rats (Teraokas et al., 1996). Pirfenidone showed protective effects against gastric ulcers and mucosal irritation in rats exposed to large doses of phenylbutazone or aspirin.

Preclinical toxicity: The laboratory animal studies performed on several species evaluated acute, subacute and subchronic effects of pirfenidone. For the several species exposed to very high or fatal systemic dosages of pirfenidone, CNS side effects (ataxia, loss of skeletal tone, loss of righting reflex, reduction in respiratory rate and amplitude) were observed. Death was precipitated by acute respiratory failure. No significant gastrointestinal erosion was observed in animals treated with high doses of oral pirfenidone.

Acute oral toxicity of pirfenidone	
Species	LD ₅₀ mg/kg body weight
Rodents (mice, rats, hamsters, guinea pigs)	600-900
Dogs	300
Cats	500

Similarly, topical preparation containing 2.0% pirfenidone in aqueous solution, failed to produce significant eye irritation in albino rabbits. Subacute (two week, one month and two months) and subchronic (three months) administration of oral pirfenidone to rats showed that the maximum tolerated dose of pirfenidone was in excess of 300 mg/kg/day. Pirfenidone caused no deaths at dosages as high as 1,000 mg/kg/day. No

significant changes that could be attributed to pirfenidone treatment were observed in the general condition or appearance of treated animals, on ophthalmologic evaluation, on hematologic determinations and on gross and microscopic examinations at autopsy. Reproduction and teratogenicity studies in rodents showed no difference in the incidence of pregnancies, or the size of the litters, or adverse effects on embryo/fetal development in comparisons of the control and the pirfenidone-treated groups. In the standard and *in vitro* Ames test for mutagenicity and carcinogenicity, a wide range of concentrations of Pirfenidone in the culture media failed to show any mutagenic or carcinogenic potential. Carcinogenicity studies in rats and mice exposed to pirfenidone for 104 weeks found an increase in the incidence of uterine adenocarcinomas (in rats but not mice), hepatocellular adenomas (in rats and mice), and hepatocarcinomas and hepatoblastomas (in mice but not rats). These doses are equivalent to 2250-9000 mg/m² BSA /day in humans. The relevance to humans is unknown at this time (InterMune 2007)

1.2.7 HUMAN STUDIES PIRFENIDONE

Pirfenidone was well tolerated in 10 healthy adult men after a single dose of 400 mg.

Subacute tolerance of pirfenidone administered orally was evaluated in twenty normal adults (18 men, 2 women). Pirfenidone was administered for 22 days at increasingly higher daily doses, starting with 300 mg/day (divided in three daily doses) for three days and reaching a maximum of 2400 mg daily for three days. The drug was well tolerated even at the maximal oral dose. Three of the subjects reported mild side effects including tiredness and transient mild gastric disturbance, photosensitivity rash and palpitations. At entry and at the end of the study, physical examination, electrocardiogram, blood chemistries and urinalyses were performed and no clinically significant changes were found compared to premedication baseline and normal clinical values (Margolin, 2001).

Open and Controlled Trials:

To investigate for the clinical usefulness of pirfenidone, a prospective, phase II clinical trial in 54 patients with "end stage" pulmonary fibrosis of different etiologies was undertaken. The mean age of patients was 62. Pirfenidone was given in dose 2400 mg/day for 3 to 36 months. Approximately 75% of the ill patients had clinical signs of improvement within six months after beginning this treatment. The patients reported reduction of incidence of coughs, reduction in supplemental oxygen requirement at rest, reduced dyspnea during conversation or ambulation, resumption of normal daily tasks, weight gain, and decreased incidence of hospital admissions and prolongation of survival. There was a clear improvement in pulmonary function gauged by chest X-ray, spirometry and CO diffusion. The improvement continued while the patients were maintained on the daily oral dosages of pirfenidone for 12 to 24 more months. The incidence of adverse effects was low and relatively mild, consisting of occasional drowsiness improved by caffeinated beverages, gastric discomfort remedied by antacids or food, or dermal photosensitivity (Raghu et al., 1999).

Pirfenidone has been used in several open studies: in three patients with peritoneal sclerosis for 6 to 18 months, in four patients with benign prostatic hypertrophy for three months, one patient with systemic lupus erythematosus for 14 months, 9 patients with scleroderma, 11 patients with rheumatoid arthritis, 10 patients with acute trauma and 3

patients with ophthalmic inflammation. In all a positive response was noted with minimal side effects. In two patients with psoriasis, the treatment with oral and local Pirfenidone did not have any positive effects. Pirfenidone also showed promising effects in treatment of multiple sclerosis in one patient, prompting involvement of another 20 individuals with progressive multiple sclerosis in an open-label clinical trial (Margolin, 2001; Bowen et al. , 2003). The effects are thought to be mediated by an anti-TNF-alpha (tumor necrosis factor-alpha) activity of pirfenidone, well supported by in vitro study (Cain et al., 1998). A pilot study evaluating oral pirfenidone in the treatment of desmoid tumors in familial adenomatous polyposis syndrome has been recently completed. No drug toxicity was observed in the 14 patients entered. Of seven of patients who received drug for at least 18 months, two experienced a reduction in the size of all desmoid tumors, two experienced symptomatic improvement, and three experienced no change in symptoms or tumor size (Lindor et al., 2003). In three patients with keloidal scars 0.7% pirfenidone ointment was applied and the surgical wound healed effectively with no recurrence of keloid over a 12-month follow-up interval (Okada Y, 1993).

Other double-blinded controlled studies evaluating pirfenidone's cytoprotective and anti-inflammatory activities have been completed. These studies have been done in patients with resistant perennial allergic rhinitis and sinusitis compared with placebo, in patients with rheumatoid arthritis compared with oxyphenbutazone and in patients with neurodermatitis compared with betamethasone. Pirfenidone was better than placebo in the first trial and at least as effective as the active drug in the last two studies. Pirfenidone was well tolerated in daily dose of 2400 mg, and no major toxicity has been encountered with its use.

Two double-blind controlled clinical protocol of pirfenidone for adult patients with idiopathic pulmonary fibrosis are currently underway, sponsored by InterMune, Inc.

Based on these preliminary results for pirfenidone in other conditions, and the scientific rationale for pirfenidone's use in plexiform neurofibromas, a Phase II study has been undertaken in adults with NF1 and progressive plexiform neurofibromas, coordinated by Mayo Clinic. This study, headed by Dr. Dusica Babovic-Vuksanovic, who is a co-principal cooperative group investigator on the present study, has entered 24 patients to date. Pirfenidone (2400 mg/day divided in three doses) was well tolerated in all enrolled patients except for three individuals who experienced toxicity (significant nausea or upset stomach) and in whom therapy was discontinued, and one other patient whose dose was reduced due to persistent nausea. On this trial pirfenidone was administered at reduced dose for the initial treatment days, and subsequently escalated to full dose to prevent nausea, which was observed when patients were started at the full dose of pirfenidone. At the end of treatment, 11 of the 17 patients (65%) who completed 24 months of treatment had stable disease, three had minor response, and three had tumor progression. The seven patients who did not complete 24 months of therapy were stable at their last evaluation, with the exception of 1 patient who had a partial response to therapy after 12 months. Ten patients reported improvement in neurologic symptoms (Babovic-Vuksanovic et al., 2006).

In summary, clinical investigations (phase I and phase II) in open clinical trials in adults have shown that pirfenidone exerts noteworthy anti-fibrotic actions. A maximum

tolerated dose of pirfenidone has not been determined in ongoing clinical trials in adults, but at the dose used in clinical trials (daily dosing with no rest period: 2400 mg/day divided in three daily doses) pirfenidone appears to be well tolerated even after prolonged administration.

Based on the results of the adult trials with pirfenidone, a phase I trial of pirfenidone in children with NF1 and plexiform neurofibromas was initiated and completed. Four patients were entered on the starting dose level of 750 mg/m²/day (250 mg/m²/q8h), and twelve patients were entered at the second dose level of 1500 mg/m²/day (500 mg/m² q8h). The formulation of pirfenidone as 200 mg and 400 mg capsules only, did not allow for smaller dose increments in this trial. The median age of the patients entered was 10.5 years (range 3 years to 19 years). Overall, pirfenidone was well tolerated. No dose-limiting toxicities were observed at the first level. Non dose-limiting toxicities at least possibly related to pirfenidone included diarrhea (n=1), fatigue (n=1), and gastritis (n=1). All 12 patients entered at the second dose level were evaluable for toxicity. Two patients developed dose-limiting toxicity during the first treatment cycle, which is used to define the maximum tolerated dose or the dose of pirfenidone, which achieves comparable drug exposure (AUC) to adults. One patient developed dose-limiting persistent (> 7 days) grade 2 diarrhea, which subsided after treatment with pirfenidone was held, and thus appeared to be related to pirfenidone treatment. Pirfenidone was restarted at reduced dose for this patient and tolerated well. One additional patient developed dose-limiting persistent grade 2 nausea associated with vomiting, which subsided after pirfenidone was held. Pirfenidone was restarted at a reduced dose for this patient. Non dose-limiting toxicities observed during the first treatment cycle included nausea (n=4), vomiting (n=7), diarrhea (n=1), fatigue (n=3), abdominal pain (n=2), pruritus (n=1), palpitations (n=1), and dyspepsia (n=1). In three patients nausea and vomiting developed after the initial doses of pirfenidone, which resolved quickly after drug was held. Pirfenidone was well tolerated in all three patients when restarted at initially reduced dose and subsequently full dose. These toxicities were thus not considered dose-limiting. Two patients developed grade 3 toxicities after the first treatment cycle of pirfenidone: One patient developed grade 3 hypokalemia (potassium 2.8 mmol/L) on the third treatment cycle of pirfenidone. The potassium level was low normal (3.4 mmol/L, lower limit of normal 3.3 mmol/L) at the time of trial entry, and hypokalemia may thus be related to pirfenidone treatment. Pirfenidone was held, the patient was started on potassium supplementation, and after documentation of normal serum potassium, pirfenidone was restarted at reduced dose. The patient has tolerated the reduced pirfenidone dose well, and the potassium level has remained normal initially with and subsequently without supplementation of potassium. One additional patient with stable preexisting optic and thalamic glioma developed a grand mal seizure on the fifth treatment cycle with pirfenidone. This patient had no prior seizure history. Pirfenidone treatment was held, anti-seizure medication was initiated, and no seizure has been observed since. A MRI of the brain was performed and demonstrated no disease progression based on outside and NCI review. The patient restarted pirfenidone at full dose and has not developed further seizures. This toxicity is possibly related to pirfenidone. One patient with a history of syncope prior to the start of treatment with pirfenidone experienced more frequent episodes of fainting beginning during cycle # 19. No decrease in the frequency of syncope was noted while pirfenidone was held for a 2-week period, and treatment with pirfenidone was re-initiated (Babovic-Vuksanovic et al., 2007).

Thus, of 12 evaluable patients entered at the second dose level in the phase I trial, two patients experienced dose-limiting toxicity felt to be related to pirfenidone. The second dose (1500 mg/m²/day) will thus be the phase II dose for this proposed trial. Due to the initial nausea and emesis in 3 of 12 patients entered on the second dose level, and experience of the Mayo Clinic with initial nausea following administration of pirfenidone, which could be overcome by administration of pirfenidone at reduced dose for the initial days of treatment, pirfenidone will be administered at reduced dose for the first week of treatment in the proposed phase II trial (Section 3.2).

Analysis of plasma pharmacokinetics has been completed for all 16 patients entered on the phase I trial, and defined the comparable dose of pirfenidone as 1500 mg/m²/day (500 mg/m² q8h) (see table below in Section 1.2.8 Clinical PK of pirfenidone).

1.2.8 CLINICAL PHARMACOKINETICS OF PIRFENIDONE

Acute oral tolerance of pirfenidone in humans has been evaluated in 10 healthy adult men. Following the single dose of 400 mg, a significant amount of pirfenidone was found in the serum at 15 minutes after ingestion (average 4.0 mcg/ml). At one, four and six hours, the average serum level was 5.6 mcg/ml, 2.3 mcg/ml and 1.6 mcg/ml, respectively. These data indicate that the highest serum levels of pirfenidone occurred between one and three hours. The serum half-life was 2.9 hours. Pulse rate, respiratory rate and blood pressures were monitored at 15 minutes, one hour and four hours after the pirfenidone dose. Laboratory parameters including hematology, biochemistry and urinalyses were measured and none of these values differed significantly from the pretreatment determination or from the normal value range (Margolin, 1999).

After oral administration, pirfenidone is readily absorbed from the gastrointestinal tract, distributed into many tissues and metabolized by the liver and dermis layer of the skin. The primary metabolite of pirfenidone is the derivative with a hydroxy substitution in the para position of the phenyl group. Since pirfenidone is quite rapidly metabolized and eliminated from the body's circulation and tissues, it does not accumulate in the body, even when given repeatedly for many months (Margolin 2001).

In the phase I study of pirfenidone for children with NF1 and plexiform neurofibromas, the primary objectives were to define the toxicities and the dose of pirfenidone that produces comparable drug exposure (AUC) to adults. The comparable dose of pirfenidone was defined as the dose level at which the mean AUC in children is within one standard deviation of the mean AUC in adults who were treated with 800 mg pirfenidone three times daily, the dose that demonstrated activity in adults with conditions other than NF1.

A comparison of the drug exposure to pirfenidone measured as AUC for healthy adults, adults with renal dysfunction due to focal segmental glomerulosclerosis, and children entered on the phase I trial of pirfenidone for NF1 and plexiform neurofibromas is shown below.

Comparison of pirfenidone drug exposure (AUC) in adults and children:

Pirfenidone dose		Patients	N	AUC ($\mu\text{g}\cdot\text{h}/\text{ml}$) Mean \pm SD
Fixed Dose (mg) Adult	mg/m ² Dose Pediatric			
400	267	Adult healthy	10	21 \pm 10
400	267	Adult renal dysfunction	12	16 \pm 10
375	250	Children NF1	4	12 \pm 3
800	533	Adult renal dysfunction	8	36 \pm 21
750	500	Children NF1	12	56 \pm 43

The results demonstrate that drug exposure in children with NF1 at the starting dose level of 250 mg/m²/dose is within one standard deviation of drug exposure in healthy adults and adults with segmental glomerulosclerosis treated at 400 mg three times daily. At the 1500 mg/m²/day (500 mg/m²/dose) dose level drug exposure in children is also within one SD above the mean AUC in 8 adults treated with a similar dose. The 500 mg/m²/dose (1500 mg/m²/day) dose level is considered the comparable dose to the dose active in adults for the pediatric phase I trial, and will be the dose for the proposed pediatric phase II study, provided it will be well tolerated in the expanded patient cohort (see below).

1.2.9 PROPOSED PEDIATRIC PHASE II TRIAL OF PIRFENIDONE

This study will be conducted as a single stage, single arm phase II trial with time to progression as the primary endpoint. The natural history of the growth of plexiform neurofibromas is unknown. For this reason, a double-blinded, placebo-controlled, cross-over trial design is used to determine the activity of the farnesyltransferase inhibitor R115777 in an ongoing phase II trial for children with NF1 and progressive plexiform neurofibromas (CC protocol number 01-C-0222). The proposed phase II pirfenidone trial will use the initial placebo arm from this trial, containing 30 patients, as a historical control to determine the effect of pirfenidone on time to disease progression (see Section 5.4.2 Statistics and Feasibility).

Pirfenidone will be administered at a dose of 1500 mg/m²/day (500 mg/m²/dose) which was determined in the pediatric phase I trial of pirfenidone for patients with NF1 and plexiform neurofibromas. Pirfenidone will be administered three times daily (q8h) for 28 days with no rest period between cycles (28 day cycles). The dose of pirfenidone will be 500 mg/m²/dose every 8 hours (1500 mg/m²/day), which appears to produce an AUC in children that is higher than the AUC in adults treated with 800 mg pirfenidone three times daily, the dose that showed activity in adults with conditions associated with excessive fibrosis (pulmonary fibrosis, peritoneal sclerosis, scleroderma). During the first week of the first treatment cycle only pirfenidone will be

administered at reduced dose to prevent nausea and vomiting observed in few patients with initial doses of pirfenidone in the pediatric phase I and adult phase II trial for NF1.

Volumetric MRI data analysis of MRI studies from all participating institutions will be performed at the NCI POB using MEDx software to determine changes in tumor volume, and disease progression will be defined as a $\geq 20\%$ increase in tumor volume (see Section 1.2.2). Volume measurements will be compared to conventional 2-D MRI analysis and 1-D MRI analysis to assess its reproducibility and sensitivity in determining disease status of plexiform neurofibromas. The protocol described in Appendix 4 will be used to image plexiform neurofibromas.

Patients will be able to continue on study for as long as no disease progression or intolerable toxicity is documented, or other off study criteria are met (Section 3.7).

The quality of life of patients treated with pirfenidone 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. However, the data will be useful for evaluating the ability of this new tool to measure changes in quality of life over time in children with NF1. 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. Quality of life will not be evaluated in children younger than 6 years or older than 18 years.

Tumor biopsies will only be obtained on this trial if clinically indicated. Attempts will be made to contribute tumor specimens obtained on this trial to an already-existing tissue bank. Tumor specimens of plexiform neurofibromas will undergo central pathology review, including detailed morphological, ultrastructural immunohistochemical, and mRNA gene expression profile analysis. Tumor samples will be made accessible to the scientific community after obtaining IRB approval in order to collect more information on the pathology, genetics, and cell biology of plexiform neurofibromas (Appendix 5).

1.2.10 UPDATE OF THE PEDIATRIC PHASE II TRIAL OF PIRFENIDONE

Protocol 04-C-0080 enrolled 36 patients from July 21, 2004 to July 11, 2007, and enrollment on this trial is thus complete. Pirfenidone has been well tolerated. Only 2 patients required dose reductions for dose-limiting toxicities: nausea (n=1) and grade 3 neutropenia (n=1). As of March 2008, the median number of completed treatment cycles for all patients enrolled is 10 (range 3-42 cycles). Currently nine patients remain on study: NCI POB (n=3), Children's National Medical Center, Washington, DC (n=2), Children's Memorial Hospital, Chicago, IL (n=2), Dana-Farber Cancer Institute, Boston,

MA (n=1), and Cleveland Clinic, Cleveland, OH (n=1). The median number of completed treatment cycles for these patients is 17 (9-37 cycles). The body surface area of these patients ranges from 0.66 to 1.88 m².

Initially, pirfenidone was supplied by Solanan Inc. as 200 and 400 mg capsules, and dosing for this trial was devised for identical doses three times daily on a continuous dosing schedule. The biopharmaceutical company InterMune has taken over the development of pirfenidone and will provide pirfenidone, and starting no later than May 19th, 2008, as pirfenidone shipments are requested by active sites, they will be provided by InterMune, Inc. until the trial is complete. The date for sites to begin dispensing InterMune drug supply may vary by site, depending on each site's availability of existing Solanan/Marnac supply, their procurement of IRB approval, and timing of patient re-consent. Drug supply from InterMune will be in form of 267 mg capsules. The protocol is therefore being revised in March 2008 to provide new dosing guidelines.

2.0 ENROLLMENT PROCEDURES

2.1 ELIGIBILITY CRITERIA (ELIGIBILITY CHECKLIST APPENDIX 1)

2.1.1 INCLUSION CRITERIA

2.1.1.1 Age: ≥3 years and ≤21 years of age. Required body surface area (BSA) : ≥ 0.31 m².

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) or significant cosmetic problems, 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):

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 NFI are eligible at the time of recurrence or progression of an inoperable plexiform neurofibroma. 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 medical therapy.

Patients who received prior medical treatment for their plexiform neurofibroma(s) must have recovered from the toxic effects of all prior therapy before entering this study. The Cancer Therapy Evaluation Program Common Terminology Criteria (CTCAE-3) Version 3.0 will be used for toxicity assessment. A copy of the CTCAE version 3.0 can be downloaded from the CTEP home page (<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: Performance Status: Patients should have a life expectancy of at least 12 months. Patients > 10 years must have a Karnofsky performance level ≥ 50 , and children ≤ 10 years must have a Lansky performance level ≥ 50 . (See Appendix 2). Patients who are wheelchair bound because of paralysis should be considered "ambulatory" when they are up in their wheel chair.

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 (all transfusion independent).

2.1.1.7 Hepatic Function: Patients must have a bilirubin within normal limits and SGPT $\leq 2x$ 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 ≥ 70 mL/min/1.73 m².

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 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 discussions. 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, when appropriate, 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 Patients must be able to take pirfenidone by mouth. Capsules can be opened and content mixed with food for easier consumption in small children.

2.1.1.12 Patients (both male and female) must be willing to practice birth control (including abstinence) during and for two months after treatment, if of a child-bearing age. For purposes of the protocol, all patients greater than 9 years of age or those showing pubertal development will be considered of childbearing age.

2.1.1.13 Ability and to undergo MRI and no contraindication for MRI examinations following the MRI protocol outlined in Appendix 4.

2.1.2 EXCLUSION CRITERIA

2.1.2.1 Pregnant or breast feeding females are excluded, because the toxic effects and pharmacology of pirfenidone 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 pirfenidone or are likely to interfere with the study procedures or results.

2.1.2.3 An investigational agent within the past 30 days.

2.1.2.4 Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumor, immunotherapy, or biologic therapy (for example interferon).

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

2.1.2.6 Prior treatment with pirfenidone.

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

2.2 PRE-TREATMENT EVALUATION (SEE APPENDIX 3)

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 is listed in table form in Appendix 3.

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. Height, weight and body surface area must be recorded.

The BSA should be calculated using the formula used at the participating institution from the average of 3 repeated measurements of weight and height on the same day.

2.2.2 HEMATOLOGY: Complete blood counts, differential, platelet count.

2.2.3 CHEMISTRIES: Electrolytes (including sodium, potassium, chloride, CO₂, calcium, phosphorus and magnesium), creatinine, BUN, glucose, SGOT, alkaline phosphatase, SGPT, and bilirubin.

2.2.4 URINE OR SERUM PREGNANCY TEST: For all females of child-bearing potential (females greater than 9 years of age or those showing pubertal development). This test is to be performed within 72 hours prior to enrollment on the trial.

2.2.5 RADIOGRAPHIC EVALUATION (APPENDIX 4): MRI scan of the progressing plexiform neurofibroma(s) within 2 weeks of 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 4 will be used each time MRI examinations are performed to assess the effect to pirfenidone.

2.2.6 TISSUE PROCUREMENT: Biopsy of plexiform neurofibroma, only if clinically indicated. (Tissue sent as in appendix 5).

2.2.7 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 and ≤ 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. To allow for more meaningful analysis of the QOL questionnaires, a “background information sheet” will be completed by the parent one time, preferably at trial entry. This sheet includes information about education, current educational services, behavioral/psychiatric medications, visibility of NF1 tumors, and severity of NF1 symptoms. Quality of life will not be evaluated in children younger than 6 years or older than 18 years.

2.3 PATIENT REGISTRATION

Patients must be registered by contacting Ms. Anne Goodwin or Ms. Wendy Goodspeed at the Pediatric Oncology Branch (POB) (phone number, 301-594-4762, e-mail: goodwina@mail.nih.gov or goodspew@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@nih.gov) must also be contacted to discuss the patient prior to entry on study. The POB will ship a module with the necessary materials to administer the quality of life assessment to each participating institution at the time of receipt of IRB approval of each site.

The completed Eligibility Checklist (Appendix 1) must be faxed to the POB c/o Ms. Anne Goodwin or Ms. Wendy Goodspeed (Fax: 301-480-8871). All patients (from all institutions) will be registered with Harris Technical Services (phone: 301-402-1732, fax: 301-480-0757) by the POB research nurse, and an identification number will be assigned to each patient by the POB research nurse. The POB research nurse will notify the trial sponsor Dr. Babovic-Vuksanovic about registration of each patient entered on the trial by faxing eligibility checklist and trial entry document.

The POB research nurse must be notified when a participating patient is removed from the protocol. The POB research nurse will notify the trial sponsor Dr. Babovic-Vuksanovic when a patient is removed from the protocol.

3.0 IMPLEMENTATION OF STUDY

3.1 STUDY DESIGN

3.1.1 OVERALL TRIAL DESIGN

This is an open label phase II trial of oral pirfenidone in pediatric and young adult patients with NF1 and inoperable, progressive plexiform neurofibromas that have the potential to cause significant morbidity. Patients will receive pirfenidone orally as capsules three times a day (“approximately” q8hours) for cycles of 28 days with no rest period between cycles (28 day treatment cycles). The investigational agent to be used in this study (pirfenidone) is not approved by the Food and Drug Administration (FDA) for commercial use; however, the FDA has permitted its use in this research study. The trial will be conducted in compliance with the GCP and applicable regulating requirements. Based upon the data from the pirfenidone phase I study in children, the dose of pirfenidone will be 500 mg/m² q8 hours (1500 mg/m²/day). Patients will remain on trial for as long as there is no disease progression and no other off study criteria have been met (Section 3.7).

This study is designed to determine the time to disease progression while on a chronic oral dose of pirfenidone (28 day cycles with no rest periods between cycles). In order to determine if pirfenidone benefits patients with NF1 and progressive plexiform neurofibromas time to disease progression on pirfenidone will be compared to time to disease progression on the placebo arm of the ongoing phase II trial of the farnesyltransferase inhibitor R115777 for children with progressive plexiform neurofibromas (Section 5.4.2).

In addition, this trial will evaluate the toxicity profile of pirfenidone in children and young adults with NF1 and progressive plexiform neurofibroma(s).

3.1.2 MONITORING TIME TO PROGRESSION AND RESPONSE

This phase II trial is designed to determine the time to tumor progression and response rate with pirfenidone in patients with NF1 and progressive plexiform neurofibromas. The primary endpoint will be time to progression. At the time of study entry the progressing plexiform neurofibroma(s) will be identified as index lesion(s), and followed for progression by 3-D MRI. Results obtained with 3-D MRI analysis will be compared to conventional 2-D MRI and 1-D MRI analysis for their ease of use, sensitivity, and reproducibility. In addition, if possible, all known additional, measurable plexiform neurofibroma(s) will be followed for progression by 3-D MRI. Results obtained with 3-D MRI analysis will be compared to conventional 2-D MRI and 1-D MRI analysis for their ease of use, sensitivity, and reproducibility. The imaging protocol outlined in Appendix 4 will be used each time MRI scans are performed to assess response to pirfenidone. MRI scans are performed prior to cycles 1, 4, 7, 10, and then after every 6 cycles while on study. All MRI studies required per protocol will be submitted to the NCI POB for assessment of response by volume measurement within 2 weeks of study acquisition. The NCI POB will notify the participating site of the volumetric measurement and response assessment. Until response assessment at the NCI POB is completed, patients will remain on treatment with pirfenidone. If a patient is removed from study because of clinical evidence of disease progression, the MRI scans should be repeated if they had not been performed within the past 6 weeks.

3.1.3 DEFINITION OF TUMOR PROGRESSION

- A $\geq 20\%$ increase in the volume (by 3D-MRI) of at least one of the index plexiform neurofibroma(s) compared to the pretreatment volume measured prior to the start of treatment.
- 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 (NCI, POB).
- Patients with other evidence of disease progression than outlined above should also be discussed with the Principal Investigator.

3.2 DRUG ADMINISTRATION

3.2.1 SUPPLY OF PIRFENIDONE FROM SOLANAN, INC./MARNAC, INC.

Pirfenidone will be supplied in 200 mg and 400 mg capsules by Solanan, Inc./Marnac Inc. under the IND # 60,584 held by Dr. Dusica Babovic-Vuksanovic. Pirfenidone will be administered orally with food three times daily (approximately every 8 hours) for 28-day cycles with no rest period between cycles (28-day treatment cycle). The pirfenidone dose will be 500 mg/m² q8 hours (1500 mg/m²/day). BSA will be calculated using the formula used at the treating institution.

Each patient's dose will be rounded to the nearest 200 mg using the pirfenidone dose nomogram below based on the body surface area. Each treatment of the three daily doses will be identical.

Dosing nomogram for pirfenidone				
BSA*	0.31-0.6	0.61-1.0	1.01-1.4	≥1.41
Dose [†]	200	400	600	800

* BSA, body surface area in m².

[†] Actual dose in mg (capsules sizes 200 and 400 mg) administered every 8 hours

During the first week of the first treatment cycle only, pirfenidone will be administered at a reduced dose to prevent nausea and vomiting, which was observed in few patients with the initial doses of pirfenidone in the pediatric phase I and adult phase II trial for NF1. The reduced dosing for the first week will be as follows:

Pirfenidone full dose	Pirfenidone reduced dose week 1, cycle 1
200 mg TID	200 mg BID
400 mg TID	200 mg TID
600 mg TID	400 mg TID
800 mg TID	400 mg TID

The formulation of pirfenidone as 200 and 400 mg capsules only does not allow for a more consistent dose reduction. Following the first week of treatment at reduced dose, pirfenidone will be administered at full dose.

3.2.2 SUPPLY OF PIRFENIDONE FROM INTERMUNE, INC.

Starting no later than May 19th, 2008, when pirfenidone shipments are requested by study sites they will be supplied as 267 mg capsules by InterMune Inc. Since this dosage form and all related information supportive of its use has been submitted under InterMune's IND #67,284, InterMune is authorizing the cross reference of this trial's IND #60,584 to InterMune's IND #67,284. Pirfenidone will be administered orally with food three times daily (approximately every 8 hours) for 28-day cycles with no rest

period between cycles (28-day treatment cycle). The pirfenidone dose will be 500 mg/m² q8 hours (1500 mg/m²/day). BSA will be calculated using the formula used at the treating institution.

Each patient's dose will be rounded to the nearest 267 mg using the pirfenidone dose nomogram below based on the body surface area (BSA). In order to allow for precise dosing with the new formulation (267 mg/capsule) dosing cannot always be maintained with three identical doses. Pirfenidone will therefore be administered three times daily as outlined in the nomogram below.

Pirfenidone dosing nomogram							
BSA (m ²)	≤0.61	0.62-0.79	0.8-0.97	0.98-1.15	1.16-1.32	1.33-1.5	≥1.51
Dose (mg/day)	801	1068	1335	1602	1869	2136	2403
Dose (Capsules/day)	3	4	5	6	7	8	9
Dose [†] (Capsules/dose)	1-1-1	1-1-2	1-2-2	2-2-2	2-2-3	2-3-3	3-3-3

[†]Capsules/dose to be administered approximately every 8 hours

At follow-up evaluations, pirfenidone doses will be adjusted for changes in body surface area according to the dosing nomogram for pirfenidone.

Dose modifications for patients who experience toxicities are outlined in Section 3.3.

Pirfenidone capsules may be opened and the content mixed with food for easier consumption in young children.

Pirfenidone should be re-taken if vomiting occurs within 15 minutes of taking the dose, but not if vomiting occurs more than 15 minutes after taking pirfenidone.

Patients or their guardians will keep a diary to document the intake of each dose of pirfenidone and potential side effects. The patient diary should be reviewed with the patient's family at each required clinical study evaluation. In addition, leftover study medication should be collected at each on study evaluation, and drug should be accounted for at this time (Appendix 6). These diaries will be forwarded to Ms. Anne Goodwin or Ms. Wendy Goodspeed (Pediatric Oncology Branch, NCI, Fax: 301-480-8871, Phone: 301-594-4762) after every 3 treatment cycles.

3.3 TREATMENT MODIFICATIONS

3.3.1 FOR PIRFENIDONE FROM SOLANAN, INC. (200-MG AND 400-MG CAPSULES)

Patients who experience **grade 2 toxicity** (CTCAE -3) related to pirfenidone should have pirfenidone withheld until the toxicity resolves (grade ≤1) and then restarted at the same dose level. If the grade 2 toxicity recurs, the pirfenidone dose should be withheld again until the toxicity resolves (grade ≤1) and then reduced as follows: For patients receiving 200 mg TID, 400 mg TID, 600 mg TID, or 800 mg TID, the dose will be administered BID, which is an equivalent to a 33% dose reduction. Each treatment cycle should be no longer than 28 days. Doses withheld while recovering from toxicity should not be made up. If the grade 2 toxicity recurs after a dose reduction the patient should be taken off protocol.

Patients who experience **grade 3 toxicity** related to pirfenidone should have their dose withheld. If the toxicity returns to grade ≤1 within 14 days, patients may resume pirfenidone at a dose reduced as follows: For patients receiving 200 mg TID, 400 mg TID, 600 mg TID, or 800 mg TID, the dose will be administered BID, which is an

equivalent to a 33% dose reduction. Each treatment cycle should be no longer than 28 days. Doses withheld while recovering from toxicity should not be made up. If the toxicity persists at grade ≥ 2 for >14 days without administration of pirfenidone or the grade 3 or 4 toxicity recurs at the lower dose level, the patient should be removed from the study (see Section 3.7).

Patients who experience **grade 4 toxicity** related to pirfenidone will be removed from the study.

3.3.2 FOR PIRFENIDONE FROM INTERMUNE, INC. (267-MG CAPSULES)

Patients who experience **grade 2 toxicity** (CTCAE -3) related to pirfenidone should have pirfenidone withheld until the toxicity resolves (grade ≤ 1) and then restarted at the same dose level. If the grade 2 toxicity recurs, the pirfenidone dose should be withheld again until the toxicity resolves (grade ≤ 1) and then reduced as outlined for patients with grade 3 toxicity in the table below. Each treatment cycle should be no longer than 28 days. Doses withheld while recovering from toxicity should not be made up. If the grade 2 toxicity recurs after a dose reduction the patient should be taken off protocol.

Patients who experience **grade 3 toxicity** related to pirfenidone should have their dose withheld. If the toxicity returns to grade ≤ 1 within 14 days, patients may resume pirfenidone at a dose reduced as outlined in the table below:

Full Dose		Reduced Dose		
Capsules/day	Capsules/dose [†]	Capsules/day	Capsules/dose [†]	% Dose reduction
3	1-1-1	2	1-0-1	33.3
4	1-1-2	3	1-1-1	25
5	1-2-2	3	1-1-1	40
6	2-2-2	4	1-1-2	33.3
7	2-2-3	5	1-2-2	28.6
8	2-3-3	6	2-2-2	25
9	3-3-3	6	2-2-2	33.3

[†]Capsules/dose to be administered approximately every 8 hours

Each treatment cycle should be no longer than 28 days. Doses withheld while recovering from toxicity should not be made up. If the toxicity persists at grade ≥ 2 for >14 days without administration of pirfenidone or the grade 3 or 4 toxicity recurs at the lower dose level, the patient should be removed from the study (see Section 3.7).

Patients who experience **grade 4 toxicity** related to pirfenidone will be removed from the study.

3.4 ON STUDY EVALUATION (APPENDIX 3)

3.4.1 HISTORY AND PHYSICAL EXAMINATION: History and full physical examination, with evaluation of signs of toxicity from pirfenidone, will be repeated prior to cycles 1, 2, 3, 4, and subsequently after every 3 treatment cycles as long as the patient remains on study. Height, weight, body surface area and performance status (if

changed from baseline) must be recorded. Visible plexiform neurofibromas should be directly measured (tape measure), if possible.

3.4.2 HEMATOLOGY: Complete blood counts, differential, platelet prior to cycles 1, 2, 3, 4, 7, 10, and subsequently after every 6 treatment cycles long as the patient remains on study.

3.4.3 CHEMISTRIES: Electrolytes (including sodium, potassium, chloride, CO₂, calcium, phosphorus and magnesium), creatinine, BUN, glucose, SGOT, alkaline phosphatase, SGPT, gamma-GTP, and bilirubin prior to cycles 1, 2, 3, 4, 7, 10, and subsequently after every 6 treatment cycles long as the patient remains on study.

3.4.4 RADIOGRAPHIC EVALUATION (APPENDIX 4): Evaluate the index lesions by MRI prior to cycle 1, 4, 7, 10 and then every 6 cycles thereafter while on study. The imaging protocol outlined in Appendix 4 will be used each time MRI examinations are performed to assess progression or response to pifredone. In patients with clinical suspicion of disease progression, MRI analysis should be performed earlier using the protocol outlined in Appendix 4.

3.4.5 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, prior to cycles 4, 7, and then after every 6 cycles. 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. To allow for more meaningful analysis of the QOL questionnaires, a "background information sheet" will be completed by the parent one time, preferably at trial entry. This sheet includes information about education, current educational services, behavioral/psychiatric medications, visibility of NF1 tumors, and severity of NF1 symptoms. The QOL questionnaire will not be administered to patients > 18 years. The "background information sheet", and patient and parent response forms should be photocopied after completion and copies sent to Dr. Pamela Wolters, Ph.D., Building 82, Room 109, 9030 Old Georgetown Road, Bethesda, MD 20892-8200, ideally within 48 hours and no later than 2 weeks after completion of the questionnaire. Any questions regarding the administration of the IPI Scale should be addressed to Dr. Pam Wolters, Ph.D. at phone: 301-496-0561, fax; 301-402-1734, e-mail: woltersp@mail.nih.gov.

3.5 CONCURRENT THERAPIES

Other cancer chemotherapy, radiation therapy, immunotherapy, biologic therapy, hematopoietic growth factors or investigational agents cannot be administered to patients receiving pifredone.

Use of corticosteroids for control of symptoms related to the underlying NF1 or for other reasons will be allowed, as no effect on the growth of plexiform neurofibromas is expected.

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.

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 (for example, availability of new surgical treatment option for a 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 principal investigator.

3.6.2 TOXICITY

Recurrent grade 2, 3 or 4 toxicity after dose reduction or persistent toxicity grade ≥ 2 for >14 days without administration of drug that is considered primarily related to study drug. Persistent (>14 days) grade 2 toxicity should be discussed with the PI prior to removing the patient from the study.

The protocol Principal Investigator should be notified immediately in the event of severe or life-threatening toxicity (Dr. Brigitte Widemann, 301-496-7387, 301-496-1211 page operator). The POB will then contact Dr. Babovic-Vuksanovic at (507) 284-3215 and Dr. Roger J. Packer at (202) 884-2120. The Medical Monitor will be formally contacted by Dr. Babovic-Vuksanovic.

3.6.3 TUMOR PROGRESSION

Any patient with clinical or radiographic evidence of progressive disease (see Section 3.1.3) on treatment, as documented by a $\geq 20\%$ increase in tumor volume on 3-D MRI, following any treatment cycle will be removed from the study (see Sections 3.1.3 and 5.2). The POB research nurses, Ms. Anne Goodwin or Ms. Wendy Goodspeed, must be notified when a patient has tumor progression and goes off-study at 301-594-4762.

3.7 POST THERAPY 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 last 6 weeks (2 weeks for physical examination and laboratory assessment).

- History and physical examination, performance status, and measurement of visible or palpable tumor lesions).
- Laboratory Assessment: Complete blood count, differential and platelet count, electrolytes, creatinine, calcium, magnesium, phosphorus, SGPT, bilirubin, and urinalysis.

- MRI Scan of the plexiform neurofibroma(s) and any other progressing lesions using the protocol outlined in Appendix 4.
- Quality-of-Life Scale, see Instruments.
- Case report form and patient diaries.

4.0 SUPPORTIVE CARE

GENERAL: Appropriate antibiotics, blood product support, and general supportive care will be used as indicated. Antiemetics and drugs to manage diarrhea (for example loperamide) may be used intermittently, but for no more than 7 consecutive days in a treatment cycle. Hematopoietic growth factors cannot be administered to patients receiving pirfenidone.

5.0 DATA COLLECTION AND EVALUATION

Dr. Roger Packer, who has received a Clinical Trial Award by the U.S. Department of Defense to fund aspects of this trial, will be the Cooperative Study Group Principal Investigator. Dr. Babovic-Vuksanovic is the IND holder for this study (IND #60,584). She will sponsor this trial, and will serve as Cooperative Study Group Co-Principal Investigator. The trial will be coordinated by the Pediatric Oncology Branch of the NCI with Dr. Brigitte Widemann as Principal Investigator. Dr. Tracy Glauser, M.D., Associate Professor for neurology at the Cincinnati Children's Hospital, will serve as Medical Monitor for this trial. In Spring 2008, the supplier of drug for this study will transition from Solanan, Inc./Marnac, Inc. to InterMune, Inc. InterMune is authorizing the cross-reference of this study's IND to InterMune's IND #67,284 for pirfenidone.

5.1 DATA COLLECTION

The POB, NCI will coordinate the clinical trial and data collection, and supply the data to the trial sponsor Dr. Dusica Babovic-Vuksanovic via case report forms. Data will be entered into the NCI, Center for Cancer Research (CCR) C3D database. Documentation and date of IRB approval must be provided to the POB, NCI prior to initial patient entry from each institution. The completed Eligibility Checklist (Appendix 1) must be faxed to Ms. Anne Goodwin or Ms. Wendy Goodspeed at (301) 480-8871 prior to patient entry onto the trial.

5.1.1 CASE REPORT FORMS

All case report forms and patient diaries will be identified by a study number, not names or initials. This will be done to protect patient confidentiality.

Unless otherwise stated, all forms should be submitted to:

Pediatric Oncology Branch, NCI
c/o Ms. Anne Goodwin or Ms. Wendy Goodspeed
Bldg. 10 CRC, Room 1-5742
10 Center Drive, MSC 1101
Bethesda, MD 20892-
Phone: 301-594-4762
FAX: (301) 480-8871

Case Report Forms: Case Report Forms have been developed by Dr. Babovic-Vuksanovic in collaboration with the POB. CRFs will be completed at the treating

institution after each patient evaluation and submitted within 2 weeks of each required evaluation to Ms. Anne Goodwin or Ms. Wendy Goodspeed, NCI, POB. Participating sites will be contacted to provide source documents or additional information if necessary. Data will be entered into the NCI, CCR C3D database.

Eligibility Checklist (Appendix 1): To be completed at study entry and forwarded to Ms. Anne Goodwin or Ms. Wendy Goodspeed (301) 480-8871 (phone 301 402 1848).

Patient Diaries (Appendix 6): Patients or their guardians will keep a diary to document the intake of each dose of pirfenidone and potential side effects. These diaries will be forwarded to Ms. Anne Goodwin or Ms. Wendy Goodspeed after each required evaluation.

QOL Assessment (NIH IPI Scale) Forms: The “background information sheet”, and patient and parent response forms should be photocopied after completion and copies sent to Ms. Dr. Pamela Wolters, Ph.D., FAX: (301)-402-1734, Building 82, Room 109, 9030 Old Georgetown Road, Bethesda, MD 20892-8200, ideally within 48 hours and no later than 2 weeks after completion of the questionnaire. Any questions regarding the administration of the IPI Scale should be addressed to Dr. Pam Wolters, Ph.D. at phone: 301-301-496-0561, e-mail: woltersp@mail.nih.gov.

MRI studies and protocols (Appendix 4): All MRI studies requested per protocol will be submitted to the NCI POB within 2 weeks of acquisition for volume analysis. At the same time, a copy of the MRI protocol used to obtain the MRI study will be sent to the NCI POB, or faxed to Ms. Anne Goodwin or Ms. Wendy Goodspeed. The goal is to electronically submit imaging studies via InSite One (Appendix 4), but transfer via CD or optical disk will be acceptable.

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

5.2 RESPONSE CRITERIA

Response is assessed at the time that follow-up 3D-MRI scans are performed (prior to cycle 4, 7, 10, and then after completion of every 6 cycles thereafter). 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 Terminology Criteria for Adverse Events, Version 3.0. The Cancer Therapy Evaluation Program Common Terminology Criteria (CTCAE-3) Version 3.0 will be used for toxicity assessment. A copy of the CTCAE version 3.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). The CTCAE 3.0 does not have to be appended to the protocol, however, all appropriate treatment areas should have access to a copy of the CTCAE version 3.0.

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 this Phase II trial is to determine whether the use of pifrenidone in pediatric patients with NF1 is able to increase time to disease progression. This study will be conducted as a single stage, single arm phase II trial with time to progression as the primary endpoint. The natural history of the growth of plexiform neurofibromas is unknown. For this reason, a complex trial design (double-blinded, placebo-controlled, cross-over trial) is currently used in an ongoing phase II trial (01-C-0222) of the farnesyltransferase inhibitor R115777 for children with NF1 and progressive plexiform neurofibromas to determine the potential benefit of R115777.

Twenty-five patients have been enrolled to date on the ongoing phase II trial of R115777/placebo for patients with NF1 and progressive plexiform neurofibromas. Most patients have been entered at the NCI, POB. The accrual goal is 60 patients, and steps are currently being taken, which will likely allow more institutions to open the study and should result in an increased accrual to the trial. Using a volume increase of $\geq 20\%$ to define progression of a plexiform neurofibroma, 7 patients developed disease progression on treatment phase A after a median of 9 months (range 6-26 months), and 11 patients have stable disease on treatment phase A after a median of 9 months (range 5-23 months). Of the patients who crossed over to treatment phase B, three developed progression after 4, 6, and 9 months, respectively, and were removed from the protocol. Another 3 patients remain stable on treatment phase B at 6, 9, and 13 months, respectively. One patient was removed from the study for dose-limiting grade 3 neutropenia, and another patient was removed from the study, when the biopsy of a focal increasing mass within the plexiform neurofibroma was found to be a malignant peripheral nerve sheath tumor. Enrollment on this trial is complete as of the end of 2007.

The proposed phase II pifredone trial will use the initial placebo arm from the R115777 trial, containing 30 patients, as a historical control.

The method described in Dixon and Simon (*J Clin Epidemiol* 41: 1209-1213, 1988) will be used to determine the sample size required in the present study. It will be assumed that the median time to progression of the placebo arm for the R115777 patients is 6 months, and that the eligibility criteria and distribution of potential prognostic factors for the present trial are identical to those of the R115777 trial. It is further assumed that accrual of 2.5 to 3 patients per month can be enrolled onto this trial, and that it will be of interest to identify a doubling of the median time to progression, from 6 to 12 months. A Kaplan-Meier analysis using a log-rank test is the primary method of analysis to compare the two arms. Using an intended one-sided $\alpha=0.05$, and with 50% of the 30 patients on the previous trial having progressed, at a median of 6 months, then accrual of 36 patients on the present study will provide at least 80% power to detect a doubling against the control arm from the prior trial.

Even though 30 patients have to be enrolled on the placebo arm of the ongoing phase II trial of R115777 for NF1 for a solid analysis of time to disease progression, interim analyses of time to progression will be performed while patients are still enrolled on the trial and continue on the first treatment phase. As long as the median time to disease progression on the placebo arm can be defined with reasonable precision using Kaplan-Meier analysis, a new estimate of time to disease progression can be made while the trial is still ongoing and prior to completion of the first treatment phase in all patients. The protocol may then be amended to use this estimate to adjust the sample size for the pifredone phase II trial should it be longer than anticipated.

Because this trial design uses a historical comparison, it is possible that some difference in patient characteristics may explain any differences identified. However, since the identical institutions will be participating, the identical eligibility criteria will apply, the primary trial endpoint will be assessed in identical way, and the study will be initiated immediately after accrual is completed to the trial of R115777, it is anticipated that differences in patient characteristics and related factors will be minimal. Nonetheless, an analysis to compare the characteristics of patients on both arms will be undertaken and if any important differences are identified (e.g., a difference in an important prognostic factor with a p-value of <0.10 , two-sided), then a Cox proportional hazards

model analysis may be performed to determine whether pirfenidone is able to be associated with increased time to progression after adjusting for important prognostic factors.

With accrual of 2.5 to 3 patients per month, it is expected that accrual of 36 patients can be completed in approximately 12-14 months, and that analysis could be performed approximately 12 months after the last patient was enrolled.

As a secondary objective, 3-D MRI analysis will be performed in the evaluation of plexiform neurofibromas, and will be compared to conventional 1-D MRI and 2-D MRI data analyses. The exact method used to perform the volumetric MRI analysis is described in Section 1.2.2, and Appendix 4 describes the imaging protocol. Since both a phase I trial and a phase II trial of pirfenidone will be undertaken, the results from both studies will be considered in the overall evaluation of the three MRI techniques relative to each other. Since this analysis will be interpreted as exploratory, all findings will be considered as hypothesis generating and would require additional evaluation in subsequent patients in order to provide confirmation.

“Quality-of-life” of patients treated with pirfenidone will be explored using the NIH Impact of Pediatric Illness scale, which assesses the impact of disease and treatment on children’s behavior. The ability of this new assessment tool to measure changes in a child’s quality of life will also be assessed at baseline and at fixed intervals, as outlined in the description of the protocol. The assessments will be done using exploratory techniques, and any findings identified in either the Phase I or Phase II trial will be considered hypothesis generating.

5.5 MULTI-INSTITUTIONAL GUIDELINES

5.5.1 IRB APPROVALS

The PI from each participating institution will provide the Study Coordinator (POB, NCI) with a copy of the initial IRB protocol approval and the yearly IRB continuing reviews. The Study Coordinator will submit these to the NCI IRB and to Dr. Roger Packer, who will submit these documents to the US Army IRB. Registration will be halted at a participating institution if a current continuing approval is not on file at the NCI POB.

As this trial receives funding by the US Army, approval of the protocol and of all protocol amendments will also be obtained from the HSRRB in addition to the institutional IRB prior to implementation.

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

Any deviation to the protocol that may have an effect on the safety or rights of the subject or the integrity of the study must be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.

A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these

documents become available.

The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to USAMRMC ORP HRPO.

5.5.2 AMENDMENTS AND CONSENTS

The PI from each participating institution will provide the Study Coordinator (NCI, POB) with a copy of IRB approval of all amendments to the protocol or consent. The Study Coordinator will provide these institutional reviews to Dr. Roger Packer, who will submit these documents to the US Army IRB. As this trial receives funding by the US Army, approval of all protocol amendments will be obtained from the HSRRB in addition to the institutional IRB prior to implementation.

5.5.3 PATIENT REGISTRATION

All patients entered will be registered by the POB with the CCR Central Office (ORKAND). The completed Eligibility Checklist (Appendix 1) 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 Dr. Babovic-Vuksanovic, and drug has been supplied by Solanan, Inc./Marnac Inc. Starting no later than May 19, 2008, any drug shipped for this study will be supplied by InterMune, Inc. Case report forms developed by Dr. Babovic-Vuksanovic and the Pediatric Oncology Branch will be used for submitting clinical data to the coordinating center. Data must be submitted to the Coordinating Center within 2 weeks of completing each required evaluation while the patient is on study. This information will be entered into the NCI CCR C3D system, an electronic database for ongoing clinical trials coordinated at the NCI. This System gives access only to persons directly involved in specific clinical trials (such as PI, associate investigators, research nurse for the trial, and data manager for the trial), and is password protected. Hard copies of CRF's, informed consents, and other patient identifying materials will be kept in locked filing cabinets.

Tumor samples obtained on this trial will be stored at Washington University as outlined in Appendix 5. MRI data will be stored at InSite One (contracted for transfer and storage of MRI data), and at the NCI POB. Only InSite One and the NCI POB will have access to the MRI data (Appendix 4). Representatives from the NCI, Solanan Inc., InterMune, Inc., Dr. Babovic-Vuksanovich, the FDA, and the U.S. Army Medical Research and Materiel Command will have access to the data and research records.

Data will be stored for at least 2 years after the NDA is approved for marketing. If an NDA is not filed, or is disapproved, all data will be stored for 2 years after the investigation is discontinued and the FDA is notified.

All adverse events (as defined in Section 7.3.2) from participating institutions will be submitted to the NCI IRB by the Study Coordinator. The NCI POB will forward adverse

event reports to Dr. Babovic-Vuksanovic and to Dr. Roger Packer. The Medical Monitor, Dr. Tracy Glauser, M.D., will be formally contacted by Dr. Babovic-Vuksanovic. The US Army IRB will be contacted by Dr. Roger Packer.

Dr. Tracy Glauser, the medical monitor will operate as a patient advocate and is independent of the clinical study team. He will oversee the progress of the protocol, especially issues of individual subject/patient management and safety. The medical monitor is required to review all unanticipated problems involving risks to subjects or others, including all serious and unexpected adverse events associated with the protocol as defined in Section 7.3.2. The monitor provides an unbiased written report of the event.

3-D-MRI analysis will be performed centrally by the POB, NCI.

5.5.5 DATA AND CENTER AUDITS

The trial will be audited by the NCI CCR via contract for compliance and safety. Independent monitors will visit participating sites and review case report forms and source documentation. Missing or spurious information and protocol deviations will be communicated in a report to the trial coordinating center. Protocol deviations, which may result in compromise to safely administer study drug, or to determine study endpoints will be included in the annual protocol review for the NCI and US Army IRB.

All unexpected and serious adverse events will be forwarded to the Medical Monitor by Dr. Dusica Babovic-Vuksanovic as defined in Section 7.3.2.

Volumetric MRI analysis will be used to determine disease progression, and patients will not be removed from study based on 1-D or 2-D MRI measurements or based on clinical measurement of superficial lesions. 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 pirfenidone could pose to the fetus or newborn. This trial is designed to determine whether pirfenidone is able to increase time to disease progression in children and young adults with NF1 and progressive plexiform neurofibromas and, therefore, children will be entered onto this research trial.

6.2 PARTICIPATION OF CHILDREN

This trial is designed to determine whether pirfenidone is able to increase time to disease progression in children and young adults with NF1 and 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, Pediatric Neurology, and Pediatric Genetics Clinics.

6.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The primary objective of this trial is to determine whether pirfenidone is able to increase time to disease progression in children and young adults with NF1 and progressive plexiform neurofibromas. Pirfenidone has been well tolerated in adults at doses that show activity of pirfenidone in fibrosing conditions. The equivalent dose level (1500 mg/m²/day) has been well tolerated in the ongoing pediatric phase I trial of pirfenidone. Pharmacokinetic analysis demonstrated that drug exposure at this dose level is comparable to drug exposure in adults receiving the same dose. The 1500 mg/m²/day dose level will thus be used in the proposed phase II trial. The benefit may include improved physical and neurologic functions, improved physical appearance or even prolongation of life, for those patients with plexiform neurofibromas, which are life-threatening.

6.4 RISK/BENEFIT ANALYSIS

The primary objective of this Phase II trial is to determine whether the use of pirfenidone in pediatric patients with NF1 and progressive plexiform neurofibromas is able increase time to disease progression. Patients entered on the trial will be treated with therapeutic intent and response to the therapy will be closely monitored. The pirfenidone study has the intent to benefit patients. Pirfenidone has been effectively used in adult patients with fibrosing conditions and plexiform neurofibromas are marked by excessive fibroblast proliferation. In addition, in the Phase II study of pirfenidone in adults with progressive plexiform neurofibromas, none of the treated patients had further progression of lesions, as determined by a volumetric MRI analysis, and some patients have experienced symptomatic improvement. It is intended that patients responding to treatment will have an improvement in their deficits or dysfunctions caused by the plexiform neurofibroma. Furthermore, by just entering the study, patients will be followed very carefully, in an organized coherent fashion, which will also benefit their overall care.

Therefore, this protocol involves greater than minimal risk to children, but presents the potential for direct benefit to individual subjects.

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, an associate investigator, or an investigator assigned by the PI 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 coordinated by the NCI, Pediatric Oncology Branch, and receives funding by the U.S. Army. No research samples are collected on this trial with the exception of patients who undergo surgery to their plexiform neurofibroma for clinical reasons. For these patients the plan is to obtain a tumor specimen not required for clinical care in order to perform detailed analyses as outlined in Appendix V. Handling and storage of these research specimens is described in detail in Appendix V.

7.0 DATA REPORTING

Unless otherwise stated, all forms should be submitted to:

Ms. Anne Goodwin or Ms. Wendy Goodspeed, R.N.
Pediatric Oncology Branch, National Cancer Institute
Building 10 CRC, Room 1-5742
10 Center Drive
Bethesda, MD 20892-1101
Phone (301) 594-4762
FAX (301) 480-8871

7.1 PATIENT REGISTRATION

See Section 2.3. The eligibility checklist is in Appendix 1.

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). Patient diaries (Appendix 6) should be provided to patients and their families and submitted after completion of each required evaluation. Data will be entered into the NCI, CCR C3D database.

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 Investigator Brochure and informed consent for this trial. Known toxicities observed to date are listed in Section 8.1.10.

All observed or volunteered adverse events, regardless of suspected causal relationship to study drug, will be recorded on 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 NCI Common Terminology Criteria for Adverse Events Version 3 (CTCAE-3), 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 7.3.2-7.3.4, adverse events will then be reported to the NCI POB using a routine report (case report forms) or an expedited reporting mechanism using the FDA Medwatch form, available on the FDA website <http://www.fda.gov/medwatch/safety/3500a.pdf> in addition to the case report forms.

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

All adverse events occurring during the study, whether or not attributed to study drug, observed by the investigator or reported by the subject, will be recorded on the case report form. Medically significant adverse events considered related to the investigational product (pirfenidone) by the investigator will be followed until resolved or considered stable. The following attributes must be assigned: description; dates of onset and resolution; severity; assessment of relatedness to study drug, other suspect drug, or device; and action taken.

The following adverse events require expedited reporting:

- All adverse events that are both serious and unexpected
- Adverse event that might influence the benefit-risk assessment of pirfenidone

Expedited reports are to be submitted to the NCI POB using the FDA Medwatch form available on the FDA website <http://www.fda.gov/medwatch/safety/3500a.pdf>.

A list of all known toxicities of pirfenidone can be found in the protocol document (Section 8.1.10).

All adverse events requiring expedited reporting must be reported to:

Brigitte Widemann, M.D.
Pediatric Oncology Branch
Bldg. 10/Rm. 13NC103
Phone: (301) 496-7387
Pager: (301) 496-9310
FAX: (301) 480-8871
E-mail: bw42y@nih.gov

In addition, all adverse events, serious or not, which result in the subject's permanent withdrawal from study drug or from the study should be reported to the study Dr. Brigitte Widemann.

Reporting to the NCI IRB:

The NCI PI is responsible for reporting to the NCI IRB events that occur in participants enrolled at all participating sites and that meet the requirements for expedited reporting within 7 days of notification of the adverse event.

The protocol PI will report to the NCI-IRB:

- All serious adverse events (SAEs) as defined in Section 7.3.1 for NCI patients that are **not** in the consent form, but are possibly, probably or definitely related to the research. An 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 not included in the SAE category above. Deaths that occur within 30 days of the last dose of pifrenidone.
- All grade 3 and 4 (CTCAE) events that are not in the consent and that are possibly, probably or definitely related to the research, but not included in the SAE category above.

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

The study PI will forward these adverse event reports to the trial sponsor Dr. Babovic-Vuksanovic, who will report these events to the FDA, and to the Medical Monitor, and to Dr. Roger Packer, who will report these events to the US Army IRB.

The study PI (NCI, POB) will forward all reportable adverse events (as defined above) to the responsible investigators at participating sites.

Additionally, any SAE reports from this study that are assessed as possibly related, probably related, or related to pifrenidone will be forwarded by the trial sponsor, Dr. Babovic-Vuksanovic, to the Drug Safety Risk Management Department at InterMune, Inc. (SAE@InterMune.com).

The investigator at participating institutions should notify their IRB of reportable serious adverse events occurring at the site and other adverse event reports received, in accordance with local procedures.

7.3.3 ADVERSE EVENT REPORTING TO US ARMY

This trial receives funding by a Grant of the U.S. Army. Per US Army request, adverse events will therefore also be reported by Dr. Roger Packer to the US Army as follows: All adverse events, which require expedited reporting (as defined in Section 7.3.2), and all unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

7.4 MEDICAL MONITOR AND DATA SAFETY MONITORING BOARD (DSMB)

Dr. Tracy Glauser, M.D., associate professor for pediatric neurology at the Cincinnati Children's Hospital, will be medical monitor for this study. He is a qualified physician, other than the Principal Investigator, not associated with this particular protocol, and able to provide medical care to research subjects for conditions that may arise during the conduct of the study. He will monitor the subjects during the conduct of the study. He will review all adverse events, which require expedited reporting (see Section 7.3.1) associated with the protocol and provide an unbiased written report of the event within 10 calendar days of the initial report. The medical monitor is also required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the USAMRMC ORP HRPO.

Contact information for Dr. Tracy Glauser is as follows:

Cincinnati Children's Hospital
Department of Neurology OSB-3
3333 Burnett Avenue
Cincinnati, OH 45229
Phone: 513-559-4738
Fax: 513-475-3980

Dr. Roger Packer (cooperative group PI), Dr. Dusica Babovic-Vuksanovic (cooperative Group Co-PI and trial sponsor), Dr. Brigitte Widemann (trial coordinating center), Dr. Tracy Glauser (Medical Monitor), Dr. Kim Hunter-Schaedle (National Neurofibromatosis Foundation Clinical Trial Coordinator, and Mr. E Stern (Lawyer of the National Neurofibromatosis Foundation will form the DSMB. The 3 members directly associated with the study (Dr. Babovic-Vuksanovic, Dr. Packer, and Dr. Widemann) will serve as non-voting members. The members who are independent of

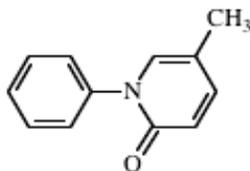
the study (Dr. Hunter-Schaedle, Dr. Glauser, Mr. Stern) will serve as voting members. The DSMB will review the study progress regularly. Patients entered on the trial and adverse events will be reviewed to ensure that the study is implemented as outlined in Section 3.0. A conference call will be held at least every 4 months.

8.0 PHARMACEUTICAL INFORMATION PIRFENIDONE

8.1 PIRFENIDONE

8.1.1 CHEMICAL NAME: 5-methyl-1-phenyl-2-(1H)-pyridone

8.1.2 CHEMICAL STRUCTURE:



8.1.3 MOLECULAR WEIGHT: 185.2

8.1.4 FORMULATION:

Pirfenidone supplied by Solanan, Inc./Marnac, Inc.: 200 mg and 400 mg capsules.

Pirfenidone supplied by InterMune, Inc.: 267 mg, size 1, white, opaque, hard gelatin capsules.

8.1.5 STORAGE:

For pirfenidone supplied by Solanan, Inc./Marnac Inc.: At room temperature.

For pirfenidone supplied by InterMune, Inc.: Pirfenidone 267 mg capsules are packaged in 200 cc high-density polyethylene bottles (180 capsules per bottle) and sealed with a 38 mm child-resistant induction seal closure system. Drug should be stored at controlled room temperature between 15° and 30° C (59° to 86°F); it should neither be refrigerates nor frozen.

8.1.6 STABILITY:

For pirfenidone supplied by Solanan, Inc./Marnac Inc.: The crystalline pirfenidone powder, and gelatin capsules containing pirfenidone have remained stable when evaluated at elevated temperatures or stored for many months at room temperature.

For pirfenidone supplied by InterMune, Inc.: 24 months at room temperature (27±2° C). The contents of pirfenidone 267-mg capsules is as follows: pirfenidone 267 mg (82.15%), croscarmellose sodium 26.5 mg (8.15%), microcrystalline cellulose 24 mg (7.38%), povidone 6 mg (1.85%), magnesium stearate 1.5 mg (0.46%). The total capsule weight is 325 mg.

8.1.7 ROUTE OF ADMINISTRATION: Oral. The capsules may be opened and the content mixed with food if a patient is unable to swallow the intact capsule; however, the entire capsule content must be administered.

8.1.8 Dose: Pirfenidone will be administered orally as capsules with a meal three times daily (approximately every 8 hours). The pirfenidone dose level is 1500

mg/m²/day (500 mg/m²/dose) for 28-day cycles with no rest period between cycles.

For pirfenidone supplied by Solanan, Inc./Marnac Inc., each of the three daily doses will be identical and rounded to the nearest 200 mg (see nomogram Section 3.2.1).

For pirfenidone supplied by InterMune, Inc., pirfenidone dosing will be rounded to the nearest 267 mg (see nomogram Section 3.2.2).

8.1.9 DRUG INTERACTIONS: In vitro data suggest a low risk of drug interactions in patients, but the possibility cannot be ruled out of mild interactions with drugs that are extensively metabolized by CYP1A2, such as drugs including theophylline, caffeine, and (R)-warfarin. Care is advised when these drugs are co-administered with pirfenidone.

8.1.10 KNOWN TOXICITIES:

In laboratory animals exposed to very high or fatal doses of pirfenidone CNS side effects (ataxia, loss of skeletal tone, loss of righting reflex, reduction in respiratory rate and amplitude) were observed. Death was precipitated by acute respiratory failure. Carcinogenicity studies in rats and mice exposed to pirfenidone for 104 weeks found an increase in the incidence of uterine adenocarcinomas (in rats but not mice), hepatocellular adenomas (in rats and mice), and hepatocarcinomas and hepatoblastomas (in mice but not rats). No reports of liver or uterine tumors in patients participating in clinical trials with pirfenidone have been reported to date.

In adult patients gastric disturbance, upper abdominal pain, abdominal distension, dyspepsia, nausea, vomiting, diarrhea, anorexia, gastroesophageal reflux, heartburn, elevation of gamma-GTP, photosensitivity, rash, palpitations, increased heart rate, dizziness, headache, fatigue, somnolence, and cold syndrome were observed. Lightheadedness and syncope with possible attribution to pirfenidone was observed in several adult patients with head and neck cancer on NCI protocol 01-C-0143. On this protocol patients received pirfenidone concurrently with radiation therapy to the head and neck.

In children with NF1 entered on the phase I trial of pirfenidone nausea, vomiting, diarrhea, abdominal pain, fatigue, and palpitations were observed. Possibly related to pirfenidone treatment, a decrease in the serum potassium level was observed in one patient, and a grand mal seizure was observed in another patient with preexisting stable optic and thalamic tumor (see Section 1.2.7 for detailed description of toxicities observed). One patient with a history of syncopes prior to initiation of treatment with pirfenidone experienced an increased frequency in syncopes during cycle #19 of treatment with pirfenidone. The frequency of syncopes did not decrease when pirfenidone was held for a 2 week period, and pirfenidone was restarted. It was felt to be unlikely that pirfenidone contributed to the frequency of syncopes.

In 3 children entered on this ongoing phase II trial of pirfenidone for children with progressive plexiform neurofibromas and NF1, grade 2 behavioral changes including decreased attention, acting more defiant, immature, and impulsive were noted. These changes were felt to be unlikely related to pirfenidone, and discontinuation of pirfenidone for a period of 2 weeks did not result in changes in

behavior in 2 of these patients. Pirfenidone has been well tolerated as of 3/2008. The toxicity profile is similar to adults with nausea and vomiting as most frequent AEs. Other toxicities include fatigue, diarrhea, rash, dizziness. Dose limiting toxicities were observed in 2 patients (grade 3 nausea n=1, and grade 3 neutropenia n=1).

8.2 DRUG ORDERS

8.2.1 PIRFENIDONE SUPPLIED BY SOLANAN, INC./MARNAC INC.

Questions about drug orders should be addressed to Solanan, Inc./Marnac Inc. (Ms. Judy Lexvold) by calling 214-692-8544 Monday through Friday between 8:30am and 4:30pm Eastern Time. Participating sites can order an adequate starter supply of pirfenidone by contacting Solanan, Inc./Marnac Inc. (Ms. Judy Lexvold, phone: 214-692-8544, fax: 214-692-8510). Solanan, Inc./Marnac Inc. will ship drug to the research pharmacist at the participating site. The research pharmacist/pharmacy of each institution will be responsible for drug labeling and dispensing to the patient, through the participating institution's principal investigator or their designate.

8.2.2 PIRFENIDONE SUPPLIED BY INTERMUNE, INC.

Pirfenidone will be provided by InterMune Inc. Questions about drug orders should be addressed to InterMune, Inc. (Ms. Brenda Hamilton) by calling 415-466-4416 or e-mailing bhamilton@intermune.com. InterMune, Inc. will ship drug to the research pharmacist at the participating site. The research pharmacist/pharmacy of each institution will be responsible for drug labeling and dispensing to the patient, through the participating institution's principal investigator or their designate.

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11.0 APPENDICES

APPENDIX 1: ELIGIBILITY CHECKLIST FOR PIRFENIDONE PHASE II PROTOCOL

Patient initials and ID number: _____

Date of birth: _____ Race: _____ Gender: _____

Patient measurements: Weight (kg): _____ Height (cm): _____ BSA (m²): _____
(Average of 3 measurements): _____

Institution: _____ Physician: _____

NF1 diagnostic criteria: Plexiform neurofibroma: _____ ≥6 Café-au-lait spots: _____
Freckling: _____ Optic glioma: _____
≥ 2 Lisch nodules: _____ Bony dysplasia: _____
1st degree relative with NF1: _____

Disease progression by either 3-D (≥20%), 2-D (≥ 13%), or 1-D (≥6%) measurements:

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: _____
Lesion of at least 3 cm in 1D: 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: _____ Chemo: GCSF: _____

Performance score: _____ Life expectancy ≥12 mo: Yes: _____ No: _____

Hematologic parameters: ANC: _____ Hgb: _____ Plt: _____

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: _____ Pregnancy test date: _____

Other significant illnesses: Yes: _____ No: _____ Prior pifrenidone: Yes: _____ No: _____

Investigational agent last 30 days: Yes: _____ No: _____

Active MPNST or other cancer: Yes: _____ No: _____

Ongoing XRT, chemo, GCSF, hormonal, immuno, biological Rx: Yes: _____ No: _____

Agrees to return for follow-up: Yes: _____ No: _____

Able to take oral medication: Yes: _____ No: _____

Willing to practice birth control: Yes: _____ No: _____ N/A: _____

Able to undergo MRI and no contraindication: Yes: _____ No: _____

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

APPENDIX 2: PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA					
Karnofsky and Lansky performance scores are intended to be multiples of 10					
ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX 3: REQUIRED STUDY EVALUATIONS PRIOR TO STARTING TREATMENT, DURING, AND POST TREATMENT WITH PIRFENIDONE

Observation	Pretreatment	Pre Cycles 2, 3, 4, 7	Pre Cycle 10, and then after every six cycles	Post Study
History & physical exam	X	X	after every 3 cycles	X
Performance status	X	If changed	If changed	X
Body surface area	X	X	after every 3 cycles	
CBC, platelets, differential*	X	X	X	X
Electrolytes, creatinine, BUN	X	X	X	X
Glucose, Ca ⁺² , Mg ⁺² , PO ₄ *	X	X	X	X
SGOT, SGPT, gamma-GTP, AP, bilirubin	X	X	X	X
Urine pregnancy test	Females			
3D-MRI of index lesions	X	Cycles 4 & 7 only	X	X
QOL assessment	X	Cycles 4 & 7 only	X	X
Review of Patient Diaries [†] :		X	after every 3 cycles	X

*Each blood draw for hematology and chemistries will require a maximum of 10 cc blood.

[†] Review of patient diaries to include compliance and toxicity monitoring.

APPENDIX 4: PROTOCOL FOR REQUIRED PRE STUDY AND ON STUDY MRI STUDIES

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

The goal will therefore be to use 3-D 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 while on study.

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.

All MRI studies requested per protocol will be submitted to the NCI POB within 2 weeks of acquisition for volume analysis. At the same time, a copy of the MRI protocol used to obtain the MRI study will be sent to the NCI POB, or faxed to Ms. Anne Goodwin or Ms. Wendy Goodspeed (301-480-8871).

MRI Protocol- Spine

PATIENT ID NUMBER: _____

Note: Only the series outlined below are required for volumetric analysis of plexiform neurofibromas and must be performed within protocol specifications as indicated below. Additional series may be obtained as indicated per institutional PI.

1. 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		

2. 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		

Date: _____ Signature (responsible MRI technician): _____

Fax completed form to: Ms. Anne Goodwin at: 301-480-8871 (phone: 301-594-4762)

MRI Protocol- Head/Neck

PATIENT ID NUMBER: _____

Note: Only the series outlined below are required for volumetric analysis of plexiform neurofibromas and must be performed within protocol specifications as indicated below. Additional series may be obtained as indicated per institutional PI.

1. 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		

2. 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		

Date: _____ Signature (responsible MRI technician): _____

Fax completed form to: Ms. Anne Goodwin at: 301-480-8871 (phone: 301-594-4762)

MRI Protocol-Trunk/Extremities

PATIENT ID NUMBER: _____

Note: Only the series outlined below are required for volumetric analysis of plexiform neurofibromas and must be performed within protocol specifications as indicated below. Additional series may be obtained as indicated per institutional PI.

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): _____

Fax completed form to: Ms. Anne Goodwin at: 301-480-8871 (phone: 301-594-4762)

Data Analysis:

- All MRI data will be analyzed at the Pediatric Oncology Branch of the NCI under guidance of Dr. Nicholas Patronas (head neuroradiologist). After review of the MRI studies with Dr. Patronas to define tumor containing areas, the MRI data from each scan will be processed to assess the volume of the index plexiform neurofibroma(s). The tumor will be traced on subsequent contiguous MR slices, the numbers summed and then multiplied by the slice thickness to obtain a numerical volume measurement. The tumor will be identified by high signal on the STIR images not corresponding to known normal anatomic structures and corresponding with the 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 1-D, and 2-D data analysis will be done by 3 physicians trained in 1-D, 2-D, and 3-D MRI data analysis at the Pediatric Oncology Branch, NCI at an Image Review Workstation using MEDx software (Sensor Systems Inc.). Volumetric measurements will be used to determine disease progression as outlined in Sections 1.2.2, 3.1.2, and 3.1.3. 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 1-D and 2-D MRI measurements, 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. All MRI studies requested per protocol will be submitted to the NCI POB within 2 weeks of acquisition for volume analysis. At the same time, a copy of the MRI protocol used to obtain the MRI study will be sent to the NCI POB, or faxed to Ms. Anne Goodwin or Ms. Wendy Goodspeed.

Arrangements for distribution of images from all participating institutions to the POB, NCI will be made by InSite One.

InSite One 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.

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 5: PATHOLOGY ANALYSIS OF PLEXIFORM NEUROFIBROMAS

Pathological analysis of plexiform neurofibromas:

The plexiform neurofibroma analysis component consists of three parts: (1) the central diagnostic neuropathology review with accompanying light- and electron-microscopic effort to identify the actual cell populations comprising the tumor, (2) immunohistochemical and FISH analysis of tumor specimens, and (3) mRNA gene expression profiling. 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.

Contribution of Tumor Specimens to a Central Tumor Repository:

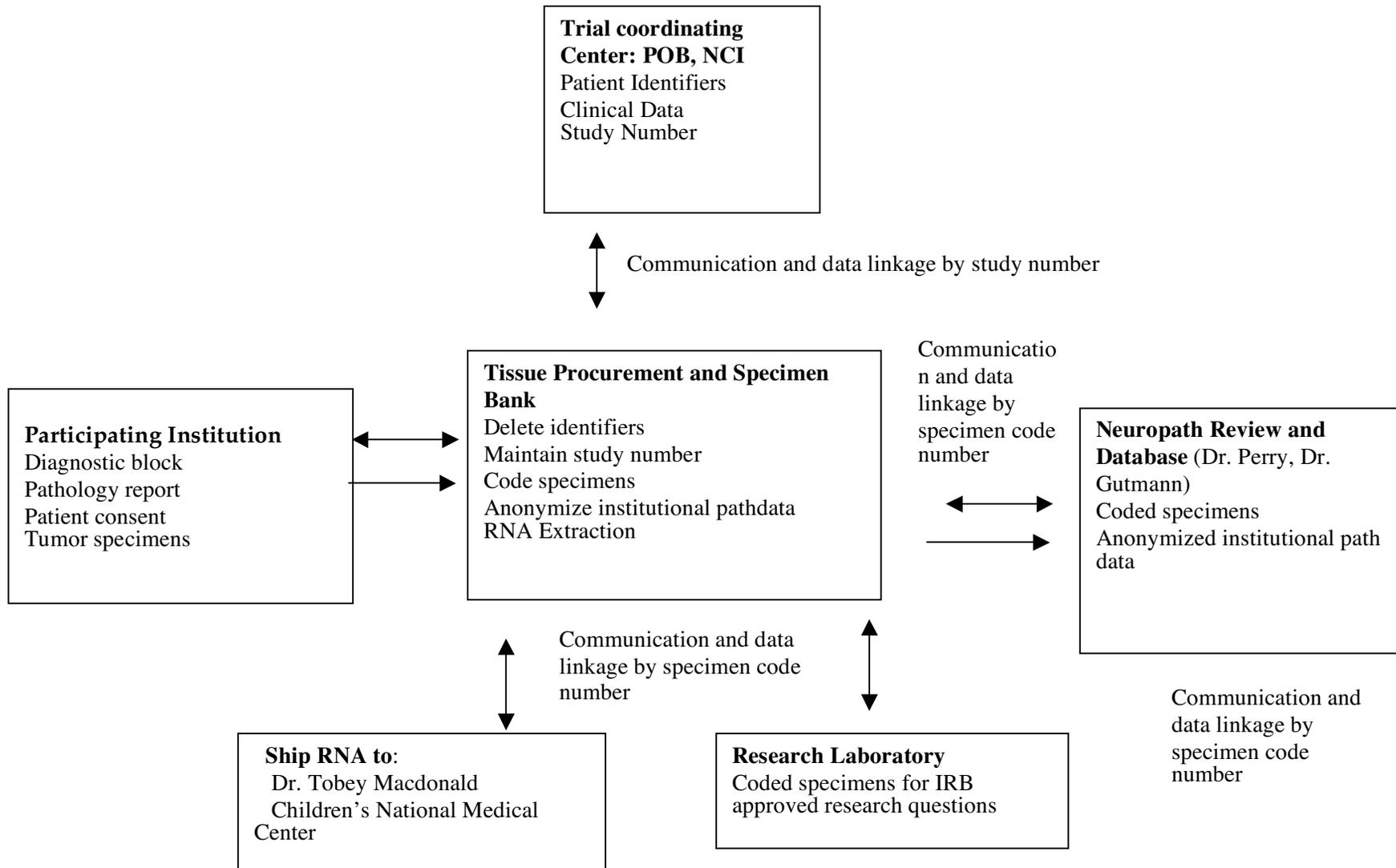
All tumor samples not required for routine clinical analysis obtained on this study will be sent to the tissue procurement facility.

Tissue Acquisition: 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.

Tissue shipment: All patient specimens 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. Tobey MacDonald (gene expression analysis) 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. 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. Study participants will not receive further notice of future uses of samples, unless a future use could involve more than minimal risk to the study participant. All research results will be kept confidential. Biospecimens will be stored until they have been exhausted by use in IRB-approved research studies, or until the patient elects to withdraw their consent, at which time the biospecimens will be destroyed. The exception to this is paraffin embedded tissue blocks, which are regarded as diagnostic material. In these cases, upon patient withdrawal or on request by the submitting institution, specimens will be returned to the medical center from which they were collected. 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.

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



APPENDIX 5A: INSTRUCTIONS FOR TISSUE ACQUISITION OF DISCRETE AND PLEXIFORM NEUROFIBROMAS

Five to seven days prior to the planned tumor biopsy please notify Ms Anne Goodwin or Ms. Wendy Goodspeed at the POB, NCI, about the planned biopsy: Phone: 301-594-4762, Fax: 301-480-8871, e-mail: gillesan@mail.nih.gov. To assist in the collection of tissue specimens, a specimen shipment kit 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.

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 still remains, 2-4 2 mm fragments, preferably from various sites representing a spectrum of gross appearances, will be placed in the provided glutaraldehyde container. These specimens will be used for electron microscopy studies.
5. 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.
6. If tissue still remains, the remainder of the specimen will be divided into 1 cm³ segments and snap frozen as described in (3).

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

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 the instructions, which will be provided with the kit.

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 6: PATIENT DIARY FOR PIRFENIDONE PHASE II

Patient ID number: _____ Dose: _____ Cycle Number: _____ Cycle Start Date: _____

Date →																						
Dose:	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Time pirfenidone dose taken →																						
Number of capsules taken* →																						
Indicate reason for missed doses →																						
SIDE EFFECTS																						
Nausea (see scale below) [†] →																						
Vomiting (# of times in 24 hr) →																						
Diarrhea (# of times in 24 hr) →																						
Skin rash →																						
OTHER SIDE EFFECTS (list below)																						
→																						
→																						

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

* For each dose write down number of capsules taken. 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 Anne Goodwin at 301-480-8871, call with questions: 301-594-4762 Parent/patient initials: _____

INSTITUTE: National Cancer Institute

STUDY NUMBER: 04-C-0080 PRINCIPAL INVESTIGATOR: Brigitte Widemann, M.D.

STUDY TITLE: Phase II Trial of Pirfenidone in Children, Adolescents, and Young Adults with Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas

Continuing Review Approved by the IRB on 06/25/07
Amendment Approved by the IRB on 04/17/08 (D)
Standard

Date Posted to Web: 04/29/08

INTRODUCTION

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

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

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

You 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 have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you 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 personal physician or other health professional. If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

You have neurofibromatosis type I (also called NF1). 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. In NF1 the defective gene is neurofibromin. The defect in the neurofibromin gene can result in formation of several types of tumors including neurofibromas (tumors involving a nerve) or plexiform neurofibroma(s) (tumors involving a nerve and the branches of that nerve). You have one or more plexiform neurofibroma(s) that appear(s) to be increasing in size over the past year and has/have the potential to cause serious medical problems.

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. There are no medical treatments, which are known to be effective for patients with NF1 and plexiform neurofibromas.

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)

STUDY NUMBER: 04-C-0080

CONTINUATION: page 2 of 8 pages

A new experimental drug called pirfenidone, has been found to be effective in treating a variety of fibrosing (scarring) conditions, and this drug targets the same growth factors that are also present in plexiform neurofibromas. Pirfenidone may therefore provide a means of controlling tumors in patients with NF1. In preliminary studies in adults with a variety of diseases pirfenidone has been well tolerated and can be given by mouth. Pirfenidone is currently undergoing testing in adults and a small number of children with NF1 and plexiform neurofibromas.

We do not know if this drug will be effective in your plexiform neurofibroma(s). Pirfenidone 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 pirfenidone can slow down the growth rate of plexiform neurofibromas in patients with NF1, (2) to determine if pirfenidone can result in shrinkage of progressive plexiform neurofibromas, and (3) to determine the types of side effects that can be produced by pirfenidone in children and young adults with NF1.

We will follow you closely throughout the study for signs of increase of the plexiform neurofibroma by regular physical examinations, laboratory tests, and MRI scans, as described in more detail below. Should the tumor be stable or decrease in size, you will continue to receive the pirfenidone for as long as it is well tolerated. You will be removed from the study if growth of the plexiform neurofibroma is noted based on the MRI scan. 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 physician. Other reasons for removal from the protocol could be if you did not tolerate pirfenidone because of side effects of the drug, if you developed another serious medical condition, which would not allow the administration of pirfenidone, or if you were unable to complete the physical exams, blood work, and scans requested as part of the protocol.

All patients on the study will receive pirfenidone orally (by mouth) as capsules with meals three times a day (approximately every 8 hours) for cycles of 28 days with no rest period. During the first week of the first treatment cycle you will receive pirfenidone at a lower dose, as it may help preventing you from getting nauseated. After the first week of treatment at a reduced dose, you will receive pirfenidone at the full dose. Capsules can be opened and the content mixed with food for easier intake in young children. Pirfenidone will be given at a similar dose to the dose which showed activity in adults with conditions other than NF1. This dose has been well tolerated by children with NF1. The daily dose will be 1500 mg/m² body surface area, which is calculated from your height and weight.

Approximately 36 patients will be entered on this clinical trial.

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

You will not be able to receive other chemotherapy, radiation therapy, immunotherapy, biologic therapy, growth factors or other experimental drugs while receiving pirfenidone on this trial.

Prior to entering this study you will have a small amount of blood drawn to measure blood counts, blood chemistries, and liver and kidney function. Females of child-bearing age will have a pregnancy test. Blood tests will be repeated prior to treatment cycle number 2, 3, 4, 7, 10, and subsequently after completion of every six treatment cycles to monitor for possible side effects of pirfenidone. At each of these visits, up to a maximum of 10 ml (2 teaspoons) of blood will be

MEDICAL RECORD**CONTINUATION SHEET for either:**

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taken. A physical examination will be performed at the same time as blood samples are obtained, but will be continued at intervals of every three treatment cycles after cycle number 10.

An MRI of your plexiform neurofibroma will be performed prior to beginning treatment with pirfenidone. The MRI will be repeated prior to treatment cycle number 4, 7, 10, and after completion of every six treatment cycles thereafter.

In addition, one important aspect of the study is to assess your quality of life. We will evaluate quality of life by giving you a questionnaire, which you would complete prior to treatment with pirfenidone, prior to treatment cycle number 4, 7, and then after completion of every 6 treatment cycles. Quality of life will not be assessed and the questionnaire will not be given to patients older than 18 or younger than 6 years of age. You will not have to answer any questions that you feel uncomfortable answering.

Should you have to undergo a biopsy or surgery of your plexiform neurofibroma, 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. These studies may help us to better understand which patients may benefit from the treatment with pirfenidone. Any results from these studies will be preliminary and will require further analysis for verification. Therefore, neither you nor anyone else will be informed about results of the studies performed on your 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 use of your specimen(s) will be for research purposes only and will not benefit you. It is also possible that the stored specimen(s) may never be used. The tissue will be identified with a code number, and will only be possible to connect with your 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 are providing for this study, may have some commercial applicability. There are no plans to provide financial compensation to you, 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 will not receive further notice of future uses of your sample, unless a future use could involve more than minimal risk to you. Any results from these studies will be preliminary and will require further analysis for verification. Therefore, neither you nor anyone else will be informed about results of the studies performed on your neurofibroma tissue. It might help people who have NF1 in the future. All research results will be kept confidential. You can decide not to allow us to obtain a tumor sample and/or store your tumor sample at the tissue repository (please see below), or withdraw your specimen from the tissue repository at any time. Just contact us and let us know that you do not want us to use your tumor sample. Then any sample that remains will be destroyed.

Donation of a tumor sample is optional, and if you decide not to have a tumor sample taken and/or stored, you can still participate in the treatment part of this study (please see below), and your care will not be affected.

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 with that information.

Pirfenidone 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.

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:**

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Please indicate below if you agree or disagree to the following study procedures for you in case you were to undergo surgery of your plexiform neurofibromas for clinical purpose (not research):

Obtain tumor sample for detailed pathological analysis: Agree: Disagree: Initials:

Storage of the tumor sample in a central tumor repository for future neurofibromatosis type 1 research:

Agree: Disagree: Initials:**ALTERNATIVE APPROACHES OR TREATMENTS**

You 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 may decide not to receive any treatment at this point in time.

RISKS OR DISCOMFORTS OF PARTICIPATION

The side effects of pirfenidone have been studied in animals, in healthy adults, in adults with fibrosing (scarring) conditions, and in adults and a small number of children with NF1.

In animal studies, which use much higher doses of pirfenidone than are to be used in this study, deaths occurred due to respiratory (breathing) failure. Other side effects noted in animals included unsteadiness and weakness. Long-term studies in rats and mice treated with pirfenidone showed that animals developed tumors of the liver. In addition, rats developed tumors of the uterus. The relevance of these tumors to humans is not known at this time. No reports of liver or uterine tumors in patients participating in clinical trials with pirfenidone have been reported to date.

Pirfenidone has been studied in approximately 850-1000 adults taking this drug on an experimental basis in other studies for other conditions. The following risks/side effects, which are believed to be associated with pirfenidone, have been infrequently observed: Rash, skin photosensitivity (skin rash in light exposed areas), temporary mild stomach upset, nausea, decreased appetite, heartburn, diarrhea, abdominal distension (bloating), abdominal discomfort, dyspepsia (indigestion), headache, tiredness, somnolence (feeling abnormally sleepy), palpitations (fast or irregular heart rate), and elevated gamma-GTP (an enzyme measured in the blood, that may indicate a problem with the liver or bile system). Because pirfenidone can make you more sensitive to sun exposure, you should wear protective clothing and sunscreen during exposure in the sun. Few patients, who received radiation treatment in addition to pirfenidone, developed lightheadedness and passed out. Overall, pirfenidone has also been well tolerated in a small number of children with NF1. The following side effects related to pirfenidone were observed in few of these pediatric patients: Diarrhea, mild nausea and vomiting of the initial doses of pirfenidone, tiredness, upset stomach, (gastritis), abdominal pain, and palpitations (fast or irregular heart rate). One patient developed a decrease in the white blood cell count. In addition two patients developed a side effect with uncertain relationship to pirfenidone: One patient with preexisting brain tumor developed a seizure, and one child experienced a decrease in the blood potassium level while on pirfenidone. Few patients were noted to develop behavioral changes (decreased attention, acting more defiant, immature, and impulsive), which were felt to be unlikely related to pirfenidone.

You may have an allergic reaction to the pirfenidone, which may cause a rash, itching, hives or wheezing. There have been no serious or irreversible side effects in adults taking this drug. Since this is a new experimental treatment, other presently unknown side effects may occur. These side effects could potentially be serious and even fatal.

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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You will be watched closely, and the drug will be discontinued if serious side effects develop. If these symptoms resolve within 2 weeks after the therapy is stopped, you may continue therapy with pirfenidone, but the dosage of medication will be decreased. If you continue to have side effects after stopping pirfenidone for two weeks, or experience side effects on a decreased dosage of pirfenidone, the medication will be stopped and you will not be able to further participate in this study. Taking other medications (including over-the-counter medications, etc.) in combination with pirfenidone may produce or worsen side effects not produced by either alone. Before taking another medication, you must talk to your study doctor.

The risks from the blood drawing to assess the effect of pirfenidone 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 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.

MRI: Magnetic resonance imaging (MRI) is a standard procedure used for imaging plexiform neurofibromas. Administration of a contrast agent is not required for analysis of plexiform neurofibromas on this research protocol. When having a MRI, you will lie motionless on a table that slides into a tunnel slightly wider than your body for about one hour. There is very little room in the MRI, however you 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) are present. However, braces are not a problem. Should you have a metal prosthesis you may be excluded from participating in the study for your own safety. All potential participants will be 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. Most of the MRI studies performed on this study would also be done as normal follow up for your plexiform neurofibroma, and not just for the study.

Pirfenidone may be harmful to an unborn child. If you are a female and old enough to get pregnant, you will be given a pregnancy test before you begin the treatment, in order to make sure that you are not pregnant. If there is a chance that you could become pregnant during this study, you should not participate in the study. If you are sexually active, you must use an appropriate and effective method of birth control while you are taking part in this study. If you become or are found to be pregnant while you are taking part in this study, you must notify one of the doctors listed on this form right away so the treatment can be discussed, and you will be withdrawn from the study. Breast-feeding mothers must stop breast-feeding. The effects of pirfenidone on female fertility are unknown.

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

Tumor Studies: A tumor sample will only be obtained if you have to undergo surgery or a biopsy of the plexiform neurofibroma for clinical reasons. With your permission, left over tumor will be sent to a central tumor repository. Although there is no immediate plan to perform studies from any tumor samples obtained, tumor material will be stored for future research. 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 only by contact with the trial coordinating center "Pediatric

PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

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MEDICAL RECORD**CONTINUATION SHEET for either:**

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

STUDY NUMBER: 04-C-0080

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Oncology Branch, NCI" in Bethesda, MD. Neither you, nor anybody else will be informed about results of testing performed on your tumor tissue. Every effort will be made to keep test results confidential. However, as the tumor and sample can be linked to your 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 have neurofibromatosis.

POTENTIAL BENEFITS OF PARTICIPATION

The potential benefit of this treatment with pirfenidone is that it may cause your 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 participant 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 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. It is expected that 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. Data obtained in this study will help determine an optimal dose of pirfenidone in children and young adults with NF1 and plexiform neurofibromas. If the pirfenidone medication proves to be effective in NF1, you and other children with NF1 will have benefit of this new therapy.

RESEARCH SUBJECT'S RIGHTS

Joining this research study is voluntary. You may ask the doctors and nurses any questions about this treatment. If you decide at any time that you 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 may be eligible to receive experimental therapy other than the drug described here, or can receive therapy consisting of symptomatic treatment only.

Your medical record may be reviewed by qualified representatives from the National Cancer Institute, by representatives from Solanan Inc/Marnac Inc, and by Dr. Dusica Babovic-Vuksanovic, who sponsors the clinical trial, and by the Food and Drug Administration (FDA). It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as part of their responsibility to protect human participants in research.

PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (10-84)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

STUDY NUMBER: 04-C-0080

CONTINUATION: page 7 of 8 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 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 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 NIH medical records. However, you should know that the Act allows release of some information from your 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. Neither the National Institutes of Health nor Clinical Center will provide long-term medical care or financial compensation for research-related injuries, except as may be provided through whatever remedies are normally available under law. This study is being funded by the Department of Defense and conducted by the United States Army. Army regulations provide that, as a volunteer in a study by the United States Army, you are authorized all necessary medical care for any injury or disease that is a direct result of your participation in the research. If you are hurt or get sick because of this research study, you can receive medical care at an Army hospital or clinic free of charge. You will only be treated for injuries that are directly caused by the research study. The Army will not pay for your transportation to and from the hospital or clinic. If you have questions about this medical care, talk to the principal investigator for this study (Brigitte Widemann, phone 301-496-7387). If you pay out-of-pocket for medical care elsewhere for injuries caused by this research study, contact the principal investigator. If the issue cannot be resolved, contact the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (Legal Office) at (301) 619-7663/2221. The Principal Investigator or his designee will assist you/your child in obtaining appropriate medical treatment under this provision if it is required. If you/your child have any questions concerning your/your child's eligibility for Army funded medical treatment you/your child should discuss this issue thoroughly with the Principal Investigator or his designee before you/your child enroll in this study. This is not a waiver or release of your/your child's legal rights.

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.

4. Problems or Questions If you have/your child has 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, Brigitte Widemann, M.D.; Building 10, Room 13N240, Telephone: (301) 496-7387. Other researchers you/your child may call are: Frank M. Balis, M.D. at (301) 496-0085; Ms. Wendy Goddspeed, RN, or Ms. Anne Goodwin, R.N. at (301) 594-4762, or if you may have any questions about the use of your tissue for future research studies, you may also contact the Office of the Clinical Director of the National Cancer Institute at (301) 496-4251.

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 want to read it again.

PATIENT IDENTIFICATION

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

• Adult Patient or • Parent, for Minor Patient

NIH-2514-1 (5-98)

P.A.: 09-25-0099

FAX TO: (301) 480-3126

File in Section 4: Protocol Consent

STUDY NUMBER: 04-C-0080

CONTINUATION: page 8 of 8 pages

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 JUNE 25, 2007 THROUGH JUNE 24, 2008.			
_____ Signature of Investigator	_____ Date	_____ Signature of Witness	_____ Date

Revision Copy

MEDICAL RECORD	MINOR PATIENT'S ASSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Attach to NIH-2514-1, Consent to Participate in a Clinical Research Study
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INSTITUTE: National Cancer Institute

STUDY NUMBER: 04-C-0080 PRINCIPAL INVESTIGATOR: Brigitte Widemann, M.D.

STUDY TITLE: Phase II Trial of Pirfenidone in Children, Adolescents, and Young Adults with Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas

Continuing Review Approved by the IRB on 06/25/07

Amendment Approved by the IRB on 04/17/08 (D)

Date Posted to Web: 04/29/08

Minor 7 through 12 years of age

We would like to invite you to take part in a research study at the National Institutes of Health (NIH). You have 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. Your tumor cannot be safely removed by surgery, and we are asking you to help us test one of these new medicines that is called pirfenidone.

The reason for this study is to find out if this medicine may slow down the growth of your tumor, or shrink it, or make you feel better, but 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. For the MRI scan you will lay on the bed, the bed slides into a long tube of the MRI scanner. The space in the tube of the MRI scanner is small and the MRI scanner makes a loud banging noise when you are getting the scan. Some people do not like being in small places or do not like the loud noise. If these things bother you, please tell us. Some people who do not like small places, do not like the loud noise or cannot lie still for an hour need medications to help them sleep while they get an MRI scan.

An important part of the study is to learn how you are doing and how you are feeling while you are taking pirfenidone. To learn this information, you will be asked questions about things like school, activities, sleeping, books, feelings etc. These questions will be asked at regular times (every few months) while you are on this study.

You will take pirfenidone by mouth as pills 3 times a day at the same time you eat your meals each day. During the first week you will receive fewer pirfenidone pills, as it may help preventing you from getting sick. After the first week you will receive the full number of pirfenidone pills. We will take small amounts of blood (less than 2 teaspoons) from you prior to starting pirfenidone, and regularly afterwards (initially every 4 weeks, then after every 3-6 months) to make sure that pirfenidone does not harm you. We will do the MRI scans to check the size of your tumor after 3 months of treatment with pirfenidone, and regularly afterwards. You may be on this study and receive pirfenidone for as long as your tumor does not grow and you have no side effects from the pirfenidone.

The new medicine might not work. It may make you feel worse. You could get an upset stomach or diarrhea. Your heart may start beating fast. You could have an allergy to the drug and get a rash or itchy bumps on your skin called hives, or it might become hard for you to breathe. You may also feel more tired or lightheaded. Your doctor and parents will watch for any problems. Be sure to tell your parents if you feel bad or if you think anything is wrong. If these problems occur, they will be treated right away.

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 (2)
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STUDY NUMBER: 04-C-0040

CONTINUATION: page 2 of 2 pages

When you have your blood drawn or when we put a small tube (catheter) in your arm to draw blood, you might feel pain or there may be bruising or, rarely, an infection.

The children who are part of the study will help us find out if the new medicine works. If this new medicine works, it may slow down or stop the growth of your tumor, and you may feel better.

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 parent's permission before we test this new medicine on you. A copy of this form will be given to you and to your parents. 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.

We will keep your records in a safe place, and only people working on the study will know your name.

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: _____

Signature of Witness: _____ Date: _____

Permanent address of study participant:

PATIENT IDENTIFICATION

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

NIH-2514-2 (4-97)

P.A.: 09-25-0099

FAX TO: (301) 480-3126

File in Section 4: Protocol Consent

INSTITUTE: National Cancer Institute

STUDY NUMBER: 04-C-0080

PRINCIPAL INVESTIGATOR: Brigitte Widemann, M.D.

STUDY TITLE: Phase II Trial of Pirfenidone in Children, Adolescents, and Young Adults with Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas

Continuing Review Approved by the IRB on 06/25/07

Amendment Approved by the IRB on 04/17/08 (D)

Date Posted to Web: 04/29/08

Minor 13 through 17 years of age

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 neurofibromatosis type 1 or NF1, which has caused a tumor (called a plexiform neurofibroma) to grow in 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 called pirfenidone helps to make your tumor smaller. This drug has been given to adults and has been found to be effective in treating medical problems similar in some aspects to the one that you now have. Pirfenidone is also being tested in adults with NF1 and plexiform neurofibromas, and has been given to a small number of children with NF1 to find out the best dose of pirfenidone for children and teenagers with NF1. We do not know yet if pirfenidone is effective. We would like to see if this same medication may help children and teenagers with NF1 and plexiform neurofibromas.

We want to answer the following questions about this new drug pirfenidone and NF1 tumors:

- 1) Will this new drug, pirfenidone slow down how fast your NF1 tumor(s) grow(s)?
- 2) Will pirfenidone make your NF1 tumor(s) smaller?
- 3) How well is pirfenidone tolerated, and what are the side effects?

STUDY NUMBER: 04-C-0080

CONTINUATION: page 2 of 5 pages

Study plan

If you participate in this study, you will undergo a physical examination, blood testing, and will have a magnetic resonance imaging (MRI) scan prior to starting pirfenidone treatment. You will be asked to complete a questionnaire consisting of 46 questions to determine how you are functioning and how you are feeling. All these tests will be repeated at regular intervals while you are on this study.

You will take a medication that you have not taken before. It is called pirfenidone and is provided as capsules, and is taken by mouth. You will take pirfenidone three times every day, but we define 28 days of taking pirfenidone as one treatment cycle. During the first week of the first treatment cycle you will receive pirfenidone at a lower dose, as it may help preventing you from getting nauseated. After the first week of treatment at a reduced dose, you will receive pirfenidone at the full dose.

You will be able to receive pirfenidone for as long as you tolerate the medicine well, and your plexiform neurofibroma does not increase in size. Pirfenidone treatment will be stopped if your tumor grows or you have side effects from the pirfenidone.

To measure the size of your tumor during treatment we will take a picture (called a MRI) of your tumor by using a large scanner. To take the picture you lay down on a bed, which slides into a tunnel in the scanner. 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. The MRI will be performed prior to treatment with pirfenidone, prior to treatment cycle number 4, 7, 10, and after completion of every six treatment cycles thereafter.

You will have a small amount of blood drawn for blood counts and chemistries and to measure your liver and kidney function. Each time, up to a maximum of 10 ml (2 teaspoons) of blood will be taken. These blood tests will be performed prior to treatment with pirfenidone, and then prior to treatment cycle #2, 3, 4, 7, and after completion of every six treatment cycles thereafter. You will also have a physical examination at regular intervals while you receive pirfenidone.

If you are a female and are old enough to become pregnant, you will also have a pregnancy test. You cannot participate in the study if there is a chance that you may become pregnant.

Should you have to undergo a biopsy or surgery of your plexiform neurofibroma, we would like to obtain a sample of the tumor. We would perform a detailed analysis of the tumor in order to better understand these tumors. Should any tumor sample be left over after performing these studies, we would like to store these samples in a central place. Your sample would be identified only by a number, not by your name. Donating a tumor sample is optional. You can decide not to allow us to obtain a tumor sample and/or store your tumor sample or have the sample removed at any time. . This will not affect your care. Donating a tumor sample will be for research purpose only and will not help you, but might help others in the future.

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: 04-C-0080

CONTINUATION: page 3 of 5 pages

Please mark below if you agree or disagree to the following in case you were to undergo surgery of your plexiform neurofibromas for clinical reasons:

- 1) Obtain tumor sample for detailed analysis: Agree: Disagree: Initials: _____
- 2) Storage of the tumor sample in a central tumor repository for future neurofibromatosis type 1 research: Agree: Disagree: Initials: _____

Risks or side effects:

Pirfenidone has been studied in approximately 850-1000 adults taking this drug in studies for other conditions. The following risks/side effects have been infrequently observed: Rash, skin photosensitivity (skin rash in light exposed areas), temporary mild stomach upset, nausea, decreased appetite, heartburn, diarrhea, abdominal distension (bloating), abdominal discomfort, dyspepsia (indigestion), headache, tiredness, somnolence (feeling abnormally sleepy, palpitations (fast or irregular heart rate), and elevated gamma-GTP (an enzyme measured in the blood, that may indicate a problem with the liver or bile system). Because pirfenidone can make you more sensitive to sun exposure, you should wear protective clothing and sunscreen during exposure in the sun. Few patients, who received radiation treatment in addition to pirfenidone, developed lightheadedness and passed out.

Overall, pirfenidone has also been well tolerated in a small number of children with NF1. The following side effects related to pirfenidone were observed in few of these pediatric patients: Diarrhea, nausea and vomiting of the initial doses of pirfenidone, tiredness, upset stomach (gastritis), abdominal pain, and palpitations (fast or irregular heart rate). One patient developed a decrease in the white blood cell count. In addition two patients developed a side effect with uncertain relationship to pirfenidone: One patient with preexisting brain tumor developed a seizure, and one child experienced a decrease in the blood potassium level while on pirfenidone. Few patients were noted to develop behavioral changes (decreased attention, acting more defiant, immature, and impulsive), which were felt to be unlikely related to pirfenidone

However, since this is a new experimental treatment, other presently unknown side effects may occur. These side effects could potentially be serious and even cause death. If you experience any severe side effects, the pirfenidone therapy will be stopped. Any side effects of the drug will be immediately treated. If these symptoms resolve within 2 weeks after the therapy is stopped, you may continue therapy with pirfenidone, but the dosage of medication will be decreased.

Taking Pirfenidone might be harmful to an unborn child. Birth control measures must be used by all females of child-bearing age (those females who are older than 9 or have begun puberty) who can become pregnant and are sexually active or by their sexual partners while in this study. These birth control measures can include contraceptive pills or use of condom and spermicide cream. Effects of pirfenidone upon an unborn child are unknown and may possibly result in serious birth defects of the unborn child. Breast-feeding mothers must stop breast-feeding their child.

During your blood tests, you may feel a small prick at the site where the needle is entering your arm. A little while after your blood draw your arm may appear bruised around where the needle was inserted. This bruising will go away within a few days. When the catheter/heparin lock is inserted, it may also cause bruising, pain or, rarely, infection.

We will let you know about any new findings during the course of your participation in this study, which may relate to your willingness to continue to participate in the study.

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: 04-C-0080

CONTINUATION: page 4 of 5 pages

Potential Benefits:

Pirfenidone might slow the growth of your tumor or even might decrease its size; however, this study may not make your health improve.

Information obtained in this study will help determine an optimal dose of pirfenidone in children with NF1 and plexiform neurofibromas. If the pirfenidone medication proves to be effective in NF1, you and other children with NF1 will have benefit from this new therapy.

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.

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 test this new medicine on you. A copy of this form will be given to you and to 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

PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (10-84)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

STUDY NUMBER: 04-C-0080

CONTINUATION: page 5 of 5 pages

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: _____