Neurofibromatosis (NF) Consortium

NF PROTOCOL 106
A Phase 2 Trial of the MEK Inhibitor PD-0325901 in Adolescents and Adults with NF1-Associated Morbid Plexiform Neurofibromas

Sponsored by:
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TABLE OF CONTENTS

Protocol Roster ........................................................................................................................................ 2
Participating Sites: ...................................................................................................................................... 3
Roles and Responsibility of Study Personnel: ........................................................................................... 6
EXPERIMENTAL DESIGN SCHEMA ......................................................................................................... 11
1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS) ............................................................................. 12
2.0 BACKGROUND AND RATIONALE ..................................................................................................... 12
  2.1 Neurofibromatosis Type 1 and Plexiform Neurofibromas ................................................................. 12
  2.2 Mitogen-activated Protein (MAP) Kinase/Extracellular signal-regulated protein kinase (ERK), and MAPK/ERK kinase (MEK) ......................................................... 16
  2.3 Pharmacokinetics and Dosing of PD-0325901 .................................................................................. 23
  2.4 Overview of Proposed Study ............................................................................................................. 23
3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES ...................................................................... 24
  3.1 Informed Consent/Assent .................................................................................................................. 24
  3.2 Screening Procedures ....................................................................................................................... 24
  3.3 Study Enrollment .............................................................................................................................. 25
4.0 PATIENT ELIGIBILITY .......................................................................................................................... 25
  4.1 Inclusion Criteria for all subjects: ...................................................................................................... 25
  4.2 Exclusion Criteria ............................................................................................................................. 27
5.0 REQUIRED DATA .................................................................................................................................. 28
  5.1 Tests and Observations ...................................................................................................................... 30
  5.2 Records to be Kept ............................................................................................................................ 30
  5.3 Role of Data Management ................................................................................................................ 30
6.0 TREATMENT PROGRAM ....................................................................................................................... 31
  6.1 Agent Information/ PD-0325901 ........................................................................................................ 31
  6.2 Treatment Overview ......................................................................................................................... 35
  6.3 Criteria for Starting Subsequent Courses ......................................................................................... 36
7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY .......................................................... 36
  7.1 Supportive Care .................................................................................................................................. 36
  7.2 Growth Factors .................................................................................................................................. 36
  7.3 Surgery ............................................................................................................................................. 36
  7.4 Concomitant Medications .................................................................................................................. 37
8.0 MODIFICATIONS FOR ADVERSE EVENTS .......................................................................................... 37
  8.1 Hematological Toxicity ...................................................................................................................... 37
  8.2 Non-Hematological Toxicity ............................................................................................................... 38
  8.3 Toxicities Requiring Removal From Protocol Therapy ..................................................................... 38
9.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED ........................................................... 38
  9.1 Required Clinical, Laboratory and Disease Evaluation ..................................................................... 38
  9.2 History and physical examination and vital signs .............................................................................. 39
  9.3 Retinal Exam ..................................................................................................................................... 39
  9.4 Hematology ..................................................................................................................................... 39
  9.5 Blood chemistry ............................................................................................................................... 39
  9.6 Serum or Urine Pregnancy Test ........................................................................................................ 39
  9.7 MRI for volumetric analysis of plexiform neurofibroma ................................................................... 40
  9.8 PD-0325901 diary ................................................................................................................................ 40
  9.9 Pharmacokinetic profile of PD-0325901 (Required) ........................................................................ 40
  9.10 Pharmacodynamic Analysis (Optional) ............................................................................................ 41
9.11 Plasma Cytokines and Growth Factors (Optional) ................................................. 41
9.12 Maximum blood volumes for pharmacokinetic and pharmacodynamic studies ................................................................................................................. 41
9.13 Quality of Life and Pain Evaluations (Required) .................................................. 41
10.0 Adverse Reporting Requirements ........................................................................ 43
  10.1 Definitions ........................................................................................................... 43
  10.2 Common Terminology Criteria for Adverse Events (CTCAE) ......................... 43
  10.3 Attribution: Definitions of relationship to study medication are as follows: 44
  10.4 Reporting Procedures for All Adverse Events ................................................... 44
  10.5 Expedited Reporting Guidelines ...................................................................... 44
  10.6 Reporting of Protocol Violations/Deviations and Unanticipated Problems 45
11.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA ........................................................................................................ 46
  11.1 Criteria for Removal from Protocol Therapy ..................................................... 46
  11.2 Off Study Criteria ............................................................................................... 46
12.0 STATISTICAL AND ETHICAL CONSIDERATIONS ............................................ 47
  12.1 Subject Accrual .................................................................................................... 47
  12.2 Statistics and Feasibility ....................................................................................... 47
  12.3 Statistical Analysis Plan ....................................................................................... 48
  12.4 Definitions of Evaluable ...................................................................................... 50
13.0 Response Criteria .................................................................................................. 50
14.0 Human Subjects Protection & Data Safety Monitoring PLAN ......................... 51
15.0 REFERENCES ........................................................................................................ 54
APPENDIX I: SCHEDULE OF EVALUATIONS ............................................................... 56
Appendix II: Performance Status Scales/Scores ......................................................... 57
Appendix III: NIH Consensus clinical Defintion of Neurofibromatosis ..................... 58
Appendix IV: Protocol for Required Pre-Study and On-Study MRI Studies ............... 59
Appendix IVa: MRI eligibility form .............................................................................. 62
Appendix V: Subject Diary On PD-0325901 Protocol .............................................. 63
Appendix VI: Pharmacokinetic, Pharmacodynamic and Cytokine STUDIES ............. 64
  Pharmacokinetic Worksheet ...................................................................................... 64
  Pharmacodynamic Worksheet ................................................................................... 66
  Plasma Cytokines and Growth Factors ................................................................ 67
Appendix VII: Consortium QOL and Pain Measures ................................................. 68
  PAIN QUESTIONNAIRE ........................................................................................... 70
QOL INSTRUMENT (TEEN REPORT) ........................................................................ 72
  For teens and young adults (16 to 20 years old) with NF-1 .................................... 72
QOL INSTRUMENT (ADULT SURVEY) .................................................................. 78
ABSTRACT/SCHEMA

Background

- Patients with Neurofibromatosis 1 (NF1) have an increased risk of developing tumors of the central and peripheral nervous system, including plexiform neurofibromas (PN), which are benign nerve sheath tumors that are among the most debilitating complications of NF1. There are no standard treatment options for PN other than surgery, which is often difficult due to the extensive growth and invasion of surrounding tissues.
- The Mitogen-activated Protein Kinase (MAPK) pathway is important for plexiform neurofibroma growth.
- Phosphorylated Extracellular signal-regulated protein kinase (p-ERK), is detected in human plexiform neurofibromas at higher levels than normal human nerve.
- The Dhh-Cre;Nf1fl/fl mouse model develops plexiform neurofibromas, and these tumors histologically mimic those of human plexiform neurofibromas\(^1\).
- Elevated phosphorylated (p)-ERK1,2 was detected in Nf1fl/fl;Dhh-cre mouse neurofibromas relative to Nf1fl/fl;Dhh-cre or wild type mouse nerve.
- PD-0325901 is a highly specific allosteric MAPK/ERK kinase (MEK) inhibitor currently in clinical cancer trials that blocks MAPK signaling.
- Lower doses of PD-0325901 in mice results in plasma concentrations similar to the concentrations achieved in adults at the dose proposed for this trial, and induced tumor volume reductions in 85% of mice.

Primary Objective

- To determine whether PD-0325901 results in objective radiographic responses based on volumetric MRI measurements in adolescents and adults with NF1 and growing or symptomatic, inoperable PN

Secondary Objectives

- To evaluate the feasibility and toxicity of protracted PD-0325901 administration in this patient population
- To estimate the objective response rate of up to 2 non-target plexiform neurofibromas to PD-0325901 by MRI.
- To characterize the pharmacokinetic profile of PD-0325901 when administered to this patient population
- To assess quality of life and pain in patients on PD-0325901

Exploratory Objectives

- To characterize the pharmacodynamics profile of PD-0325901 when administered to this patient population by assaying host tissues (dermal neurofibromas) as a surrogate for plexiform neurofibroma cells before and after drug administration.
- To characterize the activity of PD-0325901 on neurofibroma cell gene expression
- To characterize the activity of PD-0325901 on plasma cytokines and growth factors
- To correlate pERK levels with pharmacokinetic data
- To validate the PedsQL NF1 QOL Module, a disease specific QOL scale, for use in this patient population
- To determine whether subjects who respond (≥20% objective radiographic response of target lesion by 12 courses) to PD-0325901 will maintain that response for 1 year off therapy
Eligibility

- Patients ≥16 years old with NF1 and PN(s) that are progressive by serial imaging OR causing significant morbidity, and that can be analyzed by volumetric MRI.

Design

- PD-0325901 will be dosed by mouth b.i.d. at a dose of 2 mg/m²/dose with a max of 4 mg per dose (8 mg per day max). Dosing will be on a 4 week course with a 3 week on/1 week off schedule.
- Subjects will undergo volumetric assays of their target PN using MRI after every 4 courses for the first year and then every 6 courses.
- Treatment will continue for 8 courses (approximately 8 months) as long as there is at least SD.
- Treatment beyond course 8 will only be given to those with at least 15% reduction in volume of the target tumor by the end of course 8.
- Treatment beyond course 12 will only be given to those subjects who achieve a response (≥ 20% tumor shrinkage by volumetric analysis) by the end of course 12, and will be continued for a maximum of 24 total courses.
- Subjects will be removed for significant toxicity or objective progression (≥ 20% tumor growth by volumetric analysis) at any time.
EXPERIMENTAL DESIGN SCHEMA
1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1. Primary Aim
   1.1.1. To determine whether PD-0325901 results in objective radiographic responses based on volumetric MRI measurements in adolescents and adults with NF1 and growing or symptomatic inoperable PN

1.2. Secondary Aims
   1.2.1. To evaluate the feasibility and toxicity of chronic PD-0325901 administration in this patient population
   1.2.2. To estimate the objective response rate of up to 2 non-target plexiform neurofibromas to PD-0325901 by MRI
   1.2.3. To characterize the pharmacokinetic profile of PD-0325901 when administered to this patient population
   1.2.4. To evaluate quality of life and pain during treatment with PD-0325901

1.3. Objective Aims
   1.3.1. To characterize the pharmacodynamic profile of PD-0325901 when administered to this patient population using dermal neurofibromas as a surrogate for plexiform neurofibroma cells.
   1.3.2. To characterize the activity of PD-0325901 on neurofibroma cell gene expression
   1.3.3. To characterize the activity of PD-0325901 on plasma cytokines and growth factors
   1.3.4. To correlate pERK levels to pharmacokinetic data and response
   1.3.5. To validate the PedsQL NF1 QOL Module, a disease specific QOL scale, for use in this patient population
   1.3.6. To determine whether subjects who respond (≥20% objective radiographic response of target lesion by 12 courses) to PD-0325901 will maintain that response for 1 year one they come off therapy

2.0 BACKGROUND AND RATIONALE

2.1 Neurofibromatosis Type 1 and Plexiform Neurofibromas

   Neurofibromatosis type 1 (NF1) is a common autosomal dominant, progressive disorder with an incidence of 1:3500 (>80,000 persons affected in The United States). NF1 is caused by a mutation in the NF1 tumor suppressor gene. The NF1 gene was cloned on chromosome 17q11.2 and compromises 60 exons spanning 350 kb of genomic DNA. Mutation analysis of the NF1 gene allows identification of 95% of mutations with a wide spectrum of mutations (Messiaen, Callens et al 2000). To date, no phenotype genotype correlations have been made with the exception of complete loss of the NF1 gene (megabase deletions), which is associated with severe intellectual disability. The diagnosis of NF1 is clinical and based on criteria developed at the NIH consensus conference (Section 4.1.1). 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%), and malignant peripheral nerve sheath tumors (10%) \(^{2,3}\).
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 MPNSTs arise by malignant transformation of neurofibroma. Based on a recent study, the life-time risk of developing MPNST in patients with NF1 is 8-13%.

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. Between 20-44% of individuals with NF1 develop plexiform neurofibromas. 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.

A subset of plexiform neurofibromas includes paraspinal plexiform neurofibromas. These tumors tend to originate from the dorsal root ganglion and grow bidirectionally, centrally towards the neural foramen and centrifugally down the peripheral nerve. These tumors cause substantial morbidity by compression of the spinal cord and by peripheral growth, and may show progressive growth not only in young children, but also in adults. Individuals with substantial paraspinal neurofibroma burden may be a distinct subset of individuals with NF (personal communication Dr. Bruce Korf). These patients typically have no or only few cutaneous neurofibromas; have few, if any, café au lait spots; have a large number of firm subcutaneous neurofibromas; and rarely have cognitive deficits. The phase II trials of tipifarnib and pirfenidone (adult and pediatric studies) allow study entry to patients with paraspinal plexiform neurofibromas. In these clinical trials, volumetric MRI analysis of paraspinal neurofibromas is used to evaluate the potential benefit of the investigational agent.

Plexiform neurofibromas, including paraspinal neurofibromas, cause major morbidity and mortality in NF1. There is no currently accepted effective drug therapy for plexiform neurofibromas. The rate of growth of this histologically benign neoplasm has been described as unpredictable and often episodic. Recently, Widemann et al reported the time to progression (TTP) of plexiform neurofibromas on the control arm of a blinded cross-over designed trial in which patients received either placebo or tipifarnib (personal communication). The placebo arm mean TTP was 10.6 months. 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. 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, cis-retinoic acid, interferon alpha 2b, methotrexate and vinblastine, PEG interferon alpha-2b, the farnesyltransferase inhibitor tipifarnib (R115777), the antifibrotic agent pirfenidone, the RAF kinase inhibitor Sorafenib, the cKIT inhibitor Gleevec, and the mTOR inhibitor Sirolimus (personal communication) 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. While PEG interferon alpha-2b increased TTP and there have been some PN shrinkage reported with Gleevec, to date no medical treatment has reliably resulted in objective radiographic response of plexiform neurofibromas.
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 \(^{19,20}\). These methods have limited value in the assessment of treatment outcome for plexiform neurofibromas, which are frequently large, have a complex (non-spherical) shape, and have a slow, erratic growth pattern. In order to reproducibly quantify the size of these complex lesions and detect small changes in the size over time, we used MR imaging characteristics of plexiform neurofibromas to develop an automated method of lesion detection and volume measurement. Short T1-Inversion Recovery (STIR) MR images, on which plexiform neurofibromas are bright lesions compared with normal surrounding tissue, were used to develop a program for automated image analysis within MEDx (v3.41) software (Sensor Systems, Inc. Sterling, VA). Reproducibility and inter-observer variability of this automated method were determined by 2 observers who quantified volumes for plexiform neurofibromas of the orbit (n=2), face/neck (n=3), abdomen (n=1), and pelvis (n=3) on three different days (Solomon, Warren et al. 2004). For each MR image (Figure 1A), the tumor is roughly outlined manually including a rim of low signal intensity normal tissue (Figure 1B). The program then performs a histogram analysis of signal intensity pixel by pixel and a threshold that distinguishes high signal intensity tumor from normal tissue is defined (Figure 1C). Tumor contours are then determined using a gradient image, connected component analysis and automatic edge following operation (Figure 1D). There is an option for re-analysis of MR images using an average or selected threshold. Tumor volume is calculated by summing the results from all images based on the resulting 2-D contours and slice thickness; and a report is generated.

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

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</tr>
<tr>
<td>Median (range)</td>
<td>(809-1581)</td>
<td>(757-1603)</td>
</tr>
<tr>
<td>Median Inter-day CV (%)</td>
<td>3.6</td>
<td>1.6</td>
</tr>
<tr>
<td>(range)</td>
<td>(0.7-6.0)</td>
<td>(0.6-5.6)</td>
</tr>
<tr>
<td>Difference in volume between observers (%)</td>
<td>6.4 (1.4 - 11.9)</td>
<td>6.4 (1.4 - 11.9)</td>
</tr>
<tr>
<td>Correlation automated vs. manual method, R</td>
<td>0.999</td>
<td>0.999</td>
</tr>
</tbody>
</table>

This automated volumetric MRI analysis is applicable to most plexiform neurofibromas, has excellent intra- and inter-observer reproducibility and agrees with volumes determined by manual tumor tracing. This method was used in the phase II trial of the farnesyltransferase inhibitor tipifarnib, the phase I and II trials of pirfenidone, the phase I trial of peg-interferon alfa-2b, and the NF Consortium phase II trial of Sirolimus for children with NF1 and plexiform neurofibromas to assess changes in tumor size. Imaging studies on these multicenter trials are sent to the NCI, POB, where volumetric MRI analysis is performed. Tumor progression on these trials is defined as an increase in plexiform neurofibroma volume by \( \geq 20\% \).
This volume increase corresponds to much smaller changes in 1-D, or 2-D measurements as outlined in the table below:

<table>
<thead>
<tr>
<th>Response Criteria</th>
<th>RECIST Diameter, (2r)</th>
<th>WHO Product, ((2r)^2)</th>
<th>Current NF1 trials Volume, (\frac{4}{3}\pi r^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression (Increase)</td>
<td>20</td>
<td>44</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>13</td>
<td>20</td>
</tr>
</tbody>
</table>

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

2.2 Mitogen-activated Protein (MAP) Kinase/Extracellular signal-regulated protein kinase (ERK), and MAPK/ERK kinase (MEK)

**MEK and Cancer**

The MAPK pathway regulates multiple critical cellular functions including growth and senescence\(^2^1\). Dysregulation of the RAS-MAPK-MEK pathway occurs frequently in human cancer \(^2^2\). MEK1 mutations have been found in 3% of melanomas and 2.2% of colon cancers. These mutations typically lead to activation of both MEK and ERK. In addition, malignant peripheral nerve sheath tumors (MPNST), a cancer seen commonly in patients with Neurofibromatosis Type 1, have aberrations in MAPK signaling\(^2^3\).

**MEK and NF1**

The \(NF1\) gene encodes a protein, termed neurofibromin, which functions partly as a Ras-GTPase activating protein (RasGAP). Accordingly, neurofibromin loss in tumor cells leads to Ras hyperactivation. Signaling intermediates downstream of Ras are hyperactivated as a result of \(NF1\) gene inactivation and these specific proteins are critical for transmitting the Ras growth signal and for the development of neoplasia in patients with NF1. PD-0325901 is a highly specific non-competitive MEK inhibitor currently in clinical cancer trials. PD-0325901 blocked MAPK signaling based on pharmacodynamic measurement of p-ERK in MPNST xenografts and mouse neurofibroma tissue sections at intervals after PD-0325901 exposure.

**Dhh-Cre;Nf1fl/fl Mice Develop Plexiform Neurofibromas**

The \(Dhh-Cre;Nf1fl/fl\) mouse model develops plexiform neurofibromas, and these tumors histologically mimic those of human plexiform neurofibromas \(^1\). MAPK pathway activation was evaluated \textit{in vivo} by staining tissue sections for P-ERK. Elevated phosphorylated (p)-ERK1,2 was detected in \(Nf1fl/fl;Dhh-cre\) mouse neurofibromas and NPsies mouse sarcomas relative to \(Nf1fl/fl;Dhh-cre\) or wild type mouse nerve. P-ERK was also detected in all human neurofibromas \((n = 6)\) and MPNSTs \((n = 4)\) at higher levels than normal human nerve associated with a neurofibroma. In addition, malignant tumors showed higher levels of p-ERK relative to benign neurofibromas.

**PD-0325901 is a novel MEK inhibitor**
PD-0325901 is an orally bioavailable, highly specific allosteric MEK inhibitor currently in clinical cancer trials. PD-0325901 inhibits both purified MEK and cellular activation of MAPK at the low nanomolar range\(^\text{24}\). PD-0325901 has shown activity against pancreatic, colon, breast, lung and skin cancers. Phase 1 trials of this drug have shown 90% suppression of MAPK phosphorylation at doses as low as 1 mg daily.

**Mouse Neurofibroma Volume is Reduced by PD0325901**

PD-0325901 blocked MAPK signaling based on pharmacodynamic measurement of p-ERK in MPNST xenografts at intervals after PD-0325901 exposure. P-ERK disappeared by 30 minutes after dosing MPNST xenografts, remained low at 6h, and resembled pretreatment levels by 24h (see Fig 1). Pharmacodynamic assessment of PD-0325901 was at the end of the 60 day treatment period, demonstrating that the inhibitor remained efficacious throughout the experiment.

*Nf1fl/fl;Dhh-Cre* mice neurofibroma growth rates can be measured using serial volumetric magnetic resonance image (MRI) analysis. In pre-clinical studies performed by Ratner et al.\(^\text{25}\), twenty-eight tumor-bearing mice were randomly assigned to PD-0325901 treatment (10 mg/kg/day; n=18) or received control vehicle (n=10) (See Fig 2). Because this dose of MEK inhibitor has been reported to cause toxicity in human trials after prolonged exposure, lower doses of PD-0325901 were also analyzed with striking results. Sixteen mice were treated with 5 mg/kg and 15 mice with 1.5 mg/kg PD-0325901, with MRI volumetric analysis used to determine efficacy. The 1.5 mg/kg PD-0325901 dose in mice results in plasma concentrations similar to the concentrations achieved in adults at the dose proposed for this trial. Tumor volumes were reduced in mice treated with 1.5 mg/kg (10/15 mice), 5mg/kg (15/16 mice), or 10 mg/kg (14/18 mice) PD-0325901 (p<0.001 each dose). PD-0325901 was well tolerated with no apparent toxicity at any dose. In addition, cellular proliferation in neurofibromas treated with either control, 1.5 mg/kg, 5.0 mg/kg, or 10 mg/kg of PD-0325901 for 60 days was assessed by quantification of Ki67+ cells. Neurofibromas in *Nf1fl/fl;Dhh-Cre* mice treated with PD-0325901 at any dose showed a significant (***p<0.001) reduction in the percentage of Ki67+ cells relative to mice treated with control vehicle (see Fig 3).
Figure 1. *p-ERK in Dhh-Cre mouse neurofibromas*. Brown staining indicates detection of phosphorylated (p)-ERK in paraffin tissue sections. *Nf1<sup>[fl/fl]</sup>;Dhh-cre* mouse p-ERK staining is robust in carrier treated neurofibroma (A, E) but is absent 30 minutes after treatment with 10mg/kg (B) or 1.5 mg/kg (F) PD-0325901. P-ERK becomes detectable 6 hours (C) post-treatment with 10mg/kg PD-0325901 and returns to pretreatment levels by 24 hours (D). P-ERK also becomes detectable 6 hours (G) post-treatment with 1.5 mg/kg PD-0325901 but does not return to pretreatment levels by 24 hours (H). Scale bar = 50 µm; scale bar in (H) applies to (E – H); scale bar in (D) applies to (A – D). (Data from N Ratner, personal communication.)
FIGURE 2. PD-0325901 inhibits neurofibroma growth. (A – F) Serial MRI in Nf1fl/fl;DhhCre mice given vehicle (A – C) versus 10 mg/kg PD032901 (D – F). MRI was conducted on 5 month-old pre-treated mice (A,D), at treatment onset (B,E – Day 0; 7 months old), and at the end of treatment (C,F – Day 60; 9 months old). Images show representative tumor-bearing mice given vehicle control (A – C) or PD-0325901 (D – F). Note the reduction in size and intensity of bright bilateral neurofibromas treated with PD-0325901. (G) Volumetric measurements of vehicle-treated or PD-0325901-treated Nf1fl/fl;DhhCre mice indicate a decrease in neurofibroma volume treated with 1.5 mg/kg, 5mg/kg, or 10 mg/kg PD-0325901 for 2 months. The y-axis shows tumor volume in mm$^3$ quantified by measurements of MRI scans. Each bar represents the difference in tumor volume in an individual animal from Day 0 (7 months) to Day 60 (9 months). Mixed Effects Model analysis indicated statistical significance for each dose (p<0.001). (Data from N Ratner, personal communication.)
Figure 3. Molecular mechanism of PD-0325901 in Nf1<sup>fl/fl</sup>;Dhh-Cre neurofibromas and MPNST xenografts. (A) Assessment of proliferation in neurofibromas by quantification of Ki67+ cells. Neurofibromas in Nf1<sup>fl/fl</sup>;Dhh-Cre mice treated with 1.5, 5.0, or 10mg/kg PD-0325901 for 60 days showed a significant (***p<0.001) reduction in the percentage of Ki67+ cells relative to mice treated with control vehicle. (C) Labeling of Ki67+ proliferating cells (green), CNPase+ (red) Schwann cells, and DAPI+ (blue) cell nuclei in Nf1<sup>fl/fl</sup>;Dhh-Cre neurofibromas and MPNST xenografts Scale bar = 50 µm (E) Assessment of vasculature in neurofibromas and MPNSTs by quantification of MECA+ endothelial cells. Number of blood vessels per high powered field was significantly (**)p<0.01) reduced in both neurofibromas.

Neurofibromas are complex tumors, containing not only Schwann cells and vasculature, but also hematopoietic cells including mast cells and macrophages. Recent data from the Ratner lab (Prada, C., et al., Acta Neuropath, 2012, in press) indicate that roughly 30% of neurofibroma cells are macrophages. Based on this finding, it is likely that patient plasma contains growth factors/cytokines that attract these hematopoietic cells to neurofibromas. Such factors could be biomarkers of tumor burden and/or play roles in tumor growth.
Figure 4 Iba1+ macrophages in nerve and neurofibroma. (A) Staining of paraffin sections with anti-Iba1 (brown) to mark macrophages. GEM genetically engineered mouse model. (B) Quantification of Iba1+ macrophages per high-powered field (hpf) (*p=0.001). Averages from individual mice are shown as individual dots. (C) Staining of Dhh-Cre; Nf1fl/fl sciatic nerve sections with anti-Iba1 to mark macrophages (red) and with anti-GFP to mark Schwann cells (green). (D) M2 macrophages are rare in Nf1-deficient nerves and tumors. Iba1 (brown) and CD163 (purple) in paraffin sections. Green arrowheads show rare double-labeled cells. In all other cases, cells are single labeled. (E) Staining of human plexiform neurofibroma (PNF) and malignant peripheral nerve sheath tumor (MPNST) paraffin sections with anti-Iba1 (brown) to mark macrophages. (F) Average numbers of Iba1+ cells in human neurofibroma and MPNST. (G) FACS shows populations of CD11b cells (macrophages) isolated from human neurofibromas after in vitro culture; table presents quantification. Scale bar in Fig. 1A 50 μm
Human Trials with PD-0325901

A pilot study in advanced solid tumor patients (adults) evaluated PD-0325901 administered orally at 20 mg twice daily (BID) for 21 consecutive days followed by 7 days of no treatment (n=15 patients), and later at 15 mg BID for 21 consecutive days followed by 7 days of no treatment (n=4 patients) when the initial dose was not tolerated well. The study was terminated early because of an unexpected high incidence of musculoskeletal and neurological adverse events, including gait disturbance, memory impairment, confusion, mental status changes, and mild to moderate visual disturbances. Other common toxicities were diarrhea, rash, fatigue, and nausea. One patient achieved a confirmed complete response and five patients had stable disease.

A Phase 1 trial of PD-0325901 was conducted in 66 patients with advanced cancer to evaluate different doses and dosing schedules. They found that twice a day dosing sustained target suppression more completely than did once daily dosing. Common adverse events were rash, diarrhea, fatigue, nausea, and visual disturbances including retinal vein occlusion (RVO; n = 3). Acute neurotoxicity (visual disturbance, balance, and gait disorders) was common in patients receiving ≥ 15 mg BID, regardless of schedule. The maximum tolerated dose, 15 mg BID continuously, was associated with late-onset RVO outside the dose-limiting toxicity window. An alternative dose and schedule, 10 mg BID 5 days on/2 days off, was therefore expanded; one RVO event occurred. In contrast to the neurotoxic effects observed, all episodes of RVO presented quite late, after 13, 15, and 36 weeks of therapy. A retrospective analysis of relevant visual episodes found predisposing factors for retinopathy (hypertension, diabetes, hypercholesterolemia, and glaucoma) in all patients with RVO but no correlation with cumulative PD-0325901 dose. No patients on a 3 week on/1 week off dosing regimen developed RVO. Finally, they determined that doses ≥ 2 mg bid, which achieved the plasma levels consistent with target inhibition in xenograft mouse models, caused ≥60% suppression of pERK signaling in melanoma tissue from patients.

An open-label, phase II study of PD-0325901 evaluated 15 mg bid given intermittently (3 weeks on/1 week off) to 13 patients with advanced non-small cell lung cancer. Of 13 patients treated, three discontinued due to adverse events (blurred vision, fatigue, and hallucinations, respectively). The study was then altered to 5 days on/2 days off for 3 weeks, followed by 1 week off and another 21 patients were enrolled. Main toxicities included diarrhea, fatigue, rash, vomiting, nausea, and reversible visual disturbances. There were no objective responses. Seven patients had stable disease. Neither phase I nor II PD-0325901 trials have been conducted in children.

Based on these data, on the presence of the activated pathway in patients with NF1, and on the availability of a targeted inhibitor, we propose a Phase 2 study of the MEK inhibitor PD-0325901 initially limited to older adolescents and adults with NF1 and plexiform neurofibromas. Development of RVO seems to be avoidable with a 3 week on/1 week off schedule. In addition, toxicity is minimal when patients are given ≤ 5 mg bid. Finally, because murine trials show similar efficacy at the low dose of 1.5 mg/kg as at 10 mg/kg, we propose a low dose of PD-0325901 at 2 mg/m2 po bid (with a max dose of 4 mg bid) and a 3 week on/1 week off schedule.
2.3 Pharmacokinetics and Dosing of PD-0325901

A major product resulting from metabolism of PD-0325901 is the carboxylic acid metabolite, which showed comparable efficacy to the parent compound when assayed against purified MEK1 but was significantly less effective at reducing ERK phosphorylation in tumor cells. Assays for measuring both PD-0325901 and its metabolite are well established. In this study, we will obtain pK data on consenting participants and relate this to pD profiles.

2.4 Overview of Proposed Study

This phase II open label study will evaluate adolescents (≥ 16 years of age) and adults with neurofibromatosis type-1 (NF1) and plexiform neurofibromas treated with the MEK inhibitor PD-0325901. The primary aim of the study will be to assess quantitative radiographic response in a target lesion. Subjects will receive PD-0325901 by mouth on a bid dosing schedule of 2 mg/m²/dose with a maximum dose of 4 mg bid. Each course is 4 weeks duration, and subjects will receive drug on a 3 week on/1 week off schedule. Subjects may receive additional courses beyond course 8 only if there is at least 15% reduction in volume of the target tumor. Subjects who have a 20% or greater reduction in target tumor volume at the end of 12 courses can continue on therapy for up to an additional year (maximum of 24 total courses). However, subjects who do not achieve at least 15% reduction in volume of the target tumor after 8 courses (~8 months) will be considered treatment failures and taken off study.

Subjects will have retinal screening performed before starting PD-0325901 and regularly while on study drug. Patients with glaucoma, intraocular pressure >21 mmHg, or any other significant abnormality (excluding chronic, stable ophthalmological findings secondary to Optic Pathway Glioma) on ophthalmic examination (performed by an ophthalmologist) will not be eligible. Patients who have received radiation or cytotoxic therapy within 4 weeks of study entry and patients who have received radiation to the orbit at any time previously, will not be eligible for the study. Patients with other concurrent severe and/or uncontrolled medical disease will also be excluded. In addition, pregnant women will not be eligible for enrollment and subjects of reproductive age will be required to practice birth control while on treatment.

Subjects entered on the trial will be carefully monitored for the development of PD-0325901 associated toxicities. Stopping rules for toxicity are outlined in section 8.

In all consenting subjects entered on this trial, a complete pharmacokinetic profile of PD-0325901 after administration will be evaluated during course 1. Involvement with this part of the study will be required.

Consenting subjects with dermal neurofibromas will have punch biopsies of dermal neurofibromas at two time points to determine if the PD-0325901 is affecting the biologic target. Involvement with this part of the study will be optional.

Since plexiform neurofibromas may significantly impact the lives of patients with NF1, this study will evaluate the effects of the disease and treatment with PD-0325901 on the quality of life (QOL) of adolescents and adults. Involvement in this part of the study will
be required. The Pediatric Quality of Life Inventory (PedsQL) Neurofibromatosis Type 1 Module will be used to assess the QOL of subjects (Nutakki et al, personal communication). The PedsQL NF1 Module is a self-reported disease-specific QOL scale developed for adolescents and adults with NF1. It assesses 16 domains of functioning including physical functioning, emotional functioning, social functioning, cognitive functioning, physical appearance, worry, pain and hurt, fatigue, and daily activities. Preliminary data collected on this scale indicates good reliability and validity in adults (Nutakki et al, personal communication). The preliminary data in a small sample of adolescents also looks promising (N. Swigonski, personal communication, October 10, 2012). Data collected from this trial may be used toward validating this instrument since no disease specific QOL measure for NF1 currently exists, but such a tool is critically needed. Pain will be assessed using the Numeric Rating Scale-11 (NRS-11), which is an 11-point self-report scale of pain intensity. In addition, the Brief Pain Inventory Pain Interference Scale is a 7-item self-report questionnaire that measures the extent to which pain interferes with daily functioning. Both of these brief measures have been recommended to assess different aspects of pain in clinical trials. A brief description of the QOL and pain scales being used in this protocol is attached in Appendix VII.

For subjects who respond to PD-0325901 (≥20% tumor volume reduction of target lesion by 12 courses), an MRI scan of the target lesion is requested (but not required) at 4 and 12 months after stopping drug (as long as the subject is still on protocol) in order to determine whether response is maintained post-therapy. These studies will not be requested from subjects who experience disease progression while on study drug.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

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

3.1 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject or the subject’s parent(s) or guardian if the subject is a child, and a signed informed consent and assent will be obtained according to institutional and federal guidelines. Assents will be tailored for those aged 16-17 years (or until the age of majority in the state of the clinical center). In addition, study participants should sign the institution’s HIPAA Consent and the institution’s Release of Medical Information Waiver if not already included in the study consent document.

3.2 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. Documentation of the informed consent for screening will be maintained in the subject’s research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.
Before the subject can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. The completed eligibility checklist should be faxed or scanned and emailed to the NF Operations Center to confirm eligibility prior to subject enrollment.

3.3 Study Enrollment

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

4.0 PATIENT ELIGIBILITY

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

4.1 Inclusion Criteria for all subjects:

4.1.1 All subjects must have EITHER the clinical diagnosis of NF1 using the NIH Consensus Conference criteria (see Appendix III), OR have a constitutional NF1 mutation documented in a CLIA/CAP certified lab.

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

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

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

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

4.1.4. **Age:** Subjects must be ≥ 16 years of age at the time of study entry.

4.1.5. **Durable Power of Attorney:** Adults who are unable to provide informed consent will NOT be enrolled on this study.

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

4.1.7. **Prior Therapy**
Subjects are only eligible if complete resection of a plexiform neurofibroma with acceptable morbidity is not feasible, or if a subject with surgical option refuses surgery.

Subjects 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 evaluable by volumetric analysis (see section 4.1.3).

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

a. **Myelosuppressive chemotherapy:** Must not have received within 4 weeks of entry onto this study.

b. **Hematopoietic growth factors:** At least 7 days since the completion of therapy with a growth factor that supports platelet, red or white cell number or function.

c. **Biologic (anti-neoplastic agent):** At least 14 days since the completion of therapy with a biologic agent. For agents that have known adverse events occurring beyond 14 days after administration, this period must be extended beyond the time during which adverse events are known to occur. These subjects must be discussed with the Study Chair on a case-by-case basis.

d. **Investigational Drugs:** Subjects must not have received an investigational drug within 4 weeks.

e. **Steroids:** Subjects with endocrine deficiencies are allowed to receive physiologic or stress doses of steroids if necessary.

f. **XRT:** ≥ 6 months from involved field radiation to index plexiform neurofibroma(s);
≥ 6 weeks must have elapsed if subject has received radiation to areas outside index plexiform neurofibroma(s). Subjects who have received radiation to the orbit at any time are excluded.

g. Surgery: At least 2 weeks since undergoing any major surgery and must be recovered from effects of surgery.

4.1.8. Organ Function Requirements

4.1.8.1. Adequate Bone Marrow Function Defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 1500/µL
- Platelet count ≥ 100,000/µL
- Hemoglobin ≥ 10.0 gm/dL

4.1.8.2. Adequate Renal Function Defined as: maximum serum creatinine 1.5 mg/dL OR a creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m²

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

4.2 Exclusion Criteria

4.2.1 Exclusion Criteria
- Chronic treatment with systemic steroids or another immunosuppressive agent. Subjects with endocrine deficiencies are allowed to receive physiologic or stress doses of steroids if necessary.
- Evidence of an active optic glioma or other low-grade glioma, requiring treatment with chemotherapy or radiation therapy. Subjects not requiring treatment are eligible for this protocol.
- Patients with malignant glioma, malignant peripheral nerve sheath tumor, or other malignancy requiring treatment in the last 12 months.
- Subjects who have received radiation to the orbit at any time previously
- Subjects with glaucoma, intraocular pressure >21 mmHg, or any other significant abnormality on ophthalmic examination (performed by an ophthalmologist). Ophthalmological findings secondary to long-standing Optic Pathway Glioma such as optic nerve pallor or strabismus will NOT be considered significant for the purposes of the study.
- Tumor not able to be reliably evaluated by volumetric analysis.
- Other concurrent severe and/or uncontrolled medical disease, which could compromise participation in the study (e.g. uncontrolled diabetes, uncontrolled hypertension, severe infection, severe malnutrition, chronic liver or renal disease, active upper GI tract ulceration, congestive heart failure, etc.)
- Subjects who have an uncontrolled infection.
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of PD-0325901 (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).
- Subjects unable to swallow capsules whole, as study drug may not be crushed or opened.
- Women who are pregnant or breast feeding.
- Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method during the period they are receiving the study drug and for 3 months thereafter. Abstinence is an acceptable method of birth control. Women of childbearing potential will be given a pregnancy test within 7 days prior to administration of PD-0325901 and must have a negative urine or serum pregnancy test.
- History of noncompliance to medical regimens
- Subjects unwilling to or unable to comply with the protocol, or who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study
- Prior treatment with a MEK inhibitor of any kind

5.0 REQUIRED DATA

IRB Approvals

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

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

Amendments and Consents

The PI from each participating institution will provide the NF Consortium Operations Center with a copy of IRB approval of all amendments to the protocol or consent. The NF Consortium Operations Center will provide these institutional reviews to the USAMRMC ORP HRPO.

As this trial receives funding by the US Army, substantive amendments to the research protocol and any amendments that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation and site distribution. The USAMRMC ORP HRPO defines a substantive amendment as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.
Data Collection and Toxicity Reporting

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

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

Cincinnati Children’s Hospital Medical Center will receive pharmacokinetic and pharmacodynamic samples together with completed worksheets.

Upon analysis of these studies, results will be transmitted to the NF Consortium Operations Center for entry into the study databases.

Representatives from the FDA and the U.S. Army Medical Research and Material Command will have access to the data and research records as required.

Julia Glade Bender, M. will serve as the medical monitor. She will serve as a patient advocate and is independent of the clinical study team. She will oversee the progress of the protocol, especially issues of individual subject/patient management and safety. The medical monitor is required to review all unanticipated problems involving risks to subjects or others, including all serious and unexpected adverse events associated with the protocol as defined in Section 10.0. She will be automatically notified by the data entry system as soon as any SAE is entered into the study system. The monitor provides an unbiased written report of the event and may request additional information if needed for her determination.

Handling of Research Samples

This study is conducted at NF Consortium Sites and coordinated by the NF Consortium Operations Center. Sample labeling, collection and initial processing will be conducted as outlined in the study Section 9, as well as in Appendix VI. Blood samples obtained for pharmacokinetic and pharmacodynamic studies and skin samples for pharmacodynamic studies will be sent to Cincinnati Children’s Hospital Medical Center for analysis. Samples will be stored in designated monitored freezers and will be identified by the protocol specific subject ID number. Once analyzed for the studies outlined in this protocol, any remaining samples will be stored by the Cincinnati Children’s Hospital until the study is complete and the manuscript describing the study has been accepted for publication. Any use of samples not outlined in Section 9 or Appendix VI will require Study Leadership approval and prospective IRB review and approval. The study will remain open and status reported to the IRB until all samples have been analyzed, reported or destroyed. Unintentional loss or destruction of any samples will be reported to the IRB as part of annual continuing reviews. MRI studies of PN will be obtained as described in Appendix IV and will be sent on CD to the NCI POB. MRI studies will be loaded on one of three Sun Workstations, which are password protected and allow access only to Drs. Dombi, Widemann, or associate investigators on the trial. CDs will be stored in locked filing cabinets. Data results will be electronically submitted to the Operations Center for curation in the study database.
Data and Center Audits

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

All unexpected and serious adverse events will be forwarded to the Medical Monitor, the Study PI and the USAMRMC ORP HRPO by the NF Consortium Operations Center as defined in Section 10.0.

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

5.1 Tests and Observations

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

5.2 Records to be Kept

Subject Registration and Case Report Forms

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

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

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

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

5.3.2 It is the responsibility of the NF Operations Center to assure the quality of data for this study in partnership with the study investigators. This role extends from protocol development to generation of the final study database.

6.0 TREATMENT PROGRAM

6.1 Agent Information/ PD-0325901

6.1.1 Source and Pharmacology:

Absorption
Absorption of PD-0325901 following oral administration of a single dose is moderate to high with an absolute bioavailability of 29.5% in rats, 103% in dogs, and 43.7% in monkeys.

In humans, the plasma pharmacokinetics of PD-0325901 was characterized by rapid absorption, with peak concentrations occurring within 1 to 2 hours of dosing, generally dose-proportional changes in exposures, and an average elimination half-life of 8.6 hours (range 5 to 18 hours across dosing cohorts). The plasma half-life of the carboxylic acid metabolite PD-0315209 was longer than that for the parent.

Food effects
There was minimal effect of food on PD-0325901 pharmacokinetics. Food appeared to reduce PD-0325901 peak plasma concentrations, but the effect on AUC was variable.

Distribution
There was no apparent accumulation of PD-0325901 in plasma following 13 weeks of dosing to rats and dogs.

Plasma protein binding for \(^{14}\text{C}\)PD-0325901 was high with unbound fractions of \(\leq 0.0129\) (mouse), \(\leq 0.0328\) (rat), \(\leq 0.00948\) (dog), \(\leq 0.00905\) (monkey), \(\leq 0.00254\) (human).

PD-0325901 showed a marked preferential distribution to plasma over red blood cells. Following oral administration to Long Evans rats, \(^{14}\text{C}\)PD-0325901 distributed extensively to tissues, with concentrations in most tissues lower than that in blood; distribution of radio-equivalents in brain demonstrated distinct regional localization with highest levels in striatum, hippocampus, and olfactory bulb. Drug equivalents were not retained in pigmented tissues.

Metabolism
In vitro metabolism of \(^{14}\text{C}\)PD-0325901 involves glucuronidation and oxidation of parent compound. A carboxylic acid metabolite (PD-0315209, M15) was found both in vitro and in vivo (rats, dogs, and monkeys). In rats, biliary excretion is the major route of elimination for the absorbed compound and/or its metabolites.
In vitro studies using pooled human liver microsomes demonstrated low potential of PD-0325901 to inhibit activities of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 based on IC50 values relative to the plasma concentration achieved in humans.

**Excretion**


### 6.1.2 Formulation and Stability

The dosage form is a hard gelatin capsule. The capsule shell is composed of gelatin, titanium dioxide, and black iron oxide. The active composition consists of PD-0325901 and preceded ingredients. The capsules will be packaged in appropriate packaging material and storage conditions.

**Tablet size:** 1mg

**Molecular Weight:** 482.19 g/mol

**Chemical Structure:**

![Chemical Structure Diagram]

**CAS Name:** N-[(2R)-2,3-dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-benzamide

**Systematic (IUPAC) Name:** N-((R)-2,3-dihydroxypropoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

**Molecular Formula:** C₁₆H₁₄N₂O₄F₃I

**Physical Description:** White to tan or pink powder

### 6.1.4 Supplier

Pfizer
235 East 42nd Street
New York, NY 10017
1-212-733-2323

### 6.1.5 Toxicities
The primary PD-0325901 toxicities in nonclinical studies are to the GI tract (rat, dog, rabbit, and monkey), skin (rat, dog, and monkey), cornea (rat), CNS (dog), liver (rat), gallbladder (monkey), bone (rat), and systemic mineralization (rat). Systemic mineralization in the rat was associated with dysregulation of calcium and phosphorus homeostasis. Injury to the mucosa of the GI tract was the dose-limiting toxicity in non-rodents. Results of the safety pharmacology studies were generally unremarkable. PD-0325901 was not mutagenic in bacteria or clastogenic in vitro or in vivo.

As of 20 June 2012 (data cut-off date), 3 studies evaluating the safety, efficacy, and/or PK of PD-0325901 had been undertaken. Study A4581001 was a Phase 1/2 study in cancer patients, with 79 patients dosed (66 in Phase 1 and 13 in Phase 2). Study A4581002 was a Phase 2 study in patients having advanced NSCLC (N = 13). In addition, a formal food effect study in healthy subjects (N = 23) evaluated the effect of food on plasma pharmacokinetics of PD-0325901. Doses have been administered on an intermittent (i.e. 3 weeks on/1 week off) or continuous daily dosing schedule. Frequently reported treatment-related adverse events have included diarrhea, acneiform skin rash, edema, visual disturbances (consisting of blurred vision, reduced acuity, halos, floaters, colored spots or flashes of light), nausea, and fatigue. As of 20 June 2012, two patients on the Phase 1 study were diagnosed with significant findings on eye examinations: 1 with a Grade 3 eye disorder, 1 with a Grade 3 retinal vein occlusion. There were also 6 patients with Grade 2 visual adverse events including 1 case of retinal vein occlusion, 1 case of optic neuropathy and 1 case of retinal hemorrhage. None of the patients on the 15-20 mg bid intermittent dosing Phase 2 part of the study had greater than a Grade 1 visual adverse event.

Among 13 subjects enrolled on a 15 mg bid 3 weeks on/1 week off schedule (Schedule 1-see Table 2), the most frequently reported treatment-related adverse events (AEs) were gastrointestinal disorders (11 subjects, 84.6%), including diarrhea (7 subjects, 53.8%), nausea and vomiting (each in 6 subjects, 46.2%), and dry mouth (2 subjects, 15.4%). Seven of 13 subjects (53.8%) experienced at least one Grade 3, treatment-related AE according to the CTCAE criteria. No subjects experienced treatment-related Grade 4 or Grade 5 AEs. Treatment-related Grade 3 AEs included inappropriate antidiuretic hormone secretion, diarrhea, pneumonia, hypocalcemia, confusional state, hallucination, dyspnea, lung infiltration, and rash, each in 1 subject (7.7%).

Among 21 subjects enrolled on a 15 mg bid 5 days on/2 days off for 3 weeks followed by 1 week off schedule, the most frequently reported AEs were also gastrointestinal disorders, which occurred in all subjects (n = 21, 100%). These AEs included diarrhea (16 subjects, 76.2%), vomiting (7 subjects, 33.3%), nausea (6 subjects, 28.6%), constipation (4 subjects, 19.0%), and abdominal pain, abdominal pain (upper), and dry mouth, each experienced by 3 subjects (14.3%). One subject (4.8%) experienced dyspepsia during this study. 6 of 21 subjects (28.6%) experienced at least one treatment-related Grade 3 AE, and 3 subjects (14.3%) experienced at least one treatment-related Grade 4 AE. Treatment-related Grade 3 AEs included atrial flutter, diarrhea, hiatus hernia, bronchitis, alanine aminotransferase increased, aspartate aminotransferase increased, syncope, confusional state, dyspnea, hypoxia, and hypotension, each in 1 subject (4.8%); and fatigue and dehydration in 2 subjects (9.5%). Treatment-related Grade 4 AEs included diarrhea, dehydration, pneumonia aspiration, pulmonary embolism, pulmonary hypertension, and deep vein thrombosis, each in 1 subject (4.8%).
**Table 1** Adverse drug reactions occurring in patients receiving PD-0325901 in Phase 1/2 Studies*

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Disorders</td>
<td>Retinal vein occlusion, retinal hemorrhage, optic ischemic neuropathy</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, paresthesia</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle disorder (neck drop), muscular weakness</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Confusional state</td>
</tr>
</tbody>
</table>

*Table 7-1 in PD-0325901 Investigator Brochure September 2012

**Table 2:** Study A4581002 (Phase 2) Treatment-related Adverse Events Experienced by ≥ 10% of Subjects on Either Dosing Schedule (Maximum Grade, All Cycles)*

<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>Schedule 1 N (%)</th>
<th>Schedule 2 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td>9 (69.2)</td>
<td>7 (33.3)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>5 (38.5)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10 (76.9)</td>
<td>21 (100)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0.0)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (53.8)</td>
<td>16 (76.2)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2 (15.4)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2 (15.4)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (38.5)</td>
<td>6 (28.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (38.5)</td>
<td>7 (33.3)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face edema</td>
<td>2 (15.4)</td>
<td>4 (19.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (30.8)</td>
<td>10 (47.6)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>2 (15.4)</td>
<td>4 (19.0)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>1 (7.7)</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (30.8)</td>
<td>7 (33.3)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusional state</td>
<td>6 (46.2)</td>
<td>6 (28.6)</td>
</tr>
<tr>
<td>Hallucination</td>
<td>4 (30.8)</td>
<td>4 (19.0)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (15.4)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3 (23.1)</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis acneform</td>
<td>7 (53.8)</td>
<td>15 (71.4)</td>
</tr>
</tbody>
</table>

*Table 7-1 in PD-0325901 Investigator Brochure September 2012*
6.2 Treatment Overview

This phase II study will evaluate adolescents (≥ 16 years of age) and adults with neurofibromatosis type-1 (NF1) and plexiform neurofibromas treated with the MEK inhibitor PD-0325901. The primary aim of the study will be radiographic response. Subjects will receive PD-0325901 by mouth on a bid dosing schedule of 2 mg/m²/dose with a maximum dose of 4 mg bid. Each course is 4 weeks duration with a 3 week on/1 week off schedule. Subjects may receive additional courses beyond course 8 only if there is at least 15% reduction in volume of the target tumor. Subjects who have a 20% or greater reduction in target tumor volume at the end of 12 courses can continue on therapy for up to an additional year (maximum of 24 total courses). Subjects who have not had at least 15% reduction in volume of the target tumor by the end of the 8th course will be removed from protocol therapy. Subjects who have not had at least 20% tumor shrinkage by volumetric analysis by the end of the 12th course will be removed from protocol therapy.

**PD-0325901 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 the drug.**

Subjects or their parents/guardians will keep a diary to document each dose of PD-0325901 and potential side effects. The subject diary should be reviewed with the subject's family at each required clinical study evaluation. The subjects should use the diary in Appendix V or a suitable document developed by the local institution. In addition, leftover study medication should be collected at each on study evaluation, and drug should be accounted for at this time (Appendix V). Food did not seem to have a significant effect on PD-0325901 pK. **Medication may be taken either with or without food.**

PD-0325901 is an antineoplastic agent and should be handled and administered with care. **Inhalation of powder or contact with skin and mucous membranes, especially those of the eyes, must be avoided.** Should accidental eye contact occur; copious irrigation with water should be instituted immediately followed by prompt ophthalmologic consultation. **Should accidental skin contact occur; the exposed area should be irrigated immediately with copious amounts of water for at least 15 minutes.**

**PD-0325901 capsules must be swallowed whole.** Subjects should not open or crush them for any reason.

Starting Dosing Nomogram

<table>
<thead>
<tr>
<th>BSA m²</th>
<th>≥0.9-1.24</th>
<th>1.25-1.74</th>
<th>≥1.75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose (mg)</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Tablets: 1 mg

PD-0325901 will be held for subjects who experience toxicity as per section 8.
6.3 Criteria for Starting Subsequent Courses

Unless the subject has developed toxicity requiring interruption or withdrawal from protocol therapy (see section 8.0), a course may be repeated every 28 days if the subject has at least stable disease and has again met laboratory parameters (when study evaluations are required) as defined in the eligibility section.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

Subjects must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the subject are allowed, including drugs given prophylactically (e.g. antiemetics), with the following exceptions:

- No other investigational therapy should be given to subjects
- No chronic treatment with systemic steroids or another immunosuppressive agent (see section 7.4) with the exception of subjects with endocrine deficiencies who are allowed to received physiologic or stress doses of steroids, if necessary.

Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered.

7.1 Supportive Care

Appropriate antibiotics, blood products, fluids, electrolytes and general supportive care are to be used as necessary. Antiemetics, other than systemic steroids, are allowed. Corticosteroids are permissible as premedication for blood product transfusions, or as treatment for an acute allergic reaction.

7.2 Growth Factors

Growth factors that support platelet or white cell number or function can only be administered for culture proven bacteremia, clinical sepsis, or invasive fungal infection with neutropenia. The Study Chair should be called when growth factors are initiated.

7.3 Surgery

Subjects undergoing surgical procedures should have the study drug held for 2 weeks prior to the procedure, if feasible, and for 2 weeks after. Surgery to a non-target plexiform neurofibroma does not require removal from protocol therapy (i.e. subject can continue on therapy once he/she recovers from surgery, as described above).
7.4 Concomitant Medications

Other than for subjects receiving physiologic replacement doses of steroids due to endocrine deficiencies, corticosteroid therapy is ONLY permissible as premedication for blood product transfusions, or as treatment for an acute allergic reaction.

8.0 MODIFICATIONS FOR ADVERSE EVENTS

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

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

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

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (v4.0).

Any subject experiencing a toxicity (as described below in sections 8.1 and 8.2) that is possibly, probably, or definitely related to PD-0325901 should have the drug held until the toxicity has completely resolved. In addition, the site should notify the study chair (brian.weiss@cchmc.org) and NF Operations Center immediately of any DLT.

8.1 Hematological Toxicity

8.1.1 During All Courses:

If a subject experiences, at least possibly related to the investigational drug, EITHER ≥ grade 3 neutropenia (ANC < 1,000), anemia (Hb < 8), or thrombocytopenia (platelets < 50,000) OR clinically significant grade 2 neutropenia, anemia, or thrombocytopenia that does not resolve within 72 hours after initiation of maximal medical management, the drug will be withheld. Subjects should continue to be seen and have complete blood counts obtained every 1-2 weeks until recovery (≤ Grade 1) is documented. Upon resolution of the toxicity (≤ Grade 1), PD-0325901 may be restarted using the following nomogram:

<table>
<thead>
<tr>
<th>Dose reduction</th>
<th>Percent decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose (mg)</td>
<td>Reduced dose (mg)</td>
</tr>
<tr>
<td>2 BID</td>
<td>2 mg AM; 1 mg PM</td>
</tr>
<tr>
<td>3 BID</td>
<td>2 mg BID</td>
</tr>
<tr>
<td>4 BID</td>
<td>3 mg BID</td>
</tr>
</tbody>
</table>
Subjects will not have the dose re-escalated in subsequent cycles. If the subject has hematological toxicity (as explained above) at the reduced dose, then they should be removed from protocol therapy.

8.2 Non-Hematological Toxicity

8.2.1 During All Courses

If a subject experiences, at least possibly related to the investigational drug, EITHER ≥ Grade 3 non-hematological toxicity OR clinically significant grade 2 non-hematological toxicity that does not resolve within 72 hours after initiation of maximal medical management, the study drug will be withheld. Subjects should continue to be seen and have appropriate labs/observations obtained every 1-2 weeks until recovery (≤ Grade 1) is documented. Upon resolution of the toxicity (≤ Grade 1), PD-0325901 may be restarted using the nomogram in 8.1.1. Subjects will not have the dose re-escalated in subsequent cycles. If the subject has non-hematological toxicity at the reduced dose, then they should be removed from protocol therapy.

8.3 Toxicities Requiring Removal From Protocol Therapy

Any toxicity defined in section 8.1 or 8.2 that is at least possibly related to study medication that recurs on a reduced dose of PD-0325901. No subject may be dose-reduced more than once.

Any ≥ Grade 3 toxicity that is at least possibly due to study drug that does not resolve to ≤ Grade 1 within 2 weeks requires removal from protocol therapy.

Development of retinal vein occlusion will also require removal from protocol therapy.

Development of glaucoma, intraocular pressure >21 mmHg, or any other significant abnormality on ophthalmic examination (performed by an ophthalmologist) while on study treatment will require removal from protocol therapy. Ophthalmological findings secondary to long-standing Optic Pathway Glioma such as optic nerve pallor or strabismus will NOT be considered significant for the purposes of the study.

The study chair or co-chair should be contacted for any questions regarding toxicity.

9.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Pre and on study evaluations are described in Appendix I.

9.1 Required Clinical, Laboratory and Disease Evaluation

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

9.2 History and physical examination and vital signs

Physical examination will be performed prior to entry, at the end of course 1 (+1 week); post course 2 (+1 week), 3 (+1 week), 4 (+1 week), 8 (+2 weeks), 12 (+2 weeks), 18 (+2 weeks) and 24 (+2 weeks). In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above. The exam must comprise a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system). Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded.

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight.

9.3 Retinal Exam

Subjects will have a retinal exam consisting of slit lamp examination with binocular indirect ophthalmoscopy at baseline and after the first and second course (+2 weeks), then after every two courses for the first year (+2 weeks), then after every third course for the second year (+2 weeks) while on study drug. Subjects with evidence of disease (retinal vein occlusion) will need full evaluation (such as fluorescein angiography and/or optical coherence tomography). In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above.

9.4 Hematology

CBC must include hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential. CBC must be performed within two weeks prior to entry on trial, at the end of courses 1 +1 week, 2 +1 week, 3 +1 week, 4 +1 week, 8 +2 weeks, 12 +2 weeks, 18 +2 weeks and 24 +2 weeks. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above.

9.5 Blood chemistry

Blood chemistry must include sodium, potassium, chloride, bicarbonate, calcium, phosphorous, glucose, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, and CPK. Blood chemistries should be drawn within two weeks prior to study entry, at the end of courses 1 ±1 week, 2 ±1 week, 3 ±1 week, 4 ±1 week, 8 ±2 weeks, 12 ±2 weeks, 18 ±2 weeks and 24 ±2 weeks. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above.

9.6 Serum or Urine Pregnancy Test

Standard pregnancy tests will be given to all females of childbearing age within 7 days prior to starting treatment medication. In addition, tests will be administered at the end of course 4 ±2 weeks, 8 ±2 weeks, 12 ±2 weeks, 18 ±2 weeks, and 24 ±2 weeks to ensure that females are not
pregnant while on the study medication. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above.

9.7 MRI for volumetric analysis of plexiform neurofibroma

Evaluate the plexiform neurofibromas(s) by MRI within 4 weeks prior to course 1 and after courses 4 ±2 weeks, 8 ±2 weeks, 12 ±2 weeks, 18 ±2 weeks, and 24 ±2 weeks while on study and at end of study ±2 weeks. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above. To evaluate the durability of response, subjects who responded while on treatment (>20% target lesion shrinkage by 12 cycles), will be recommended but not required to have a follow-up MRI scan at approximately 4 months and 12 months following completion of therapy. If a subject starts another tumor-directed therapy during the one year follow-up time, then they are off-study (and no further MRIs requested).

The imaging protocol outlined in Appendix IV will be used each time MRI examinations are performed to assess progression or response. In subjects with clinical suspicion of disease progression, MRI analysis should be performed earlier using the protocol outlined in Appendix IV. If because of unforeseen reasons, an MRI time window is passed, but not yet at the time of the opening of the subsequent window, the MRI should be performed and the protocol violation noted.

9.8 PD-0325901 diary

A diary will be kept by the subject and/or proxy (see Appendix V). A document developed by the local institution can be used as a substitute for Appendix V. The diary will be reviewed with the treating physician at the history/physical visit after completion of courses 1±1 week, 2 ±1 week, 3 ±1 week, 4 ±1 week, 8 ±2 weeks, 12 ±2 weeks, 18 ±2 weeks and 24 ±2 weeks. In addition, at the end of treatment ±2 weeks if this is not encompassed in the times above.

9.9 Pharmacokinetic profile of PD-0325901 (Required)

A complete pharmacokinetic profile will be obtained on all subjects. Involvement with this part of the study will be required. Plasma pharmacokinetics will be studied on day 1 of course 1.

Blood samples (3 ml) will be drawn for the pharmacokinetic profile before, and during PD-0325901 therapy on day 1 of course 1 at the following times: before the Day 1 morning dose (pre-dose), and at 30 min, 1 hr, 2 hrs, 3 hrs, 4 hrs, 6 hrs, 8 hrs, and 10-12 hrs after the Day 1 morning dose of PD-0325901, prior to administration of the evening dose.

There will be a total of 9 samples drawn. Samples are stable for at least 8 months at -80 °C. Drug analysis: PD-0325901 concentrations will be analyzed in plasma by Advion Laboratories. Specimens will be maintained by Advion Laboratories until the end of the study, then remaining specimens will be destroyed. Procedures for obtaining, processing, and shipment of blood samples are outlined in Appendix VI.
9.10 Pharmacodynamic Analysis (Optional)

As a marker of the effects of PD-0325901, ERK phosphorylation will be measured in dermal neurofibromas using methods described by Ratner et al. Dermal neurofibromas are nerve tumors associated with dermal and epidermal nerves. Many NF1 patients develop dermal neurofibromas around the time of puberty. The cellular composition of dermal neurofibromas is indistinguishable from that of plexiform neurofibromas; therefore, dermal neurofibromas may be useful as an accessible surrogate tissue for analysis of therapeutic efficacy.

Three millimeter punch biopsies of 1-2 dermal neurofibromas (2 dermal neurofibromas per timepoint is preferred) will be made prior to initiating therapy with PD-0325901 and during week 3 of course 1 at least 30 min but no more than 6 hours after taking the morning dose. At each time point, one tumor will be fixed in formalin for paraffin embedding, and shipped on wet ice. At the same time, one tumor will be frozen in liquid nitrogen and stored at -80°C and shipped separately, on dry ice. If only one tumor is biopsied, the sample should be placed in formalin. Time of tumor removal after drug dose will be noted. Any remaining specimens will be stored for future research with subject consent. Details regarding sample processing and shipment are provided in Appendix VI.

9.11 Plasma Cytokines and Growth Factors (Optional)

Procedure: 10 ml blood will be drawn into EDTA tubes before treatment initiation, during week 3 of course 1 and during week 3 of course 4. The sample will be collected at least 30 min but no more than 6 hours after taking the morning dose. Any remaining specimens will be stored for future research with subject consent.

9.12 Maximum blood volumes for pharmacokinetic and pharmacodynamic studies

Institutional guidelines will be followed for maximum blood volumes for research samples. The table below provides details regarding blood volumes obtained for research studies during course 1. All subjects should have blood samples obtained for pharmacokinetic analysis.

<table>
<thead>
<tr>
<th>Type of test</th>
<th>Volume per sample (ml)</th>
<th>Number of samples (volume for all samples, ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>3</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Plasma Cytokine Measurement</td>
<td>10</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Total volume for research samples course 1</td>
<td></td>
<td>12 (57)</td>
</tr>
</tbody>
</table>

9.13 Quality of Life and Pain Evaluations (Required)

This study will evaluate quality of life, pain intensity, and pain interference in subjects during treatment with PD-0325901. The Pediatric Quality of Life Inventory (PedsQL) NF1 Module (Adult and Teen self-report forms) will be used to assess disease-specific QOL. Pain intensity will be assessed by self-report with the Numeric Rating Scale-11 (NRS-11) and pain interference will be measured by the Brief Pain Inventory (BPI) Pain Interference Scale. The following table summarizes the quality of life and pain questionnaires to be completed by age of the subjects.
Quality of Life and Pain Questionnaires to be Completed by Age of Subject at Study Entry

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Age of Subject (years) at Study Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16-20*</td>
</tr>
<tr>
<td></td>
<td>21+*</td>
</tr>
<tr>
<td>Disease Specific QOL</td>
<td></td>
</tr>
<tr>
<td><strong>Subject:</strong> PedsQL NF1 Module-Teen or Peds QL NF1 Module-Adult</td>
<td>X</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td><strong>Subject:</strong> NRS-11 Pain Intensity and BPI-Pain Interference</td>
<td>X</td>
</tr>
</tbody>
</table>

Background Information Forms to be Completed by the Subject

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Age of Subject (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background Information</strong></td>
<td>16+**</td>
</tr>
<tr>
<td><strong>All subjects</strong></td>
<td></td>
</tr>
<tr>
<td>QOL Background Form</td>
<td>X</td>
</tr>
</tbody>
</table>

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

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

To allow for more meaningful analysis of the QOL data, the subject (≥16 years) also will complete a self-report background information form at study entry and each QOL assessment. This form will collect general information such as their level of education, work status, psychiatric diagnoses, and pain medications, as well as the visibility of NF1 tumors and severity of NF1 symptoms.

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

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

10.0 ADVERSE REPORTING REQUIREMENTS

10.1 Definitions

- **Adverse Events**: An adverse event is any new, undesirable medical occurrence or change (worsening) of an existing condition in a subject that occurs during treatment, whether or not considered to be product related. Therefore, adverse events are treatment emergent signs or symptoms. Elective hospitalizations for pretreatment conditions (e.g., elective cosmetic procedures) are not adverse events. Non-clinically significant abnormal laboratory values should not be reported as adverse events; however, any clinical consequences of the abnormality should be reported as adverse events. All adverse events must be noted on the case report forms and submitted to the operations center within 2 weeks of completion of every treatment course.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification (within 24 hours) to the site PI and clinical coordinator, as well as the NF Operations Center. Follow-up of the adverse event, even after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.

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

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

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

10.2 Common Terminology Criteria for Adverse Events (CTCAE)
This study will utilize the CTCAE of the National Cancer Institute for reporting and grading of adverse events. A copy of the current version of the CTCAE version 4.0 can be downloaded from the CTEP home page: http://ctep.cancer.gov/reporting/ctc.html

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

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

The expected adverse events related to administration of PD-0325901 are listed in Section 6.1.5. All other adverse events not attributed to study drug will be considered unexpected. Adverse events attributable to study drug will be reported if the adverse events are at an intensity that is more severe than previously documented or considered significant by the investigator.

10.4 Reporting Procedures for All Adverse Events

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

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

Adverse events will be assessed by the treating investigator for relationship to the study drug (unrelated, unlikely, possible, probable, or definitely related).

10.5 Expedited Reporting Guidelines

**The following adverse events require expedited reporting:**

- All adverse events that are both serious and unexpected per section 6.1.5
- Adverse events that, in the opinion of the treating physician, might influence the benefit-risk
assessment of administration of PD-0325901 as outlined in the protocol

- All grade 5 adverse events
- A serious adverse event that occurs within 30 days of the last dose of the investigational agent
- Expedited AE reporting timelines defined:

  “24 hours; 24 hours – The investigator must initially report the AE within 24 hours (or immediately if the event is fatal or life-threatening) of learning of the event to the Study Chair (brian.weiss@chmc.org) and NF Operations Center followed by a complete written report within 24 hours of the initial 24-hour report.

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

NF Consortium Operations Center
Clinical Research Manager: Vivien Phillips, RN 205-934-5376
Program Director: Karen Cole – Plourde, BS 205-934-5140
Research Compliance Manager: Roy McDonald, MPH 205-975-4075
Direct Email: nfconsortium@uab.edu

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

MedWatch
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178

10.5.1 Pfizer Expedited Reporting Guidelines
- Even though there may not be an associated SAE, exposure to the Pfizer Product during pregnancy and exposure to the Pfizer Product during lactation are reportable.
- The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Pfizer Product through 28 calendar days after the last administration of the Pfizer Product or longer if so specified in the Protocol. In addition, investigators should submit SAEs to Pfizer any time after the administration of the last dose of the Pfizer Product, if the Investigator suspects a causal relationship between the Pfizer Product and the SAE.
- Investigators will assist Pfizer in investigating any SAE and will provide any follow-up information reasonably requested by Pfizer.
- The NF Operations Center will forward any SAE report within 24 hours (or immediately if the event is fatal or life-threatening) of learning of the event to Pfizer followed by a complete written report within 24 hours of the initial 24-hour report.

10.6 Reporting of Protocol Violations/Deviations and Unanticipated Problems

Site reporting to NF Operations Center
Sites will report unanticipated problems and/or protocol deviations that impact subject safety or the scientific integrity of the study to the Operations Center promptly at NFConsortium@uab.edu. Other protocol violations and deviations should be reported to the NF Operations Center annually.
NF Protocol #106 - Version 1.3
07/20/2018

NF Operations Center reporting requirements
The Operations Center will report unanticipated problems that impact subject safety or the
scientific integrity of the study to the USAMRMC ORP HRPO promptly. Unanticipated
problems will also be reported to the protocol team, Medical Monitor, and DSMB.

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

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

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

11.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

11.1 Criteria for Removal from Protocol Therapy

a. Progressive disease (See Section 13)
b. Completion of course 24 of therapy
c. <15% reduction in target tumor volume after course 8 of therapy
d. <20% reduction in target tumor volume after course 12 of therapy
e. Refusal of further protocol therapy by subject/parent/guardian
f. Non-compliance that in the opinion of the investigator does not allow for ongoing
   participation.
g. Physician determines it is not in the subject’s best interest.
h. Patient becomes pregnant
i. Participant is prescribed a non-allowed concomitant medicine during study.
j. Withdrawal of protocol consent
k. Any surgical procedure on a target PN.
l. PD-0325901-related toxicity requiring removal (see Section 8).

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

11.2 Off Study Criteria

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

a) Thirty days after the last dose of PD-0325901 (but note that subjects with ongoing toxicity
should be followed until the toxicity resolves or 30 days, whichever is longer)

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

For all subjects (supercedes “a” or “b”):
c) Death
d) Lost to follow-up
e) Withdrawal of consent for any further data submission.
f) Initiation of subsequent other medical treatment directed towards the plexiform neurofibroma
g) Initiation of medical treatment (e.g. chemotherapy, biologic therapy, radiation therapy) directed towards other NF1-related tumor such as an optic pathway glioma

12.0 STATISTICAL AND ETHICAL CONSIDERATIONS

12.1 Subject Accrual

Subjects of both genders, from all racial and ethnic groups are eligible for this trial if they meet the criteria outlined in Section 4.0. To date, there is no information that suggests differences in drug metabolism or disease response among racial or ethnic groups or between the genders, indicating that results of the trial will be applicable to all groups. 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 subject safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand, and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, age, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

12.2 Statistics and Feasibility

The primary objective of this study is to determine if there is an adequate level of disease responsiveness to PD-0325901 in adolescents and adults with NF1 and inoperable plexiform neurofibromas.

Sample Size

Minimum: 9 evaluable subjects Maximum: 19 evaluable subjects Target: 17 evaluable subjects. To allow for 10% unevaluable subjects, a maximum of 19 subjects will be enrolled. We anticipate enrollment to be completed in 24 months with primary outcome measure defined in 30 months.

The sample size for this trial is based on three primary factors: safety based on risk versus benefit; efficacy of 25% response rate and power of 80% to achieve feasibility if this rate were true. In order to balance these factors, we propose a two stage Simon Optimal Design\(^3\). Two stage designs are designed to provide an overall Type I error that is based on the probability of stopping at the end of Stage 1 plus the conditional probability of rejecting the drug given one passed Stage 1 to get to Stage 2. Thus, the overall Type I error was set at 5% and power at 80%. We assume a null hypothesis success rate of 5% versus a treatment with a 25% response rate.
Stage 1 will consist of 9 subjects to provide evidence of effectiveness and safety. If at least 1 of the 9 subjects achieves a radiographic response (> 20% reduction in tumor volume) the study will be allowed to recruit the total sample size of 17 evaluable subjects. The Stage I boundary is the same 0 of 9. The second stage of the design requires only 3 or more of the 17 subjects to have a positive response. If the null hypothesis is true, there is a 63% chance of terminating after Stage 1. If the probability of success is actually 0.25, there is a 92% chance that 1 or more subjects will exhibit a 20% reduction in tumor volume at Stage 1. Thus, it is expected that the trial will continue with continuous recruitment if the 25% success rate is correct.

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

12.3 Statistical Analysis Plan

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

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

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

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

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

An early stopping rule will be invoked to potentially prevent accrual of subjects onto the study in the event that PD-0325901 is associated with a higher than acceptable rate of dose-limiting toxicity (DLT) requiring removal from study (set at 10% or higher) during the first 2 courses. Toxicity will be continuously monitored. As per the 2nd table below, if at any time >2 of the first 10 subjects or 4 or more of the first 15 total subjects are removed for toxicity as per Section 8.3, then accrual will be stopped until the DSMB reviews safety and efficacy data for the study and recommends termination or despite the DLT (because of the benefit:risk assessment or other reasoning) recommends reopening recruitment.

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

Using these rules and the binomial distribution, the chance of putting the trial on hold and potentially stopping early within the first 10 subjects:
<table>
<thead>
<tr>
<th>True probability of toxicity</th>
<th>Chance of stopping early</th>
</tr>
</thead>
<tbody>
<tr>
<td>.10</td>
<td>7%</td>
</tr>
<tr>
<td>.20</td>
<td>32%</td>
</tr>
<tr>
<td>.25</td>
<td>47%</td>
</tr>
<tr>
<td>.30</td>
<td>62%</td>
</tr>
<tr>
<td>.35</td>
<td>74%</td>
</tr>
<tr>
<td>.40</td>
<td>83%</td>
</tr>
</tbody>
</table>

In addition, any episode of retinal vein occlusion will halt enrollment until the DSMB reviews the case and the study and recommends termination or despite the DLT recommends reopening recruitment.

### 12.4 Definitions of Evaluable

#### 12.4.1 Evaluable for Toxicity

12.4.1.1 Any subject who received ≥ one dose of PD-0325901 and had a ≥ Grade 3 PD-0325901-associated toxicity is evaluable for toxicity.

12.4.1.2 In the absence of a ≥ Grade 3 toxicity, any subject who completed one full course of therapy is evaluable for toxicity.

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

#### 12.4.3 Evaluable for Pharmacokinetics – Any subject who has at least 4 samples drawn for pharmacokinetics is evaluable for pharmacokinetics.

#### 12.4.4 Evaluable for Pharmacodynamics – Any subject who has a dermal neurofibroma biopsy for pharmacodynamics prior to starting therapy plus at least one other dermal neurofibroma biopsy is evaluable for pharmacodynamics.

#### 12.4.5 Evaluable for Plasma Cytokines/Growth Factors – Any subject who has at least one sample drawn for plasma cytokines/growth factors prior to starting therapy plus at least one other sample drawn is evaluable for plasma cytokines/growth factors.

### 13.0 RESPONSE CRITERIA

Response is assessed by the NCI-POB at the time that follow-up 3D-MRI scans are performed (after course 4, 8, 12, and then after completion of every 6 courses thereafter). For the purpose of
determining the level of response (complete, partial, etc.) measurements from the follow-up scans are compared to the target lesion size in the pretreatment MRI scan using 3D data analysis.

Complete Response (CR): A complete resolution of the target plexiform neurofibroma for ≥ 4 weeks

Partial Response (PR): A ≥20% reduction in the volume of the target plexiform neurofibroma lesion for ≥4 weeks.

Stable Disease (SD): A <20% increase, and < 20% decrease in the volume of the target plexiform neurofibroma lesion for ≥4 weeks.

Progressive Disease (PD): A ≥ 20% increase in the volume (by 3D-MRI) of the target plexiform neurofibroma compared to the pretreatment volume.

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. Subjects 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.

Subjects with other evidence of disease progression than outlined above should also be discussed with the Principal Investigator.

14.0 HUMAN SUBJECTS PROTECTION & DATA SAFETY MONITORING PLAN

Rationale for Subject Selection
Neurofibromatosis type 1 is a genetic disorder and the incidence of the disease in the various racial and ethnic groups may vary. This may impact on our ability to recruit sufficient numbers of subjects within each group to this trial. Subject accrual in regards to gender, and racial and ethnic groups is described in Section 4.0. None of these groups are excluded from participation in the trial. Females who are pregnant or breast feeding will not be eligible for entry onto the trial because of the potential risks that PD-0325901 could pose to the fetus or newborn. This trial is designed to determine the activity of PD-0325901 in adolescents and adults with NF1 and inoperable PN and therefore, subjects <18 years old will be entered onto this research trial. Individuals will be enrolled at one of the sites that participate in the NF consortium. Subjects may also be referred from outside centers but treatment will be directed at an NF consortium site.

Participation of Subjects < 18 years of age
The primary endpoint of this trial is to determine whether PD-0325901 can result in tumor shrinkage in adolescents and adults with PN. Therefore adolescents who meet eligibility criteria for this trial will be entered in the study.

Evaluation of benefits and risks/discomforts
The potential benefit from participation in this trial is the stabilization or reduction in the size of the PN, relief of symptoms caused by the PN, and prolongation of life. The primary risk to the subjects from participation in this trial is from PD-0325901 toxicity (Section 6.1.5). Toxicities from PD-0325901 are outlined in Section 6.1.5 and are typically reversible when they occur.
Subjects enrolled on this trial will be carefully monitored for the development of toxicities, and guidelines for discontinuation of drug, and a toxicity stopping rule are in place. Blood samples will be obtained on this trial for required pharmacokinetic and optional pharmacodynamics studies. Samples will be identified by a code number that can be traced to the subject only by contacting the trial coordinating center. However, as the blood samples are linked to the subject’s name, a small risk persists that unauthorized persons could gain access to information. Some testing may eventually reveal information that could result in discrimination with health or life insurance or employment. We believe that these risks are minimal since it is already known that subjects enrolled on the study have neurofibromatosis. All research results will be kept confidential. Results from the pharmacodynamic studies will be considered preliminary and will require further analysis for verification. Therefore, results will not be communicated with the research subjects. Subjects also have the right to withdraw the blood specimens obtained for research purposes at any time.

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

Risk/benefit analysis
The primary objective of this phase II trial is to define the objective response rate of PN treated with PD-0325901, and thus subjects entered on the trial will be treated with therapeutic intent and response to the therapy will be closely monitored. Therefore, this protocol involves greater than minimal risk, but presents the potential for direct benefit to individual subjects. The potential benefit of this treatment with PD-0325901 is that it may stop or slow down the growth of PN, or shrink PN. In addition PD-0325901 may lessen the symptoms, such as pain, that are caused by the tumor. The MRI data in this study will be analyzed by a special approach called “volumetric MRI,” in addition to being read in a standard manner by a radiologist. The volumetric MRI approach will provide more precise measurement of the size of PN, and therefore will give more complete and objective information on which to base any possible future treatment decisions. Volumetric MRI is currently not available on a routine clinical basis.

Consent and assent process and documentation
The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts and benefits, and potential alternative therapies will be carefully explained to the subject and the subject’s parents or guardian if he/she is a child, and a signed informed consent document will be obtained. Consent will be obtained by the site PI or an associate investigator on the trial according to state and institutional guidelines. Age appropriate assent forms for adolescents from 16 through 17 years have been developed for use in this trial. This is a multi-institutional trial, and the NF Operations Center will require evidence of local IRB approval and of USAMRMC ORP HRPO approval of the protocol prior to allowing for accrual of subjects at that institution. This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

Medical Monitor and Data Safety Monitoring Plan
The trial PI and clinical coordinator will review the study progress regularly. Subjects entered on the trial and adverse events will be reviewed to ensure that the study is implemented as outlined in the protocol. Monthly reports will be generated by the NF Consortium to assess completeness of data. There will be monthly phone conferences between the NF Consortium and the Principal Investigator to address QA issues. A Data Safety Monitoring Board has been established for the purpose of ensuring data compliance and regular monitoring of this trial.
Julia Glade Bender, MD will be medical monitor for this study. She is a qualified physician and is not associated with this particular protocol. She will work closely with the Principal Investigator to monitor the participants' treatment while on this study.

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

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

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

There may be more than one medical monitor (e.g., if different skills or experiences are necessary). The monitor may be an ombudsman or a member of the data safety monitoring board. At a minimum, the medical monitor:
- may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research;
- shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor’s report;
- shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

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


APPENDIX I: SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>STUDIES TO BE OBTAINED</th>
<th>Pre-Study*</th>
<th>Course 1</th>
<th>Subsequent courses</th>
<th>Completion of Rx</th>
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<tbody>
<tr>
<td>Informed Consent Assent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility Checklist</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>X</td>
<td>End†</td>
<td>Post course 2, 3, 4, 8, 12, 18, and 24 †</td>
<td>X</td>
</tr>
<tr>
<td>Physical Exam with vital signs (including T, P, RR, BP)</td>
<td>X</td>
<td>End†</td>
<td>Post course 2, 3, 4, 8, 12, 18, and 24 †</td>
<td>X</td>
</tr>
<tr>
<td>Height*, weight, BSA</td>
<td>X</td>
<td>End†</td>
<td>Post course 2, 3, 4, 8, 12, 18, and 24 †</td>
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</tr>
<tr>
<td>Performance Status (see Appendix II)</td>
<td>X</td>
<td>End†</td>
<td>Post course 2, 3, 4, 8, 12, 18, and 24 †</td>
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<tr>
<td>Retinal Exam†</td>
<td>X</td>
<td>End†</td>
<td>Post course 2, 4, 6, 8, 10, 12, 15, 18, 21, 24†</td>
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</tr>
<tr>
<td>PD-0325901 Diary Review</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, differential, platelets</td>
<td>X</td>
<td>End†</td>
<td>Post course 2, 3, 4, 8, 12, 18, and 24 †</td>
<td>X</td>
</tr>
<tr>
<td>Electrolytes including BUN, Creatinine, glucose, blood chemistry including albumin, total protein, alkaline phosphatase, SGOT, SGPT, bilirubin, CPK</td>
<td>X</td>
<td>End†</td>
<td>Post course 2, 3, 4, 8, 12, 18, and 24 †</td>
<td>X</td>
</tr>
<tr>
<td>Urine/Serum Pregnancy*</td>
<td>X</td>
<td></td>
<td>Post course 4, 8, 12, 18, and 24 †</td>
<td>X</td>
</tr>
<tr>
<td>MRI including volumetric analysis</td>
<td>X (within 7 days prior)</td>
<td></td>
<td>Post course 4, 8, 12, 18, 24 †</td>
<td>X†</td>
</tr>
<tr>
<td>Health-related quality of life and pain assessments</td>
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<td></td>
<td>Post course 4, 8, 12, 18, 24 †</td>
<td>X†</td>
</tr>
<tr>
<td>PD-0325901Pharmacokinetics*</td>
<td>X</td>
<td>Day 1</td>
<td></td>
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<tr>
<td>Pharmacodynamic studies</td>
<td>X</td>
<td>Week 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Cytokines</td>
<td>X</td>
<td>Week 3</td>
<td>Week 3 of course 4</td>
<td></td>
</tr>
</tbody>
</table>

† See section 9 for definitions of end of course.
1. All studies to determine eligibility must be performed within 2 weeks prior to enrollment unless otherwise indicated below (See section 9.0). Consent must be obtained prior to enrollment but does not expire at 2 weeks.
2. Height only required at baseline
3. Slit lamp examination with binocular indirect ophthalmoscopy
4. For females of childbearing age
5. Subjects who had a response (≥20% target lesion shrinkage by 12 cycles) are requested but not required to have an MRI performed at 4 months and 12 months after stopping drug if they are still on study.
6. Subjects will have multiple blood draws at this time
## PERFORMANCE STATUS CRITERIA

Karnofsky performance scores are intended to be multiples of 10

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal, no complaints, no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity, minor signs or symptoms of disease.</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease.</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self, unable to carry on normal activity or do active work.</td>
</tr>
<tr>
<td>60</td>
<td>Required occasional assistance, but is able to care for most of his/her needs.</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care.</td>
</tr>
<tr>
<td>40</td>
<td>Disabled, requires special care and assistance.</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled, hospitalization indicated. Death not imminent.</td>
</tr>
<tr>
<td>20</td>
<td>Very sick, hospitalization indicated. Death not imminent.</td>
</tr>
<tr>
<td>10</td>
<td>Moribund, fatal processes progressing rapidly.</td>
</tr>
</tbody>
</table>
APPENDIX III: NIH CONSENSUS CLINICAL DEFINITION OF NEUROFIBROMATOSIS

- Six or more café-au-lait spots (≥0.5 cm in prepubertal subjects or ≥1.5 cm in postpubertal subjects)
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axilla or groin
- Optic glioma
- Two or more Lisch nodules
- A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex)
- A first-degree relative with NF1
APPENDIX IV: PROTOCOL FOR REQUIRED PRE-STUDY AND ON-STUDY MRI STUDIES

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

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

Pre-study imaging evaluation:

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

2. Perform 3-D MRI sequences on the selected index lesions as outlined in the MRI acquisition protocols below.

On study imaging evaluation:

Unless clinically indicated otherwise obtain MRI of the index lesion(s) (target and non-target) only as outlined in the MRI acquisition protocol below after course 4, 8, 12, 18, and 24 while on study.

MRI protocols:

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

If necessary, participating institutions may modify the MRI sequences to optimize differentiation of tumor and surrounding tissue. Modifications should be noted, such that the same imaging protocol, and, if possible, the same MRI scanner, can be used for all subsequent MRI studies.

All MRI studies requested per protocol will be submitted to the NCI POB within 1 week of acquisition for volume analysis.

<table>
<thead>
<tr>
<th>Volumetric sequence for PN**</th>
<th>Axial STIR</th>
<th>Head-Neck or Small## Trunk-Extremity PN</th>
<th>Large## Trunk-Extremity PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo Train Length</td>
<td>5 - 15</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>TR</td>
<td>3000 - 6000</td>
<td>6000</td>
<td>4000</td>
</tr>
</tbody>
</table>
**Spinal/paraspinal PN should be imaged with the appropriate protocol based on tumor size. Tumors that include the neck and trunk, for which the majority of the tumor is in the trunk, should be imaged with the Large Trunk-Extremity PN protocol.

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

Please contact Dr. Dombi if there are questions regarding the appropriate coverage or imaging protocol.
**Data Analysis:**
- All MRI data will be analyzed at the Pediatric Oncology Branch of the NCI. The MRI data from each scan will be processed to assess the volume of the index plexiform neurofibroma. 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 subject’s volumetric measurement obtained from the initial MRI will serve as the baseline against which to assess incremental changes in volume that occur during the subsequent intervals. Volumetric measurements and 1-D, and 2-D data analysis will be done by 3 physicians trained in 1-D, 2-D, and 3-D MRI data analysis at the Pediatric Oncology Branch, NCI at an Image Review Workstation using MEDx software (Sensor Systems Inc.). Volumetric measurements will be used to determine disease progression as outlined in Section 13. Drs. Dombi and Widemann will inform Participating Investigators, the Principal Investigator, and the NF Consortium Operations Center about the results of the MRI study by written report.

**Image and Data Acquisition:**
- In order to perform quantitative analysis the Pediatric Oncology Branch must receive the imaging data from the investigator sites. All MRI studies requested per protocol will be submitted to the NCI POB within 1 week of acquisition for volume analysis. The Pediatric Oncology Branch will check all materials received for completeness and will notify the site if data, images, or information are missing or incomplete. Dr. Dombi will confirm for each patient in screening that the MRI imaging is adequate and that the target PN is measurable and amenable to volumetric MRI analysis.
- Address for shipment of imaging studies:
  Dr. Eva Dombi, MD
  NCI, POB
  10 Center Drive, Building 10, room 1-5750
  Bethesda, MD 20892-1101
  Phone: 301-451-7023
  e-mail: dombie@mail.nih.gov
APPENDIX IVa: MRI ELIGIBILITY FORM

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

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

PID#1:_________ Date of MRI: ___________

Location of target plexiform: _______________________________________________

From:
Name of Investigator: ______________________________
Study Center: _______________________________
Phone #: _______________________________
Email Address: _______________________________

From Eva Dombi, MD:
The target PN is measurable and amenable to volumetric analysis:
Yes:_____________ No: ____________
Comments: _______________________________________________
<table>
<thead>
<tr>
<th>Week #</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Time dose taken:**

**Indicate reason for missed doses**

### SIDE EFFECTS

- **Nausea (see scale below)**
  - □ Mild
  - □ Moderate
  - □ Severe

- **Vomiting (# of times in 24 hr)**

- **Diarrhea (# of times in 24 hr)**

- **Rash (see scale below)**

### OTHER SIDE EFFECTS (list below)

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

* If you miss a dose write "M" in the box.
* Rate nausea mild if you are able to eat and drink a reasonable amount, moderate if you can eat and drink but the amount is substantially decreased, or severe if you are unable to eat and drink.
* Describe Location of Rash (i.e. Face, arms, legs etc)

Parent/ patient signature

Date
APPENDIX VI: PHARMACOKINETIC, PHARMACODYNAMIC AND CYTOKINE STUDIES

Pharmacokinetic Worksheet

Subject Consortium ID number: _____________
BSA (m²): _______ PD-0325901 dose (mg) _______ mg given: ____________

Blood samples (3 ml) will be drawn for the pharmacokinetic profile during PD-0352901 therapy on Day 1 of Course 1 at the following times: before the morning dose of PD-0325901 (pre-dose), and at 30 min, 1 hr, 2 hrs, 3 hrs, 4 hrs, 6 hrs, 8 hrs, and 10-12 hrs after the Day 1 dose of PD-0325901. For each pharmacokinetic profile there will be a total of 9 samples drawn.

Procedure: Samples will be drawn as 3 mL whole blood into K2EDTA (lavender top) tubes
- After collection, samples should be gently inverted 15 times to completely mix whole blood and anticoagulant
- Blood samples should then be immediately placed into an ice bath so that they are kept at 2-8 degrees Celsius
- Whole blood samples should be centrifuged at 4 degrees Celsius for 10 minutes at 1,700 x g to separate the plasma from the red blood cells
- Transfer plasma layer using a clean disposable pipette into the appropriately labeled 3.6mL cryovial
- Immediately store plasma sample in a -70 degrees Celsius freezer until shipment. Once frozen, samples should not be allowed to thaw, including during shipment.
- **Time from blood collection to freezing of plasma should not exceed 30 minutes**

Samples will be shipped on dry ice **Monday thru Thursday** to Cincinnati Children’s Hospital Medical Center.
Please ensure completion of all fields of PK worksheet and sample collection log prior to shipping, and include these documents in sample shipment.
Samples with completed worksheet and sample log should be shipped using express next day priority delivery to the following address and to the attention of:

**Laboratory of Applied PK and Pharmacogenetics (Dr. Vinks)**
Cincinnati Children’s Hospital Medical Center
3333 Burnet Ave., Rm R2469
**Attn. David Hahn, PhD**
Cincinnati, OH 45229
Phone:  513-636-1905
Fax:      513-636-1955
David.Hahn@cchmc.org

Please send email notification of shipment including tracking number on day samples are shipped.
All Questions regarding sample shipment(s) may be addressed to David Hahn.
The Vinks laboratory will store the PK samples and ship in batches to Advion Laboratories for analysis. Pharmacokinetic modeling will be performed by Dr. Vinks’ Pharmacometrics Core.

Sample Collection Log

Subject ID #:_________________

Course 1, Day 1, Date: ___________ Day: ____________ Time of dose: _________

<table>
<thead>
<tr>
<th>Sample #</th>
<th>Hours</th>
<th>Scheduled Sample Time</th>
<th>Actual Sample Time</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>pre dose</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
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<td></td>
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</tr>
<tr>
<td>6</td>
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</tr>
<tr>
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<tr>
<td>8</td>
<td>8.0</td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>10.0-12.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The next PD-0325901 dose will be administered after obtaining the 12 hour sample (Sample 9).

Please include completed Appendix VI - PK worksheet and Sample Collection Log with your shipment
Pharmacodynamic Worksheet

Pharmacodynamic Analysis of Dermal Neurofibromas

Procedure:
Three millimeter punch biopsies of 1-2 dermal neurofibromas (2 dermal neurofibromas per timepoint is preferred) will be made prior to initiating therapy with PD-0325901 and during week 3 of course 1 at least 30 min but no more than 6 hours after taking the morning dose. At each time point, one tumor will be fixed in 10% neutral buffered formalin (or its equivalent) for paraffin embedding, and shipped on wet ice. At the same time, one tumor will be frozen in liquid nitrogen and stored at -80˚C and shipped separately, on dry ice. If only one dermal fibroma is biopsied, it should be placed in formalin fixative as above. Time of tumor removal after drug dose will be noted.

To Summarize:
1. Place first punch biopsy sample in a 15ml conical tube and add 5ml of 10% neutral buffered formalin. Label tube with Subject ID, Course, course day, date of sample, and date and time of last PD dose. Ship sample with freezer ice packs.

2. Place second punch biopsy in a cryovial (screw on the top), or aluminum foil, Subject ID, Course, course day, date of sample, and date and time of last PD dose, and drop into liquid nitrogen (Flash freezing the sample). Immediately store at -80 and ship separately on dry ice.

Samples will be shipped as soon as possible to Cincinnati Children’s Hospital Medical. Samples should be shipped with express next day priority delivery to the following address and to the attention of:

Ratner Laboratory
Cincinnati Children’s Hospital Medical Center
S Dock
240 Albert Sabin Way
Cincinnati, OH 45229
c/o Nancy Ratner S7.250
Phone: 513-636-3502
Fax: 513-803-1083
Email: lindsey.aschbacher-smith@cchmc.org

Please include this completed worksheet with the sample shipment:

<table>
<thead>
<tr>
<th>Subject ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course</td>
</tr>
<tr>
<td>Course day</td>
</tr>
<tr>
<td>Date of sample</td>
</tr>
<tr>
<td>Date and time of last PD-0325901 dose:</td>
</tr>
</tbody>
</table>
Plasma Cytokines and Growth Factors Worksheet

CYTOKINE STUDIES

BSA (m2)  PD-0325901 dose (mg)  Date/time:
given

Plasma Cytokines and Growth Factors Procedure:
10 ml blood will be drawn into EDTA tubes before treatment initiation, during week 3 of course 1 and during week 3 of course 4. The sample will be collected at least 30 min but no more than 6 hours after taking the morning dose. To summarize:

- Pre-study measurement needed
- Course 1, week 3: collection 30 minutes to 6 hours after taking the morning dose
- Course 4, week 3: collection 30 minutes to 6 hours after taking the morning dose

- After collection, samples should be gently inverted 15 times to completely mix whole blood and anticoagulant
- Blood samples should then be immediately placed into an ice bath so that they are kept at 2-8 degrees Celsius
- Whole blood samples should be centrifuged at 4 degrees Celsius for 10 minutes at 1,700 x g to separate the plasma from the red blood cells
- Transfer plasma layer using a clean disposable pipette into the appropriately labeled 3.6mL cryovial
- Immediately store plasma sample in a -70 degrees Celsius freezer until shipment. Once frozen, samples should not be allowed to thaw, including during shipment.

- Time from blood collection to freezing of plasma should not exceed 30 minutes

Samples will be shipped on dry ice Monday thru Thursday. Samples will be shipped to Cincinnati Children’s Hospital Medical Center. Samples should be shipped with express next day priority delivery. Samples will be shipped to the following address:
Cincinnati Children’s Hospital Medical Center
S Dock, Ratner Laboratory S7.348
240 Albert Sabin Way
Cincinnati, OH 45229
c/o Nancy Ratner S7.250  Phone: 513-636-3502
Email: Lindsey.Aschbacher-Smith@cchmc.org

Other email contacts in the lab: Nancy.Ratner@cchmc.org; Jianqiang.Wu@cchmc.org; Huiqing.Li@cchmc.org; Adam.Miller@cchmc.org; and Tilat.Rizvi@cchmc.org

Please include this completed worksheet with the sample shipment:

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Course day</td>
<td></td>
</tr>
<tr>
<td>Date of sample</td>
<td></td>
</tr>
<tr>
<td>Date and time of last PD-0325901 dose:</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX VII: CONSORTIUM QOL AND PAIN MEASURES

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

NF1 Disease Specific QOL Measure

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

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

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

Feasibility, measured by the percentage of missing responses, was 4.8 % for all scales on the adult version of the PedsQL™ NF1 Module. Internal consistency reliability for the Total Scale score (alpha =0.97) and Scale reliabilities ranging from 0.72 to 0.96 were acceptable for group comparisons. The PedsQL™ NF1 module distinguished between NF1 adults with excellent to very good, good, and fair to poor health status. Thus, preliminary data demonstrates the initial feasibility, reliability and validity of the PedsQL™ NF1 module in adult patients (Nutakki et al., personal communication). The preliminary data in a small sample of adolescents also looks promising with good feasibility (percentage of missing responses was 8.9%) and a total scale reliability of 0.96 (N. Swigonski, personal communication, October 10, 2012).

Pain Measures

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

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

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

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

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

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

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

Participant's Study ID:
Protocol:
Course Number:

**Numeric Rating Scale (NRS-11)—Pain Intensity**

Below are lines with numbers from 0 to 10 where 0 means no pain and 10 means the worst pain you can imagine.

1. For this question, please circle the one number that best describes your most important tumor pain at its *worst* during the past week. Please rate your pain for the same tumor throughout the study (specify the location of the tumor: ________________________).

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>
   No pain|   |   |   |   |   |   |   |   |   |   | Worst pain you can imagine

2. For this question, please circle the one number that best describes your overall tumor pain at its *worst* during the past week.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>
   No pain|   |   |   |   |   |   |   |   |   |   | Worst pain you can imagine

**Brief Pain Inventory (BPI)—Pain Interference**

3. For the following questions, a "0" means that pain did not interfere with (get in the way of) the activity and a "10" means that pain completely interfered.

Circle the one number that describes how much, during the past week, tumor pain has interfered with your ________.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Does not interfere</th>
<th>Completely interferes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.  General activity</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>2.  Mood</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>3.  Walking ability</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>4.  School, work, or chores</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>5.  Relations with other people</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>6.  Sleep</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>7.  Enjoyment of life</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>
NF1 QOL BACKGROUND INFORMATION SHEET

Participant’s Study ID: __________________________
Course Number: __________________________

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

Today’s Date: ___________ Date of Birth: ______ Gender: M F Race: ______

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

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

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

Learning/Psychiatric Diagnosis: Have you ever been diagnosed by a doctor or other health professional with any of the following? (Check an answer for each one).
Attention deficit/hyperactivity disorder……………………………… □ yes □ no □ don’t know
Learning disability (specify: ) □ yes □ no □ don’t know
Depression…………………………………………………………………… □ yes □ no □ don’t know
Anxiety………………………………………………………………………… □ yes □ no □ don’t know
Other (specify: ) □ yes □ no □ don’t know

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

Visibility of tumor(s): When dressed, are your plexiform neurofibroma tumor(s) visible?
(Please check one).
□ mild: No visible tumor(s) outside of the normal clothing areas, and gait and posture appear normal when casually observed by others.
□ moderate: Tumor(s) is visible on the neck, face, or hands, or other areas not typically covered by clothes, and/or gait or posture is somewhat affected.
□ severe: Large tumor(s) is visible on the neck, face or hands, or other areas not typically covered by clothes and/or gait or posture is severely affected.

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

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

**DIRECTIONS**

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

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

There are no right or wrong answers.
If you do not understand a question, take your best guess.
Thank you for your help!
Please select which of the following describes you the best:

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

How old are you? (in years) ______________

Do you have plexiform neurofibromas?

- Yes
- No
- Don’t know

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

In general, how would you rate your health?

- Excellent
- Very Good
- Good
- Fair
- Poor

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

On average, how many different medications do you take for your NF-1 in a day? ____________
In the past ONE month, how much of a problem has this been for you...

<table>
<thead>
<tr>
<th>PHYSICAL FUNCTIONING (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Having headaches</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Feeling physically weak</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Walking more than one block</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Climbing stairs</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Running</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Doing a sports activity or exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Lifting something heavy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Doing chores around the house</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EMOTIONAL FUNCTIONING (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling anxious</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Feeling sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Feeling angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Feeling frustrated</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Feeling helpless or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOCIAL FUNCTIONING (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling isolated from others</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Getting support from others</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Having enough energy for social activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COGNITIVE FUNCTIONING (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Keeping attention on things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Remembering what people tell you</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Remembering what you just heard or read</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Thinking quickly</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Solving math problems</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Writing school papers or reports</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Remembering what you were just thinking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Participant’s Study ID:

Protocol:

Course Number:

Visit Date: ____________________________
<table>
<thead>
<tr>
<th>COMMUNICATION (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Telling the doctors and nurses how you feel</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Asking the doctors and nurses questions</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Talking with others about your disorder</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WORRY (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Worrying about neurofibromas</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Worrying about side effects from medical treatments</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Worrying about whether or not medical treatments are working</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Worrying that neurofibromas will grow bigger or reoccur</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Worrying about my future or the risk of having children with Neurofibromatosis Type 1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Worrying about the risk of other health related issues associated with Neurofibromatosis Type 1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PERCEIVED PHYSICAL APPEARANCE (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling that I am not good looking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Not wanting other people to see my neurofibromas</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Being embarrassed about others seeing my body</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PAIN AND HURT (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aching or hurting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Aching or hurting a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Not sleeping because of pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PARESTHESIAS (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A burning sensation in some part of my body</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. A tingling sensation in some part of my body</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Participant’s Study ID: 

Protocol: 

Course Number: 

Visit Date: ______________________
<table>
<thead>
<tr>
<th>SKIN IRRITATION (problems with...)</th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Itching</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Itching a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting a skin rash when exposed to sun</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Tolerating temperature changes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Rough skin</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SENSATION (problems with...)</th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vision in one or both eyes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Seeing well enough with glasses or contact lenses</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Hearing in one or both ears</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Speech</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MOVEMENT AND BALANCE (problems with...)</th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bending my body</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Moving one or both legs</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Using or moving one or both arms</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Keeping balance when sitting/standing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCHOOL ACTIVITIES (problems with...)</th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Writing or drawing with a pen or pencil</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Carrying school books</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Using a mouse or keyboard on the computer</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAILY ACTIVITIES (problems with...)</th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Putting on shoes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Buttoning my shirt</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Combing my hair</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Getting into the bathroom to use the toilet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Undressing to use the toilet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Getting in and out of bathtub or shower</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Brushing my teeth</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Eating with a fork and knife</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
9. Using a phone  |  0 | 1 | 2 | 3 | 4  
10. Shopping    |  0 | 1 | 2 | 3 | 4  
11. Managing money | 0 | 1 | 2 | 3 | 4  
12. Driving     |  0 | 1 | 2 | 3 | 4  
<table>
<thead>
<tr>
<th>FATIGUE <em>(problems with...)</em></th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling tired</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Resting a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Having enough energy to do things that I like to do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TREATMENT ANXIETY <em>(problems with...)</em></th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Getting scared about going to the doctor</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Getting scared about going to the hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Being responsible for my medicines or therapy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Managing my Neurofibromatosis Type 1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please write any comments that you have about how NF-1 affects your health and well-being. Please write any comments about the survey and whether or not it captures how NF-1 affects people’s health and well-being.
QOL INSTRUMENT (ADULT SURVEY)
For adults (≥ 21 years old) with NF-1

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

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

There are no right or wrong answers.
If you do not know an answer, take your best guess.
Thank you for your help!
Please select which of the following describes you the best (you can choose more than one):

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

How old are you? (in years) ________________

Do you have plexiform neurofibromas?

- Yes
- No
- Don’t know

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

In general, how would you rate your health?

- Excellent
- Very good
- Good
- Fair
- Poor

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

On average, how many different medications do you take for your NF-1 in a day? _________
In the past ONE month, how much of a problem has this been for you...

<table>
<thead>
<tr>
<th>PHYSICAL FUNCTIONING (problems with...)</th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling physically weak</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Walking more than one block</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Climbing stairs</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Running</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Doing a sports activity or exercise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Lifting something heavy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Doing chores around the house</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EMOTIONAL FUNCTIONING (problems with...)</th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling anxious</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Feeling sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Feeling angry</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Feeling frustrated</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Feeling helpless or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOCIAL FUNCTIONING (problems with...)</th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Getting support from others</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Having enough energy for social activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COGNITIVE FUNCTIONING (problems with...)</th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Keeping attention on things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Remembering what people tell you</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Remembering what you just heard/read</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Thinking quickly</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Remembering what you were just thinking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMMUNICATION (problems with...)</th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Telling the doctors and nurses how you feel</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Asking the doctors and nurses questions</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Talking with others about your disorder</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Participant’s Study ID: ____________________________

Protocol: ____________________________

Course Number: ____________________________

Visit Date: ____________________________
### WORRY (problems with...)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Worrying about my neurofibromas</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Worrying about side effects from medical treatments</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Worrying about whether or not medical treatments are working</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Worrying that neurofibromas will grow bigger or reoccur</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Worrying about my future or the risk of having children with Neurofibromatosis Type 1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Worrying about the risk of other health related issues associated with Neurofibromatosis Type 1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### PERCEIVED PHYSICAL APPEARANCE (problems with...)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling that I am not good looking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Not wanting other people to see my neurofibromas</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Being embarrassed about others seeing my body</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### PAIN AND HURT (problems with...)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aching or hurting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Aching or hurting a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Not sleeping because of pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### PARESTHESIAS (problems with...)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A burning sensation in some part of my body</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. A tingling sensation in some part of my body</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### SKIN IRRITATION (problems with...)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Itching</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Itching a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Getting a skin rash when exposed to sun</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Tolerating temperature changes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Rough skin</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Participant’s Study ID:

Protocol:

Course Number:

Visit Date: ____________________________
<table>
<thead>
<tr>
<th>SENSATION (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vision in one or both eyes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Seeing well enough with glasses or contact lenses</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Hearing in one or both ears</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Speech</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MOVEMENT AND BALANCE (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bending my body</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Moving one or both legs</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Using or moving one or both arms</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Keeping balance when sitting or standing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAILY ACTIVITIES (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Putting on shoes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Buttoning my shirt</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Combing my hair</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Getting into the bathroom to use the toilet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Undressing to use the toilet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Getting in and out of bathtub or shower</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Brushing my teeth</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Eating with a fork and knife</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Using a phone</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Shopping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Managing money</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Driving</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>FATIGUE (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling tired</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Resting a lot</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Having enough energy to do things that I like to do</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>TREATMENT ANXIETY (problems with...)</td>
<td>Never</td>
<td>Almost Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Almost Always</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------</td>
<td>--------------</td>
<td>-----------</td>
<td>------</td>
<td>--------------</td>
</tr>
<tr>
<td>1. Getting scared about going to the doctor</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Getting scared about going to the hospital</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Being responsible for my medicines or therapy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Please write any comments that you have about how NF-1 affects your health and well-being. Please write any comments about the survey and whether or not it captures how NF-1 affects people’s health and well-being.

<table>
<thead>
<tr>
<th>SEXUAL FUNCTIONING (problems with...)</th>
<th>Never</th>
<th>Almost Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
<th>Not Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fatigue or lack of energy affecting your satisfaction with your sex life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. Pain affecting your satisfaction with your sex life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Ability to have children with a fertile partner</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>