Informed Consent Cover Page for FDAAA consent posting:

Official Title: ***A Pilot Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of escalating multiple oral doses of AG-348 in Subjects with Stable Sickle Cell Disease***

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PRINCIPAL INVESTIGATOR: Swee Lay Thein, M.D.

STUDY TITLE: A Pilot Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of escalating multiple oral doses of AG-348 in Subjects with Stable Sickle Cell Disease

STUDY SITE: NIH CLINICAL CENTER (CC), NHLBI

Cohort: *Standard*

Consent Version: *09/01/2020*

WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes the research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you to in making your decision about participating in this study. Additional information that may help you make a decision can be found in other sections of the document. Taking part in research at the NIH is your choice. It is completely voluntary.

The purpose of this research study is to test the tolerability and safety of an investigational medication called AG-348 in people with sickle cell disease. "Investigational" means that the drug has not been approved by any authority that regulates new medicines, including the US Food and Drug administration (FDA).

The study will last approximately 14 weeks and includes 8 visits to the NIH Clinical Center (CC) Visit 1 will be determining your eligibility

• At visits 2, 3, 4, 5, and 6, you will receive study medication and you will have to stay at the NIH for 2 days (1 night) at a time. This way we can watch you closely -to see if you develop any reaction to the study drug when increasing or decreasing your dose. You will receive a study diary and bottle of study pills to take home at each visit. You will take the study drug every 12 hours (for example, 9 AM and 9PM) and record in the diary when you take the study drug as well as any symptoms you experience. You will bring back your diary and study drug bottle at each of these visits, even if the bottle is empty.

- You will stop medication at visit 7
- At visit 8, you will be followed up to see if you are doing okay
- Lab tests will be done on all the visits
- Side Effects of Study Drug

There are many side effects and risks related to this drug, but this drug has been used in other studies before and most of these risks are known and can be addressed.

- The most common side effects are:

  headache

  insomnia

  nausea.

- At the highest dose level, you may experience in addition to the above vomiting hot flashes and fever
- Other possible risks that may be related to the study drug are:

  the decrease in bone mineral density (decrease in bone mass)

  withdrawal hemolysis (stopping the drug quickly may destroy your red blood cells)

  changes in liver enzymes (ALT and AST)

  changes in levels of certain fats (triglycerides)

  changes in certain hormone levels (testosterone-related and estrogen-related hormones)

  acute pain crisis caused by withdrawal of study drug (stopping the drug quickly may destroy your red blood cells)

- Compensation for your time and inconvenience is offered.
- You can discuss with your doctor to see if there are other alternative studies that you can participate in if you decide not to participate in this one. You will not be able to continue any other medication should you take part in this study

The remaining document will now describe this research study in more detail. The additional information should be considered before you make your choice. Members of the study team will talk with you about all the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your

family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY THIS STUDY IS BEING DONE?

This is a research study. The purpose of this research study is to test the tolerability and safety of a new medication called AG-348 in people with sickle cell disease. We also want to evaluate the amount of study drug that gets into the blood and how long it stays in the blood; what the study drug does in the body; and look for signs as to whether the study drug is working. Laboratory research has shown that AG-348 will help with speeding up the activities in the red blood cell that helps transport oxygen throughout the body.

We are asking you to join this research study because you have SCD. If you are a NIH employee, you will be given the NIH Information Sheet on Employee Research Participation.

AG-348 is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) or other regulatory authorities around the world to treat alone or in combination with any drug in this group of people. The drug AG-348, is also known as AGI- 1480 and AGX-0841. This drug activates an enzyme called pyruvate kinase in the red blood cell that is very necessary for its function in transporting oxygen as well as maintaining its structure. We would like to see if the study medication is safe to give to subjects with sickle cell disease and how this medication works in their bodies. AG-348 is a capsule taken by mouth.

So far, AG-348 has been studied in in healthy volunteers and currently under study in people who lack the pyruvate kinase protein. In both healthy subjects and people with pyruvate kinase deficiency, the drug is generally well tolerated and shown to be safe.

AG-348 is manufactured by Agios Pharmaceuticals Inc. We have a research agreement with this company that allows them to give us this drug. We will not accept any money from Agios Pharmaceuticals Inc. to conduct this study.

WHAT WILL HAPPEN DURING THE STUDY?

If you decide to take part in this study, you will be asked to come to the Clinical Center of the National Institutes of Health for Screening and visits 1 through 8. You will receive 4 different doses of the study drug, 5, 20, 50, and 100 milligrams at different time points.

We will give you a list of study contacts and phone numbers to keep with your diary and a wallet card, in case you have any questions or have an emergency while you are in the study.

The next section describes what will happen at each visit:

SCREENING -VISIT 1:

A member of the study team will tell you about the study and ask you some questions to determine if you are eligible for this study. After you agree to be in the study and sign this consent form, we will do the following:

- Medical History and Physical Examination
- Blood Collection: We will take blood from a vein in your arm using a needle. The amount of blood drawn is considered a safe amount for adults per NIH guidelines. We will use your blood to test or confirm if you have SCD. We will also use your blood to run some standard clinical labs.
- Urine Collection: We will use your urine to test for standard laboratory tests and pregnancy if you are a female of child bearing age.

STUDY VISITS:

Lab tests will be performed at all visits and the study medication will be given to you at the following doses at each visit. You will stay at the NIH for 1 night each for visits 2-6. The lab tests will show if it is safe for you to continue to the next increased dose of the drug.

Visit 2 (inpatient) – You will have an IV placed in your arm and a blood draw. We will provide you with **5 milligrams** of AG-348 to take by mouth. After taking the study drug you will have a blood draw through your IV after 1, 2, 4, and 8 hours. After the last blood draw, you will be discharged home and will take the next dose of 5 milligrams of AG-348 at home. Before you leave, we will provide you with 2-weeks' worth of study medication and a study diary to take home with you.

About Taking the Study Medication:

AG-348 comes in the form of a tablet that you will take twice a day, every 12 hours (for example, 9AM and 9PM). The study tablets are to be taken by mouth and swallowed whole with water. The tablets are not to be crushed, chewed, or dissolved in water. The study drug may be taken with or without food. Keep the study medication in its original bottle.

If you miss a dose by 4 hours or less, you should still take that dose. If a you miss a dose by more than 4 hours, you should skip that dose and take your next dose at the usual time.

If you do not tolerate the drug and it is not safe for you to continue, we will gradually reduce the study drug and continue to follow you to monitor your safety until the end of the study.

Bring the bottle of study medication with you to every visit until Visit 8.

About the Study Diary:

We will give you a study diary to record when you take the study medication. You will also keep track of any symptoms until the end of the study. Bring your study diary to every visit until the end of the study.

Visit 3 (inpatient) – Bring your bottle of study medication and study diary. You will have

an IV placed in your arm and a blood draw. We will provide you with **20 milligrams** of AG-348 to take by mouth. After taking the study drug you will have a blood draw through your IV after 1, 2, 4, and 8 hours. After the last blood draw you will be discharged home and will take the next dose of 20 milligrams of AG-348 at home. You will spend the night and be discharged the following morning. Before you leave we will provide you with 2-weeks' worth of study medication and return your study diary to you to take home.

Visit 4 (inpatient) **-** Bring your bottle of study medication and study diary. You will have an IV placed in your arm and a blood draw. We will provide you with **50 milligrams** of AG-348 to take mouth. After taking the study drug you will have a blood draw through your IV after 1, 2, 4, and 8 hours. After the last blood draw you will be discharged home and will take the next dose of 50 milligrams of AG-348 at home. Before you leave we will provide you with 2-weeks' worth of study medication and return your study diary to you to take home.

Visit 5 (inpatient) **-** Bring your bottle of study medication and study diary. You will have an IV placed in your arm and a blood draw. We will provide you with a total of **100 milligrams** of AG-348 (2 tablets of 50 milligrams) to take mouth. After taking the study drug you will have a blood draw through your IV after 1, 2, 4, and 8 hours. After the last blood draw, you will be discharged home and will take the next dose of 100 milligrams of AG-348 at home. Before you leave we will provide you with 2-weeks' worth of study medication and return your study diary to you to take home.

Visit 6 (inpatient)**-** Bring your bottle of study medication and study diary. You will have an IV placed in your arm and a blood draw. We will provide you with **100 milligrams** of AG-348 to take mouth on the morning of your taper. After taking the study drug you will have a blood draw through your IV after 1, 2, 4, and 8 hours. After the last blood draw you will be discharged home, where you will begin taking 50 milligrams twice a day. Before you leave we will provide you with sufficient study medication for your drug taper and return your study diary to you to take home.

The morning after your inpatient stay you will begin to gradually reduce the dose over 15 days (dose tapering) until you are no longer taking the study medication. The schedule for the dose taper will be as follows: 100 mg in the morning (provided inpatient) and 50 mg in the evening for the first day, followed by 50 mg twice a day for 2 days, 50 mg once a day for 3 days, 20 mg twice a day for 3 days, then 20 mg once a day for 3 days, then 5 mg once a day for 3 days until you come in for Visit 7. You will be instructed to contact the study team right away if you develop any changes in your symptoms or overall health, or if you feel that you may be experiencing a sickle cell pain crisis. If this happens, we may change the schedule for your dose taper.

Visit 7 - Lab tests

Visit 8 – (4 week follow-up) Lab tests

The approximate amounts of blood to be collected at each visit at pre-dose, 1 hour, 2nd hour, 4th hour, and 8th hour for each study visit (except during the 1st visit/screening, and visits 7 and 8) as follows:

Visit	Amount of blood
Screening/Visit 1	2 tbsp
Visit 2	5 tbsp
Visit 3	5 tbsp
Visit 4	5 tbsp
Visit 5	5 tbsp
Visit 6	5 tbsp
Visit 7	5 tbsp
Visit 8	5 tbsp
Total	2.3 cups

tbsp=tablespoon; tsp=teaspoon

Genetic Testing for Research:

We will take DNA from the blood samples you provide. We will test your DNA for the PKLR gene which is inherited that can cause differences in response to the study drug. We may also test one, many or other of your genes to see if we can find any genes that interact with the PKLR variant and SCD. Methods for looking at genes are constantly changing and we plan to continue to use new and improved techniques as they become available to look for all possible changes in genes that may help explain the differences in response to the drug, and possibly in symptoms of SCD. We may also test your DNA for other genes we know that may affect symptoms of SCD. Because we don't know much about how these genes can affect sickle cell disease, the results of our research studies will not be provided to you or your referring doctor.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement will last for about 14 weeks in total.

Please refer to the previous section to review the study visits. 3 outpatient visits usually will range from 4 to 6 hours in length. 5 inpatient visits require a 24-hour hospital stay.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

Up to 25 people may participate in this study at the NIH Clinical Center.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

a) **Blood collection**:

There may be some discomfort on your arm when we collect your blood with a needle. There is a small chance that you will get a bruise, feel lightheaded, faint, or have an infection at the place where you were pricked.

b) Genetic and DNA analysis:

Issues related to your confidentiality: Some people are concerned that information about

them from their medical records could be given out without them knowing about it. Possible problems might include insurance or employment discrimination. Steps to protect your information are detailed below. These problems may also occur if you give out information yourself or agree to have your research records given out. Information from this study will be identified with a code number instead of your name. The key for this code will be stored in a locked file cabinet.

There may be a risk that genetic information taken as part of participation in research could be misused for discriminatory purposes. However, state and federal laws provide some protections against genetic discrimination.

We may publish results of this research study in scientific journals and public databases, including your medical history and other medical information but the information provided in the publications will be anonymous. It is possible but unlikely that you and/or a family member could be identified because of such publications.

Researchers who will have access to genetic information about you will take measuresto maintain the confidentiality of your genetic information.

c) AG-348 side effects:

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. Your doctor may reduce or delay dosing with the study drug to ensure your safety. Many side effects go away soon after you stop taking an experimental drug. In some cases, side effects can be serious, long lasting, or may never go away. You should talk to your study doctor about any side effects that you have while taking part in the study.

The following table shows safety data from an ongoing clinical study of patients with pyruvate kinase deficiency (PKD). In this study a total of 52 patients were treated with

doses of study drug up to 300 mg twice a day (higher than the doses that will be used in this study) and 42 of the patients were treated for at least 6 months. The list below shows the adverse events that were seen in more than 10 % of patients (most of them were not serious).

At the highest doses it is possible that these side effects may be more frequent or more severe.

Side effects seen in more than 10% of the 79 patients with PKD receiving the study drug

- Headache (44.3% of patients)
- Nausea (34.2% of patients)
- Insomnia (Difficulty falling asleep or staying asleep) (34.2% of patients)
- Nasopharyngitis (The common cold) (27.8% of patients)
- Fatigue (Feeling tired) (24.1% of patients)

- Vomiting (Throwing up) (17.7% of patients)
- Alanine aminotransferase increased (Increased liver enzymes "ALT") (16.5% of patients)
- Oropharyngeal pain (Sore throat) (15.2% of patients)
- Back pain (15.2% of patients)
- Diarrhea (Loose stool) (13.9% of patients)
- Influenza (The "flu") (13.9% of patients)
- Cough (12.7% of patients)
- Hot flush (Sudden feeling of warmth) (12.7% of patients)
- Dizziness (12.7% of patients)
- Upper respiratory tract infection (A common viral infection that affects the nose, throat, and airways) (12.7% of patients)
- Pyrexia (Fever) (11.4% of patients)
- Arthralgia (Joint Pain) (11.4% of patients)
- Hypertriglyceridemia (High levels of a type of fat found in blood) (11.4% of patients)
- Dyspepsia (indigestion/heartburn) (11.4% of patients)
- Asthenia (Weakness) (10.1% of patients)
- Gastroenteritis (the "stomach flu", an inflammation of the lining of the intestines caused by a virus, bacteria, or parasites) (10.1% of patients)
- Dysmenorrhea (painful menstrual periods) (10.1% of patients)

CERTAIN RISKS ARE KNOWN TO BE CAUSED BY THE USE OF THE STUDY DRUG:

Bone mineral density decrease was reported in 3.8% of PKD patients: Bone mineral density is a measure of how strong your bones are. A decrease in bone mineral density could lead to an increased risk of bone fractures. A serious decrease in bone mineral density has been reported in one patient who took the study drug for more than six months.

Withdrawal hemolysis was reported in 2.5% of PKD patients: PKD causes your red blood cells to be destroyed (hemolysis). If the study drug works very well for you (increases your hemoglobin level), and you quickly stop taking the study drug, the hemolysis may come back quickly and you could feel sick. Hemolysis also occurs in sickle cell disease (SCD), and it is possible that stopping the study drug too quickly could lead to an increase in hemolysis or an acute pain crisis (see below). It is important that you do not stop taking

the study drug without checking with your study doctor first unless it is absolutely necessary for emergency medical care and you are instructed to stop treatment by an emergency medical care professional. If you think you may be running out of study drug, you should contact the study site immediately.

Insomnia, trouble falling asleep and/or staying asleep, was reported in 34.2% of PKD patients and 44.4% of Thalassemia patients. In the ongoing study described above, insomnia and trouble falling asleep were reported. These events were seen more often in patients receiving 300 mg twice a day, a higher dose of the study drug than the doses (5, 20, 50, and 100 mg) that will be used in this study.

Changes in liver enzymes (ALT and AST) in blood have been seen in some patients receiving the study drug. These increases may be early signs of liver damage. Your doctor will use blood tests to check your liver enzymes throughout the study. If you experience an increase of liver enzymes (ALT or AST) which meets certain criteria the study doctor will prescribe additional tests. These tests may include:

- Blood tests for viruses that can infect the liver and cause increases in liver enzymes. Examples of such viruses include Cytomegalovirus (CMV), Epstein Barr Virus (EBV), Hepatitis A, B and C, and Human Immunodeficiency Virus (HIV).
- Blood tests for markers of autoimmunity. Autoimmunity is when the body has an immune response that causes the body to attack itself.
- Imaging tests to see if there are any blockages or other problems with your liver: such as liver ultrasound, Magnetic Resonance Imaging (MRI) of liver, Computed Tomography (CT) scan of liver, /or Magnetic resonance cholangiopancreatography.

Changes in levels of certain fats (triglycerides) in blood have been seen in some patients receiving the study drug. Long term exposure to very large increases in certain fats may lead to inflammation of your pancreas (pancreatitis) which may be serious. Your doctor will check the level of fat in your blood throughout the study.

Changes in certain hormone levels (testosterone-related and estrogen-related hormones) in blood have been seen in some patients receiving the study drug. These hormone changes can contribute to osteoporosis, which is a weakening of the bones. Your doctor will check your hormone levels throughout the study (blood tests).

Changes in hemoglobin levels. We anticipate an increase in hemoglobin when you take the study drug, and will monitor the increase very carefully as excessive increase may not be beneficial. As the response to the study drug and tolerance to the level of increased hemoglobin varies between individuals, we will monitor your symptoms in response to the increase and may have to reduce the dose of study drug to suit you.

In addition, the following risk may be caused by use of the drug:

Acute pain

It is possible that you may have an acute pain crisis, particularly when going through the dose taper portion of the study. This severe pain is known as acute vaso-occlusive crises (VOC). To reduce this possible risk, we will decrease the dose of the study drug over time during the drug taper. If you start experiencing acute pain or symptoms of a VOC, you should let your study doctor know immediately. If this happens, we may decrease the study drug dose even slower in order to prevent the development of a VOC.

d) Interactions with other drugs

Sometimes different drugs can interact with each other in the body and cause side effects when used together, which do not occur when each drug is used alone. It is important that you discuss all medications, including prescribed medications, over-the-counter medications, and supplements (like vitamins), as well as grapefruit products that you are taking before you start the study and also tell your doctor of any changes in your medications during the study. Your study doctor will let you know if you need to stop taking certain medications or switch to another medication while you are taking the study drug.

What are the risks related to pregnancy?

You should not become pregnant or father a baby while in this study because the effects on an unborn baby are unknown. If you are a woman who can have children, you will have a pregnancy test before you can be in this study. If you are pregnant or breast feeding, you cannot be in this study. Tell one of the study staff members right away if you suspect that you have become pregnant while in the study or, if you are a man, you suspect that your partner has become pregnant. If you are a female and become pregnant during the study you will be required to discontinue study drug, in consultation with your study doctor.

You may be able to remain in the study and off of study drug during the pregnancy and while you are breast feeding, and be allowed to restart the drug at the end of the pregnancy and when you have completed breast feeding, if the study is still ongoing.

Whether you are a man or a woman, you need to either remain abstinent from sexual intercourse, (if this is part of your usual lifestyle), or use highly effective methods of birth control while in this study and for at least 28 days after the last dose of study drug for women and 90 days following the last does of study drug for men. Check with your study doctor about the methods of birth control to use.

Based on animal studies, the study drug may affect fertility in males and females. In animals, these effects were reversible after discontinuation of the study drug. The study drug may also affect the ability to maintain pregnancy.

If you are a female and become pregnant during the study you will be required to

discontinue study drug, in consultation with your study doctor.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study. The purpose of this study is to find doses of the drug AG-348 that are safe and tolerable in patients with SCD. Even if you benefit from taking the study drug, we will need to take you off of the drug at the end of the study.

However, in the future, other people might benefit from this study because once we find a dose that can be tolerated and safe, we will start a clinical study of AG-348 to evaluate its efficacy in improving the anemia and reducing the hemolysis that is related to SCD. The knowledge acquired from the study will also help understand the sickling process itself, and perhaps provide information on future treatments for targeting the sickling process.

WHAT OTHER OPTIONS ARE THERE FOR ME?

You do not have to participate in this study if you do not want to. You may withdraw from this study at any time. If you decide to withdraw from the study, we would like to keep your test results to properly analyze this research study. If you have concerns about this, please speak with members of your research team.

If you decide not to participate in this research study, other treatments or medications may be available for the treatment of SCD. There may also be other clinical research studies in which you may choose to participate. You may discuss these alternatives with your doctor and decide whether to participate in this study. Please note that some treatments are forbidden during the course of this study. Therefore, before you start any new medication you must notify your doctor responsible for the study at the NIH. Your doctor will tell you if anynew information about AG- 348 become available during the course of the study

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

You will be provided with the results of the standard clinical labs but the results of our research studies will not be provided to you or your referring doctor.

EARLY WITHDRAWAL FROM THE STUDY

Discontinuing Participation:

- If you decide to stop participating in this study, you may request this by either

informing the investigators or by writing to the research team to the address at the end of this consent (under Problems and Questions on last page of consent). You will not be asked for further information or samples.

- If we are unable to contact you or reach you.
- When the study has completed.

Discontinuing Treatment (You can still be part of the study and will be followed until end of study):

- If the study drug affects the safety of your health or if the study doctor decides that it is in your best interest for you to be off the drug.

- Pregnancy or unwillingness to use acceptable forms of contraception.

Research Subject's Rights: You are free to refuse to undergo any of these tests. You may withdraw from the study at any time. If you decide to participate and later change your mind, you are free to stop participation at any time. You will not be penalized or lose benefits to which you are otherwise entitled. Refusal to participate will not affect your legal rights or the quality of health care that you may receive at this center.

Explanation of Conditions for Early Withdrawal: If new previously undisclosed information emerges during the study that would exclude you from the study, the investigators looking after you will discuss these with you.

WHAT WILL HAPPEN WHEN THE RESEARCH STUDY IS OVER?

The data from this study will be preserved for future use until it is no longer of scientific value. Future research use of data not defined in the research protocol may occur only after IRB review and approval or an exemption from the NIH Office of Human Subjects Research Protections (OHSRP). Refusal of a research subject participant to permit future use of data will be honored.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

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

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Food and Drug Administration (FDA) and the Office for Human Research

Protections, which are involved in keeping research safe for people.

- National Institutes of Health Intramural Institutional Review Board

This study is protected by a Certificate of Confidentiality. The researchers with this certificate may not release or use data or information about you under certain circumstances. Please refer to the OTHER IMPORTANT INFORMATION section near the end of this consent form for more information on this type of protection.

WILL YOU SAVE MY SAMPLES OR DATA FOR USE IN OTHER RESEARCH STUDIES?

As part of this study, we are obtaining specimens and data from you. We plan to use these specimens and data for studies going on right now, as well as studies in the future. These studies may provide additional information that will be helpful in understanding sickle cell disease or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you. By agreeing to let us use your specimens and data, you give the NIH any rights you may have in the specimens and data.

We may share your specimens and data with other researchers. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or industry sponsors of research.

We may put your research data in a large database which will be freely available to the public that anyone can use. These data repositories might or might not be located at the NIH. This data is intended for other researchers to use and learn from but anyone can gain access to it, including law enforcement. The information in this database could include but is not limited to genetic information, ethnicity and sex. This public information will not be labeled with your name or other information that could be used to easily identify you. This information when combined with information from other public sources could be used to identify you, though we believe it is unlikely that this will happen.

In addition to the use and sharing of your specimens and data described above, we might remove any information from your specimens and data that can identify you such as name, address, or medical record number, and then use the specimens and data for additional research studies at the NIH or other places. If we do this, we might not contact you to ask your permission or otherwise inform you.

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top ofthis document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your samples. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw the specimens and data.

How Long Will My Samples and Data be Stored by the NIH?

Your blood samples will be stored at NIH indefinitely.

Risks of Storage and Sharing of Samples and Data

When we store your samples and data, we take precautions to protect your information from others that should not have access to it. When we share your samples and data, we will do everything we can to protect your identity by removing information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your data or samples.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will I receive compensation for participation in the study?

You will receive the following compensation your participation in this study for your time and inconvenience. The amount of compensation, if any, is guided by NIH policies and guidelines.

Procedure(s)/Test(s)	IU*	Amount	Frequency	Total amount
EKG	1	$10	2	$20
Oxygen monitoring during inpatient stay	1	$10	5	$50
Medical History and Physical Exam	2.5	$25	8	$200
Urinalysis	1	$10	2	$20
Blood Draw	1	$10	9	$90
Blood Draw through an IV	1	$10	30	$300
IV placement	1	$10	5	$50
Diary	1	$10	7	$70
Drug Administration, General	2	$20	5	$100
Inpatient visit $40 per night	N/A	$40	5	$200
OUTPATIENT- **1st HOUR**	NA	$20	4	$80
OUTPATIENT TIME- **Not to Exceed More than 4 Hours**	3	$30	3	$90
TOTAL				**$1,270**

The NIH has guidelines for the participation of its staff in research protocols. If you are a NIH staff member, please refer to the NIH Manual Chapter 2300-630-3 which details the NIH leave policy for NIH employees who participate in NIH protocols. Participants who are NIH staff members should be aware of these guidelines and discuss any questions they have with the research team.

If you are unable to finish the study, you will receive compensation for the parts you completed as indicated in the table above.

With few exceptions, study compensation is considered taxable income that is reportable to the Internal Review Service (IRS). A "Form 1099-Other Income" will be sent to you if your total payments for research participation are $600 or more in a calendar year. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

Will I receive reimbursement or direct payment by NIH as part of my participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

This study does not offer reimbursement for, or payment of, travel, lodging or meals.

Will taking part in this research study cost me anything?

NIH does not bill health insurance companies or participants for any research or clinical care that you receive at the NIH Clinical Center.

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.

- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.

- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.

- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

CONFLICT OF INTEREST

The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf . You may ask your research team for additional information or a copy of the Protocol Review Guide.

This protocol may have investigators who are not NIH employees. Non-NIH investigators

are expected to adhere to the principles of the Protocol Review Guide but are not required to report their personal financial holdings to the NIH.

Cooperative Research and Development Agreement (CRADA)

None of the researchers involved with this study have a direct financial interest related to this study. The NIH and members of the research team are making products to be usedin research. This means that it is possible that the results of this study could lead to payments to the NIH and to NIH scientists. By law, the NIH and government scientists are required to receive such payments for their inventions. You will not receive any money from the development of these products.

Agios Pharmaceuticals Inc. is providing the drug AG-348 for this study to NIH without charge. No NIH employee involved in this study receives any payment or other benefits from Agios Pharmaceuticals Inc.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

OTHER IMPORTANT INFORMATION

Confidentiality

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

If we share your specimens or data with other researchers, in most circumstances we will remove any information that shows your identity before sharing them. You should be aware that there is a slight possibility that someone could figure out the information is about you.

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (CoC). NIH researchers must use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. NIH researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

There are several circumstances in which the Certificate does not provide protection. These include when information:

1. is disclosed to people connected with the research, for example, information may

be used for auditing or program evaluation internally by the NIH; or

2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);

3. is necessary for your medical treatment and you have consented to this disclosure;

4. is for other research;

5. is disclosed with your consent

In addition, identifiable, sensitive information collected or compiled during research and protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent. You should understand that a CoC does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider, or other person obtains your written consent for us to disclose the research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures.

The protections of the Certificate apply to all copies of the identifiable, sensitive information collected or compiled during the research. Therefore, if an NIH investigator shares a copy of your identifiable, sensitive information with any other investigator or institution (whether a collaborator on this study, or researcher conducting secondary research in the future) that party must agree to comply with the disclosure restrictions under the Certificate of Confidentiality described above.

Additionally, the Federal Privacy Act generally protects the confidentiality of your NIH medical records. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Swee Lay Thein, MD; sweelay.thein@nih.gov, 301-402-6699. You may also call the NIH

Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only: This section is only required if you are doing the oral short-consent process with a non-English speaking subject and this English consent form has been approved by the IRB for use as the basis of translation.

Witness:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

_____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.