The language in the following sections cannot be altered for sites relying on UAB IRB:

- ***PURPOSE OF THE RESEARCH***
- **HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**
- **WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?**
- **HOW LONG WILL I BE IN THE STUDY?**
- **CAN I STOP BEING IN THE STUDY?**
- **WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THIS STUDY?**
- **ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**
- **WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?**
- **WILL I BE PAID FOR TAKING PART IN THIS STUDY?**
- **WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?**
- **<u>OPTIONAL CONSENTS</u>**

Site specific language may be added if institutionally required.

SITE NAME

Protocol Title:	A Phase II Study of Binimetinib in Children and Adults with NF1 associated Plexiform Neurofibromas (PNOC 010) (The Neurofibromatosis Clinical Trials Consortium)
IND Number:	132519
IRB Protocol #:	IRB-170616001
Sponsor:	Department of Defense, U.S. Army
Sponsor Protocol #:	NF108
Support from:	Array BioPharma, Inc.
Principal Investigator:	SITE PI

PURPOSE OF THE RESEARCH

This is a clinical trial, a type of research study. Your study doctor, Dr. SITE PI, and his/her associates from the SITE and SITE DEPARTMENT will explain the clinical trial to you.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to participate in this study because you have neurofibromatosis type 1 (also called NF1), and one or more tumors called plexiform neurofibroma(s) (PNs) that can cause serious medical problems. Plexiform neurofibromas, which are tumors that arise from nerves, occur commonly in people with NF1. Some PNs may never grow. However, some PNs grow and can cause significant problems.

The only known effective treatment for PNs is surgery, but many times complete surgical removal of a PN is not possible, because of the large size, location or number of the tumors. There are no medical treatments that are known to be effective for people who have both NF1 and PNs. We want to see if the drug binimetinib (also called MEK162) is safe and has beneficial effects in people who have NF1 and plexiform neurofibromas.

The purpose of this study is find out whether the study drug, binimetinib, will shrink your plexiform neurofibroma and what effects, good and/or bad, it has on you and your neurofibroma.

Plexiform neurofibromas are rare, non-cancerous tumors that grow around nerves in patients with neurofibromatosis type 1 and cause problems by compressing organs and nerves. Plexiform neurofibromas can be life-threatening due to their size and location and cause difficult breathing and reduced mobility.

Currently plexiform neurofibromas are treated with surgery and/or medicines. Due to the location, size, and shape of the neurofibroma, many tumors cannot be completely removed with surgery. Besides surgery, there currently are no known standard treatments for plexiform neurofibromas.

The study researchers also want to assess quality of life and pain in participants on binimetinib.

The study drug binimetinib is considered experimental, because it is not approved by the Food and Drug Administration (FDA).

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 50 people will take part in this study at multiple sites across the United States, and about ## people will participate at SITE.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

Before you begin the main part of the study...

Eligibility Screening

In order to take part in this clinical study, you will have exams and tests done to make sure you are eligible to participate in the study. These exams and tests will be done at approximately 1 or 2 study visits. The study staff will discuss the eligibility criteria with you in more detail during screening.

These tests will be done even if you do not join the study as part of your normal care. We will use the results of the tests to see if you are eligible for the study. The MRI scans performed during screening will also be used as baseline tests for comparison to scans that are done later during study treatment.

You will also have some procedures that are only being done because you are in the study. If you have had some of these exams, tests or procedures recently, they may not need to be repeated. This will be up to your study doctor. If you are not eligible, your study doctor will discuss other treatment options with you.

- Physical exam
- Complete medical history including baseline symptoms and history of prior treatments
- Review of what medications you are taking
- Assessment of your ability to perform everyday tasks
- Neurological Exam
- Blood draw (about two tablespoons) for routine safety tests
- Serum or urine pregnancy test for females of childbearing age
- Eye exam
- Electrocardiogram (ECG) and ECHO or multigated acquisition (MUGA) scan of your heart
- MRI of neurofibroma tumors

Upon Study Entry – Before first course of study therapy

- Blood draw (about two teaspoons) for cytokine and growth factor studies (optional)
- Blood draw (about two teaspoons) for biological specimen banking (optional)
- Questionnaires: All participants in this study will assess general health-related quality of life (QOL) and pain (pain intensity and pain interference) using patient-reported outcomes (PROs).
- Functional evaluation: Depending on the location of your plexiform neurofibroma, specific functional assessments will be performed. The functional assessments may include a 6-Minute Walk-Test if you have a plexiform neurofibroma affecting your legs or airway; or evaluation of muscle strength and range of motion if you have plexiform neurofibroma affecting your arms or legs. The study team will review all evaluations that apply to you in detail with you. You will also be asked to complete the symptom checklist and some pain, quality of life and physical functioning forms. Bowel/bladder dysfunction or visual function will be evaluated in subjects in whom these functions are affected.
- Photography of visible PN (optional): If you agree to take part, photographs of visible PN will be taken. Photos will be taken before treatment and then after courses 4, 8, 12, 18, and 24.

During the main part of the study...

If the Eligibility Screening exams, tests and procedures show that you can be in the main part of the study, and you choose to take part, then you will begin treatment. The study doctor will discuss with you your responsibilities as a participant. All participants will receive the study drug twice daily. We will ask you to keep a log of the pills or amount of liquid you take with a diary. We define one treatment course as 28 days. We will work with you to schedule end of course visits outlined below. Binimetinib can be taken with or without food. If you vomit after taking a dose, you should **not** retake the dose.

End of course 1, 2, 3, 4, 6, 8, 10, 12, 15, 18, 21, and 24

- History and physical exam
- Vital signs
- Review of any side effects you may be experiencing
- Assessment of your ability to perform everyday tasks
- Review of what medications you are taking
- Blood draw (about two tablespoons) for routine safety tests related to study drug
- Serum or urine pregnancy test for females of childbearing age

End of course 4, 8, 12, 18, and 24

- Eye exam
- MRI of neurofibromas
- ECHO and ECG
- Functional evaluation: Depending on the location of your plexiform neurofibroma, specific functional assessments will be performed. The functional assessments may include a 6-Minute Walk-Test if you have a plexiform neurofibroma affecting your legs or airway; or evaluation of muscle strength and range of motion if you have plexiform neurofibroma affecting your arms or legs. The study team will review all evaluations that apply to you in detail with you. You will also be asked to complete the symptom checklist and some pain, quality of life and physical functioning forms. Bowel/bladder dysfunction or visual function will be evaluated in subjects in whom these functions are affected.
- Questionnaires: assessing general health-related quality of life (QOL) and pain (pain intensity and pain interference) using patient-reported outcomes (PROs).
- Photography of visible PN (optional)

If your doctor thinks you are responding well to treatment after your MRIs at course 12, you will continue to take the study drug twice daily for up to two years.

End of course 1 and 4

- Blood draw (about two teaspoons) for cytokine and growth factor studies (optional)

End of course 4 and 12

- Blood draw (about two teaspoons) for biological specimen banking (optional)

End of Treatment Visit

If you and/or your doctor decide to end your participation on this study before completion of the 24 courses, we will ask you to come in for the following evaluations (on the last day of treatment if not assessed within 14 days before).

- History, physical and neurological exam
- Vital signs
- Binimetinib diary review
- Eye exam
- Review of any side effects you may be experiencing
- Assessment of your ability to perform everyday tasks
- Review of what medications you are taking
- Blood draw (about two tablespoons) for routine safety tests related to study drug
- MRI exam
- Functional evaluation
- Questionnaires
- Serum or urine pregnancy test for females of childbearing age (if last day of treatment)
- Blood draw (about two teaspoons) for biological specimen banking (optional)
- Photography of visible PN (optional)

When you are finished receiving binimetinib…

If you had any ongoing side effects at the end of therapy, around 30 days after your last day of treatment, your study team will check in with you for an evaluation of any adverse events and to review any medications you are taking. This may be done in the clinic or over the phone.. During the follow up period, we will collect information about your disease status, whether you have started any new treatment, and your survival status.

To evaluate whether the response to binimetinib lasts after stopping it, if your tumor responded while on treatment, you should have a follow-up MRI scan at approximately 4 months and 12 months after receiving your last dose of binimetinib. This MRI scan does not have to be done at your study site. If the MRI is done outside of your study site, you will need to ask for a copy of the MRI to provide to your study doctor. If you start another tumor-directed therapy during the one year follow-up time, then we will not ask you for further MRI scans.

HOW LONG WILL I BE IN THE STUDY?

You will take the study drug twice daily, and if your doctor thinks you are responding well after course 12 (~12 months), you will continue taking it twice daily for a total of about 24 months. If you had any ongoing side effects at the end of therapy, around 30 days after your last dose of binimetinib, your study team will check in with you. If you have ongoing side effects we will continue to check in with you as clinically necessary. You will be followed by chart review for up to one year following treatment. If your tumor responded while on treatment, you will be asked to have follow-up MRI

scans at approximately 4 months and 12 months. Thus, you may be in the study for up to approximately three years (36 months).

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping, so that your doctor can evaluate you for any risks from the study drug. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THIS STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away. There also is the risk of death. If death occurs, an autopsy will be requested, but is not required.

You should talk to your study doctor about any side effects you experience while taking part in the study.

Of note, several of the initial adult subjects on the study chose to remove themselves from study for rashes that they felt were intolerable. Thus, the starting (and maximum) dose of binimetinib for future adult subjects on the study was lowered.

Binimetinib is an investigational drug and not all of the side effects are known. Serious side effects, including death, are possible. The long-term effects of binimetinib are also unknown.

Side effects in cancer patients treated with binimetinib (in any treatment group) may include those described below.

Most likely side effects (greater than 20% incidence):

- *Eye disorders (see below) which may affect vision
- Feeling weak, tired, or lacking in energy
- Rash, acne or skin irritation including redness, raised bumps, dryness or itching
- Swelling throughout your body or in specific areas such as your abdomen, arms, legs, hands, feet, face or eyes.

Less likely side effects (greater than 10% up to 20% incidence):

- Muscle spasms, muscle pain or inflammation

Side effects that occurred at a lower rate (1% up to 10% incidence):

- Alteration in how things taste or loss of the ability to taste
- Nosebleeds or bleeding in the digestive/intestinal tract
- Blood clots in veins in the legs, in veins of the eyes, or in arteries of the lungs
- *Decrease in the heart's ability to pump blood (decreased ejection fraction or left ventricular dysfunction)
- Diarrhea
- Dizziness
- Fever
- High blood pressure
- Increase in a lab test called creatine phosphokinase (an enzyme found in the blood) that may indicate muscle inflammation or damage)
- Infection of the hair follicles, or nails
- Weakness of the neck muscles resulting in difficulty holding the head up
- Nausea, vomiting
- Reduction in red blood cells
- Skin cracking
- Stomach pain
- Increase in lab test that may suggest liver inflammation or damage

***Additional information about eye disorders and decreased ejection fraction side effects:**

Eye disorders: Binimetinib has caused mild to moderate visual changes in some participants. These changes include swelling and/or inflammation in and around the eyes and changes in the retina. While this type of visual impairment may resolve, there is a risk that the visual changes may continue. Blurred vision, "seeing floaters" and, in some cases, loss of vision may be observed with binimetinib. There is the possibility that these changes could affect the activities of your daily life (i.e. driving a car or operating machinery). Participants with a history of or current retina blood vessel abnormalities will not be able to participate in this study. It is important to tell your doctor about any pre-existing eye problems you have and visual changes that occur while taking the study drug as your doctor may decide to change or stop your treatment with the study drug.

Decreased ejection fraction: A decrease in ejection fraction has been reported in studies with binimetinib. This means that the heart's ability to pump blood throughout the body is decreased. This adverse event has also been described with other similar compounds. Your cardiac function will be evaluated before and during the study. Participants with severe and recent cardiac abnormalities or events should not receive binimetinib.

Rare but important serious side effects seen in participants receiving binimetinib (less than 1%):

- A patient experienced acute liver failure (the liver rapidly lost its ability to function normally) leading to death. Due to this event and the observed increase in the value of liver enzymes, your liver function will be evaluated frequently.
- Severe increase in blood pressure that can lead to a stroke ("hypertensive crisis") was described in a single agent study with binimetinib. Increase of blood pressure may be a potential risk when receiving binimetinib. Participants at risk for high blood pressure will be monitored closely. If necessary these participants will receive specific treatment for hypertension.
- Cases of serious adverse events of inflammation of the lung tissue (pneumonitis) have been reported in clinical studies of binimetinib. Difficulty breathing, often accompanied by a cough and fever, is the most common symptom of pneumonitis. Please inform your doctor should you experience any of the symptoms described above.
- A severe skin reaction including serious illness with blistering of the skin, mouth, eyes and genitals has been reported in a patient who received binimetinib in combination with another investigational drug (BYL719). It is possible that one of these drugs may have caused this reaction. Please contact your physician immediately in case of such symptoms.
- A small number of participants in clinical trials developed hives and/or swelling in the throat, also known as angioedema, which can be a sign of an allergic reaction. Your doctor should be notified immediately if you experience tightness in your throat which may be associated with difficulty breathing.
- Severe muscle damage with breakdown of muscle tissue (rhabdomyolysis) which may result in organ damage such as kidney failure.

Side effects seen in patients receiving binimetinib but it is not clear if they are related to receiving binimetinib:

- Sores of the mouth, lip or tongue
- Blockage or tear in the intestine (especially if you have had cancer or surgery in this area of your body) that can cause pain, bloating, constipation, and vomiting

<u>There may be additional side effects related to binimetinib that your treating team still does not know. It is very important to tell them if you have any bad experiences while on this study.</u>

Other risks:

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, infection, and fainting.

MRI risks: Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocketknives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.
Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear earplugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this study.

Contrast agent (gadolinium) risks: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than on in one thousand), participants are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.
Participants with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in participants with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

<u>Information for Women of Childbearing Potential, Nursing Mothers, and/or Men Capable of Fathering a Child</u>

You should not become pregnant or father a baby while on this study because we are not sure how the drugs in this study might affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. There is not enough medical information to know what the risks might be to a breast-fed infant or to an unborn child carried by a woman who takes part in this study. Therefore all women who can become pregnant and are sexually active, or their sexual partners, must use birth control measures while in this study and for 3 months after the last administration of binimetinib. The following birth control measures are acceptable:

- intrauterine device (IUD),
- birth control pills,

• barrier device.

Females of childbearing potential must have a pregnancy test before taking part in this study. For the pregnancy test, you will give a blood sample taken from a vein in your arm with a needle 7 days before the study. You may also submit a urine sample. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study

Confidentiality risks: There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researcher believe the chance these things will happen is very small, but cannot promise that they will not occur.

Risks associated with genetic testing: If you agree to allow blood and/or tumor tissue to be banked for future research (see "optional consent" below), the research studies on your samples may involve genetic analyses, and these data may be shared with other researchers. The risks related to genetic analyses can be to individuals or to groups. These harms include stigmatization and insurability. To reduce this risk, only coded samples will be stored and used for research. Information about this study will not be recorded in your medical record.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by all employers.

Unknown Risks: The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.
For more information about risks and side effects, ask your study doctor.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

Taking part in this study may or may not make your health better. There is a chance your health may get worse while on study. While doctors hope binimetinib will be more useful against plexiform neurofibromas compared to the usual treatment, there is no proof of this. We do know that the information from this study will help doctors learn more about binimetinib as a treatment for plexiform neurofibromas. This information could help future patients.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

The study doctor will discuss with you the alternatives to participation and their risks and benefits. Your other choices may include:

- Getting treatment or care for your plexiform neurofibromas without being in a study. You may have alternative treatment options such as surgery to treat your plexiform neurofibromas.
- Taking part in another study.
- Getting no treatment.

Please talk to your doctor about your choices before deciding if you will take part in this study.

HOW WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The University of Alabama at Birmingham (UAB) Institutional Review Board (IRB). An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- SITE INSTITUTION
- Members of the Pacific Pediatric Neuro Oncology Consortium
- Members of the Neurofibromatosis Consortium
- Array BioPharma, Inc.
- The Department of Defense
- The National Cancer Institute (NCI) and other government agencies, e.g., the Food and Drug Administration (FDA), involved in overseeing research and the Office for Human Research Protections (OHRP)
- The research monitor located at Memorial Sloan Kettering Cancer Center

A Data and Safety Monitoring Board (DSMB), a research monitor and a site monitor will be reviewing the data from this research throughout the study. The investigator will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Study tests that are performed by research laboratories and information gathered directly from you by the researchers will be part of your research records but will not be added to your medical record.

If you do not have a SITE medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your SITE medical record.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of SITE affiliated entities so costs for clinical services can be appropriately paid for by either the study account or by your insurance.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Array BioPharma, Inc., the makers of binimetinib, is supplying the drug at no cost to you, and providing support to conduct this study.

Some of the services you will receive are being done only because you are participating in this research study. Examples of these 'research only' services include: cytokine studies and some of the functional evaluations. Those services will be paid for by the study and will not be billed to you or your health insurance company. If you believe you have received a bill for a research related procedure contact the study team and the SITE BILLING OFFICE that sent the bill.

In addition, some of the services you will receive during this research study are considered to be "routine clinical services" that you would have received even if you were not participating in the research study. Examples are physical exams, the routine laboratory tests and all the tumor imaging. These services will be billed to your health insurance company, and you will be responsible for paying any deductibles, co-payments or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs.

INSTITUTION SPECIFIC LANGUAGE:

(This is a space holder only)

If you have any questions, your doctor and the study team will be able to provide you with answers. For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call **1-800-4-CANCER (1-800-422-6237)** and ask them to send you a free copy.

WILL I BE PAID FOR TAKING PART IN THIS STUDY?
You will not be paid for taking part in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
It is important that you tell your study doctor, SITE PI, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at PHONE NUMBER.

Treatment and Compensation for Injury: The SITE, Department of Defense, Array BioPharma, Inc., and the Neurofibromatosis Consortium have made no provision for monetary compensation in the event of injury from the research, and in the event of such injury, treatment will be provided, but is not free of charge.

SITE PI or his/her designee will assist you in obtaining appropriate medical treatment if it is required. If you have any questions, please discuss this issue thoroughly with the SITE PI or his/her designee before you enroll in this study. This is not a waiver or release of your legal rights.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits.

Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor, SITE PI or his/her associates at SITE PI PHONE NUMBER.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the SITE HUMAN SUBJECTS PROTECTION OFFICE at OFFICE NUMBER.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

INSTITUTION SPECIFIC LANGUAGE:

(This is a space holder only)

OPTIONAL CONSENT

Consent for Cytokine and Growth Factor studies

We would like to collect additional blood samples to see if the study drug is causing changes to molecules in your blood called growth factors and cytokines. Growth factors work to help cells grow and cytokines help your immune system turn on and off. The researchers want to see if the study drug causes any changes in the amount of growth factors and cytokines in your blood. If you agree to take part, we will collect an additional 10 milliliters of blood (2 teaspoons) before you start taking the study drug, and then after courses 1, and 4.

The choice to consent to participate in the cytokine and growth factor studies is optional and is up to you. You may still participate on this clinical trial if you choose to decline.

Please think about your choice. After reading, **put your initials** next to the "Yes" or "No" statement.

If the subject/parent does not speak English, the person obtaining consent should initial the subject's/parent's choice below.

_____ I will allow additional blood to be taken for research purposes.

_____ I will NOT allow additional blood to be taken for research purposes.

Consent for Photography of Visible PN

If you agree to take part, photographs of visible PN will be taken to see if the visible tumors shrink with treatment. Photos will be taken at pre-treatment, and then after courses 4, 8, 12, 18, and 24.

Your photographs will be labeled with a unique study identification number, instead of your name. Your photographs will be stored electronically at SITE and transmitted to UAB with the rest of the information collected during your participation on this trial. Your photographs may contain recognizable facial images and may be printed. If your photo is published or presented at scientific meetings, your name and other personal information will not be used.
The choice to consent to photographs of visible PN is optional and is up to you. You may still participate on this clinical trial if you choose to decline.

Please think about your choice. After reading, **put your initials** next to the "Yes" or "No" statement.

If the subject/parent does not speak English, the person obtaining consent should initial the subject's/parent's choice below.

_____ I will allow photographs of visible PN to be taken for research purposes.

_____ I will NOT allow photographs to be taken for research purposes.

_____ I will allow my photographs to be published or presented at scientific meetings.

_____ I will NOT allow my photographs to be published or presented at scientific meetings.

Consent for Use of Study Data for Future Research:

If you agree, we would like to keep your data for future research about NF1 and PNs, treatments for these conditions, and ways to prevent these conditions.

The data will be labeled with a unique study identification number, instead of your name. The data will be used for research purposes only and will not benefit you. It is also possible that the stored data may never be used. Results of research done on your data will not be available to you or your doctor. The results might help people who have NF1 and/or PNs in the future.

Please think about your choice. After reading, **put your initials** next to the "Yes" or "No" statement.

If the subject/parent does not speak English, the person obtaining consent should initial the subject's/parent's choice below.

_____ Yes, I will allow my study data to be kept for use in future research about PN and other diseases.

_____ No, I will NOT allow my study data to be kept for use in future research about PN and other diseases.

Consent for Biological Specimen for Banking

We would like to collect additional blood and tumor tissue sample. The researchers want to bank these samples for future studies. Your samples will be only identified with your study number. The samples will be shipped to and stored at Children's Hospital of Philadelphia. If you agree to take part, we will collect an additional 10 milliliters of blood (2 teaspoons) before you start taking the study drug, and then after courses 4, 12 and at the end of treatment. Tumor Tissue will be collected if you are undergoing a clinically indicated procedure and agree to provide your tumor tissue for banking.

The choice to consent to participate in the biological specimen for banking is optional and is up to you. You may still participate on this clinical trial if you choose to decline.

Please think about your choice. After reading, **put your initials** next to the "Yes" or "No" statement.

If the subject/parent does not speak English, the person obtaining consent should initial the subject's/parent's choice below.

_____ I will allow additional blood to be taken for research purposes.

_____ I will NOT allow additional blood to be taken for research purposes.

_____ I will allow tumor tissue to be taken for research purposes.

_____ I will NOT allow tumor tissue to be taken for research purposes.

Consent for Use of Leftover Blood for Future Research:
Donating your blood for future research is completely voluntary.

You will have blood collected as part of your participation in this clinical trial prior to starting the study drug, and after courses 1 and 4 for analysis of cytokines, or biomarkers of tumor burden and response to therapy. After the study has been completed, instead of discarding your leftover specimens, with your permission, we will save (bank) them for possible future research to learn more about cancer and other diseases. Any leftover blood samples will be coded and stored indefinitely at Cincinnati Children's Hospital Medical Center.

The research that may be done with your blood specimens are not designed specifically to help you. It might help people who have plexiform neurofibromas and other diseases in the future.

Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care. If the research is published or presented at scientific meetings, your name and other personal information will not be used.

Things to Think About

If you decide now that your blood can be collected for research, you can change your mind at any time. Just contact the study doctor, SITE PI, at the INSTITUTION, INSTITUTION ADDRESS, SITE PI's EMAIL and let us know that you do not want us to use your blood.
Then any samples that remain will no longer be used for research. We will destroy any remaining identifiable specimens and information if they are no longer needed for your care. However, if any research has already been done using portions of your specimens, the data will be kept and analyzed as part of those research studies.

Your blood will be used only for research and will not be sold. The research done with your blood specimen may help to develop new products in the future. You will not receive any payment or financial benefit from any products, tests, or discoveries derived from these samples.

Making Your Choice

Please think about your choice. After reading, **put your initials** next to the "Yes" or "No" statement. If you have any questions, please talk to your doctor or nurse, or call our research review board at SITE NUMBER.

The choice to let us keep any leftover blood for future research is optional and is up to you. No matter what you decide to do, it will not affect your care.

If the subject/parent does not speak English, the person obtaining consent should initial the subject's/parent's choice below.

_____ Yes, I will allow my leftover blood to be kept for use in future research about PN and other diseases.

_____ No, I will NOT allow my leftover blood to be kept for use in future research about PN and other diseases.

DOCUMENT OF CONSENT:

PARTICIPATION IN RESEARCH IS VOLUNTARY.

You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled. You are not waiving any of your legal rights by signing this consent form.

My signature below indicates that I agree to participate in this study. I am aware that I will receive a copy of this signed agreement:

- I have had enough time to read the consent or have the consent form read to me and think about participating in this study;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

PARTICIPANT NAME: _____
(Print Name)

_____ _____
Date Participant's Signature for Consent

_____ _____
Date Signature of Participant 14 Years of Age and Older

_____ _____
Date Signature of Parent or Guardian

_____
Name of Legally Authorized Representative (if applicable) / Relationship of Legally Authorized Representative to Participant

_____ _____
Date Signature of Legally Authorized Representative (if applicable)

_____ _____
Date Witness Signature
(Only required if the participant is a non-English speaker)

Waiver of Assent

The assent of _____ (name of child/minor) was waived because of:

Age _____

To be completed by person obtaining consent:

For Adult Participants:

☐ The participant is an adult and provided consent to participate.

☐ The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

- ☐ gave permission for the adult participant to participate
- ☐ did not give permission for the adult participant to participate

For Minor Participant:

☐ The parent or legally authorized representative gave permission for the minor to participate.

☐ Parent or legally authorized representative is illiterate.

The consent form was read to the parent or legally authorized representative who was given the opportunity to ask questions.

☐ The parent or legally authorized representative did not give permission for the minor to Participate.

Signature of Individual obtaining consent: _____

Printed name of above:_____

Date: _____

Space is reserved for your institutional HIPAA Authorization, if your institution attaches this to the informed consent form.

Site Name
RE-TREATMENT ADDENDUM CONSENT FORM

Protocol Title:	A Phase II Study of Binimetinib in Children and Adults with NF1 associated Plexiform Neurofibromas (PNOC 010) (The Neurofibromatosis Clinical Trials Consortium)
IND Number:	132519
IRB Protocol #:	IRB-170616001
Sponsor:	Department of Defense, U.S. Army
Sponsor Protocol #:	NF108
Support from:	Array BioPharma Inc., a wholly owned subsidiary of Pfizer Inc.
Principal Investigator:	Site PI Name, degree

PURPOSE OF THE RESEARCH

The purpose of this addendum is to provide you an opportunity to re-start taking the study drug binimetinib again. You are being asked to participate in this re-treatment study because unfortunately your tumor(s) started growing again after you stopped taking the study drug. Since the study drug shrank your tumor last time, we want to see if binimetinib will shrink your tumor again and/or keep the tumor from growing.

The information in the main consent has not changed except for the activities described in this addendum re-treatment consent.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RE-TREATMENT STUDY?

Before you begin the main part of the re-treatment study...

Eligibility Screening

In order to take part in the re-treatment part of this clinical study, you will have exams and tests done to make sure you are eligible to participate in the re-treatment study. These exams and tests will be done at approximately 1 or 2 study visits. The study staff will discuss the eligibility criteria with you in more detail during screening.

These tests will be done even if you do not join the re-treatment study as part of your normal care. We will use the results of the tests to see if you are eligible for the re-treatment study. The MRI scans performed during screening will also be used as baseline tests for comparison to scans that are done later during study treatment.

You will also have some procedures that are only being done because you are in the re-treatment study. If you have had some of these exams, tests or procedures recently, they may not need to be repeated. This will be up to your study doctor. If you are not eligible, your study doctor will discuss other treatment options with you.

- Physical exam
- Complete medical history including baseline symptoms and history of prior treatments
- Review of what medications you are taking
- Assessment of your ability to perform everyday tasks
- Neurological Exam
- Blood draw (about two tablespoons) for routine safety tests
- Serum or urine pregnancy test for females of childbearing age
- Eye exam
- Electrocardiogram (ECG) and ECHO or multigated acquisition (MUGA) scan of your heart
- MRI of neurofibroma tumors

<u>Upon Re-Treatment Study Entry – Before first course of study therapy</u>

- Questionnaires: All participants in this re-treatment study will assess general health-related quality of life (QOL) and pain (pain intensity and pain interference) using patient-reported outcomes (PROs).

During the main part of the re-treatment study...

If the Eligibility Screening exams, tests and procedures show that you can be in the Re-Treatment part of the study, and you choose to take part, then you will begin treatment. The study doctor will discuss with you your responsibilities as a participant. You will receive the study drug twice daily at the same dose you were taking when you finished the main study. We will ask you to keep a log of the pills or amount of liquid you take with a diary. We define one treatment course as 28 days. We will work with you to schedule end of course visits outlined below. Binimetinib can be taken with or without food. If you vomit after taking a dose, you should **not** retake the dose.

After completing the 24 cycles of re-treatment...

After completing 24 courses of re-treatment, if you are receiving benefit from binimetinib, and both you and your study doctor agree that continued treatment with a MEK inhibitor is appropriate, your study doctor will transition you to receive a MEK inhibitor (which may include binimetinib) through a

commercial supply or from another source. While arrangements are being made to transition you, you may continue to remain on study to receive binimetinib for up to 12 additional courses. Your study doctor will transition you to receive a MEK inhibitor off study as soon as possible.

End of Re-Treatment course 1 (month 1)

- The study team will call you to review any side effects you may be experiencing and will discuss your drug diary.

End of Re-Treatment course 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33 and 36

- History and physical exam
- Vital signs
- Binimetinib diary review
- Review of any side effects you may be experiencing
- Assessment of your ability to perform everyday tasks
- Review of what medications you are taking
- Blood draw (about two tablespoons) for routine safety tests related to study drug
- Serum or urine pregnancy test for females of childbearing age

End of Re-Treatment course 4, 8, 12, 18, and 24

- Questionnaires: assessing general health-related quality of life (QOL) and pain (pain intensity and pain interference) using patient-reported outcomes (PROs).

End of Re-Treatment course 4, 8, 12, 18, 24, 30 and 36

- MRI of neurofibromas

End of Re-Treatment course 6, 12, 18, 24, 30 and 36

- Eye exam
- ECHO and ECG

If your doctor thinks you are not responding well to treatment after each MRI, you will stop taking the drug and will be off the re-treatment study.

End of Treatment Visit

If you and/or your doctor decide to end your participation on this re-treatment study before completion of the 24 courses, we will ask you to come in for the following evaluations (on the last day of treatment if not assessed within 14 days before).

- History, physical and neurological exam
- Vital signs
- Binimetinib diary review
- Eye exam
- Review of any side effects you may be experiencing
- Assessment of your ability to perform everyday tasks
- Review of what medications you are taking
- Blood draw (about two tablespoons) for routine safety tests related to study drug
- MRI exam
- Questionnaires
- Serum or urine pregnancy test for females of childbearing age (if last day of treatment)

When you are finished receiving binimetinib…

If you had any ongoing side effects at the end of therapy, around 30 days after your last day of treatment, your study team will check in with you for an evaluation of any adverse events and to review any medications you are taking. This may be done in the clinic or over the phone. During the follow up period, we will collect information about your disease status, whether you have started any new treatment, and your survival status.

HOW LONG WILL I BE IN THE RE-TREATMENT STUDY?

You will take the study drug twice daily, and if your doctor thinks you are responding well after each MRI scan, you will continue taking it twice daily for a total of about 24 months. If you had any ongoing side effects at the end of therapy, around 30 days after your last dose of binimetinib, your study team will check in with you. If you have ongoing side effects we will continue to check in with you as clinically necessary.

CAN I STOP BEING IN THE RE-TREATMENT STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping, so that your doctor can evaluate you for any risks from the study drug. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this re-treatment study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?

You can talk to your study doctor about any questions, concerns, or complaints you have about this re-treatment study. Contact your study doctor, Site PI Name at Site PI Telephone Number.

Site IRB/HRPP Contact Information

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

OPTIONAL CONSENT

Things to Think About

If you decide now that your re-treatment data and/or tumor sample can be collected for research, you can change your mind at any time. Just contact the study doctor, Site PI Name, at the Site Address and let us know that you do not want us to use your blood. Then any samples that remain will no longer be used for research. We will destroy any remaining identifiable specimens and information if they are no longer needed for your care. However, if any research has already been done using portions of your specimens and/or data, the data will be kept and analyzed as part of those research studies.

Your data and/or tumor sample will be used only for research and will not be sold. The research done with your data and/or tumor sample may help to develop new products in the future. You will not receive any payment or financial benefit from any products, tests, or discoveries derived from these samples.

Consent for Use of Re-Treatment Study Data for Future Research:

If you agree, we would like to keep your re-treatment data for future research about NF1 and PNs, treatments for these conditions, and ways to prevent these conditions.

The data will be labeled with a unique study identification number, instead of your name. The data will be used for research purposes only and will not benefit you. It is also possible that the stored data may never be used. Results of research done on your data will not be available to you or your doctor. The results might help people who have NF1 and/or PNs in the future.

Please think about your choice. After reading, **put your initials** next to the "Yes" or "No" statement.

If the subject/parent does not speak English, the person obtaining consent should initial the subject's/parent's choice below.

_____ Yes, I will allow my re-treatment study data to be kept for use in future research about PN and other diseases.

_____ No, I will NOT allow my re-treatment study data to be kept for use in future research about PN and other diseases.

Consent for Tumor Tissue Sample for Banking

We would like to bank a tumor tissue sample for future studies if you are undergoing a clinically indicated procedure while you are on the re-treatment study. Your samples will be only identified with your study number. The samples will be shipped to and stored at Children's Hospital of Philadelphia. Tumor Tissue will be collected if you are undergoing a clinically indicated procedure and agree to provide your tumor tissue for banking.

The choice to consent to participate in the biological specimen for banking is optional and is up to you. You may still participate on this clinical trial if you choose to decline.

Please think about your choice. After reading, **put your initials** next to the "Yes" or "No" statement.

If the subject/parent does not speak English, the person obtaining consent should initial the subject's/parent's choice below.

_____ I will allow tumor tissue to be taken for research purposes.

_____ I will NOT allow tumor tissue to be taken for research purposes.

DOCUMENT OF CONSENT:

PARTICIPATION IN RESEARCH IS VOLUNTARY.

You have the right to decline to participate or to withdraw at any point in this re-treatment study without penalty or loss of benefits to which you are otherwise entitled. You are not waiving any of your legal rights by signing this consent form.

My signature below indicates that I agree to participate in this re-treatment study. I am aware that I will receive a copy of this signed agreement:

- I have had enough time to read the consent or have the consent form read to me and think about participating in this re-treatment study;
- I am willing to participate in this re-treatment study;
- I have been told that my participation is voluntary and I can withdraw at any time

PARTICIPANT NAME: _____
(Print Name)

_____ _____
Date Participant's Signature for Consent

_____ _____
Date Signature of Participant 14 Years of Age and Older

_____ _____
Date Signature of Parent or Guardian

_____
Name of Legally Authorized Representative (if applicable) / Relationship of Legally Authorized Representative to Participant

_____ _____
Date Signature of Legally Authorized Representative (if applicable)

_____ _____
Date Witness Signature
(Only required if the participant is a non-English speaker)

Waiver of Assent

The assent of _____ (name of child/minor) was waived because of:

Age _____

To be completed by person obtaining consent:

For Adult Participants:

☐ The participant is an adult and provided consent to participate.

☐ The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

- ☐ gave permission for the adult participant to participate
- ☐ did not give permission for the adult participant to participate

For Minor Participant:

☐ The parent or legally authorized representative gave permission for the minor to participate.

☐ Parent or legally authorized representative is illiterate.

The consent form was read to the parent or legally authorized representative who was given the opportunity to ask questions.

☐ The parent or legally authorized representative did not give permission for the minor to Participate.

Signature of Individual obtaining consent: _____

Printed name of above:_____

Date: _____