CHILDREN'S ONCOLOGY GROUP

NCI Pediatric Early Phase Clinical Trials Network

A program funded by the National Cancer Institute of the National Institutes of Health

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A National Cancer Institute-supported member group of the National Clinical Trials Network

May 1, 2023

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Please find attached Amendment #1 to **PEPN2113**, *A Phase 1 and pharmacokinetic study of Uproleselan (GMI-1271, IND #139758, NSC #801708) in combination with fludarabine and cytarabine for patients with acute myeloid leukemia, myelodysplastic syndrome or mixed phenotype acute leukemia that expresses E-selectin ligand on the cell membrane and is in second or greater relapse or that is refractory to relapse therapy*, for CTEP review.

The protocol and informed consent document have been revised according to recommendations and comments issued by CTEP on June 23, 2022. This amendment also includes revisions in response to FDA Clinical Information Requests in the form of Hold and Non-Hold comments dated September 13th, 2022, October 12th, 2022, November 4th, 2022, and November 28th, 2022. Please see the table below for a complete list of the changes made in this amendment.

In addition, several other administrative changes have been made; specific changes are detailed below. Minor administrative updates (such as the correction of typographical errors or updates to the numbers of referenced sections) are tracked in the protocol but not specified below.

Please contact us if you have any questions.

Sincerely,

Lee Baker, MPH, Protocol Coordinator (for)
Maria Luisa Sulis, MD, PEPN2113 Study Chair and
Brenda Weigel, MD, PEP-CTN Group Chair

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SUMMARY OF CHANGES

I. Changes Made to the Consent Due to PCIRB Stipulations (From April 17th, 2023):

#	Section	Page(s)	Comment
1.	Why am I being invited to take part in this study?	2	The sentence was revised as follows: • AML, MDS and MPAL are ~~a~~ types of cancer that occurs in the bone marrow.
2.	What will happen on this study that is research?	4	A period was added to the following sentence: • You may continue to receive uproleselan for a total of 2 cycles unless you develop serious side effects, or your cancer worsens**.**
3.	Additional Required Research Study Tests	5	The sentence was revised as follows: • If you participate in this study, the **tissue** ~~test~~ is sent to a special laboratory called Hematologics, Inc. to perform the MRD tests.
4.	Treatment Risks	6	The first sentence of the 1st paragraph was moved down to begin a new 2nd paragraph and revised as follows: • The risks of the individual drugs given as regular **treatment** are listed in Attachment 2.
5.	Treatment Risks	6	A hyperlink was inserted to the "COG Family Handbook for Children with Cancer".
6.	Risks of Study	6	The sentence was revised as follows: • The use of chemotherapy (cytarabine and fludarabine) plus uproleselan treatment that is being studied could be less effective than the **current** standard treatment.
7.	What other options are there?	9	The last sentence of the last bullet point was moved down to begin a new paragraph to align with the template. • Please talk to your doctor about these and other options.
8.	How many people will take part in the study?	9	The total number of participants was revised from ~~51~~ to **36**.

9.	How long is the study?	9	~~If~~ was revised to **if**, as requested.
10.	Attachment 1	13	A space before "IV over 20 minutes" was removed, as requested.
11.	Possible Side Effects of Fludarabine	17	A space was deleted before "or pain with …"., as requested.

II. Changes Made to the Informed Consent by the Principal Investigator:

#	Section	Page(s)	Comment
40.	General	Throughout	The version date has been updated.
41.	Overview	1	The sentence has been revised as follows: • This is called a Phase 1 study because the goal is to find ~~the highest~~ **a** safe dose of uproleselan that can be given without causing severe side effects
42.	Overview	2	The sentence has been revised as follows: • Between 2 and 6 children will receive uproleselan at this dose. If the side effects are not too severe, ~~the next group of children will receive a higher dose~~ **6 more children will receive Uproleselan at the same dose**.
43.	Overview	2	The paragraph has been revised as follows: • ~~If you are enrolled early in this study, you may receive a lower dose than those who are enrolled later. A lower dose may be less likely to have any effect on your tumor.~~ Whatever dose you start at, your dose will not be increased. ~~If you are enrolled in this study at a higher dose level you may be more likely to have side effects.~~ If you have bad side effects, your dose may be decreased. Up to 2 different doses of uproleselan may be studied.
44.	Why is This Study Being Done?	3	The sentence has been revised as follows: • This is called a Phase 1 study because the goal is to find ~~the highest~~ **a** dose of uproleselan that we can give safely.
45.	What Will Happen on This Study That Is Research?	4	The section has been revised as follows: • The dose for the first children enrolled on the study will be based on the side effects seen in adults. Between 2 and 6 children will receive uproleselan at this dose. ~~If the side effects are not too severe, the next group of children will receive a higher dose. Dosing is done this way because we do not yet know the best dose to use in children. If you are enrolled early in this study you may receive a lower dose~~

			~~than those who are enrolled later. A lower dose may be less likely to have any effect on your tumor.~~ Whatever dose you start at, your dose will not be increased. ~~If you are enrolled in this study at a high dose level you may be more likely to have side effects.~~ If you have bad side effects, your dose may be decreased. Up to 2 different doses of uproleselan may be studied.
46.	Additional Required Research Study Tests	5	Pharmacokinetic sampling timepoints have been clarified as Cycle 1, Day 1, and Day 6.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

PEPN2113: Phase 1 and pharmacokinetic study of uproleselan (GMI-1271, IND #139758, NSC #801708) in combination with fludarabine and cytarabine for patients with acute myeloid leukemia, myelodysplastic syndrome or mixed phenotype acute leukemia that expresses E-selectin ligand on the cell membrane and is in second or greater relapse or that is refractory to relapse therapy

Study title for participants: A study to find the highest dose of uproleselan in combination with fludarabine and cytarabine for patients with AML, MDS or MPAL that has come back or does not respond to therapy and that expresses E-selectin ligand on the cell membrane.

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

Overview

You are being asked to take part in this research study because you have been diagnosed with Acute Myelogenous Leukemia (AML), Myelodysplastic Syndrome (MDS) or Mixed Phenotype Acute Leukemia (MPAL) that has either come back ("relapsed") or does not respond to therapy (is "refractory").

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

The overall goals of this study:

- **This is called a Phase 1 study because the goal is to find a safe dose of uproleselan that can be given without causing severe side effects;**
- **Learn what kind of side effects uproleselan can cause;**
- **Learn more about the pharmacology (how your body handles the drug) of uproleselan;**
- **Determine whether uproleselan is a beneficial treatment for your cancer**

The treatment involves cancer fighting medicine called chemotherapy (cytarabine and fludarabine) plus uproleselan. The treatment on this study takes about 2 months for 2 cycles of therapy. Uproleselan will be given by vein for 8 days and after 28 days your doctor will evaluate your cancer for each cycle. The entire 28-day period is called a cycle. You may continue to receive uproleselan for a total of 2 cycles unless you develop serious side effects, or your cancer worsens.

The dose for the first children enrolled on the study will be based on the side effects seen in adults. Between 2 and 6 children will receive uproleselan at this dose. If the side effects are not

too severe, 6 more children will receive Uproleselan at the same dose. Dosing is done this way because we do not yet know the best dose to use in children.

Whatever dose you start at, your dose will not be increased. If you have bad side effects, your dose may be decreased. Up to 2 different doses of uproleselan may be studied.

All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

Common side effects of chemotherapy include nausea, vomiting, hair loss, and fatigue (tiredness). Drugs may be given to try to prevent or decrease nausea and vomiting. Hair loss is usually temporary but very rarely it may be permanent. Some chemotherapy may make people permanently unable to have children. On rare occasions, people can get a second cancer from chemotherapy. This usually happens years after the chemotherapy is finished.

This study uses the investigational drug uproleselan. Some less common but notable side effects are infection, heartburn, reaction during or following a drug infusion, bruising, bleeding, and loss of appetite. The full list of risks for drug uproleselan are available in the section What side effects or risks can I expect from being in the study?

You can ask your study doctor questions about side effects at any time.

We hope that this study will help you personally, but we do not know if it will. The potential benefits to you associated with participation in this study are described in the section Are there benefits to taking part in the study?

You have a choice between another treatment for AML, MDS, or MPAL and this clinical trial.

The rest of this form provides detailed information about the study and what to expect should you decide to participate.

Why am I being invited to take part in this study?

You are being asked to take part in this research study because you have been diagnosed with AML, MDS, or MPAL that has either come back (“relapsed”) or does not respond to therapy (is “refractory”). AML, MDS and MPAL are types of cancer that occurs in the bone marrow.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services.

This study is being carried out by the Children’s Oncology Group (COG) Pediatric Early Phase Clinical Trial Network (PEP-CTN). COG is an international research group that consists of more than 200 hospitals that treat children with cancer. The PEP-CTN is the group within COG that consists of 21 hospitals and participation in this study will be limited to these hospitals.

There is a group of doctors and scientists who are working together to find new treatments for relapsed and refractory leukemia. The group is called the Pediatric Acute Leukemia (PedAL) initiative. PedAL doctors are testing several drugs that target specific types of leukemia.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between another treatment for AML, MDS, or MPAL and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your family and friends. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

What is the current standard of treatment for this disease?

We are asking if you want to participate in this study because there is not a standard treatment for your cancer at this point.

Why is this study being done?

This is a Phase 1 study of a drug called uproleselan. We are testing new experimental drugs such as uproleselan in the hopes of finding a treatment that may be effective against AML, MDS and MPAL that has come back or that has not responded to standard therapy. To enroll on this study, you need to first sign a consent form for the study APAL2020SC. This other study was explained to you in a different consent.

This study looks at how well uproleselan works when given to children and young adults with relapsed or refractory leukemia. Uproleselan is experimental because it has not been proven to work in a situation like yours. We are using uproleselan because it seems to work against cancer in test tubes and animals. Uproleselan has been used in adults and there is a lot that we do not know about it yet.

The overall goals of this study are to

- **This is called a Phase 1 study because the goal is to find a dose of uproleselan that we can give safely.**
- **Learn what kind of side effects uproleselan can cause;**
- **Learn more about the pharmacology (how your body handles the drug) of uproleselan;**
- **Determine whether uproleselan is a beneficial treatment for your cancer**

What will happen on this study that is research?

The treatment involves cancer fighting medicine called chemotherapy plus uproleselan. The treatment on this study takes about 2 months. Uproleselan will be given by vein for 8 days for about 20 minutes a day and after 28 days your doctor will evaluate your cancer. The entire 28-day period is called a cycle. On day 1, uproleselan will be given by vein once a day. On days 2-6 cytarabine and fludarabine will be given by vein once a day and uproleselan will be given by vein twice a day. On days 7 and 8, uproleselan will be given by vein twice a day. You may continue to receive uproleselan for a total of 2 cycles unless you develop serious side effects, or your cancer worsens.

Dose Escalation/ Dose Confirmation

The dose for the first children enrolled on the study will be based on the side effects seen in adults. Between 2 and 6 children will receive uproleselan at this dose. Whatever dose you start at, your dose will not be increased. If you have bad side effects, your dose may be decreased. Up to 2 different doses of uproleselan may be studied.

Diagram of Treatment

This chart shows the experimental parts of treatment on this study. Each cycle of treatment lasts 28 days and you will receive up to a total of 2 cycles of treatment.

Each Cycle (28 days)				
	uproleselan	**Fludarabine**	**Cytarabine**	**Assessment**
Day 1	once daily			
Day 2	twice a day	once daily	once daily	
Day 3	twice a day	once daily	once daily	
Day 4	twice a day	once daily	once daily	
Day 5	twice a day	once daily	once daily	
Day 6	twice a day	once daily	once daily	
Day 7	twice a day			
Day 8	twice a day			
Day 9				
…				
Day 28-35				Disease assessment

	How the drug will be given	**Days**
uproleselan	By vein	1-8
cytarabine and fludarabine	By vein	2-6

Experimental parts of treatment:

The experimental part of this study is that uproleselan is being given with cytarabine and fludarabine to patients who have relapsed or refractory AML, MDS, or MPAL. See Attachment 1 for full details of treatment on this study.

Additional Required Research Study Tests

A number of tests will be performed that are part of regular cancer care and may be done even if you do not take part in this study. A partial list is provided in Attachment 1.

The following tests will be done because you are part of this study. If you were not in the study you would probably not have these tests. You will not be charged for these tests.

Central Review of Measurable Residual Disease (MRD)
The study doctors want to look for measurable residual disease (MRD) in bone marrow and blood. MRD is a test to look for very small amounts of leukemia cells and is a standard test. If you participate in this study, the tissue is sent to a special laboratory called Hematologics, Inc. to perform the MRD tests. Your doctor will receive copies of these test results from Hematologics, Inc.

About ½ teaspoon to 1 teaspoon (2-4mL) of extra bone marrow will be drawn at the same time you are having a bone marrow procedure to assess your disease at the following times:

- End of Cycle 1
- End of Cycle 2

Pharmacokinetics:
During this study we will use some of your blood to do tests called pharmacokinetic tests. Pharmacokinetic tests determine how much of the uproleselan is in your blood. Pharmacokinetic blood samples will be required from all participants in the study. Because we cannot draw the samples from the same IV we give the drug through, we will start a separate IV to get the samples. Blood samples (2 mL or about ½ teaspoon each sample) will be collected before infusion begins and on the following timepoints.

For patients who weigh more than 10kg (approximately 22 pounds):

Day	**Timepoint**
Cycle 1 Day 1 (1st dose of uproleselan (GMI-1271))	Immediately pre-dose
	30 minutes after start of your dose (±5 minutes)
	1 hour after start of your dose (±20 minutes)
	2 hours after start of your dose (±20 minutes)
	4 hours after start of your dose (±20 minutes)
Cycle 1 Day 6	Immediately pre-dose
	30 minutes after start of your dose (±5 minutes)
	1 hour after start of your dose (±20 minutes)
	2 hours after start of your dose (±20 minutes)
	4 hours after start of your dose (±20 minutes)

For patients who weigh less than 10kg (approximately 22 pounds):

Day	**Timepoint**

Cycle 1 Day 1 (1st dose of uproleselan (GMI-1271))	Immediately pre-dose
	30 minutes after start of your dose (±5 minutes)
	1.5 hour after start of your dose (±20 minutes)
	4 hours after start of your dose (±20 minutes)
Cycle 1 Day 6	Immediately pre-dose
	30 minutes after start of your dose (±5 minutes)
	1.5 hour after start of your dose (±20 minutes)
	4 hours after start of your dose (±20 minutes)

What side effects or risks can I expect from being in the study?

Treatment Risks

All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

The risks of the individual drugs given as regular treatment are listed in Attachment 2.

Common side effects of chemotherapy include nausea, vomiting, hair loss, and fatigue (tiredness). Drugs may be given to try to prevent or decrease nausea and vomiting. Hair loss is usually temporary but very rarely it may be permanent. Some chemotherapy may make people permanently unable to have children. On rare occasions, people can get a second cancer from chemotherapy. This usually happens years after the chemotherapy is finished.

Side effects can be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. Low blood counts are described in the COG Family Handbook for Children with Cancer. Parents will be taught more about caring for their child when his or her blood counts are low.

Risks of Study

The use of chemotherapy (cytarabine and fludarabine) plus uproleselan instead of standard treatment may cause more complications.

The use of chemotherapy (cytarabine and fludarabine) plus uproleselan treatment that is being studied could be less effective than the current standard treatment.

You may lose time at school, work or home and spend more time in the hospital or doctor's office than usual. You may be asked sensitive or private questions which you normally do not discuss.

The chemotherapy used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drugs/study approach. Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

You can ask your study doctor questions about side effects at any time.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.
- The study doctor will provide you with information about other drugs you may need to avoid while receiving the study drugs.

This study uses the investigational drug uproleselan. The table(s) below show the common and the most serious side effects of the experimental treatment on this trial that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Risks and side effects related to uproleselan:

COMMON, SOME MAY BE SERIOUS
• **None**
OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving uproleselan (GMI-1271), from 4 to 20 may have:
• **Infection, especially when white blood cell count is low** • **Heartburn** • **Reaction during or following a drug infusion which may cause fever, chills, rash, low blood pressure** • **Bruising, bleeding** • **Loss of appetite** • **Pain** • **Dizziness, headache, tiredness** • **Changes in taste** • **Restlessness**
RARE, AND SERIOUS
• **None**

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

Reproductive risks
Women should not become pregnant and men should not father a baby while on this study because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex while on this study and for 3 months after the last dose of uproleselan. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some birth control methods might not be approved for use in this study. If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your treating physician immediately. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).

Are there benefits to taking part in the study?

The potential benefit of the treatment with uproleselan is that it may cause your cancer to stop growing or to shrink for a period of time. It may lessen the symptoms, such as pain, that are caused by the cancer. However, we do not know if you will benefit from taking part in this study. Information learned from this study may help future patients with cancer.

What other options are there?

Instead of being in this study, you have these options:
- **Getting treatment for your cancer without being in a study**.

- **Taking part in another study.**
- **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, instead it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

  Please talk to your doctor about these and other options.

How many people will take part in the study?

The total number of people enrolled on this study is expected to be 36.

How long is the study?

Although it is difficult to predict whom, if any child, may benefit, it is possible that people in this clinical trial may receive treatment on this study for up to 2 months (2 cycles of therapy).

We would like to continue to find out about your health for about 30 days after you enter this study. By keeping in touch with you for a while after you complete treatment, we can better understand the long-term effects of the study treatments.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study:
- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you
- if you become pregnant.

What about privacy?

We will do our best to make sure that the personal information in your medical record will be kept private. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Children's Oncology Group has a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the Children's Oncology Group will do their best to make sure that any information that goes out to others will not identify who you are. Information about this Certificate of Confidentiality is included in **Attachment 3**.

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

- **Children's Oncology Group and research partners**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research.**
- **The Institutional Review Board of this hospital**
- **National Cancer Institute Central Institutional Review Board (CIRB)**
- **The study sponsor and any drug company supporting the study or their designated reviewers.**

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

What are the costs?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

The NCI will supply uproleselan at no charge while you take part in this study. The NCI does not cover the cost of getting the uproleselan ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the uproleselan to the NCI for some reason. If this does happen, other possible options are:

- You might be able to get the uproleselan from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no uproleselan available at all, no one will be able to get more and the study would close.

If a problem with getting uproleselan occurs, your study doctor will talk to you about these options.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

You will not be paid for taking part in this study. The research may lead to new tests, drugs or other products for sale. If it does, you will not get any payment.

What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies COG if changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results, which will only be available after the study is fully completed. *A summary of the study results will also be posted on the Children's Oncology Group website (http://www.childrensoncologygroup.org/).* To receive the results, you may either (1) go to the COG website to check if results are available or (2) register your information with the COG on its web site and have an email sent to you when the results are available. Your pediatric oncology team from your hospital can give you additional instructions on how to do this. Please note, that the summary of results may not be available until several years after treatment for all people on the study is completed, and not only when you complete treatment.

Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. *XXXX* or your doctor at *XXXX*.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call *XXXX* Institutional Review Board (IRB) Administrator at *XXXX*.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at *XXXX*.

Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at https://www.childrensoncologygroup.org/index.php/cog-family-handbook.

Visit the NCI's Web site at http://www.cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

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

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Signature

I have been given a copy of all _____ pages of this form. The form includes (*number (N)*) attachments.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

Attachment 1

Study Treatment and Procedures

Methods for Giving Drugs

Various methods will be used to give drugs:

- **IV** - Drug is given using a needle or tubing inserted into a vein. Drugs can be given rapidly over a few minutes ("push") or slowly over minutes or hours ("infusion").
- **IT** - Drug used to treat the brain and spinal cord is given using a needle inserted through the back into the fluid surrounding the spinal cord.
- **PO** - Drug is given by tablet or liquid swallowed through the mouth.

Central Line

Your doctor may recommend that you get a special kind of IV called a "central line." This is a kind of IV placed into a big vein in your body, usually in the chest, that can stay in for a long time. The risks connected with central lines will be explained to you and all of your questions will be answered. If you are to have a central line inserted, you will be given a separate informed consent document to read and sign for this procedure. A description of the types of central lines is in the COG Family Handbook for Children with Cancer.

Treatment Tables

The treatment described below is the full study treatment for a single cycle of uproleselan. Treatment is planned for 2 cycles.

Drug	How the drug will be given	Days
uproleselan	IV over 20 minutes	1-8
cytarabine	IV over 1-3 hours	2-6
fludarabine	IV over 30 minutes	2-6
IT therapy (either IT cytarabine or ITT, your doctor will decide)	IT	• 1 and 28 for all patients • Also on days 7, 14, and 21 for patients who have leukemia in the brain or spinal cord
leucovorin (only for patients with Down syndrome who are receiving ITT)	PO or IV	1, 8, 15, 22, 29

*ITT – intrathecal triple therapy with methotrexate, hydrocortisone, cytarabine

Standard Tests and Procedures

The following tests and procedures are part of regular cancer care and may be done even if you do not join the study.

- Frequent labs to monitor your blood counts and blood chemistries.
- Urine tests to measure how your kidneys are functioning.
- Pregnancy test for females of childbearing age before treatment begins.
- Tests to monitor your heart and lung function.

- Bone marrow aspiration tests to see if the cancer is responding to treatment. The bone marrow procedure is described in the COG Family Handbook for Children with Cancer.
- Spinal Taps to check for cancer cells in the spinal fluid and to give chemotherapy into the spinal fluid. This is described in the COG Family Handbook for Children with Cancer.

Attachment 2

Risks of Standard Drugs Used to Treat AML, MDS, and MPAL on this trial

Possible Side Effects of Cytarabine by vein or under the skin

COMMON, SOME MAY BE SERIOUS In 100 people receiving cytarabine, more than 20 and up to 100 may have:
• **Blood clot** • **Rash** • **Swelling in the rectum which may cause rectal pain** • **Diarrhea, loss of appetite, nausea, vomiting** • **Sores in mouth and GI tract which may cause difficulty swallowing or pain** • **Fever**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cytarabine, from 4 to 20 may have:
• **Heart failure which may cause shortness of breath, swelling of ankles, cough and tiredness** • **Damage to the lungs which may cause shortness of breath** • **Infection, especially when white blood cell count is low** • **Anemia which may cause tiredness, or may require blood transfusions** • **Bruising, bleeding** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Numbness and tingling of the arms and legs** • **Muscle pain** • **Severe blood infection** • **Kidney damage which may cause swelling, may require dialysis** • **Headache** • **Dizziness** • **Flu-like syndrome with fever, bone pain, rash, redness of eyes, or chest pain** • **Chest pain** • **Hair loss** • **Liver damage which may cause yellowing of skin or eyes** • **Swelling and redness of the eye**

RARE, AND SERIOUS In 100 people receiving cytarabine, 3 or fewer may have:
• **Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness** • **Difficulty speaking, trouble standing or walking** • **Swelling and redness at the site of the medication injection (SubQ)**

Possible Side Effects of Cytarabine when given into the spinal fluid (intrathecal):

COMMON, SOME MAY BE SERIOUS In 100 people receiving cytarabine, more than 20 and up to 100 may have:
• **Nausea, vomiting** • **Fever** • **Headache**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cytarabine, from 4 to 20 may have:
• **Anemia which may cause tiredness, or may require blood transfusions** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Tiredness, dizziness, loss of coordination** • **Numbness and tingling of the arms and legs** • **Inflammation of the lining of the brain that can lead to headache, numbness and tingling**

RARE, AND SERIOUS In 100 people receiving cytarabine, 3 or fewer may have:
• **Seizure** • **Paralysis** • **Blurred vision with a chance of blindness** • **Damage to the brain that may result in a decrease in the ability to learn**

Possible Side Effects of Fludarabine:

COMMON, SOME MAY BE SERIOUS In 100 people receiving fludarabine, more than 20 and up to 100 may have:
• **Infection, especially when white blood cell count is low** • **Vomiting, loss of appetite** • **Tiredness, fever** • **Pain** • **Bruising, bleeding** • **Cough** • **Increased risk of unusual infections lasting more than 6 months**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving fludarabine, from 4 to 20 may have:
• **Anemia, kidney problems which may cause tiredness, bruising, or swelling** • **Visual disturbances*** • **Nausea, chills** • **Feeling of "pins and needles" in arms and legs** • **Damage to organs (brain, lungs, others) which may cause tiredness, changes in thinking or shortness of breath** • **Confusion**

RARE, AND SERIOUS In 100 people receiving fludarabine, 3 or fewer may have:
• **Coma, seizures (with high dose)** • **Blindness*** • **Kidney damage which may require dialysis**

*Rarely, fludarabine has been associated with damage to or inflammation of the optic nerve (the nerve from the brain to the eye) which can cause blurred vision with a chance of blindness, decreased vision, other visual disturbances, or pain with eye movements.

Possible Side Effects of Leucovorin:

COMMON, SOME MAY BE SERIOUS In 100 people receiving leucovorin, more than 20 and up to 100 may have:
• **Diarrhea, nausea, vomiting** • **Sores in mouth which may cause difficulty swallowing** • **Tiredness**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving leucovorin, from 4 to 20 may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**

RARE, AND SERIOUS In 100 people receiving leucovorin, 3 or fewer may have:
• **None**

Possible Side Effects of Triple Intrathecals - Methotrexate, Cytarabine (ARA-C) and Hydrocortisone when given into the Spinal Fluid (Intrathecal):

COMMON, SOME MAY BE SERIOUS In 100 people receiving triple intrathecals (methotrexate, cytarabine, hydrocortisone), more than 20 and up to 100 may have:
• **Nausea, vomiting** • **Fever** • **Headache**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving triple intrathecals (methotrexate, cytarabine, hydrocortisone), from 4 to 20 may have:
• **Inflammation of the lining of the brain that can lead to headache, stiff neck, numbness and tingling** • **Bruising, bleeding** • **Pain** • **Numbness and tingling of the arms and legs** • **Tiredness, sleepiness, dizziness, loss of coordination, confusion** • **Rash**

RARE, AND SERIOUS In 100 people receiving triple intrathecals (methotrexate, cytarabine, hydrocortisone), 3 or fewer may have:
• **Damage to the brain that may result in a decrease in the ability to learn** • **Seizure** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Paralysis, weakness** • **Blurred vision with a chance of blindness** • **Bleeding into the space of the spine at the site of the injection**

Attachment 3

Certificate of Confidentiality

The Children's Oncology Group is covered by a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.
The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.