A Phase II, Single Center, Open-Label, Single Arm Study to Evaluate the Safety, Tolerability, and Efficacy of Disulfiram and Copper Gluconate When Added to Standard Temozolomide Treatment in Patients with Newly Diagnosed Resected Unmethylated Glioblastoma Multiforme

NCT: 03363659

January 17th, 2019

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Aurora IRB #: 17-56	
Version date: 03/22/2021	Medical Record # _____

Subject name: _____ Subject date of birth: _____

Aurora Health Care, Inc.
Consent to Participate in a Research Study

Study Title	A Phase II, Single Center, Open-Label, Single Arm Study to Evaluate the Safety, Tolerability, and Efficacy of Disulfiram and Copper Gluconate When Added to Standard Temozolomide Treatment in Patients with Newly Diagnosed Resected Unmethylated Glioblastoma Multiforme; ANII 100-1
Study Investigator	Asadullah Khan, MD (414) 384-5111
Sponsor	Aurora Neuroscience Innovation Institute

Why am I being asked to participate?

You are being asked whether you would like to voluntarily participate in a research study for patients diagnosed with glioblastoma. You are eligible to participate in this study because your tumor has unmethylated MGMT. MGMT is an enzyme that repairs the damage to DNA. When MGMT is unmethylated, it is active and counteracts the effect of temozolomide (also known by the trade name Temodar), the standard chemotherapy treatment for patients with glioblastoma. Research in animal models of glioblastoma and in patients has shown that the combination of disulfiram and copper taken orally will inactivate MGMT, allowing Temodar to work better. Disulfiram (also known by the trade name Antabuse) has been used for decades as a treatment for alcoholism. It is approved by the U.S. Food and Drug Administration (FDA) and has a long track record of safety. It is not an experimental medication. Copper is a common nutritional supplement. This clinical study will use well established agents for a different purpose: to inhibit MGMT inside glioblastoma cells so that Temodar can work better.

This form describes the study and how you can volunteer to participate. We will answer any questions you may have so that you can make an informed decision.

What is a research study?

A research study is an experiment, survey, or information collection whose purpose is to answer a specific question, such as:

- Does this work?
- Is it safe?
- What kind of treatment is better?
- How do people think or feel about this?

To answer these questions, doctors and scientists need volunteers to participate in research studies. These volunteers are called "subjects." The doctors and scientists who run the research study are called "investigators." Other people who help them run the study are called the "research team."

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Sometimes a drug being tested makes research subjects better, and sometimes it doesn't. When you are a subject, the main purpose is to see if the study drug works and if it is safe. There may be side effects or risks to you, including some we don't know about right now.

A research study has specific rules the investigator must follow. The study rules may say that subjects can't receive certain medications or treatments while they are in the study. We will explain the rules you will have to follow. If you can't or don't want to follow these rules, then you should not participate.

What is the purpose of this study?

In this study, we want to find out if adding a drug called disulfiram and the nutritional supplement copper gluconate ("copper") improves how unmethylated glioblastoma responds to treatment with Temodar.

Disulfiram/Antabuse is approved by the FDA for the treatment of people with problem drinking; however, it is not approved for the treatment of patients with glioblastoma.

Who is sponsoring this study?

The sponsor for this study is the Aurora Neuroscience Innovation Institute.

Where will this study take place?

This study will take place at Aurora Cancer Care located in the Professional Office Building located at Aurora St. Luke's Medical Center. Dr. Khan expects to enroll between 14 and 40 subjects in this study.

What is involved?

As a subject, you will be responsible for:

- attending all study visits;
- telling the investigator if you are feeling bad or worse than before;
- telling the investigator if you have any changes in medications during the study; and,
- following the directions of the investigator and research team.

If you agree to take part in this study, you will sign this consent form before any study-related procedures are performed. The investigator and research team will ask you questions and perform tests to see if you qualify to be in the study.

The following tests and procedures are part of regular medical care of patients with glioblastoma. This means you will have these whether you choose to be in this study or not.

- Medical and medication history;
- Physical examination, including a neurological examination which is a series of simple questions and tests that provide important information about the nervous system;
- ECOG Performance Status (ECOG PS) which measures changes in your ability to function;

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- Laboratory blood tests to measure blood counts, your body's metabolism, the function of your kidney and liver, and, if applicable, pregnancy testing;
- Blood tests to monitor the level of copper in your body. Blood for this test will be drawn at the same time as blood for other blood tests done to for your regular medical care; specifically at Baseline, cycle 1 day 1 and cycle 4 day 1.
- A brain MRI (magnetic resonance imaging), a test that uses powerful magnets and radio waves to create pictures of the brain;
- Surgery to remove as much of your brain tumor as possible;
- Radiation therapy to slow the grown of any remaining tumor that could not be removed during surgery;
- Taking the drug Temodar; and,
- Taking the drug, disulfiram. The medication will be taken twice each day, in the morning and in the evening. Disulfiram is not FDA approved for this indication.

The following tests and procedures are for research purposes only. This means you will only have these if you agree to be in the study:

- Taking the nutritional supplement copper at the same time that you take the medication disulfiram
- Completion of a medication diary every day to record your taking of Temodar, disulfiram and copper; and
- Completion of a brief quality of life questionnaire that will ask questions about how you are feeling physically, including if you are experiencing any pain, nausea, or feeling tired, and how you are doing emotionally, such as if you are feeling anxious or depressed. It will take you about 5 minutes to complete the questionnaire each time you are asked to do so. You may skip answering any question that makes you feel uncomfortable.

What will happen at each study visit?

Visit	**During this visit the following tests or procedures will be performed:**	**How long is this visit?**	**Reminders**
Visit 1 (At your first Multidisciplinary Clinic [MDC] visit following surgery for your brain tumor)	• Provide consent to be part of this research study; • Medical and medication history; • Physical and neurological examination; • ECOG Performance Status (ECOG PS); • Completion of the quality of life questionnaire; • Assessment about current use of corticosteroids (medications used to provide relief for inflamed areas of the body); • Laboratory blood tests; and • Brain MRI.	4 hours	None

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Visit	**During this visit the following tests or procedures will be performed:**	**How long is this visit?**	**Reminders**
At the start of your 4th week of radiation treatment	• Completion of the quality of life questionnaire • Assessment about current use of corticosteroids; and, • Assessment of any bad effects you may have experienced from taking the study medication.	5 minutes	None
About every four (4) weeks	• Physical and neurological examination; • ECOG PS; • Laboratory blood tests; • Completion of the quality of life questionnaire • Assessment about current use of corticosteroids; and, • Assessment of any bad effects you may have experienced from taking the study medication.	1 hour	None
About every eight (8) weeks	• Brain MRI	2 hours	None
At the time you stop taking disulfiram and copper	• Physical and neurological examination; • ECOG PS; • Completion of the quality of life questionnaire • Assessment of any bad effects you may have experienced from taking the study medication; and, • Brain MRI	I hour	None
About thirty (30) days after you stop taking disulfiram and copper	• Return for a visit with the study doctor to determine if you experienced any bad effects from taking the study medication.	1 hour	None

At the same time you begin receiving radiation therapy and Temodar as part of the standard treatment for your brain tumor, you will also begin taking one-half of an disulfiram tablet (125mg) two times each day with meals. You will take one tablet/capsule of copper (2mg) at the same time you take the dose of disulfiram.

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If you experience any stomach upset taking the disulfiram and copper together, you may take the copper tablet/capsule 30 minutes after your dose of disulfiram. If you forget to take the disulfiram/copper you should wait until your next scheduled dose.

You will be asked to bring your completed medication diary and any unused disulfiram and copper to each study visit.

Temodar is usually given to patients as a capsule that is taken by mouth at home. If you are unable to take Temodar by mouth, or if your insurance will not cover the costs of oral Temodar, you may be asked to come to the clinic daily for intravenous (IV) infusions of Temodar. An IV infusion is a method of delivering a medication directly into a vein through a needle inserted in your arm. Your decision to take part in this study will not influence the decision about you receiving Temodar by IV infusion. Your study doctor will discuss this with you and explain what you will need to do if you receive Temodar as an IV infusion.

After you stop the study your study doctor will recommend any follow-up based on how you're doing. At approximately two years after stopping the study your study doctor will review your medical record to check on the general state of your health and to see if your cancer has come back.

Are there any risks to me?

There may be risks, side effects and discomforts if you choose to participate in this study. These can be physical, emotional, financial or social. The ones we know about are listed below.

There may be side effects from the study medication, disulfiram. Many side effects go away, but sometimes they can be serious, long-lasting, or may never go away. There may be other side effects that we don't know about yet, so be sure to tell the investigator about any unusual symptoms.

Risks of disulfiram

Common	Rare but serious
• Drowsiness; • Feeling tired; • Headache; • Metallic or garlic-like taste in the mouth; • Skin rash or acne • Decreased sexual function in men; and • Swollen or sore tongue	• An allergic reaction (swelling of lips, shortness of breath, closing of the throat, or hives); • Extreme tiredness; • Darkening of your urine; • Yellowing of the skin or eyes; • Vision changes; • Numbness or tingling of arms and legs; • Muscle weakness; • Mental mood changes, like feeling agitated, excited or confused; and • Seizures

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Disulfiram blocks the processing of alcohol in the body and causes unpleasant effects. You should not consume any alcoholic beverages while taking the study medication. Disulfiram should not be used with any alcohol-containing products such as cough or cold medications.

Disulfiram can increase the side effects of caffeine. Avoid drinking large amounts of beverages containing caffeine (coffee, tea, colas) or eating large amounts of chocolate.

Before using disulfiram, tell your doctor or pharmacist of any prescription and nonprescription/herbal products you may be using. Do not start, stop, or change the dosage of any medicine before checking with your doctor or pharmacist first.

Risks of Copper Gluconate

Taken at the dosage used in this research study the nutritional supplement copper has not been reported to cause any side effects. Side effects from taking too much copper may include breathing problems, chest pain, stomach upset, and rash or hives.

Reproductive risks:
Women of childbearing potential will have pregnancy testing prior to starting treatment. You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you 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.

If you are sexually active, you should use a barrier method of contraception (such as condoms or diaphragm) during the trial. For women, this should continue for at least 6 months after the last dose of drug to ensure that the drug has cleared the body. For men, contraception should continue for 6 months after the last dose of drug, to ensure that all sperm present in the body during the clinical trial have been replaced.

For more information about risks and side effects, ask your study doctor**.**

Are there any benefits to me?

You may or may not benefit from being in this study. The combination of disulfiram and copper may improve your brain tumor's response to treatment with Temodar, but this cannot be guaranteed.

It is also possible that your condition could stay the same or even get worse. We hope the information learned will help other patients with glioblastoma in the future.

How much will it cost to participate?

If you have insurance, the cost of the disulfiram will be billed to your insurance. You will be responsible for the usual deductibles or co-pays required by your insurance.

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If you do not have insurance, or if your insurance does not pay for the disulfiram, you will have to pay the cost of the disulfiram you will receive while taking part in this research study.

The copper supplement you will take while taking part in this research study will be supplied to you at no cost.

You will have to pay for tests, procedures, radiation therapy, and anti-cancer medications that are a normal part of the diagnosis and treatment of your cancer and related symptoms. Taking part in this study may or may not cost more than the cost of getting regular cancer treatment.
If you have insurance, your insurance may cover some or all of these costs. You will pay any copays and deductibles, as described in your insurance plan. **You will need to contact your insurance company to find out what will be covered.** Ask the research team if you need help.

Will I be paid to participate?

You will not be paid to participate in this study.

How long will I be in the study?

You will be in the study approximately two years.

The study may be stopped early by the study sponsor. You could be asked to stop being in the study for any of the following reasons:

- for your safety
- if you do not follow our directions for this study
- if you become pregnant

If you stop being in the study early for any reason, we will ask you to do the following:

- Return for a visit with the study doctor approximately 30 days after stopping the study medication to determine if you experienced any bad effects while taking part in this study.

Do I have to be in this study?

You do not have to be in this study. If you start the study, you may stop at any time. There is no penalty or loss of benefits if you don't want to participate, and your decision won't affect your regular medical care.

You may decide to participate now, but change your mind and withdraw from the study anytime without penalty or loss of benefits. If you decide to withdraw before the last study visit, let the investigator know. There may be special procedures to follow for your safety.

You may be eligible to receive disulfiram and copper as part of your regular medical care without participating in this research study. You study doctor will be able to answer any question you have about this option.

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If you don't want to be in this study, your other options include:

- Getting treatment or care for your brain tumor without being in a study, including receiving the standard of care treatment of radiation therapy and Temodar;
- Taking part in another study, if one is available;
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible; or
- Getting no treatment at this time.

Your doctor can tell you about all your options, and their risks and benefits, before you decide if you will take part in this study.

What if I am harmed from being in the study?

If you get hurt or sick from being in this study, you should seek medical treatment as needed. Be sure to tell the investigator as soon as possible. You will not have to pay for medical treatment of any illness or injury that is caused by your participation in this study. There is no plan to pay for lost income or any non-medical costs that might result from the illness or injury.

Will my records be kept confidential?

Your study records will be kept as confidential as possible. You can find out more in the section "Information about Confidentiality and HIPAA Authorization."

What if there is new information about this study?

If we learn any new information about this study that might make you change your mind about participating, we will tell you.

If you want to know the results of the study once it is over, you can ask the investigator.

Who oversees this study?

The Aurora Institutional Review Board (IRB) has approved this study. The IRB is a group of people who review all research studies at Aurora to check that they meet federal laws and ethical standards.

IRB approval only means it is ok for the study to begin. *Only you* can decide if being in this study is the right decision. Feel free to talk about this study with your family, friends and personal doctor before you decide.

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Who do I contact?

If …	You should contact	Contact information
You are harmed by the research	Dr. Khan or Aurora Patient-Centered Research	414-384-5111 or 414-385-1873
You have questions about your rights as a research subject	Aurora IRB office	414-219-7744 (outside Milwaukee: 877-219-7744)
You have questions, problems, concerns, information, input or complaints about this research study	Dr. Khan or Aurora IRB office	414-384-5111 or 414-219-7744 (outside Milwaukee: 877-219-7744)

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Information about Confidentiality and HIPAA Authorization

Note: In this authorization document, "you" and "your data" refer to the subject. If you are a parent or guardian, please remember that "you" refers to the study subject.

Federal law provides additional protections of your medical records and related health information. That law is the *Health Insurance Portability and Accountability Act* (HIPAA). This study's HIPAA statement is provided below. You are providing your authorization if you sign this form and the accompanying consent or permission form to participate in the study.

Who will see my protected health information?

Who may have access to my information:	*Purpose:*
Any sponsor, including future sponsors, of the study and anyone working on behalf of a sponsor or future sponsor	To oversee the study and make sure the information is correct.
Advocate Aurora Health consultants and employees, including IRB members.	To protect the rights and safety of subjects and make sure the study information is correct.
Organizations that regulate research (such as the FDA, Office for Human Research Protections (OHRP), or similar government agencies in the US and other countries).	To make sure applicable laws are being followed.
Organizations that grant accreditation to hospitals and research programs.	For Advocate Aurora Health to remain accredited.

By signing this form, you are authorizing access to and sharing of personally identifiable health information. This includes direct access to your medical records at Advocate Aurora Health.

Please note that the study doctor or study staff may also share personal information about you if required by law (for example, if the study doctor or study staff suspects that you are going to harm someone or yourself; reporting of communicable disease (HIV, hepatitis, tuberculosis, etc.). If you have questions about this, please ask the study doctor.

How will my information be used for this study?

This section explains who will use and share your health information if you agree to be in this study. You must authorize this use and sharing of your information by signing this form or you cannot be in the study.

The study principal investigator and study staff will collect, use, and share identifiable health information about you for the following reasons:

- to conduct this research study;
- to review the study, and to check the safety and results of the study;

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- to seek government approval of an investigational study drug, vaccine, device or product if such was involved in the trial;
- to assist a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations, or interventions.

Information used and shared may include:

- information from your medical records related to the research or your routine medical care;
- information collected about you during the research and any follow-up related to study visits, tests, procedures, outcomes, etc.

The collected information may contain your name, address, telephone number, health plan number, date of birth, medical record numbers, dates relating to various medical procedures, and/or other identifying information.

How will my information be kept confidential?

We will keep your personal health information as confidential as possible. Your identity will be protected as required by law and according to any policies described in the study consent form you were given. Researchers may share your information with representatives and agents of the sponsor(s) for the purposes of managing and overseeing the study. Usually the health information sent to sponsors does not directly identify participants (for example, by name or address). Instead initials and a code number are used. Some personal information, such as date of birth, will usually be included but will not be used to identify you.

Once your information leaves Advocate Aurora Health we cannot control how it is used, and the law may not require outside organizations to protect the privacy of your information.

To maintain the integrity of this research, you might not have access to any health information developed as part of this study until it is completed. At that point, you generally will have access to your health information.

If this study is designed so that you are intentionally not told what treatment or study intervention you are receiving (called a blinded study), you will not have access to health information in your medical record that was collected as part of this study until those who run the study determine it is no longer necessary to keep you blinded. This usually occurs after everyone in the study has completed study treatment or intervention but can sometimes last until all study data is collected and analyzed.

How do I cancel my authorization?

You can cancel your authorization to use and share your information at any time by writing a letter to the study doctor. If you cancel your authorization, you will not be able to continue in the study. If some aspects of the study were optional, you may cancel your authorization for the optional part(s) of the

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study and still remain in the main study.

If you cancel your authorization, no new information will be collected without your permission. The study doctor and study staff will still be able to use and share your information that has already been collected to maintain the integrity of the study.

When will my authorization expire?

This authorization to use and share your information expires at the end of the research study when data analysis is complete, and study records have been destroyed.

If study information is used for scientific publications or educational purposes, all identifying information will be removed.

You will receive a signed and dated copy of this form for your records.

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Subject name: _____

- I have read this form and the research study has been explained to me.
- I have been given the chance to ask questions, and my questions have been answered. I have been told who to call if I have more questions.
- I agree to be in the research study described above.
- I will receive a copy of this consent form after I sign it. A copy will be put in my medical record and/or study record.
- I am not giving up any of my legal rights by signing this form.

_____

Subject signature Date Time

_____

Witness signature (if applicable*) Date Time

**Use when the subject cannot read the consent (for example, subject is blind, illiterate, or does not speak English). The witness must be present for the entire consent discussion. The witness signature means that the information in this document was presented to the subject, and the subject appeared to understand it.*

_____

Legally Authorized Representative signature (if applicable) Date

Relationship to Subject: Court Appointed Guardian Health Care Agent Next-of-kin

For Site Use only:

- I have carefully explained to the subject the nature and purpose of this study.
- The subject has been given enough time and an adequate place to read and review this form.
- The subject has had a chance to ask questions and receive answers about this study.

_____

Name of person obtaining informed consent (print) Title Phone number

_____

Signature of person obtaining informed consent Date Time

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Risk/Benefit/Alternatives Discussion

I have explained and discussed with the subject or his/her legally authorized representative

- The nature of the research
- Potential risks and benefits
- The alternate treatments available to the subject and the benefits and risks of each

_____

Name of person providing this information (print) Title

_____

Signature of person providing this information Date

DOCUMENTATION OF INFORMED CONSENT:

- ☐ All elements of the study contained in this document were discussed with the subject.
- ☐ The subject had the opportunity to ask questions, all questions were answered, and the subject expressed understanding.
- ☐ The subject gave written informed consent before any research-related procedures began.
- ☐ The subject received a copy of the signed and dated consent form.

_____

Signature of person obtaining informed consent Date

FILE A SIGNED COPY OF THIS FORM IN THE PATIENT'S MEDICAL RECORD (if applicable).
Keep the original in the investigator's research records.
Form IC 701A v. 8-31-15

THIS PAGE IS FOR DOCUMENTATION ONLY. IF GIVEN TO SUBJECTS, IT MAY BE BLANK.