

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: A Phase I, Open Label, Multi-Center, Dose Escalation Study of the Safety, Tolerability and Pharmacokinetic Properties of the Orally Administered Negative Enantiomer of Gossypol (AT-101) in Patients with Advanced Malignancies

PROTOCOL NO.: AT-101-CS-001
WIRB® Protocol #20041501
UAB #W041022006

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This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

This is an important consent form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this consent form. Your signature means that you have been told about the study and what the risks are.

INTRODUCTION

You are being asked to take part in this research study because you have advanced cancer that is present despite your having already received standard treatment, or for which no standard treatment is available.

The study will be conducted at the Mayo Clinic, the University of Alabama at Birmingham, and Georgia Cancer Specialists in Atlanta.

PURPOSE

Ascenta Therapeutics Inc., the sponsor of this study, has developed a drug called AT-101 as a potential treatment for cancer. AT-101 is an investigational drug. This means it is not approved by the United States Food and Drug Administration (FDA) for general use. The FDA does permit its use in studies like this one to see if it is safe and effective.

The purpose of this study is to test the safety of AT-101 in subjects with advanced cancer, find the highest dose of AT-101 that can be given without causing severe side effects, determine what doses of AT-101 should be used in future studies, learn how long AT-101 remains in your blood, and see what effects (good and bad) it has on you and your cancer.

AT-101 is a form of a drug called gossypol. Gossypol has been studied extensively in more than 9,000 subjects, mostly in China, as a male contraceptive (form of birth control) and for treating endometriosis (a condition in the tissues of the uterus or "womb") and myoma (tumors of the uterus).

Gossypol has also been studied as a cancer treatment. Four studies in the United States and Britain were done, including about 100 subjects. Those studies identified doses of gossypol that could be given to cancer subjects. Also, some subjects with brain cancer or cancer of the adrenal gland had their tumors shrunk in size when they received gossypol.

Laboratory studies suggest that the form of gossypol in AT-101 may be the more effective form in treating cancer. This study, that you are being invited to participate in, is the first study to test whether this form of gossypol, AT-101, can be safely given to cancer subjects.

This study drug is in its earliest stage of testing on humans.

NUMBER OF SUBJECTS TO TAKE PART IN THE STUDY

Up to 110 subjects will take part in this study.

WHAT WILL HAPPEN IN THE STUDY?

Before you are assigned to receive any AT-101, the study doctor will review your medical records, examine you, and perform standard blood and urine tests, an electrocardiogram (ECG-a procedure to measure your heart function), a chest x-ray and CT or MRI scans to evaluate your cancer and to determine if you are eligible to participate in the study. A blood pregnancy test will be performed for women who could become pregnant. If you are pregnant you will not be allowed to participate in this study.

If the results of all these evaluations confirm that you are eligible to take part and you continue to be willing to take part, you will be assigned to receive AT-101.

AT-101 will be given as a pill and taken by mouth. Your study doctor will assign you to receive AT-101 over a three-week period (called a treatment "cycle"). After each three-week treatment period, you may be eligible to receive additional treatment cycles provided that you have not had any severe side effects caused by AT-101, that your cancer has not worsened and that your medical condition allows you to continue to be treated with AT-101.

Subjects will be given AT-101 in escalating doses starting at 5.0 mg. Each three weeks of treatment will be followed by one week of no treatment with AT-101.

The first six subjects will also be given a single dose of 5 mg AT-101. One week later, the subjects will then be given a single dose of gossypol. This will allow researchers to compare the amount of AT-101 in the blood when given alone or in the original mixture (gossypol). The subjects will then begin the first cycle of daily dosing with 5 mg of AT-101.

Some subjects will be assigned to receive their daily dose of AT-101 once a day (Once Daily Group), some will receive AT-101 divided into two doses (one taken in the morning and one at bedtime) with varying schedules of treatment (Twice Daily Group), and others will receive AT-101 once each week (Weekly Group). Your study doctor will tell you how to take AT-101 during the study.

Subjects will be followed to see if they have any adverse (bad or harmful) side effects (also known as "toxicities") from taking AT-101. Three to six subjects will be treated at each dose level of AT-101. Based on observations from subjects who were treated so far with AT-101 in the study, the dose given to new subjects may be increased until the highest safe dose of AT-101 given once a day is determined.

The Twice Daily Group will be given AT-101 twice a day on three different schedules, for 21 of 28 days, for 3 days in a row every other week or for 3 days in a row each week. The dose of AT-101 given to the first subjects in each schedule will be based on the side effect information

learned from subjects already treated on other schedules. Based on careful observation of each group of three to six subjects, later subjects on each schedule may receive higher doses of AT-101.

Group 3 will be given AT-101 once a week. The dose of AT-101 given to the first subjects in this group will be based on the side effect information learned from subjects treated in Group 1. Based on careful observation of each group of three to six subjects, later subjects may receive higher weekly doses of AT-101. The highest dose that might be given in this group from these increases is four times the amount given to the first subjects in Group 3.

Regardless of the schedule on which you are receiving AT-101 during the study, you will be monitored for adverse changes that could represent side effects or “toxicities” of AT-101. If you experience severe side effects, your treatment will be stopped until they improve enough that you may be safely treated again with AT-101. If necessary, your dose of AT-101 will be reduced. If you have side effects that are too severe, your treatment with AT-101 will be stopped completely.

If you take part in this study, you will have a number of standard and research tests and procedures done. Tests will be done in the outpatient clinic and will include:

- Questioning about adverse medical conditions and side effects, about other medications and certain foods that you consume and standard blood count tests will be done weekly throughout the study (total volume of blood drawn at each visit is approximately 1 teaspoon);
- A brief physical examination, vital signs (blood pressure, temperature, heart rate, breathing rate), body weight, standard blood chemistry and coagulation tests to help monitor you for adverse side effects will be done weekly for the first cycle, then once every cycle and at the end of the study. Additional blood chemistry tests will be drawn during the first two cycles of treatment if you are in one of the Twice Daily for 3 Days treatment groups or the Weekly treatment groups. The total volume of blood drawn at each visit will be approximately 1 to 3 teaspoons, depending on the tests to be performed);
- A standard urine test to help monitor for adverse side effects will be done at the start of every cycle and at the end of the study;
- An ECG will be done and a troponin level (an enzyme found only in heart tissue that can measure any damage to your heart muscle) will be drawn weekly to monitor for adverse side effects,
- X-ray and CT or MRI scans to check whether your cancer is getting better or worse, will be done at the beginning of the study, after every two treatment cycles and at the end of the study;

- If available for the type of cancer you have, blood tests of “tumor markers” (substances in higher-than-normal amounts in the blood, urine, or body tissues) to help check whether your cancer is getting better or worse, will be done at the beginning of the study, every cycle and at the end of the study (total volume of blood drawn at each visit is approximately 1 teaspoon); and
- Special blood tests to measure the amount of AT-101 in your bloodstream will also be done on certain days throughout the study. On two study days (or three study days for the first six subjects in Group 1), this will require that you remain in the clinic for 8 hours and to return to the clinic on the following days for repeated blood tests. The total volume of blood drawn on these days is approximately 4 tablespoons. Your study doctor will provide you with a schedule of when these special blood tests will be done throughout the study.

On days when you are to be seen in the clinic, your study doctor will give you AT-101 at the clinic. On days when you are to take AT-101 but do not need to come to the clinic, you will take AT-101 at home. You will be given instructions on how to store your AT-101 pills and when to take them.

It is important that you take AT-101 only on the assigned days. On those days, you should take AT-101 at the same time of day, either one hour before or one hour after a meal. While you are receiving treatment with AT-101, you will also be asked to keep track of all medicines you take, including nutritional supplements and certain foods. If you are asked to take AT-101 twice each day, you should take AT-101 at the same times each day, either one hour before or one hour after a meal, with each dose approximately 12 hours apart.

You may not receive any other standard or experimental drugs, hormone treatments, or other treatments for your cancer. However, if you need radiation to control pain from your tumor, you may be able to continue with AT-101 after the radiation, depending on what the study doctor decides after reviewing your case with the sponsor’s physician.

In addition, you may not be able to receive certain drugs to improve low blood counts while you are receiving AT-101.

After you are finished taking AT-101, you may receive available treatments for your cancer. You and your regular doctor will make these decisions.

LENGTH OF STUDY

Because you may continue to receive treatment with AT-101 if you appear to be benefiting from treatment, it is not possible to know the exact amount of time you will be in this study. However, we estimate that most subjects will be in the study for 6 to 8 weeks.

RISKS AND DISCOMFORTS

While in the study, you are at risk for a number of adverse side effects, also called “toxicities” of AT-101. You should discuss these with the study doctor. Some of the possible risks of AT-101 can be predicted from the past experience of people who have received gossypol. However, there also may be other adverse effects that we cannot predict. Standard medical care, including available drugs and other treatments, will be given to try to make side effects less serious and uncomfortable. Most of these side effects are expected to be mild, but some could be severe, and it is possible that life-threatening side effects could occur. Based on the information from past studies of subjects who were given gossypol, most of these side effects will probably go away shortly after AT-101 is stopped, but in some cases it is possible that these adverse effects could be long lasting or permanent.

The following adverse side effects of AT-101 are believed possible:

Most likely effects:

Nausea, vomiting, diarrhea, abdominal pain, or poor appetite. These are expected to be mild and brief but may be severe or long lasting.

Fatigue - expected to be mild but could be moderate or worse.

Reduced ability for the bowels to work, called “ileus” by doctors. This could lead to bloating, discomfort, inability to have a bowel movement, nausea, and vomiting. It has happened to several subjects who received gossypol or AT-101, and has tended to occur after a few weeks of AT-101 administration. When ileus has occurred, it has resulted in hospitalization in some subjects. Ileus has not lasted long in most cases and went away when gossypol or AT-101 was temporarily stopped, usually within a few days or a week. However, treatment could involve having a suction tube placed through your nose or mouth into your stomach. There is a small chance that this reduced ability for the bowels to work could appear serious enough that a doctor will want to consider surgery to rule out other, more serious or life-threatening problems.

Abnormal liver function blood tests—may be mild to moderate, but some subjects may experience a severe change in liver function blood tests that could be accompanied by episodes of nausea, vomiting, and fatigue.

Decreased fertility - when given repeatedly for weeks or months, gossypol does reduce the ability of men to father a child. This effect was long lasting or permanent in some men who received gossypol. Gossypol may also reduce the ability of women to conceive a baby. It is possible that AT-101 will have similar effects. It is possible that men in particular who receive AT-101 may have long-term or permanent difficulty fathering children or even become sterile. However, it is not possible to say exactly what the chance of decreased fertility is in this study. Tests for fertility will not be done as part of this study.

Less likely effects:

Low blood potassium - some subjects who were studied while taking gossypol for prolonged periods developed low potassium. If this occurs, it is likely to be mild and easily treated by giving potassium pills (supplements) by mouth. However, low potassium can cause an abnormal heartbeat or muscle weakness that can be severe. The amount of potassium in your blood will be monitored during the study.

Dry skin or dry mouth.

Skin rash - some cancer subjects have had a severe skin rash covering much of their bodies, after receiving gossypol. The rash went away when gossypol treatment was stopped and standard medicines were used. Admission to the hospital was not required.

Dizziness.

Decreased libido (sex drive).

Pain in the testicles (men).

Unlikely effects:

Damage to the heart muscle or abnormal heartbeat - a rare but serious effect observed in animals treated with gossypol. In human subjects, AT-101 or gossypol has not caused effects on the heart that have required treatment. However, one subject, who had a previous history of heart attack, had another heart attack while receiving AT-101. That subject's doctor believed the heart attack was likely related to other medical causes besides AT-101. If this unlikely problem were to occur in this study, it could be life-threatening. You will be monitored throughout this study with certain blood tests that indicate damage to the heart, or for abnormal heartbeat rhythm.

Paralysis associated with very low blood potassium - a rare but serious effect observed in some Chinese men who received gossypol to prevent conception. This condition was reversible if treated with potassium supplements.

Low blood counts - refers to decreases in the number of certain types of blood cells, which are common in cancer studies, but have been rare and mild in past studies of gossypol. If low blood counts occur, they could increase your risk of bleeding or getting an infection. Mildly low blood counts may not require treatment at all.

Your condition may not get better or may become worse while you are in this study.

Drawing blood from your arm may cause pain, bruising, lightheadedness, and, on rare occasions, infection.

Only the study subject can take the study drug. It must be kept out of the reach of children and persons who may not be able to read or understand the label.

Reproductive Risks: It is not known whether AT-101 can affect an unborn baby. Therefore, you must not become pregnant or father a baby while on this study. If you are physically able to become pregnant or father a baby, you must use an effective method of birth control while you are receiving AT-101 and for one month afterward. For females, this includes IUD, female condom with spermicide, diaphragm, with spermicide, cervical cap, no sexual intercourse and use of a condom with spermicide. For males, this includes condoms with spermicide and vasectomy. Also, you should not breast-feed your baby while on this study. If you suspect that you have become pregnant while participating in the study, you must contact the study doctor immediately.

This information is important even though AT-101 may reduce the chance of pregnancy. Ask about counseling and more information about preventing pregnancy. For more information about risks and side effects, ask the study doctor.

POSSIBLE BENEFITS

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with cancer in the future.

COST OF PARTICIPATION

All procedures, such as routine blood test, diagnostic studies (such as, CAT scans, MRIs, etc.), physician visit charges, and laboratory procedures which are a part of the standard of care for the treatment of your disease will be charged to you or your insurance carrier in the usual way. If requested, you will be referred to a social worker or the appropriate billing office for assistance and information. The cost of procedures or tests done solely for the purpose of the study that are not part of standard of care will be paid by Ascenta Therapeutics, Inc. Ascenta Therapeutics, Inc. will provide you with AT-101 at no costs to you while you are being treated on this study. Your health insurance company may or may not pay for these charges. Charges associated with the study drug will be paid by Ascenta Therapeutics, Inc.

PAYMENT FOR PARTICIPATION

There will be no payment to you for participating in this study.

OTHER OPTIONS TO STUDY PARTICIPATION

You do not have to participate in this study to receive treatment for your condition.

This study is only being done to gather information. You may choose not to take part in this study. You could also seek another clinical study of another drug or other type of therapy.

Please talk to your regular doctor about these and other options.

Also, please note that AT-101 is not available except as part of this clinical study.

VOLUNTARY PARTICIPATION/WITHDRAWAL

Taking part in this research study is your decision. You may decide to stop at any time without penalty or loss of benefits at this site. You should tell the study doctor if you decide to stop and you will be told if any additional tests may need to be done for your safety.

In addition, the study doctors, the study sponsor's physician or UAB may stop you from taking part in this study at any time without your consent if it is in your best interest, if you do not follow the study rules, or if they study is stopped.

You may continue to receive AT-101 until any of the following occurs:

You decide you do not want to continue.

You have severe adverse effects that make it unsafe for you to continue treatment with AT-101.

Your medical condition gets worse to the point where it is unsafe for you to continue treatment with AT-101.

You get pregnant or cause a pregnancy.

Your cancer gets worse.

You are unable to follow the procedures required by the study plan; or

You need a form of treatment that is not permitted on this study.

COMPENSATION FOR INJURY

If you have side effects from the study treatment, you need to report them to the study doctor and your regular physician, and you will be treated as needed. UAB will give medical services for treatment for any bad side effects from taking part in this study. Ascenta Therapeutics, Inc. will pay for treatment of bad side effects directly related to the study drug. Such services will be of no cost to you if not covered by a health plan or insurance. No additional compensation will be routinely offered.

UAB has made no provision for monetary compensation in the event of injury resulting from the research and in the event of such injury, treatment is provided, but is not provided free of charge.

UAB does not routinely provide compensation for the costs of treating injuries resulting from the research.

SOURCE OF FUNDING

UAB is receiving support from the Sponsor for conducting this study.

NEW FINDINGS

During the course of the study, you will be informed of any important new findings (either good or bad) such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation that might change your decision to be in the study.

You do not give up any rights as a subject in a research study by taking part in this study.

QUESTIONS

Your study doctor is available to answer any questions you may have about the study. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study drug, or in case of a problem or an emergency, contact:

Dr. Andres Forero-Torres at 205-975-2837 or 205-934-3411 (24 hours) or a member of the research staff at 205-934-0309.

If you have any questions regarding your rights as a research subject, you may contact:

Western Institutional Review Board® (WIRB®)
3535 Seventh Avenue, SW
Olympia, Washington 98508
Telephone: 1-800-562-4789.
E-mail: Help@wirb.com

Or

Ms. Sheila Moore, Director of the Office of the UAB Institutional Review Board for Human Use (IRB). Ms. Moore may be reached at (205) 934-3789 or 1-800-822-8816, press the option for operator/attendant and ask for extension 4-3789 between the hours of 8:00 a.m. and 5:00 p.m. CT, Monday through Friday.

WIRB is a group of people who perform independent review of research.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you.

What information may be used and given to others?

If you choose to be in this study, the study doctor will get personal information about you. This may include information that might identify you. The study doctor may also get information about your health including:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research about
Physical exams
Laboratory, x-ray, and other test results
- Records about any study drug you received

Who may use and give out information about you?

Information about your health may be used and given to others by the study doctor and staff. They might see the information during and after the study.

Who might get this information?

Your information may be given to the sponsor of this research. "Sponsor" includes any persons or companies working for or with the sponsor or are owned by the sponsor.

For this study, "sponsor" also includes RPS, an agent for the sponsor.

Information about you and your health, which might identify you, may be given to:

- The U.S. Food and Drug Administration (FDA)
- U.S. Department of Health and Human Services (DHHS)
- Government agencies in other countries
- University of Alabama at Birmingham - The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, University of Alabama Health Services Foundation, The Children's Hospital of Alabama, Callahan Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the UAB IRB and its staff.
- Western Institutional Review Board® (WIRB®)
- The billing offices of UAB and UAB Health Systems affiliates

Why will this information be used and/or shared?

Information about you and your health, that might identify you, may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

The information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so the sponsor can receive marketing approval for new products resulting from this research. The information may also be used to meet the reporting requirements of governmental agencies. If your medical record needs to be reviewed by a foreign regulatory agency, a member of the UAB IRB staff will be present at the review of your medical record to ensure that the medical record is not removed; copied or identifiable information is recorded in any manner.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

The information may be reviewed by WIRB®. WIRB is a group of people who perform independent review of research as required by regulations.

Information may be shared with the UAB or UAB Health System affiliates billing services. This would be done so that the sponsor or your insurance can be appropriately billed for certain study activities.

What if I decide not to give permission to use and give out my health information?

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

May I review or copy the information obtained from me or created about me?

You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your information until after the research is completed.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission does not stop automatically. The use of your personal health information will continue until you cancel your permission.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information that might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others?

If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others without your permission.

If you agree to participate in this study, you will receive a signed and dated copy of this consent form.

CONSENT

I have read the information in this consent form (or it has been read to me). I have had an opportunity to ask questions. All my questions about the study and my participation in it have been answered. I willingly agree to participate in this research study.

By signing this consent form I have not waived any of the legal rights that I otherwise would have as a subject in a research study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

Print Name of Research Subject

Signature of Research Subject

Date

Time

In my judgment the subject is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent for participation in this research study.

Name of Person Conducting Informed Consent Discussion

Signature of Person Conducting Informed Consent Discussion

Date

Time

Name of Principal Investigator or Designee (if different from above)

Signature of Principal Investigator or Designee Date Time

Signature of Witness Date Time

----- Use the following only if applicable -----

If this consent form is read to the subject because the subject is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. The subject freely consented to participate in the research study.

(Printed Name of Impartial Witness)

(Date/Time)

(Signed Name of Impartial Witness)

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.