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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May 1, 2023

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Dear Ms. Kruhm,

Please find attached Amendment #1 to **PEPN2113**, *A Phase 1 and pharmacokinetic study of Uproleselan (GMI-1271, IND #[redacted], 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 Protocol Due to PCIRB Stipulations (From April 17th, 2023):

#	Section	Page(s)	Comment
1.	2.5.2	14	In the originally submitted amendment, there was duplicate language added. The language newly added language was removed for clarity.
2.	Appendix III	81	~~SGOT~~ was revised to **AST**.
3.	Appendix VI	86	The street address for Glycomimetics, Inc. was capitalized.

II. Changes Made to the Protocol by the Principal Investigator:

#	Section	Page(s)	Comment
1.	General	General	The version date has been updated.
2.	Study Committee	6	The list of study committee members has been updated.
3.	Experimental Design Schema	8	The experimental design schema is now labeled as "**Table 1 – Experimental Design Schema**".
4.	1.2.2	9	The secondary objective listed in 1.2.2 has been updated as follows: • To describe the antileukemic activity of uproleselan (GMI-1271) (**COG-CR/CRp/CRi and rates of MRD negative response after up to two cycles of therapy) in combination with fludarabine and cytarabine within the limits of a Phase 1 study.**
5.	2.5.2	14	The section has been updated as follows: • ~~If no dose limiting toxicities are observed, a second dose (20mg/kg) will be tested; this dose corresponds to the highest dose tested in adults with AML and is known to be well tolerated.~~
6.	4.1.2	19	The age criteria has been updated as follows: • Patients must be **≥1 year and** <18 years of age at the time of study enrollment.
7.	4.1.3	19	The section has been updated as follows: • Patients, with or without Down syndrome (DS), and with de novo acute myeloid leukemia, therapy-related acute myeloid leukemia, myelodysplastic syndrome **with increased blasts (MDS-IB)**, therapy-related myelodysplastic syndrome **with increased blasts (MDS-IB)** or mixed phenotype acute leukemia that expresses E-selectin ligand on the cell membrane according to APAL2020SC screening results and meet one of the following: ○ Second or greater relapse or refractory myelodysplastic syndrome (MDS) **with increased blasts (MDS-IB)**.
8.	4.1.4.1	20	The subsection has been updated as follows: • Bone marrow relapse **and MDF – MRD relapse** • A single bone marrow sample showing ≥1% leukemic blasts by multidimensional flow cytometry performed at the central laboratory **(performed only at Hematalogics through the screening study APAL2020SC)**.

9.	4.1.4.3	20	The subsection has been updated as follows: • Refractory disease **and MDF – MRD refractory** • Following a re-induction cycle after any relapse, presence of ≥1% leukemic blasts by **multidimensional** flow cytometry performed at the central laboratory (performed only at Hematologics through the screening study APAL2020SC), OR there is persistent extramedullary disease. **In cases where a bone marrow aspirate cannot be obtained because of extensive fibrosis, assessment of refractory disease will be defined as described above in 4.1.4.1 II.**
10.	4.1.7	21	The section has been updated as follows: • Patients must have fully recovered **(grade <2)** from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. • **Patients must be off calcineurin inhibitors for at least 28 days prior to the start of protocol therapy. Patients may be on physiological doses of steroids (equivalent to ≤10 mg prednisone daily for patients ≥18 years or ≤10mg/m2/day for patients <18years).**
11.	4.1.8.2	22	The section has been updated with revised renal and liver function requirements.
12.	5.1	24	The experimental design schema in Section 5.1 is now labeled as '**Table 2 – Experimental Design Schema**'.
13.	5.1.4.1	26	The Cytarabine IT dosing table is now labeled as '**Table 3 – Cytarabine IT Dosing by Age**'.
14.	5.1.4.2	26	The Intrathecal Triple Therapy (ITT) dosing table is now labeled as '**Table 4 – ITT Dosing by Age**'.
15.	5.3	27	• The title of the section has been revised as follows: ○ Dose ~~Escalation~~ **Level** Schema • The Uproleselan dosing table is now labeled as 'Table 5 – Uproleselan Dose Level Schema'. ○ Dose Level 2 has been removed • The following paragraph has been revised as follows: ○ A Dose Level **2** ~~3~~ will only be considered after evaluation of PK and toxicity at Dose Level **1** ~~2~~. If PK clearance is >30% compared to adults and if the MTD has not been reached at Dose Level **1** ~~2~~, a Dose Level **2** ~~3~~ will be considered. • The previous Section 5.3.2 (Intra-Patient Escalation) has been removed: ○ ~~Intra-patient dose escalation is not allowed.~~
16.	5.5	28	The sentence has been revised as follows: • The DLT observation period ~~for the purposes of dose-escalation~~ will be the first cycle of therapy.
17.	5.5.1.1	28	**Grade 3 tumor lysis syndrome** has been added.
18.	6.3.1.2	34	The Intrathecal Cytarabine dosing table has been labeled as '**Table 6 – Intrathecal Cytarabine Age-based Dosing**'.
19.	6.3.2.2	35	• The Fludarabine dosing table has been labeled as '**Table 7 – Fludarabine Dosing Guidelines**. • Creatinine Clearance mL/min/1.73m^2 of ~~50~~ has been revised to **70**.

20.	8.1	38	The section has been revised as follows: • The roadmap in Section 8.1 has been labeled as '**Table 8 – Required Clinical, Laboratory, and Disease Evaluation**'. • Phase 1 ~~Dose Escalation~~ Cohort.
21.	8.3.2	40	• The sampling schedule schema for patients weighing 10kg or more has been labeled as '**Table 9A – Pharmacology Sampling Schedule (for patients > 10kg)**'. • The sampling schedule schema for patients weighing less than 10kg has been labeled as '**Table 9B – Pharmacology Sampling Schedule (for patients < 10kg)**'. • Added **(±20 minutes)** to the pre-dose sample in both Table 9A and Table 9B.
22.	8.3.4	42	The following statement has been added: • **Samples should be batched and sent together after day 6, once Day 6 samples have been collected and processed as above.**
23.	8.3.6	42	The Pharmacokinetic sample shipping instructions have been updated as follows: • ~~The primary and back up aliquots will be shipped on separate days to mitigate loss (Monday - Wednesday only), via overnight carrier with the appropriate amount of dry ice.~~ • **Samples will be shipped Monday-Wednesday only via overnight carrier with the appropriate amount of dry ice. Sites will ship primary aliquots and store back-up aliquots in a freezer set at -70 to -80°C until they are asked to ship them.**
24.	9.1	43	The molecular structure of Uproleselan has been labeled as '**Figure 2 – Uproleselan (MGI-1271) Molecular Structure**'.
25.	9.1.10	45	Version 2.1, July 9, 2019[25] has been revised to Version 2.1, July 9, 2019[1].
26.	9.2	48-55	The titles of the following tables have been updated: • **Table 10 -** Toxicity: (Intravenous, SubQ, IM) • **Table 11 -** Toxicity: (Intrathecal) • **Table 12 – Cytarabine: Intrathecal Administration Guidelines by Age** • **Table 13 – Fludarabine** Toxicity • **Table 14 -** Intrathecal Triple Therapy (Methotrexate/Hydrocortisone/Cytarabine) Toxicity • **Table 15 – Methotrexate Dosing Guidelines by Age** • **Table 16 – Leucovorin Calcium** Toxicity
27.	10.1	56	The sentence has been revised as follows: • a) Treatment failure (See ~~Appendix IX~~ **Appendix VIII** for definitions).
28.	11.1	57	The section has been revised with updated information.
29.	11.2.2	57	The following statement has been removed: • If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation can proceed. The paragraph has been updated as follows: • The DLTs observed in the pharmacokinetic (PK) expansion cohort will be counted towards the total number of DLTs observed at the MTD during the dose escalation portion of the study. If ≥ 1/3 of the cohort of

			patients at the MTD (during the dose evaluation plus the PK expansion) experience DLT then the MTD will be exceeded. • **If the maximum dose level (DL1) is safe (i.e., less than 1/3 of patients experience a Cycle 1 DLT among 6 DLT-evaluable patients), then DL1 will be the RP2D.** • **Patients enrolled in the PK expansion cohort will be replaced if unevaluable for PK analysis defined as pre-dose, 30 minutes and 2 hrs after the dose on days 1 and 6 for patients with weight ≥ 10 kg; pre-dose, 30 minutes and 1.5 hrs after the dose on days 1 and 6 for patients with weight <10 kg**
30.	11.3	58	The section has been revised as follows: • Dose **Evaluation** ~~Escalation~~ and Determination of MTD • The section has been replaced with revised information.
31.	11.4	58	The following statement was added: • **If the study agent is too toxic and no MTD/RP2D is determined, then no patients will be enrolled in the PK expansion cohort.**
32.	11.5	58-59	The Planned Enrollment Report table is now labeled as '**Table 17 – Planned Enrollment Report**' and has been updated with new patient enrollment numbers.
33.	12.2	59	The section has been revised as follows: • ~~Best~~ **COG** Response **Assessment** • The patient's best response assignment will ~~depend on the achievement of both measurement and confirmation criteria~~ **be assessed according to the specific criteria defined in Appendix VIII**.
34.	12.3	60	The section has been revised with updated CNS staging.
35.	13.1	62	Table A has been updated as follows: • ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported via CTEP-AERS **with full follow-up reports submitted** within the timeframes detailed in the table below.
36.	Appendix II	79-80	The Central Monitoring plan and the appendix have been updated with the most recent CRF information.
37.	Appendix III	81	ALT grading table has been replaced with: • **Use institutional ULN for ALT and CTCAE v 5 criteria for grading.**
38.	Appendix IV	82-83	The Youth Information Sheets have been revised to replace the word "~~highest~~" with "**safe**".
39.	Appendix VIII	92-93	The appendix has been updated as follows: • **For patients enrolled onto this study with ≥5% blasts, definitions of complete, partial or incomplete count recovery will be assessed using COG-specific criteria for pediatric patients.** • ~~Definitions of complete, partial or incomplete count recovery are the same as described below.~~ • COG Response Criteria has been added. Bone Marrow Relapse criteria has been updated.

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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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Closed:

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Amendment: 1

PEPN2113

A Phase 1 and pharmacokinetic study of Uproleselan (GMI-1271, IND #[redacted], 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

Lead Organization: COG Pediatric Early Phase Clinical Trials Network (PEP-CTN)

NCI Supplied Agent: Uproleselan (GMI-1271) (NSC# 801708, IND# 139758)

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CONTACT INFORMATION		
For Regulatory Requirements	**For patient enrollments:**	**For Data Submission**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://open.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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AGENT	NSC#	Supplier
Uproleselan (GMI-1271)	801708	NCI CTEP
Cytarabine		
Fludarabine	63878	Commercial
Methotrexate	312887	Commercial
Hydrocortisone	740	Commercial
Leucovorin	10023	Commercial
	3590	Commercial

IND Number (or IND Exempt):
139758
IND Sponsor: NCI

This trial 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 your 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.
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ABSTRACT
The survival of children with relapsed acute myeloid leukemia (AML) has not improved over the past decades and remains dismal. Novel therapeutic strategies with tolerable side effects are needed. While most novel therapeutic approaches have attempted to target leukemic cell-intrinsic genomic defects, it is becoming evident that extrinsic factors such as the bone marrow microenvironment also plays a significant role. E-selectin is an adhesion molecule implicated in cancer progression, development of metastases and adhesion mediated chemotherapy resistance. Preclinical *in vivo* studies have shown that the bone marrow microvasculature of mice with AML have 5-10 fold higher expression of E-selectin compared to healthy mice and that AML blasts cells, which almost universally express the E-selectin ligand, are able to bind E-selectin more efficiently than normal hematopoietic cells. Uproleselan (GMI-1271) is a selective E-selectin competitive inhibitor which antagonizes the binding of the ligand to E-selectin. *In vivo* studies have shown that treatment with GMI-1271 in combination with cytarabine and/or daunorubicin reverses chemotherapy resistance and allows longer disease-free survival in an MLL-AF9 AML mouse model compared to mice treated with chemotherapy only or vehicle. The mechanism underlying the increased sensitivity to chemotherapy when GMI-1271 is used, is unclear but it appears to be related to the release of AML blasts and leukemia-initiating cells from the bone marrow niche to the peripheral blood. GMI-1271 has been studied in combination with mitoxantrone and cytarabine in adult patients with relapsed and refractory AML and in combination with daunorubicin and cytarabine in adult patients with newly diagnosed AML. GMI-1271 was well tolerated with no dose limiting toxicities reported at any of the tested dose levels and a maximum tolerated dose was not identified. Rates of responses compared favorably with historical controls and appeared to be related to the functional binding of E-selectin ligand expressed on the AML blasts to E-selectin expressed on the endothelial cells of the bone marrow. Importantly, and as also reported in the preclinical studies, the incidence of mucositis and related infectious events was significantly lower than in historical controls. A randomized phase 3 trial of GMI-1271 with chemotherapy in adult patients with relapsed and newly diagnosed and relapsed AML is ongoing. This is a Phase 1 and pharmacokinetic study of GMI-1271 in combination with fludarabine and cytarabine for children with relapsed and refractory AML, MDS (myelodysplastic syndrome) and MPAL (mixed phenotype acute leukemia) whose blasts express the E-selectin ligand. Patients are allowed to receive up to two cycles of therapy. Once the MTD and /or RP2D is determined, an expansion cohort will further assess the safety and preliminary activity of this combination.

EXPERIMENTAL DESIGN SCHEMA

Table 1 – Experimental Design Schema

Each Cycle (28 days)						
	Uproleselan (GMI-1271) IV	**Fludarabine IV**	**Cytarabine IV**	**Cytarabine IT**	**IT Triples**	**Leucovorin PO or IV**
Day 0				once daily[1]	once daily[1]	
Day 1	once daily					24 and 30hrs post ITT[2]
Day 2	q12hr	once daily	once daily			
Day 3	q12hr	once daily	once daily			
Day 4	q12hr	once daily	once daily			
Day 5	q12hr	once daily	once daily			
Day 6	q12hr	once daily	once daily			
Day 7	q12hr			Weekly[1]	Weekly[1]	
Day 8	q12hr					24 and 30hrs post ITT[2]
Day 9						
…						
Day 14				Weekly[1]	Weekly[1]	
Day 15						24 and 30hrs post ITT[2]
Day 21				Weekly[1]	Weekly[1]	
Day 22						24 and 30hrs post ITT[2]
Day 28				Weekly[1]	Weekly[1]	
Day 29[3]						24 and 30hrs post ITT[2]

[1] Choice between IT Cytarabine OR IT Triples is up to the treating physician's discretion. Weekly intrathecal chemotherapy treatments are for CNS 2/3 patients ONLY. A minimum of 4 and a maximum of 6 intrathecal treatments may be given (count includes day 0 IT and may carry over into Cycle 2 of chemotherapy).

[2] Down syndrome patients ONLY. Administer 24 & 30 hours after each IT Triples.

[3] End of cycle bone marrow for disease assessment may be performed any day between Day 28-35.
[4] Day 28 lumbar puncture can be done at the same time as the end of cycle bone marrow assessment between day 28-35.

A cycle of therapy is considered to be 28 days. Upon count recovery, patients may receive a second cycle of uproleselan (GMI-1271) in combination with fludarabine and cytarabine if there is evidence of clinical benefit in the opinion of the treating physician and eligibility criteria are met for organ function criteria.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose or recommended Phase 2 dose of uproleselan (GMI-1271) administered in combination with fludarabine and cytarabine to patients with AML, myelodysplastic syndrome (MDS) or mixed phenotype acute leukemia (MPAL) whose blasts express the E-selectin ligand and that are in second or greater relapse or refractory to relapse therapy.

1.1.2 To characterize the pharmacokinetics of uproleselan (GMI-1271) in combination with fludarabine and cytarabine in patients with refractory and/or relapsed AML, MDS or MPAL.

1.1.3 To define and describe the toxicities of uproleselan (GMI-1271) in combination with fludarabine and cytarabine among patients with relapsed and/or refractory AML, MDS or MPAL.

1.2 Secondary Aims

1.2.1 To describe the expression of E-selectin ligand on the surface of myeloid leukemic blasts at relapse prior to initiation of uproleselan (GMI-1271) in combination with fludarabine and cytarabine and at completion of the cycle.

1.2.2 To describe the antileukemic activity of uproleselan (GMI-1271) (COG-CR/CRp/CRi and rates of MRD negative response after up to two cycles of therapy) in combination with fludarabine and cytarabine within the limits of a Phase 1 study.

1.3 Exploratory Aims

1.3.1 To determine the largest relative reduction in myeloid leukemic blast percentage in the bone marrow, calculated from baseline at time of enrollment to up to two cycles of therapy.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development in Pediatric Population

Improvement in supportive care measures and optimization of stem cell transplantation have led to an improved survival for children with relapsed acute myeloid leukemia. However, the risk of subsequent relapse and refractoriness to salvage therapy has not changed in the past decades and the outcome of these patients remains dismal[1-3]. Thus, novel therapeutic strategies with tolerable side effects are needed to eradicate the disease. While most studies have attempted to target the intrinsic genomic defects responsible for leukemogenesis and resistance to treatment, it is becoming evident that extrinsic factors such as the bone marrow microenvironment, also play a significant role in relapsed disease. We propose to investigate the safety and tolerability of GMI-1271, an E-selectin inhibitor with minimal toxicity and promising activity in adults with AML, in combination with fludarabine and high-dose cytarabine and to characterize its pharmacokinetic properties in patients with refractory or second or greater relapse of AML, MDS or MPAL.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

2.2.1.1 Physiologic roles of E-selectin:

E-selectin is a transmembrane, calcium-dependent lectin that mediates cell-cell adhesion. E-selectin binds to the terminal sialyl Lewis^x tetrasaccharide displayed at the end of a glycan epitope expressed by human leukocytes and human leukemic cells[1, 2]. Following inflammation or tissue injury, E-selectin is expressed on endothelial cells where it facilitates the recruitment of leukocytes and their extravasation across the endothelium to reach the extravascular tissue[2]. E-selectin has also an important role in the regulation of hematopoietic stem cells (HSC) homeostasis within the HSC niche. Following hematopoietic stress, endothelial cells in the perivascular HSC niche rapidly upregulate the expression of E-selectin and through the binding to the E-selectin ligands expressed on the HSC, signal the HSCs to proliferate and replenish the hematopoietic system. Consistent with these roles, mice deficient of both E and P selectins succumb to bacterial infections, are less likely to develop allergic reactions and exhibit defective engraftment of wild type HSC[1, 3, 4]. Furthermore, HSCs of *E-selectin* knock-out mice or wild type mice treated with GMI-1271, a selective E-selectin competitive inhibitor which antagonizes the binding of the ligand to E-selectin, show reduced turnover, increased quiescence, and increased self-renewal potential and resistance to chemotherapy[5]. Additionally, during the course of these experiments, it was noted that *E-selectin* knock-out mice treated with 5-fluorouracil or radiotherapy survived longer than wild type mice, had a faster recovery of neutrophils following myelosuppressive chemotherapy and did not develop weight loss. Further investigation demonstrated that absence of E-selectin almost completely abrogated chemotherapy induced intestinal mucositis which instead was severe in wild type mice. In conclusion, the prolonged survival of *E-selectin* knock-out mice was likely due to the absence of mucositis and the decreased incidence of sepsis[6].

2.2.1.2 Role of E-Selectin in AML

Several adhesion molecules, including E-selectin, have been implicated in cancer progression, metastases and development of cell adhesion mediated drug resistance[7-9]. The bone marrow microvasculature in mice with AML have 5-10 fold higher expression of E-selectin on the cell surface compared to healthy mice and compared to AML in matched *Sele*$^{-/-}$ (E-selectin knock-out) hosts. *In vitro* coculture studies demonstrate that TNF-α produced by AML blasts leads to upregulation and increased expression of E-selectin on endothelial cells[10]. Additionally, in a murine model of AML generated by transduction of the *MLL-AF9* fusion gene in the HSCs, leukemic blasts upregulated E-selectin ligand expression following transformation, suggesting a relationship between leukemic blasts and the bone marrow microenvironment. Indeed, inhibition of E-selectin binding to its ligand by the E-selectin inhibitor GMI-1271, effectively mobilized leukemic blasts, but not hematopoietic progenitor cells, from the bone marrow to the peripheral blood in the MLL-AF9 murine model and sensitized leukemic blasts to cytarabine. Notably, mobilization to the peripheral blood was more pronounced for leukemia regenerating cells than for leukemic blasts. Similar results were obtained when AML was induced in *E-selectin* knock-out mice as well as in several other AML mouse models[10]. These results support the notion that the vascular bone marrow niche can regulate sensitivity to chemotherapy and that E-selectin, in particular, can retain leukemic blasts and leukemic stem cells in the bone marrow niche providing resistance to chemotherapy.

2.2.2 Preclinical *In Vitro* Studies

Proinflammatory cytokines released by the AML blast cells increase E-selectin expression of the endothelial cells of the bone marrow, raising the possibility that AML cells hijack the bone marrow niche to create a protective environment for their survival and resistance to therapy. *In vitro* studies of AML blasts adherent to a series of immobilized recombinant adhesion molecules human IgG1-Fc proteins demonstrated that adhesion to E-selectin was associated with more than 4-fold increase in survival following exposure to cytarabine compared to blasts adherent to other adhesion molecules or control. Furthermore, chemoresistance mediated by E-selectin binding was specific as it could be reverted by the addition of RME-1, an E-selectin blocking antibody[10]

2.2.3 Preclinical *In Vivo* Studies

The role of the vascular niche in mediating resistance to therapy and supporting a survival benefit in AML was elucidated in a well-established MLL-AF9 mouse model of aggressive AML. First, E-selectin binding potential was shown to be significantly higher in AML blasts than in normal hematopoietic stem cells. Second, to explore the effect of E-selectin in promoting survival of leukemia regenerating cells, cohorts of E-selecting knock-out mice ($Sel^{-/-}$) and wild type mice carrying MLL-AF9 AML and treated with GMI-1271 or vehicle were exposed to high dose cytarabine for 24 hours and femoral bone marrow cells were then harvested and transplanted in recipient mice in limiting dilutions; the proportion of recipients that developed AML was significantly higher in the cohort of mice transplanted with cells originated from wild type mice carrying a functional E-selectin compared to those transplanted from $Sel^{-/-}$ or GMI-1271 treated mice providing evidence that E-selecting binding promotes chemo-resistance and survival, a process that can be inhibited by the administration of GMI-1275. Importantly, treatment with the E-selectin inhibitor GMI-1271 was also shown to synergize with conventional chemotherapy; wild type mice carrying MLL-AF9 AML treated with combination chemotherapy (doxorubicin and cytarabine) and GMI-1271 had significantly longer disease-free survival compared to mice treated with combination chemotherapy alone or with vehicle. Lastly, in a patient derived xenograft model of AML, treatment with GMI-1271 reversed adhesion-mediated chemotherapy resistance to cytarabine and daunorubicin[11]. The exact mechanisms by which E-selectin mediates chemoresistance have not been fully elucidated. Preliminary studies analyzing the transcriptome of leukemic blasts following exposure to GMI-1271 have suggested that E-selectin may activate the AKT and NF-kB pro-survival signaling pathway supporting an escape mechanism to the apoptotic effect of chemotherapy[10].

2.2.4 Preclinical Adsorption, Distribution, Metabolism, Elimination and Toxicology (ADMET) Studies

The pharmacokinetic (PK) profile of GMI-1271 has been evaluated after intravenous administration in mice, rats, and monkeys; PK profile of GMI-1271 in combination with daunorubicin and cytarabine has also been evaluated in mice in which it showed no apparent change in the concentration of GMI-1271 or of daunorubicin and cytarabine, suggesting the lack of interaction between the three drugs. In mice, PK of GMI-1271 was non-dose-dependent and GMI-1271 was rapidly cleared with a $t_{1/2}$ of approximately one hour and without accumulation after daily or twice daily doses. GMI-1271 is widely distributed after IV administration to mice except for brain, bone, skeletal muscle, and testis. It does not undergo hepatic metabolism, is minimally bound to protein, does not bind to melanin and is excreted in the urine for about 2/3 of the dose in mice; in humans, GMI-1271 is almost entirely renally excreted intact. Single dose and repeat single dose toxicity analysis for up to 91 days was conducted. GMI-1271 was very well tolerated with minimal, reversible non-adverse effects observed. There were no effects on body weight, organ weight, or food consumption; no effects also on the ophthalmologic, cardiovascular, nervous, and respiratory systems. Uproleselan (GMI-1271) had no mutagenic effects, and does not absorb visible or UV

light to exert phototoxicity; carcinogenicity, reproductive and developmental toxicity studies have not been conducted.

2.3 Adult Studies

2.3.1 Clinical studies with GMI-1271in AML

GMI-1271 is a specific E-selectin competitive inhibitor which antagonizes the binding of the ligand to E-selectin. Based on the nearly universal expression of E-selectin ligand on human AML leukemic blasts and the *in vivo* preclinical studies suggesting the potential benefit of GMI-1271 as a chemo-sensitizer, several clinical trials have been developed to investigate the activity of GMI-1271 in patients with AML. A Phase 2 trial (NCT02306291) enrolled a first cohort of patients with relapsed and refractory AML (n=47) who received GMI-1271 with mitoxantrone, etoposide and cytarabine (MEC) and a second cohort of treatment naïve patients (n=25) who received GMI-1271 with cytarabine and daunorubicin (7+3). The combinations were well tolerated. Approximately 30-35% of patients experienced Grade 3 and 4 adverse events attributed to GMI-1271 with febrile neutropenia, anemia, thrombocytopenia and sepsis being the most common events; other common adverse events, mostly Grade 1 and 2, were fatigue, nausea, vomiting and diarrhea. Importantly, no Grade 3 and 4 events of mucositis were reported in newly diagnosed patients and in only 2% of patients with relapsed and refractory AML (historically approximately 20%). Forty-one percent of patients with relapsed and refractory AML achieved complete remission (CR) or CR with incomplete count recovery (CRi) which compared favorably with the reported CR rate of 25% in a similar population[12]; importantly, 69% of patients who achieved CR or CRi had no minimal residual disease (MRD) in the bone marrow. The median OS was 8.8 months. Among treatment naïve patients, 72% achieved CR or CRi, as compared to approximately 50% CR rate achieved with daunorubicin and cytarabine alone in a similar patient population[13]; additionally, 56% of patients achieving CR/CRi were MRD negative; the median overall survival was 12.6 months and the median event free survival was 9.2 months. Based on these encouraging results a randomized Phase 3 trial of GMI-1271 in combination with chemotherapy for patients with relapsed and refractory AML(NCT03616470) and newly diagnosed (NCT03701308) was initiated and is ongoing[14] to better assess the contribution of GMI-1271 to safety and efficacy.

2.3.2 Pharmacokinetic and pharmacodynamic studies

Clinical studies of GMI-1271 have thus far been conducted solely in healthy adult subjects and adult patients with AML (NCT02306291), multiple myeloma (NCT02811822), and deep vein thrombosis (NCT02744833). A Phase 1 trial of GMI-1271 in combination with mitoxantrone, etoposide and cytarabine for adult patients with relapsed and refractory AML demonstrated that the combination is safe and well tolerated (NCT02306291)[15, 16]. Three dose levels were tested: 5 mg/kg (starting dose), 10 mg/kg and 20 mg/kg. No dose limiting toxicity (DLT) was reported and the recommended Phase 2 dose was determined to be 10 mg/kg. The choice of 10 mg/kg, as recommended Phase 2 dose in adults, was based on target saturation, population pharmacokinetic modeling, preclinical toxicity studies, and the absence of dose-limiting toxicities at any dose level. Pharmacokinetics (PK) were linear with a dose proportional increase in exposure and similar to the PK data obtained in healthy volunteers, suggesting that concomitant administration of chemotherapy did not affect PK. Minimal accumulation of GMI-1271 was observed, as expected based on the short half-life, and clearance varied based on renal function but not on body weight in adults. As observed in preclinical studies, no time-related changes in pharmacokinetic metrics were observed at any dose level; additionally, no defined relationship was identified between exposure and safety or clinical efficacy outcomes over the dose range of 5 to 20 mg/kg (See Fig. 1 A-B); no relationship was demonstrated between the fraction of time above IC50 and IC90 and response across all tested doses; as shown in Fig. 1 C-D, the fraction of time above IC50 ranged from 30% to 100% and the fraction above IC90 ranged from 10% to 100% with no correlation with response.

Notably, all pharmacokinetics parameters of exposure in humans were superior to those attained in mice at efficacious doses, including the fraction of time above IC50 and IC90. Correlative studies

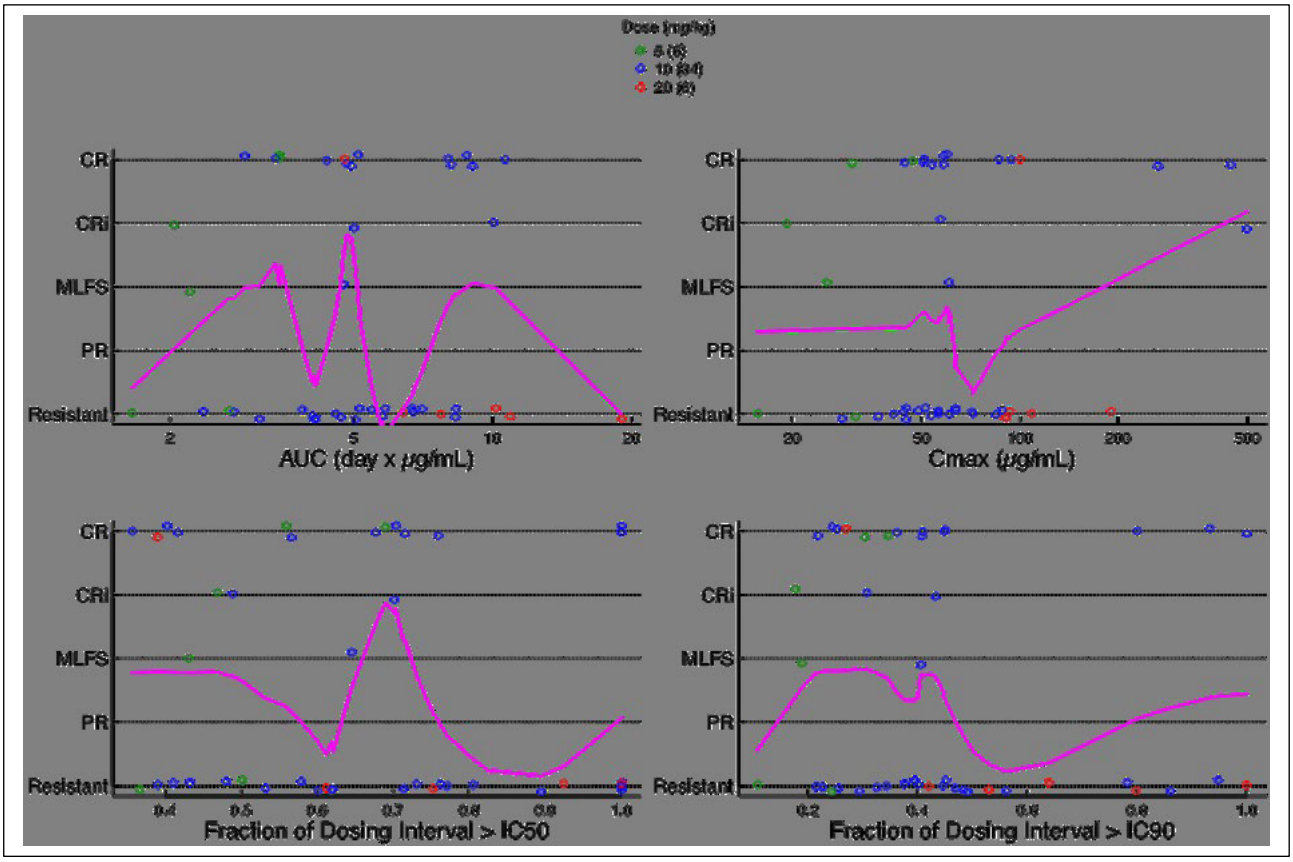


Figure 1 A-D: Exposure-Response from Study GMI-1271-201

showed that E-selectin ligand was expressed in blasts from all patients with AML and was higher in patients with relapsed and refractory AML. Functional binding of E-selectin ligand on AML blasts to E-selectin expressed in endothelial cells correlated with response to therapy[15, 16].

2.4 Pediatric Studies

There are no pediatric studies.

2.5 Overview of Proposed Pediatric Study

2.5.1 E-selectin ligand expression and enrollment into APAL2020SC trial

Patients younger than 18 years with second or greater relapsed or refractory AML, MDS or MPAL enrolling on this study must have been previously enrolled onto the APAL2020SC screening trial. A bone marrow or peripheral blood sample at time of enrollment onto APAL2020SC will be evaluated for presence of disease as well as for expression of E-selectin ligand on the membrane of the myeloid blasts. Presence of disease will be assessed by multidimensional flow cytometry (MFC) with a "different from normal technique". "Difference from normal" utilizes a standardized panel of monoclonal antibodies, quantitative immunofluorescence, and multidimensional data analysis to define the composition of bone marrow specimens. The standardized panel includes the following reagents: CD45 [2D1(BD), PerCP], CD34 [8G12(BD), APC], CD11b [D12(BD), PE], HLA-DR [L243(BD), FITC], CD36 [FA6.152(BD), FITC], CD38 [HB7(BD), FITC], CD16

[3G8FITC], CD13 [L138(BD), PE], CD14 [MΦ/P9(BD), FITC), CD33 [P67.6(BD), PE], CD7 [4H9(BD), FITC], CD56 [MY31(BD), PE], CD117 [104D2(BD), PE]), CD64 [22(BD), PE CD123 [9F5(BD), PE] CD19 [4G7(BD), FITC. E-selectin ligand expression will be measured quantitatively by MFC on myeloid blasts identified with a "different from normal" technique along with native autofluorescence for the myeloid blasts and for normal lymphocytes (as negative controls). E-selectin ligand expression is assessed in the PE fluorochrome along with this standardized panel utilizing a chimeric E-selectin-Ig construct provided by GlycoMimetics Inc and the HECA-452 antibody. Once the AML population is identified, the mean fluorescence intensity of the E-selectin ligand can be determined. The threshold to define "positive" or "negative" expression of E-selectin will be set as an expression above twice the native autofluorescence in 30% of myeloid blasts.

2.5.2 Rationale for starting dose and dose finding

This is a Phase 1 study of uproleselan (GMI-1271) in combination with fludarabine and cytarabine (FLA) for pediatric patients with relapsed and refractory acute myeloid leukemia, myelodysplastic syndrome and mixed phenotype acute leukemia that expresses the E-selectin ligand on the cell membrane. Given the absence of a definable relationship between exposure and response in adults with AML, the absence of DLTs at any dose level when GMI-1271 was administered in combination with conventional chemotherapy, and to stay consistent with the adult approach, the proposed starting dose for pediatrics is 10 mg/kg. Further dose escalation will be studied if the clearance of GMI-1271 in children is found to be 30% faster than in adults with the goal of aligning drug exposure in children to that attained in adults. In the event that excessive DLTs are experienced at dose level 1, a lower dose of 5 mg/kg will be tested. A rolling six design will be used for dose finding in this study[17], and a PK expansion cohort at that MTD/RP2D will improve the accuracy of the pharmacokinetic model. The population PK model based on the full adult dataset will be updated to include actual pediatric data from this trial, and an assessment of the pharmacokinetics in pediatrics will be performed after this first study in pediatric patients. A weight-based dosing regimen for pediatrics is recommended based on the lack of pharmacokinetic data in this pediatric AML population. Given the safety profile in adults patients, it is unlikely that DLTs will determine the RP2D. The proposed trial instead focuses on collecting adequate PK data and identifying a RP2D based on clearance parameters (clearance within 30% of adults) and plasma exposure levels compared with the adult data. A single dose of GMI-1271 will be administered on day 1 of therapy, followed by a q12 hours administration for 5 days in combination with FLA, followed by q12 hours administration for two more days as single agent (15 total doses). A pharmacokinetic (PK) study will be performed.

2.5.3 Rationale for selection of fludarabine and cytarabine (FLA) as backbone chemotherapy

We propose to use FLA as chemotherapy backbone for several reasons. The combination of fludarabine and cytarabine has been extensively used as re-induction therapy in adult and pediatric AML; it has been safely used in combination with experimental agents in children with high-risk AML and it represents an optimal regimen for patients who have already received high cumulative doses of anthracycline. Two studies evaluated the activity of FLAG (FLA with GCSF) in children with first relapse or primary refractory AML. A large prospective randomized trial conducted by the international BFM group showed that 59% of patients achieved CR after two cycles of FLAG[18]. In a recently published retrospective study of children with relapsed or refractory AML following therapy on study JPLSG AML05, the CR rate following FLAG was 65.8% [19]. The regimen was overall well tolerated without excessive unexpected toxicity.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in Oncology Patient Enrollment Network (OPEN). Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their FDA Form 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Please see Appendix I for detailed CTEP and CTSU Registration Procedures including: Registration and Credential Repository (RCR), requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1 Current Study Status

Investigators should refer to the COG website to determine if the study is currently open for accrual.

3.2 IRB Approval

U.S. sites participating in the PEP-CTN network are required to use the NCI CIRB as of March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the FDA Form 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the FDA Form 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI-CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see **Appendix I**.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp.org

in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review.

3.3 Patient Registration

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry in the OPEN system once authorization for the release of protected health information (PHI) has been obtained.

If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.4 Reservation and Contact Requirements

Prior to enrolling a patient, a reservation must be made following the steps below and the Study Chair or Vice Chair notified. (The patient will need a COG patient ID number in order to obtain a reservation). Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Patients must be enrolled within 7 calendar days of making a reservation.

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE**' a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

   Refer to the 'Slot Reservation Site User Guide' posted under the 'Help' tab in OPEN for detailed instructions:
   https://www.ctsu.org/open/Site_Resources/Training/Users_Manual/CTSU-OPEN-SlotReservationSiteUserGuide.pdf

3.5 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child. All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines

3.6 Eligibility Checklist

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

3.7 Institutional Pathology Report

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number

and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission. The APAL2020SC Hematologics CAP/CLIA report will be available through the Hematolinx portal which will include e-selectin ligand expression results.

3.8 Study Enrollment

Prior enrollment on the PedAL Screening Protocol, APAL2020SC, is required for enrollment on PEPN2113.

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria.

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.9 Dose Assignment

The dose level will be assigned via OPEN at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.

Laboratory Studies:
All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated.

Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility.

If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

Clinical Studies:
All clinical studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Imaging studies, bone marrow biopsy and/or aspirate, biopsy of extramedullary site (if the bone marrow is not involved by disease) and lumbar puncture must be obtained within 14 days prior to enrollment (repeat the tumor imaging if necessary).

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be enrolled until September 8th.

4.1 Inclusion Criteria

4.1.1 Patient must be enrolled on APAL2020SC - Pediatric Acute Leukemia (PedAL) Screening Trial – Developing New Therapies for Relapsed Leukemias - A Leukemia & Lymphoma Society and COG Groupwide Screening Protocol.

4.1.2 Age
Patients must be ≥1 year and <18 years of age at the time of study enrollment.

4.1.3 Diagnosis
Patients, with or without Down syndrome (DS), and with *de novo* acute myeloid leukemia, therapy-related acute myeloid leukemia, myelodysplastic syndrome with increased blasts (MDS-IB), therapy-related myelodysplastic syndrome with increased blasts (MDS-IB) or mixed phenotype acute leukemia that expresses E-selectin ligand on the cell membrane according to APAL2020SC screening results and meet one of the following:

- Second or greater relapse or refractory AML as defined below, including isolated extramedullary disease (EMD), but excluding isolated central nervous system (CNS) or isolated testicular disease.
- Second or greater relapse or refractory myelodysplastic syndrome (MDS) with increased blasts (MDS-IB).

- Second or greater relapse or refractory mixed phenotype acute leukemia (MPAL).

Note: Documentation of E-selectin expression by multidimensional flow cytometry (MDF) at the central laboratory (Hematologics, Inc.) on the most recent bone marrow sample prior to the diagnosis of the current relapsed or refractory disease is acceptable for eligibility to this study in the event of isolated extramedullary disease, inability to obtain a bone marrow aspirate or lack of leukemic blasts in the peripheral blood.

4.1.4 Disease Status

4.1.4.1 *Bone marrow relapse and MDF – MRD relapse:*

(patients must meet one of the following criteria to be defined as having relapse disease)

I. A single bone marrow sample showing ≥1% leukemic blasts by multidimensional flow cytometry performed at the central laboratory (performed only at Hematalogics through the screening study APAL2020SC).

II. In cases where a bone marrow aspirate cannot be obtained because of extensive fibrosis, blast count can be obtained from touch imprints or estimated from an adequate bone marrow core biopsy; blast count must be ≥5% to be eligible. A complete blood count documenting the presence of at least 1,000/ µL (i.e., a WBC count ≥ 10,000/µL with ≥ 10% blasts or a WBC count of ≥ 5,000/µL with ≥ 20% blasts) circulating leukemic cells (blasts) can also be used if a bone marrow aspirate or biopsy cannot be performed.

4.1.4.2 *Extramedullary relapse:*

Biopsy proven extramedullary disease after documented complete remission.

4.1.4.3 *Refractory disease and MDF – MRD refractory:*

Following a re-induction cycle after any relapse, presence of ≥1% leukemic blasts by multidimensional flow cytometry performed at the central laboratory (performed only at Hematologics through the screening study APAL2020SC), OR there is persistent extramedullary disease. In cases where a bone marrow aspirate cannot be obtained because of extensive fibrosis, assessment of refractory disease will be defined as described above in 4.1.4.1 II.

4.1.5 Therapeutic Options

Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

4.1.6 Performance Level

Karnofsky ≥50 for patients >16 years of age and Lansky ≥50 for patients ≤16 years of age.
Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.
See https://www.cogmembers.org/site/pages/default.aspx?page=Prot_reference_materials under Standard Sections for Protocols.

4.1.7 Prior Therapy

4.1.7.1 Patients must have fully recovered (grade <2) from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the numerical eligibility criteria are met, eg, blood count criteria, the patient is considered to have recovered adequately.

a. Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive: See DVL homepage on the COG Members site for commercial and investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.
   - ≥ 14 days must have elapsed after the completion of other cytotoxic therapy, with the exception of hydroxyurea.
     NOTE: Cytoreduction with hydroxyurea must be discontinued ≥ 24 hours prior to the start of protocol therapy.

b. Anti-cancer agents not known to be myelosuppressive (eg, not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent. See the DVL homepage on the COG Members site for commercial and investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.

c. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.

d. Corticosteroids: See Section 4.2.3.1. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

e. Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g., pegfilgrastim) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

f. Interleukins, Interferons and Cytokines (other than Hematopoietic Growth Factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than Hematopoietic Growth Factors)

g. Stem cell Infusions (with or without TBI):
   - Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion: ≥ 84 days after infusion and no evidence of GVHD.
   - Patients must be off calcineurin inhibitors for at least 28 days prior to the start of protocol therapy. Patients may be on physiological doses of steroids (equivalent to ≤10 mg prednisone daily for patients ≥18 years or ≤10mg/m2/day for patients <18years).
   - Autologous stem cell infusion including boost infusion: ≥ 30 days.

h. Cellular Therapy: ≥ 30 days after the completion of any type of cellular therapy (eg, modified T cells, NK cells, dendritic cells, etc.).

i. XRT/External Beam Irradiation including Protons: ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation.

j. Patients must not have received prior exposure to uproleselan (GMI-1271). NOTE: Prior therapy with fludarabine and/or cytarabine is permitted.

4.1.8 Organ Function Requirements

4.1.8.1 Adequate Bone Marrow Function Defined As:

a. For patients with leukemia:

- Platelet count ≥ 25,000/uL (may receive platelet transfusions).

4.1.8.2 Adequate Renal Function Defined as:

1) Estimated GFR (eGFR) ≥ 70 mL/min/1.73 m^2

"Bedside" Schwartz formula (2009):

eGFR = 0.413 x (height (cm) /serum creatinine (mg/dL))

An online calculator is available through the National Kidney Foundation at https://www.kidney.org/professionals/kdoqi/gfr_calculatorped

OR

2) Measured GFR ≥ 70 mL/min/1.73 m^2. If *measured GFR is used, it must be performed using direct measurement with a nuclear blood sampling method or small molecule clearance method (iothalamate or other molecule per institutional standard).*

4.1.8.3 Adequate Liver Function Defined as:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age.
- SGPT (ALT) < 3x ULN (unless attributed to leukemic involvement).
- Albumin ≥ 2 g/dL.

4.1.8.4 Adequate Cardiac Function Defined as:

- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by gated radionuclide study.

4.2 Exclusion Criteria

4.2.1 Patients with any of the following diagnoses

- Patients with isolated relapsed or refractory CNS disease or isolated relapsed or refractory testicular disease
- Patients with acute promyelocytic leukemia (APL)
- Patients with juvenile myelomonocytic leukemia (JMML)
- Patients with a known congenital bone marrow failure syndrome

4.2.2 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies, OR because there is yet no available

information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use two effective methods of birth control, including a medically accepted barrier or contraceptive method (eg, male or female condom) for the duration of the study and for 3 months after the last dose of uproleselan (GMI-1271). Abstinence is an acceptable method of birth control.

4.2.3 Concomitant Medications

4.2.3.1 Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid (see Section 4.1.7.1.d).

4.2.3.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

4.2.3.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible except patients receiving hydroxyurea, which may be continued until 24 hours prior to start of protocol therapy.

4.2.3.4 Anti-GVHD Agents Post-transplant: Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial.

4.2.4 Infection
Patients who have an uncontrolled infection are not eligible.

4.2.5 Patients who have received a prior solid organ transplantation are not eligible.

4.2.6 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

4.3 CNS Status Definition

CNS1 Disease
CNS1 (negative) at diagnosis of relapsed/refractory disease is defined as no blasts in cytospin CSF regardless of CSF WBC or RBC counts **AND** no clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome) **AND** no radiographic evidence of intracranial or intradural mass.

CNS2 Disease
CNS2 disease at diagnosis of relapsed/refractory disease is defined as blasts present in cytospin CSF with CSF WBC < 5/μL.

CNS3 Disease
CNS3 disease at diagnosis of relapsed/refractory disease is defined as blasts present in cytospin CSF with CSF WBC ≥ 5/uL **AND/OR** clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome) **OR** radiographic evidence of an intracranial or intradural mass consistent with a chloroma. Retinal hemorrhage and extra-ocular orbital masses are not considered CNS leukemia.

5.0 TREATMENT PLAN

5.1 Overview of Treatment Plan

Table 2 – Experimental Design Schema

Each Cycle (28 days)						
	Uproleselan (GMI-1271) IV	**Fludarabine IV**	**Cytarabine IV**	**Cytarabine IT**	**IT Triples**	**Leucovorin PO or IV**
Day 0				once daily[1]	once daily[1]	
Day 1	once daily					24 and 30hrs post ITT[2]
Day 2	q12hr	once daily	once daily			
Day 3	q12hr	once daily	once daily			
Day 4	q12hr	once daily	once daily			
Day 5	q12hr	once daily	once daily			
Day 6	q12hr	once daily	once daily			
Day 7	q12hr			Weekly[1]	Weekly[1]	
Day 8	q12hr					24 and 30hrs post ITT[2]
Day 9						
…						
Day 14				Weekly[1]	Weekly[1]	
Day 15						24 and 30hrs post ITT[2]
Day 21				Weekly[1]	Weekly[1]	
Day 22						24 and 30hrs post ITT[2]
Day 28				Weekly[1]	Weekly[1]	
Day 29[3]						24 and 30hrs post ITT[2]

[1] Choice between IT Cytarabine OR IT Triples is up to the treating physician's discretion. Weekly intrathecal chemotherapy treatments are for CNS 2/3 patients ONLY. A minimum of 4 and a maximum of 6 intrathecal treatments may be given (count includes day 0 IT and may carry over into Cycle 2 of chemotherapy).

[2] Down syndrome patients ONLY. Administer 24 & 30 hours after each IT Triples.

[3] End of cycle bone marrow for disease assessment may be performed any day between Day 28-35.

[4] Day 28 lumbar puncture can be done at the same time as the end of cycle bone marrow assessment between day 28-35.

A cycle of therapy is considered to be 28 days. A cycle may be repeated for a total of 2 cycles, up to a total duration of therapy of approximately 2 months.

Drug doses of uproleselan (GMI-1271) should be adjusted based on the weight measured within 7 days prior to the beginning of each cycle. Drug doses of fludarabine and cytarabine should be adjusted based on the BSA (calculated from the height and weight) or weight (patients < 1 year) measured within 7 days prior to the beginning of each cycle. Drug doses of intrathecal cytarabine, methotrexate and hydrocortisone should be based on the age of the patient at the time of administration.

See Section 5.6 for Therapy Delivery Maps for each cycle. Additional IT cytarabine or IT triples will be administered for CNS2 and CNS3 patients weekly according to the schedule in the Therapy Deliver Maps in Section 5.6.

5.1.1 Uproleselan (GMI-1271): IV over 20 minutes (±2 minutes)

Days: 1-8
On Day 1, uproleselan (GMI-1271) will be administered as a single dose 24 hours ± 2 hours prior to the first dose of chemotherapy. Since patients will receive a single dose of IT cytarabine or ITT on Day 0 of Cycle 1, it is recommended, but not required, that systemic therapy begin at least 24 hours after the intrathecal therapy.

On Days 2-6, uproleselan (GMI-1271) will be administered every 12 hours ±1 hour starting 2 hours ± 15 minutes *prior* to initiation of chemotherapy (fludarabine and cytarabine).

On Days 7-8, uproleselan (GMI-1271) will be administered every 12 hours ±1 hour as single agent.

At least 22 hours ± 2 hours should pass between uproleselan (GMI-1271) dose on Day 1 and the first uproleselan (GMI-1271) dose on day 2. A total of 15 uproleselan (GMI-1271) doses will be administered on Days 1-8.

If ≤6 hours have elapsed since the time of the planned dose, the dose should be given. If uproleselan (GMI-1271) and chemotherapy are held for more than 72 hours for medical reasons, the study chair or vice chair should be consulted before restarting uproleselan (GMI-1271). If chemotherapy is held for less than 72 hours and is restarted, uproleselan (GMI-1271) may be restarted when chemotherapy is restarted, and the original schedule continued if possible. For questions on restarting uproleselan (GMI-1271), the chair or vice chair should be consulted.

5.1.2 Fludarabine: IV over 30 minutes once daily

Days: 2-6
Dose: age-based dosing

Age at enrollment	Dose
< 1 year	1 mg/kg/dose
≥ 1 year	30 mg/m^2/dose

5.1.3 High Dose Cytarabine: IV infusion over 1-3 hours once daily

Days: 2-6
Dose: age-based dosing

Age at enrollment	Dose
< 1 year	67 mg/kg/dose
≥ 1 year	2000 mg/m^2/dose

Please note: Begin cytarabine infusion 4 hours after the start of the fludarabine infusion. Following/during high-dose cytarabine, chemical conjunctivitis may occur. **Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose and continuing for 24 hours after the last dose of cytarabine.** If patient does not tolerate steroid eye drops, artificial tears may be administered on an every 2-4 hour schedule. See the Chemotherapy Administration Guidelines (CAG) on the COG website at:

https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

5.1.4 Intrathecal Therapy: IT

CNS 1 patients: Day 0 and 28
CNS 2/3 patients: Days 0, 7, 14, 21, 28

All patients will receive intrathecal therapy with either IT cytarabine (Section 5.1.4.1) or triple intrathecals with methotrexate/hydrocortisone/cytarabine (ITT) (Section 5.1.4.2) in this study according to the schedule above. The choice between IT cytarabine vs triple IT therapy is up to the treating physician's discretion.

Patients will receive a single dose of IT cytarabine or ITT on Day 0 of Cycle 1. It is recommended, but not required, that systemic therapy with uproleselan (GMI-1271) begin at least 24 hours after the intrathecal therapy.

If the patient received IT cytarabine or triple IT therapy during their diagnostic workup within 14 days of starting protocol therapy, then they do not need additional Day 0 IT therapy.

CNS2/3:
Patients with CNS2/3 will receive IT cytarabine or ITT once weekly starting on Day 0 until the CSF is clear of blasts (CNS1 status) on 2 consecutive LPs. The choice between IT cytarabine vs triple IT therapy is up to the treating physician's discretion. A minimum of 4 weekly intrathecal treatments must be given with a maximum of 6 weekly intrathecal treatments per cycle; these weekly treatments may carry over into Cycle 2 as needed to achieve CNS1 status. If the patient received IT cytarabine or ITT during diagnostic workup within 14 days of starting protocol therapy, then that intrathecal treatment can count as the Day 0 dose and counts within the minimum of 4 and maximum of 6 intrathecal treatments.

5.1.4.1 Cytarabine: IT

CNS 1 patients: Day 0 and 28*
CNS 2/3 patients: Day: 0, 7, 14, 21, 28*
Dose: age-based dosing

Table 3 – Cytarabine IT Dosing by Age

Age	Dose
< 1 year	20 mg
≥ 1 to < 2 years	30 mg
≥ 2 to < 3 years	50 mg
≥ 3 years	70 mg

5.1.4.2 Intrathecal Triple Therapy (ITT): Methotrexate (MTX)/Hydrocortisone (HC)/Cytarabine (ARAC)

CNS 1 patients: Day 0 and 28* only
CNS 2/3 patients: Days 0, 7, 14, 21, 28*

Table 4 – ITT Dosing by Age

Patient Age	Methotrexate	Hydrocortisone	Cytarabine
< 1 year	6 mg	12 mg	18 mg
≥ 1 to < 2 years	8 mg	16 mg	24 mg
≥ 2 to < 3 years	10 mg	20 mg	30 mg
≥ 3 years	12 mg	24 mg	36 mg

It is recommended, but not required, that weekly intrathecal therapy begin at least 24 hours after high dose cytarabine.

Note: CNS 2 and CNS 3 patients will receive additional IT cytarabine OR IT triples once weekly until the CNS is clear of blasts on 2 consecutive LPs, with a minimum of 4 IT cytarabine OR IT Triples doses administered.
*Day 28 IT chemotherapy can be administered at the time of end of cycle bone marrow assessment between Day 28 and 35.

5.1.5 Leucovorin : Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days: 1, 8, 15, 22 and 29
Dose: 5 mg/m^2/dose x 2 doses given 24 and 30 hours after each **triple IT therapy** dose with methotrexate/hydrocortisone/cytarabine. Leucovorin administration is not necessary for patients receiving IT cytarabine.

Leucovorin rescue will be given after each ITT dose for patients with Down syndrome. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days up to 2 total cycles if the patient; 1) has at least stable disease; and, 2) all pre-cycle studies required per Section 8.1 are obtained and eligibility criteria as defined in Section 4.0 are met; and, 3) is otherwise eligible to continue agent administration per the requirements in Section 6.0

For patients in MRD negative remission, it is required that patients have an ANC >200/µL or a sustained platelet count >20,000/µL before proceeding with cycle 2.

5.3 Dose Level Schema

5.3.1 Uproleselan (GMI-1271) Dosing:
The starting dose will be 10 mg/kg with dose levels for subsequent groups of patients as follows.

Table 5 – Uproleselan Dose Level Schema

Dose Level	Uproleselan (GMI-1271) dose
-1	5 mg/kg
1*	**10 mg/kg**

Starting dose level

A Dose Level 2 will only be considered after evaluation of PK and toxicity at Dose Level 1. If PK clearance is >30% compared to adults and if the MTD has not been reached at Dose Level 1, a Dose Level 2 will be considered.

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at Dose Level -1. If Dose Level -1 is not well tolerated, further de-escalation will not occur. The study will be closed to accrual.

5.4 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair. For laboratory values in CTCAE with grading definitions including both baseline and ULN definitions, utilize the ULN for CTCAE grading.

5.5 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy. The DLT observation period will be the first cycle of therapy. Please refer to Section 13.5.4 for AE resolution definitions

Dose limiting hematological and non-hematological toxicities are defined differently.

5.5.1 Non-hematological dose-limiting toxicity

5.5.1.1 Any Grade 3 or greater non-hematological toxicity attributable to protocol therapy with the specific exclusion of:

- Grade 3 tumor lysis syndrome
- Grade 3 nausea and vomiting < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT, that returns to Grade ≤ 1 prior to the time for the next treatment cycle. See Appendix III for liver function grading parameters in children and adolescents
- Grade 3 fever
- Grade 3 infection
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation.
- Grade 3 sepsis
- Grade 3 rash
- Grade 3 mucositis

5.5.1.2 Non-hematological toxicity that causes a delay of ≥ 14 days between treatment cycles.

Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.5.2 Hematological dose limiting toxicity

5.5.2.1 **In patients evaluable for hematological toxicity (see Section 11.2.1), hematological dose limiting toxicity is defined as:**
Failure to recover a peripheral ANC > 200/µL and non-transfusion dependent platelets > 20,000/µL by 43 days after the first treatment day with fludarabine and cytarabine, not due to malignant infiltration (including MRD by central flow cytometry analysis) or ≥Grade 3 infection or sepsis. Failure to recover peripheral counts due to disease involvement of the bone marrow will not be considered dose-limiting.

5.5.2.2 **Note**: Grade 3 or 4 febrile neutropenia will not be considered a dose-limiting toxicity.

5.6: THERAPY DELIVERY MAPS (TDMS) FOR CYCLE 1-2

Therapy Delivery Map – Cycle 1-2 A cycle of therapy is considered to be 28 days. A cycle may be repeated for a total of 2 cycles, up to a total duration of therapy of approximately 2 months. Refer to section 4.1 for eligibility criteria to start cycle 1. For patients in MRD negative remission, it is required that patients have an ANC >200/μL or a sustained platelet count >20,000/μL before proceeding with cycle 2.
This form is to be completed and uploaded into RAVE at the end of every cycle.

Accession #

Patient COG ID number

Institution

Extensive details are in Section 5.1 (treatment overview). This TDM extends to three pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
IT Cytarabine (AraC)	Intrathecal (IT)	Age-based dosing: < 1 year: 20 mg ≥ 1 to < 2 years: 30 mg ≥ 2 to < 3 years: 50 mg ≥ 3 years: 70 mg	Days 0^, 7*, 14*, 21*, 28^	**^All patients.** First time point given at the time of diagnostic lumbar puncture OR Day 0 for all patients. Note that Day 28 LP with IT chemotherapy of Cycle 1 counts as Day 0 LP with IT of Cycle 2. If the patient received IT cytarabine or triple IT therapy during their diagnostic workup within 14 days of starting protocol therapy, then they do not need additional Day 0 IT therapy. ***CNS 2/3 patients ONLY.** A minimum of 4 and a maximum of 6 weekly (count includes day 0 IT) intrathecal treatments may be given. The choice between IT Cytarabine OR IT Triples is up to the treating physician's discretion. See Section 5.1 for administration guidelines.
IT Triples (Methotrexate [MTX], Hydrocortisone [HC], Cytarabine [AraC]) (ITT)	IT	Age-based dosing: < 1 year: MTX 6 mg, HC 12 mg, ARAC 18 mg ≥ 1 to < 2 years: MTX 8 mg, HC 16 mg, ARAC 24 mg ≥ 2 to < 3 years: MTX 10 mg, HC 20 mg, ARAC 30 mg ≥ 3 years: MTX 12 mg, HC 24 mg, ARAC 36 mg	Days 0^, 7*, 14*, 21*, 28^	**^All patients.** First time point given at the time of diagnostic lumbar puncture OR Day 0 for all patients. Note that Day 28 LP with IT chemotherapy of Cycle 1 counts as Day 0 LP with IT of Cycle 2. If the patient received IT cytarabine or triple IT therapy during their diagnostic workup within 14 days of starting protocol therapy, then they do not need additional Day 0 IT therapy. ***CNS 2/3 patients ONLY.** A minimum of 4 and a maximum of 6 weekly (count includes day 0 IT) intrathecal treatments may be given. The choice between IT Cytarabine OR IT Triples is up to the treating physician's discretion. See Section 5.1 for administration guidelines.
Leucovorin (LCV) %	PO or IV	5 mg/m^2/dose q6hr x 2 doses	1, 8, 15, 22, 29	**% Down-syndrome patients who are receiving ITT ONLY.** Administer 24 & 30 hours after each IT Triples dose. See Section 5.1 for administration guidelines.
Uproleselan (GMI-1271) IND# 139758	IV over 20 minutes ±2 min.	Day 1: 10 mg/kg x 1 dose Days 2-8: 10 mg/kg Q12H	1, 2-8	Day 1: Administer 24 hours ±2 hours prior to the first dose of Fludarabine. Days 2-8: Administer every 12 hours ±1 hour starting 2 hours ±15 minutes prior to initiation of Fludarabine. Total number of doses: 15
Fludarabine (FLU)	IV over 30 minutes	Age-based dosing: Age (yrs) — Dose < 1 — 1 mg/kg/dose once daily ≥ 1 — 30 mg/m^2/dose once daily	2-6	
Cytarabine (HD ARAC)	IV over 1-3 hours	Age-based dosing: Age (yrs) — Dose < 1 — 67 mg/kg/dose once daily	2-6	Begin administration 4 hours after the start of the fludarabine infusion.

Cycle 1-2

		≥ 1	2000 mg/m^2/dose once daily		Use eye drops as described in Section 5.2.

NOTE;The choice of intrathecal therapy, between cytarabine or cytarabine/methotrexate/hydrocortisone on Day 0 and on subsequent days for patients with CNS2 and CNS3 is at the discretion of the treating physician. CNS2 and CNS3 patients will receive additional IT cytarabine OR IT triples once weekly until the CNS is clear of blasts on 2 consecutive LPs, with a minimum of 4 IT cytarabine OR IT Triples doses administered (maximum of 6 intrathecal treatments).

Assigned Dose Level _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	IT ARAC _____ mg	IT Triples ARAC___ mg MTX___mg HC___mg	LCV PO/IV _____mg	GMI-1271 IV _____ mg	FLU IV ____mg	HD ARAC IV ____mg	Studies
			Enter calculated dose above and actual dose administered below						
		PRE	_____mg^	____mg^ _____mg^ ____mg^					a-k, m
		1			____mg% ____mg%	_____mg			n
		2				____mg ____mg	_____mg	_____mg	
		3				____mg ____mg	_____mg	_____mg	
		4				____mg ____mg	_____mg	_____mg	d
		5				____mg ____mg	_____mg	_____mg	
		6				____mg ____mg	_____mg	_____mg	n
		7	_____mg*	____mg* _____mg* ____mg*		____mg ____mg			a, d-g, m
		8			____mg% ____mg%	____mg ____mg			
		9							
		10							
		11							d
		12							
		13							
		14	_____mg*	____mg* _____mg* ____mg*					a, d-g, m
		15			____mg% ____mg%				
		16							
		17							d
		18							
		19							
		20							
		21	_____mg*	____mg* _____mg* ____mg*					a, d-g, m
		22			____mg% ____mg%				
		23							
		24							d
		25							
		26							
		27							
		28	_____mg^	____mg^ _____mg^ ____mg^					a, b, d-h, l-m, o
		29			____mg% ____mg%				

Please refer to Section 8.1 for the specific timing of these observations.

Cycle 1-2

Required Observations

a. History, Physical exam (including VS). Prior to Cycle 1 and every week during Cycle 1. Prior to Cycle 2 and as clinically indicated during Cycle 2.
b. Wt /Ht/BSA. Prior to Cycle 1 and prior to Cycle 2.
c. Performance Status. Prior to Cycle 1 and prior to Cycle 2.
d. CBC/diff/platelets. Prior to Cycle 1 and twice weekly during Cycle 1. Prior to Cycle 2 and as clinically indicated during Cycle 2.
e. Electrolytes including Ca++, Mg++, PO4. Prior to Cycle 1 and weekly during Cycle 1. Prior to Cycle 2 and as clinically indicated during Cycle 2.
f. Creatinine. Prior to Cycle 1 and weekly during Cycle 1. Prior to Cycle 2 and as clinically indicated during Cycle 2.
g. ALT, AST, bilirubin. Prior to Cycle 1 and weekly during Cycle 1. Prior to Cycle 2 and as clinically indicated during Cycle 2.
h. Albumin. Prior to Cycle 1 and prior to Cycle 2.
i. Pregnancy test and Urinalysis. Prior to Cycle 1. As clinically indicated during Cycle 2.
j. ECHO or gated radionuclide study. Prior to Cycle 1 and prior to Cycle 2 .
k. EKG. Prior to Cycle 1 and prior to Cycle 2.
l. Bone marrow aspirate. End of Cycles 1-2 may be performed between Days 28-35. See Section 8.2 for details.
m. CSF for cell count, cytospin. Prior to Cycle 1, with every LP, and end of Cycle 1-2.
n. Pharmacokinetics. See Section 8.3 for timing details
o. Radiographic evaluation of extramedullary disease, if applicable. End of Cycles 1-2 may be performed between Days 28-35. See Section 12.4 for details.

Cycle 1-2

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modification.

In the event that one study drug is held or delayed for toxicity, all systemic chemotherapy should be held or delayed. For guidance on intrathecal therapy, see Section 6.3.1.2.

6.1 Dose Modifications for Hematological Toxicity

6.1.1 Patients who experience a hematologic dose limiting toxicity defined as failure to recover a peripheral blood ANC>200/µL and non-transfusion dependent platelet count>20,000/µL by 43 days after the start of the cycle, not due to malignant infiltration or severe infection will be allowed to proceed to Cycle 2 at the next lower dose level at the discretion of the treating physician and study chair or vice-chair. If patient is starting at Dose Level -1, further de-escalation will not occur and the patient must be removed from protocol therapy.

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 Patients who have any dose-limiting non-hematological toxicity (as defined in Section 5.5.1) may continue on protocol therapy upon meeting eligibility lab requirements (see Section 4.0) or Grade ≤ 2 but should receive subsequent doses at the next lower dose level. If patient is starting at Dose Level -1, further de-escalation will not occur and the patient must be removed from protocol therapy.

6.2.2 If a non-hematological dose-limiting toxicity recurs after one dose reduction, the patient must be removed from protocol therapy.

6.2.3 Patients who have a dose-limiting non-hematological toxicity that does not resolve to Grade ≤ 2 or eligibility within 43 days after the start of the cycle, must be removed from protocol therapy.

6.3 Modifications and supportive care recommendations for toxicity related to standard therapy

6.3.1 Neurological Toxicity

6.3.1.1 Cytarabine

The most common neurotoxicity related to fludarabine or cytarabine administration is an acute cerebellar syndrome that may manifest itself as ataxia, nystagmus, or dysarthria. However, seizures and encephalopathy have also occurred following therapy with high dose cytarabine. Patients experiencing Grade 3 or 4 CTCAE version 5.0 nervous system disorders should be removed from protocol therapy.

6.3.1.2 Intrathecal Chemotherapy

This protocol will utilize intrathecal triples (ITT) including methotrexate, hydrocortisone and cytarabine. Experience with ITT in ALL therapy demonstrates that there is a risk for methotrexate induced leukoencephalopathy. The timing of this toxicity often occurs 1-2 weeks after intrathecal administration. This CNS toxicity may present with a wide range of symptoms and severity. Seizures or

transient stroke-like symptoms (weakness, hemiparalysis, aphasia) are most common but more severe encephalopathies are possible. There is no standard management approach and clinical judgment by the treating physician of each individual case is required for management. In general, evaluation of systemic disorders or infection (blood cultures, electrolytes, organ function and/or examination of the CSF) is important to exclude other contributing factors. Brain imaging is often helpful. Generally CT scans are normal. MRI abnormalities may be present (although sometimes these findings lag behind clinical manifestations) and may show findings consistent with posterior reversible encephalopathy or other white matter changes. The benefit of treatment with dextromethorphan remains unproven but may be used per the treating physician's discretion.

For patients who experience neurologic toxicity following intrathecal therapy, the treating physician has several options for future intrathecal treatments. In patients with ongoing neurologic symptoms, it is reasonable to hold or delay the subsequent intrathecal treatment(s) to allow recovery. In patients who have improvement of the CNS toxicity, the treating physician should consider the severity and duration of symptoms to decide whether to continue ITT as scheduled in protocol therapy or to replace the ITT with IT cytarabine.

In cases where the decision is to proceed with additional ITT, it is recommended to include leucovorin rescue with the subsequent intrathecal treatment at a dose of 5 mg/m^2 IV/PO x 2 doses at 24 and 30 hours after the LP.

In cases where the decision is made to replace with IT cytarabine, the following doses should be used (based on prior COG AML protocols including AAML1031): Intrathecal Cytarabine Age-based dosing:

Table 6 – Intrathecal Cytarabine Age-based Dosing

Age	Dose
< 1 year	20 mg
≥ 1 to < 2 years	30 mg
≥ 2 to < 3 years	50 mg
≥ 3 years	70 mg

If the event does not recur, resumption of ITT therapy should be considered for subsequent intrathecal therapy.

For patients who do not return to their pre-event baseline neurological status or for those with recurrent events, or evidence of progressive encephalopathy, additional evaluations may be warranted and the treating physician may consider a more prolonged or definitive change in therapy.

6.3.2 Renal Toxicity

6.3.2.1 Cytarabine

Patients with nephrotoxicity secondary to antibiotics, or antifungals, may have prolonged excretion of cytarabine leading to more severe marrow and extramedullary toxicity.

- Patients with a serum creatinine > 2 mg/dL or > 2x normal for age should be hydrated orally or intravenously. Following hydration, the patient must have a creatinine clearance ≥ 60 mL/min/1.73m² as measured preferably by a nuclear GFR scan, timed urine collection for creatinine clearance, or calculated by the Schwartz formula before proceeding with cytarabine therapy.
- If the creatinine clearance is abnormal (< 60 mL/min/1.73m²) then Cycle 2 high dose cytarabine should be reduced by 50% for each daily dose. With this approach, previous research has shown the prevention of subsequent neurotoxicity in recipients of high dose cytarabine in the face of renal insufficiency[21].

6.3.2.2 Fludarabine

Renal clearance accounts for about 40% of the total body clearance of fludarabine and clearance of the primary active metabolite is decreased in patients with renal impairment. Renal elimination appears to become more important at high dosages of the drug. The dose of fludarabine needs to be adjusted in patients with moderate renal impairment. The following are suggested guidelines for dose adjustment of fludarabine in renal impairment:

Table 7 – Fludarabine Dosing Guidelines

Creatinine Clearance mL/min/1.73m²	Daily Fludarabine Dose
> 70	No adjustment required
30-70	Administer 80% of calculated dose
≤ 30	Withhold Fludarabine
Hemodialysis	Administer 25% of calculated dose
Continuous ambulatory peritoneal dialysis (CAPD)	Not recommended
Continuous renal replacement therapy (CRRT)	Administer 80% of calculated dose[22]

6.3.3 Rash

6.3.3.1 Cytarabine

- **Hand-Foot Syndrome**
  Hand-foot syndrome has been reported in patients treated with high-dose cytarabine. Patients who develop hand-foot syndrome may receive topical emollients (such as Aquaphor) as well as topical or systemic steroids or antihistamines if appropriate. Oral administration of vitamin B6 (pyridoxine) can also be used for these patients- BSA < 0.5 m²: 50 mg per day; BSA 0.5-1 m²: 100 mg per day; BSA 1.1-1.5 m²: 200 mg per day, and BSA > 1.5 m²: 300 mg per day.
- **Ara-C Syndrome including Fever, Rash, or Conjunctivitis**
  Do not withhold cytarabine for fever if it is likely to have been caused by the cytarabine. However, blood cultures should be obtained even if fever is thought to be likely due to cytarabine. Institution of antibiotics for fever associated with cytarabine infusion is at the discretion of the treating physician (see fever management recommendations in the COG Supportive Care Guidelines). For rash or conjunctivitis, withhold cytarabine for Grade 3-4 toxicity until resolved to ≤ Grade 1. Make up missed doses and consider concurrent treatment with hydrocortisone or

dexamethasone, and/or with dexamethasone ophthalmic drops for conjunctivitis only.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy other than protocol therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Please see COG Supportive Care guidelines at https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines. See Section 7.5, "Concomitant Medications" for drugs that should not be used concomitantly due to potential interactions with uproleselan (GMI-1271).

Hospitalization/Hospital Environment

Hospitalization following each course of chemotherapy is strongly recommended until the absolute phagocyte count (sum of the neutrophils, bands and monocytes) is rising for 2 successive days, and the patient is afebrile and clinically stable. An additional discharge criterion of an absolute neutrophil count (ANC) of at least 200/µL is also suggested.

It is recommended that patients should be assigned to rooms with special air filtration systems such as high efficiency particulate air filters (HEPA) or clean-air rooms with constant positive pressure airflow if at all possible.

Infectious Diseases Prophylaxis

In an effort to decrease the rates of infection, prophylactic antimicrobials and antifungals are strongly encouraged as outlined below. Signs and symptoms of infection (including fever) should prompt rapid switch from prophylactic treatment to empiric or directed therapy.

Antifungal Prophylaxis

The COG trial ACCL0933 compared prophylactic treatment with caspofungin versus fluconazole during chemotherapy treatment for AML in children and adolescents. The echinocandins, (eg., micafungin, caspofungin) have extensive safety and dosing studies in children, and they have both anti-yeast and anti-mold activity (covering both *Candida* and *Aspergillus* species which are the more common causes of fungal infection in children receiving AML therapy). ACCL0933 demonstrated that the five-month cumulative incidence of proven or probable invasive fungal disease was significantly lower in those treated with caspofungin compared to fluconazole (3.1% vs. 7.2%; p=0.03).[23] A reduction in invasive *aspergillus* seemed to account for the majority of the difference in invasive fungal infection rates between the two groups.

On the current protocol, it is strongly encouraged that patients receive antifungal prophylaxis. Data from ACCL0933 supports prophylaxis with an echinocandin such as caspofungin or micafungin. Prophylaxis dosing is per institutional standard, but on ACCL0933 caspofungin was administered starting 1-3 days after completion of the systemic chemotherapy and continued until demonstration of ANC recovery (>100-500/uL) after nadir. Intravenous dosing of caspofungin used on the trial was as follows:

Caspofungin IV 70 mg/m^2/day on day 1 (max 70 mg/day) followed by 50 mg/m^2/day (max dose 50 mg/day).

The use of azole antifungals is permitted per treating physician discretion.

Antibacterial Prophylaxis

Bacterial infections, including bacteremia, are common during AML therapy. The COG trial ACCL0934 randomly assigned participants to levofloxacin prophylaxis versus no antibiotic prophylaxis and compared the rates of infection in patients undergoing 2 courses of treatment for acute leukemia (AML and relapsed ALL) or those receiving a hematopoietic stem cell transplant (HSCT). The study was stopped early at an interim analysis due to the significantly decreased rate of bacteremia within the acute leukemia group for those who received levofloxacin versus those without prophylaxis (21.9%vs 43.4%; risk difference, 21.6%; 95%CI, 8.8%-34.4%, P = 0.001).[24] In secondary analysis, the trial also reported that patients in the levofloxacin prophylaxis group were less likely to have fever and neutropenia and less likely to test positive for *C. Difficile* (likely due to less need for broad spectrum antibiotics for empiric treatment). There were no significant differences in invasive fungal disease or musculoskeletal toxic effects at 2 months or 12 months. Importantly, among bacteremia isolates there was no evidence of increased antimicrobial resistance in the levofloxacin group other than resistance to levofloxacin/fluoroquinolones.

Thus, on the current protocol, it is strongly encouraged that patients receive antibiotic prophylaxis and preferably with levofloxacin.

On ACCL0934, levofloxacin was administered starting on day 1 of each chemotherapy treatment course and continued until evidence of count recovery (ANC >200/uL after nadir). Levofloxacin can be dosed per institutional standards. ACCL0934 utilized the following levofloxacin dosing:

- Age 6 months to < 5 years: Levofloxacin PO/IV 10 mg/kg twice daily
- Age ≥ 5 years: Levofloxacin PO/IV 10 mg/kg once daily with maximum dose of 750 mg/day

7.4 Use of myeloid growth factor support

The use of a myeloid growth factor (GCSF or GMCSF) is not required and can be used at the discretion of the treating physician. The use of PEGfilgastrim is not permitted.

7.5 Concomitant Medications

To minimize the risk of neurotoxicity, it is recommended but not required that intrathecal therapy is administered at least 24 hours before or after systemic chemotherapy.

Because there is a potential for interaction of uproleselan (GMI-1271) with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies during Cycle 1. Uproleselan is a substrate for the efflux transporters P-gp and MRP2, may be a weak substrate for BCRP. Strong inhibitors of these efflux transporters (eg.,

amiodarone, azithromycin, carvedilol, clarithromycin, cyclosporine, delavirdine, dronedarone, efavirenz, eltrombopag, emtricitabine, itraconazole, ketoconazole, lapatinib, lopinavir and ritonavir, probenecid, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil) should be used with caution or avoided if reasonable alternatives exist. The study chair and/or vice chair should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently updated medical reference for a list of drugs to avoid or minimize use of. Appendix X – Patient Drug Interactions Handout and Wallet Card should be provided to patients.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol)

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT), AST, and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow biopsy and/or aspirate, biopsy of extramedullary site (if the bone marrow is not involved by disease) and lumbar puncture must be obtained within 14 days prior to enrollment.

Table 8 – Required Clinical, Laboratory and Disease Evaluation

STUDIES TO BE OBTAINED (Phase 1 Cohort)	Pre-Study	During Cycle 1	Prior to Cycle 2	During Cycle 2
History	X	Weekly	X[3]	
Physical Exam with vital signs	X	Weekly	X[3]	X[4]
Height, weight, BSA	X		X[3]	
Performance Status	X			X[4]
CBC, differential, platelets[1]	X	Twice Weekly (every 3 to 4 days)[1]	X[3]	X[4]
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X[3]	X[4]
Creatinine, ALT, bilirubin	X	Weekly	X[3]	X[4]
Albumin	X		X[3]	
Pregnancy Test[2]	X			X[4]
Urinalysis	X			X[4]

ECHO or gated radionuclide study	X		X[3]	
EKG	X		X[3]	
Bone Marrow Aspirate for flow cytometry and MRD assessment. See Section 8.2	X	End of Cycle 1		End of cycle 2
Radiologic assessment of extramedullary disease, if applicable	X	End of Cycle 1		End of Cycle 2
CSF for cell count and cytospin	X	With every LP		End of cycle 2
Pharmacokinetics See Section 8.3 for timing		X		

[1] If patients develop Grade 4 neutropenia or thrombocytopenia, CBC/differential/platelets should be checked every 3 to 4 days until recovery to Grade ≤ 3.
[2] Women of childbearing potential require a negative pregnancy test prior to starting treatment; See Section 4.2.2
[3] Studies may be obtained within 72 hours prior to the start of the subsequent cycle.
[4] As clinically indicated.

8.2 Bone Marrow for Flow Cytometry of Measurable Residual Disease (MRD) (Required)

8.2.1 Description of Studies and Assay

Bone marrow MRD will be evaluated at the end of each cycle using flow cytometry for disease assessment. Samples should be sent directly to Hematologics Inc. following the instructions below. If the MRD sample is not evaluable per Hematologics, sites will be informed. It is critical that a repeat bone marrow examination should be performed until a result can be obtained. Optimally, a specimen should be submitted while a patient has an absolute neutrophil count (ANC) greater than 200/uL. If possible, a repeat bone marrow aspirate is recommended once the ANC has recovered.

8.2.2 Sampling Schedule

Bone marrow samples are required to be sent for MRD analysis at the following time points:

- End of Cycle 1
- End of Cycle 2

8.2.3 Sample Collection and Handling Instructions

A bone marrow aspirate is required for MRD testing. Collect a minimum of 2 - 4 mL of bone marrow in a preservative-free **sodium heparin vacutainer (green top).** Samples cannot be submitted in EDTA or shipping media as they compromise key antigens.

If sample cannot be shipped immediately (i.e., sample is drawn on a Saturday, Sunday or holiday), **store sample with equal volume of RPMI medium at room temperature and ship on the next business day.** It is recommended to use RPMI without EDTA if available.

8.2.4 Sample Labeling

Clearly label the tube as bone marrow aspirate (BMA) or peripheral blood (PB) along with study ID, COG number, patient DOB, and date sample was obtained.

8.2.5 Sample Shipping Instructions

Samples should be shipped immediately to arrive next day to Hematologics Inc. Seattle, WA at the address listed below. All specimens sent to Hematologics Inc. must be accompanied by PEPN2113 Bone Marrow MRD specimen transmittal form.

Ship samples by FedEx Priority Overnight Using the COG FedEx account listed in the FedEx Account Usage Guidelines: https://members.childrensoncology

group.org/_files/reference/FEDEXmemo.pdf. Be sure to indicate the samples are for PEPN2113 on the FedEx air bill.

Hematologics, Inc.
3161 Elliott Ave. Suite 200
Seattle, WA 98121
Phone: (800) 860-0934 or (206) 223-2700
Fax: (206) 223-5550
Weekends and After Hours: (206) 264-4459

Weekend Specimens: The lab is staffed 6 days a week. For Saturday delivery, please use a *Saturday delivery* sticker and check the *Saturday delivery* box on the address label. Both sticker and checked box are necessary to insure proper handling.

8.3 Pharmacology (Required)

8.3.1 Description of Studies and Assay

Pharmacokinetic analysis of uproleselan (GMI-1271) will be performed by GlycoMimetics. Plasma samples will be obtained at specific timepoints as indicated in the Specimen Collection table below. PK studies will be determined by a validated LC/MS/MS method.

8.3.2 Sampling Schedule

Plasma samples will be obtained at the following time points during Cycle 1:

8.3.2.1 For patients ≥10kg, blood samples will be obtained prior to drug administration and at the following time points:

Table 9A – Pharmacology Sampling Schedule (for patients > 10kg)

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

* time-points are relative to start of infusion

8.3.2.2 For patients < 10 kg samples will obtained prior to drug administration and at the following time points:

Table 9B – Pharmacology Sampling Schedule (for patients < 10kg)

Day	Timepoint
Cycle 1 Day 1 (1st dose of uproleselan (GMI-1271))	Immediately pre-dose (±20 minutes)*
	30 minutes (±5 minutes)*
	1.5 hours (±20 minutes)*
	4 hours (±20 minutes)*
Cycle 1 Day 6 (1st dose of day)	Immediately pre-dose (±20 minutes)*
	30 minutes (±5 minutes)*
	1.5 hours (±20 minutes)*
	4 hours (±20 minutes)*

* time-points are relative to start of infusion

8.3.3 Sample Collection and Handling Instructions

Blood samples

- 2 mL for patients ≥6 years
- 1 mL for patients <6 years

Blood samples will be collected in sodium citrate tubes at a site distant from the infusion for pharmacokinetic evaluation. Care should be taken that blood for PK assessment is drawn from a vein apart from the site of uproleselan (GMI-1271) infusion (e.g., from a different limb or central line).

1. Drawing from the same line as drug infusion even with a second lumen is not recommended as there is a high likelihood of getting high concentrations. It is recommended to either establish a separate line in the opposite arm or collect via individual venipuncture from the opposite arm.
2. If separate line cannot be established, it is preferred to draw samples peripherally
3. If multiple peripheral sticks are not feasible due to venous access or patient refusal, prioritize peripheral collection of the 30 min dose sample
4. If separate line or peripheral sticks are not at all possible, draw from double lumen
5. If drawing multiple samples from an intravenous (IV) line, before taking the blood sample, a 'discard' tube must be taken to clean the IV line.

Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact time that the drug is administered. If study drug is diluted, record dilution volume used.

8.3.4 Sample Processing

Blood will be drawn into sodium citrate tubes, inverted 3-4 times and stored in an ice bath until centrifugation. Samples will be centrifuged at 2000-2500 rpm at 4°C for 10 minutes. Ideally, samples should be immediately centrifuged following collection. If institutional staffing and/or logistics do not allow for this, samples may be stored (at approximately 4°C) for 48-72 hours before centrifugation.

After centrifugation, pipette half of plasma into an appropriately labelled (participant ID, day/time of collection and primary vs back-up) cryovial (primary aliquot). Pipette the remaining plasma into an additional appropriately labelled cryovials (back-up aliquot).

The aliquots will be stored in a freezer set at -70 to -80°C until shipped for analysis. Samples should be batched and sent together after day 6, once Day 6 samples have been collected and processed as above.

8.3.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., time point and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form (See Appendix VII-A & Appendix VII-B), which must accompany the sample(s).

8.3.6 Sample Shipping Instructions

Samples will be shipped Monday-Wednesday only via overnight carrier with the appropriate amount of dry ice. Sites will ship primary aliquots and store back-up aliquots in a freezer set at -70 to -80°C until they are asked to ship them.

Pyxant Labs
4720 Forge Road
Colorado Springs, Colorado 80907
Contact: Emily Munk
E-mail: emunk@pyxant.com and SampleReceipt@pyxant.com
Tel.: +1 (719) 694-0958

Upon shipment of the samples, e-mail the name of the courier, the airway bill number, and a confirmation of the number of samples in the shipment to emunk@pyxant.com and SampleReceipt@pyxant.com.

9.0 AGENT INFORMATION

9.1 Uproleselan (GMI-1271) (04/12/22)

(GMI-1271) NSC# 801708, IND # [redacted]

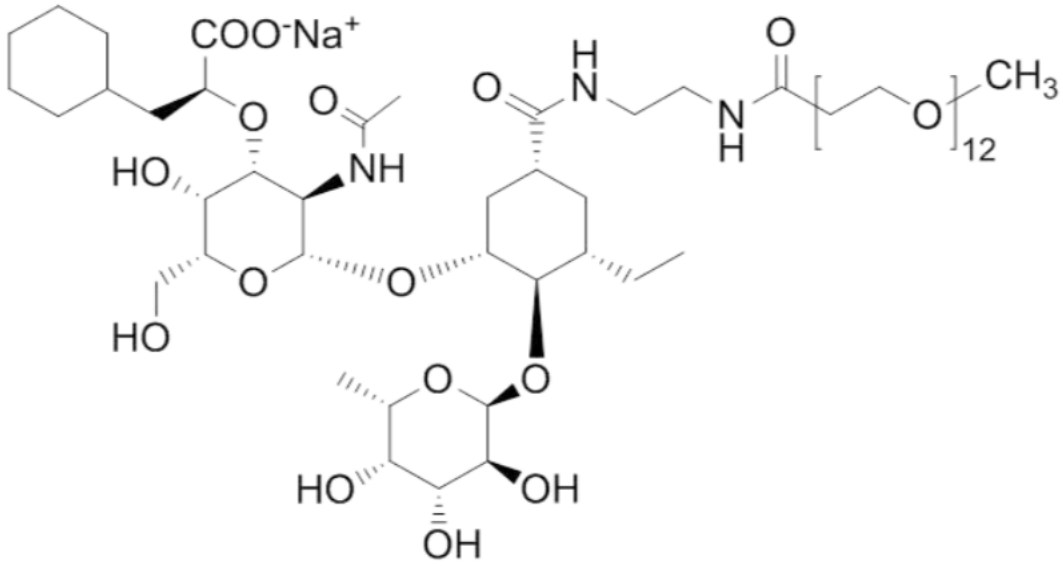
9.1.1 Structure and molecular weight

Chemical Formula: $C_{60}H_{108}N_3NaO_{27}$

Molecular Weight: 1326.5

Uproleselan (GMI-1271) is a specific E-selectin antagonist. The proposed mechanism of action is by competitive inhibition of E-selectin, thereby interrupting E-selectin-mediated interactions. Pre-clinical data collectively suggest that uproleselan-mediated disruption of E-selectin interactions between the endothelium and various tumor cells, confers increased sensitivity to cytotoxic agents by preventing these cancerous cells from remaining in the bone marrow niche and attenuating stroma-induced resistance to chemotherapy. Uproleselan (GMI-1271) blockade of E-selectin/AML binding inhibits the activation of NF-κB, attenuates the production of pro-survival signaling in AML, and restores chemosensitivity of leukemic blasts.

Figure 2 – Uproleselan (GMI-1271) Molecular Structure



9.1.2 Supplied by: GlycoMimetics, Inc. and distributed by the Pharmaceutical Management Branch, CTEP, NCI

9.1.3 Formulation

The investigational product uproleselan (GMI-1271) injection, 50 mg/mL, is a sterile, clear, colorless to slightly yellow isotonic solution for IV administration provided in single dose vials. Each 16 mL, single dose vial contains 800 mg of uproleselan (GMI-1271). The drug product is supplied in clear glass vials with 20 mm butyl rubber serum stopper with a 20 mm flip-off aluminum overseal. The drug substance is present as the sodium salt; however, the solution concentration is based on the free-acid active moiety. The sodium content of the formulation is 3.3 mg/mL. The clinical product formulation includes 10 mM Tris buffer to stabilize the pH at 7.4 (6.4 to 8.4). The investigational product should be stored according to the labeled storage conditions.

9.1.4 Storage

Uproleselan (GMI-1271) injection 50 mg/mL is stored refrigerated (2 °C to 8 °C), prior to administration.

If a storage temperature excursion is identified, promptly return uproleselan to 2°C-8°C (36°F-46°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.5 Solution Preparation

The refrigerated solution is clear, colorless to slightly yellow, and free from visible particulates. Reconstitution and dilution are not necessary. Dilution up to 10 times may be performed with normal saline. Uproleselan can be administered undiluted or diluted to a concentration not less than 5 mg/mL.

9.1.6 Stability

When prepared in syringes or IV bags without an administration set attached, uproleselan (GMI-1271) may be stored refrigerated up to 72 hours prior to administration or up to 24 hours at controlled room temperature prior to administration. Administration sets manufactured from materials of construction other than polyvinyl chloride (PVC) with di(2-ethylhexyl)phthalate (DEHP) can be primed up to 72 hours before dosing if stored refrigerated or up to 24 hours before dosing if stored at controlled room temperature. Intravenous lines consisting of PVC with DEHP should be avoided when possible. If PVC with DEHP administration sets must be used, they should be primed with uproleselan (GMI-1271) solution no more than 2 hours before dosing. It is highly recommended that uproleselan (GMI-1271) prepared prior to administration be refrigerated until 1 hour prior to dosing. While it is highly recommended that uproleselan (GMI-1271) prepared prior to administration be refrigerated until one hour prior to dosing, solutions kept at room temperature can be administered within 24 hours of preparation.

9.1.7 Potential Drug Interactions

Uproleselan is not expected to undergo extensive hepatic metabolism in humans. Uproleselan (GMI-1271) does not cause direct or time-dependent inhibition of CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Uproleselan (GMI-1271) also showed no evidence of induction of CYP1A2, CYP2B6 or CYP3A4.

Active transporter substrate analysis revealed that uproleselan (GMI-1271) is a substrate for the efflux transporters P-gp and MRP2, may be a weak substrate for BCRP, and is not a substrate of the efflux transporter BSEP. In addition, uproleselan (GMI-1271) is not a substrate for the following uptake transporters: OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2-K. Uproleselan (GMI-1271) is not an inhibitor of the efflux transporters P-gp, BCRP, or BSEP, and is not an inhibitor of the following substrate transporters: OATP1B1, OATP1B3, OAT1, OAT3, OCT2 and OCT1.

9.1.8 Patient Care Implications

Women of childbearing potential and men must use highly effective methods of contraception during the study and for 3 months after the last dose of study drug. Do not administer uproleselan (GMI-1271) to pregnant or lactating women.

9.1.9 Administration (See Section 5 for Treatment Plan and Section 6 for Dose Modifications)

Uproleselan (GMI-1271) injection should be administered IV into a peripheral line, a central catheter, or a peripherally inserted central line catheter (PICC). Infusion should take place at a steady rate over a period of 20 minutes using a syringe pump or IV pump. Microbore tubing is preferred. In-line filtration with a 0.2-micron filter is highly recommended.

Uproleselan (GMI-1271) is compatible with IV bags composed of PVC (with or without DEHP), polyolefin, or ethylene vinyl acetate, glass bottles, and syringes. IV administration sets composed of PVC without DEHP or lined with polyethylene are compatible with uproleselan (GMI-1271). IV admin sets composed of PVC with DEHP should not exceed 2 hours of contact with uproleselan (GMI-1271).

Compatibility with other therapeutic agents has not been determined; therefore, uproleselan (GMI-1271) injection should be administered via a separate IV line and should not be administered

concurrently with anything other than saline. If a flush is used, saline flush is preferred.

9.1.10 Toxicities

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Uproleselan (GMI-1271, NSC 801708)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 184 patients*. Below is the CAEPR for Uproleselan (GMI-1271).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, July 9, 2019[1]

Adverse Events with Possible Relationship to Uproleselan (GMI-1271) (CTCAE 5.0 Term) [n= 184]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Febrile neutropenia		
GASTROINTESTINAL DISORDERS			
		Abdominal pain	
	Dyspepsia		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Platelet count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		
	Headache		
	Somnolence		
PSYCHIATRIC DISORDERS			
	Restlessness		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Oropharyngeal pain		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on Uproleselan (GMI-1271) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Uproleselan (GMI-1271) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia
EYE DISORDERS - Eye disorders - Other (retinal hemorrhage)
GASTROINTEST
INAL DISORDERS - Colitis; Enterocolitis; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fatigue; Fever
INFECTIONS AND INFESTATIONS - Bacteremia; Lung infection; Sepsis
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Electrocardiogram QT corrected interval prolonged; Neutrophil count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (malnutrition); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Myalgia; Neck pain; Pain in extremity
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Dyspnea; Hypoxia; Nasal congestion; Pulmonary edema
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Rash maculo-papular

Note: Uproleselan (GMI-1271) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.1.11 Clinical Drug Request

NCI supplied agents may be requested by the eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

A starter supply of 10 vials can be requested when a patient is being screened for this study.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

9.1.12 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the

CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

9.1.13 Investigator Brochure Availability

The current version(s) of the IB(s) for the agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

9.1.14 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9.2 Cytarabine **(04/12/22)**

(Cytosine arabinoside, Ara-C, Cytosar®) NSC #63878

Source and Pharmacology:

Cytarabine appears to act through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate (Ara-CTP), an effective inhibitor of DNA polymerase. Ara-CTP is inactivated by a pyrimidine nucleoside deaminase, which converts it to the nontoxic uracil derivative (Ara-U). It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine. It has an initial distributive phase $t_{½}$ of about 10 minutes, with a secondary elimination phase $t_{½}$ of about 1 to 3 hours. Peak levels after intramuscular or subcutaneous administration of cytarabine occur about 20 to 60 minutes after injection and are lower than IV administration. Intrathecally administered doses are metabolized and eliminated more slowly with a $t_{½}$ of about 2 hours.

Table 10 - Toxicity: (Intravenous, SubQ, IM)

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, anorexia *With High Dose*: conjunctivitis	Flu-like symptoms with fever, rash	Ara-C syndrome (fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, malaise, conjunctivitis), anaphylaxis, swelling, pain and redness at the site of the medication injection (SubQ or IM injection) *With High Dose:* cardiomyopathies (vasculitis, and pericarditis), cerebral and cerebellar dysfunction including: encephalopathy, aseptic meningitis, ataxia, dysphasia, nystagmus, a decreased level of consciousness, personality changes, somnolence, seizures
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (anemia, thrombocytopenia, leukopenia, megaloblastosis, reticulocytopenia), stomatitis, alopecia	Diarrhea, hypokalemia, hypocalcemia, hyperuricemia *With High D*ose: capillary pulmonary leak syndrome (RDS, pulmonary edema)	Hepatotoxicity, sinusoidal obstruction syndrome (SOS, formerly VOD), urinary retention, renal dysfunction, pain and erythema of the palms and soles
Delayed: Any time later during therapy, excluding the above conditions			Asymptomatic nonoliguric rhabdomyolysis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cytarabine have been noted in humans. It is unknown whether the drug is excreted in breast milk.		

Table 11 - Toxicity: (Intrathecal)

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, headache	Arachnoiditis	Rash, somnolence, meningismus, convulsions, paresis
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia
Delayed: Any time later during therapy, excluding the above condition			Necrotizing leukoencephalopathy, paraplegia, blindness (in combination with XRT & systemic therapy)

Formulation:
Cytarabine for Injection is available in vials of 100 mg, 500 mg, 1 g, and 2 g containing a sterile powder for reconstitution. It is also available at a 20 mg/mL concentration with benzyl alcohol (25 mL per vial) or as a preservative free solution (5 mL, 50 mL per vial), and at a 100 mg/mL concentration with benzyl alcohol (20 mL vial) or as preservative free solution (20 mL vial). Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Cytarabine solutions should be protected from light.

Guidelines for Administration:
See Treatment and Dose Modification sections of the protocol.

IV Infusion:
Reconstitute the lyophilized powder with Bacteriostatic Water for Injection or NS injection. Solution containing bacteriostatic agent should not be used for the preparation of doses > 200 mg/m^2. May be further diluted with dextrose or sodium chloride containing solutions. May give by IV push injection, by IV infusion, or by continuous infusion.

High Dose (≥ 1000 mg/m²/dose): Administer steroid eye drops (dexamethasone or prednisolone), 2 drops each eye q6h beginning immediately before the first dose and continuing 24 hours after the last dose. If patient does not tolerate steroid eye drops, administer artificial tears on a q2-4 hour schedule.

Stability: When reconstituted with Bacteriostatic Water for Injection, cytarabine is stable for 48 hours at room temperature. Solutions reconstituted without a preservative should be used immediately. Discard if solution appears hazy. Diluted solutions in D5W or NS are stable for 8 days at room temperature; however, the diluted cytarabine should be used within 24 hours for sterility concerns.

Intrathecal:
For intrathecal administration, dilute with 5-10 mL (or volume per institutional practice) preservative free 0.9% sodium chloride injection, lactated Ringer's injection, Elliot's B solution. The volume of CSF removed should be equal to at least ½ the volume delivered.

Table 12 – Cytarabine: Intrathecal Administration Guidelines by Age

Patient Age (years)	Recommended volume	10% CSF volume	CSF Volume *
0 to < 1 year	5-10 mL	5 mL	50 ± 10 mL (babies)
≥1 to <2	5 – 10 mL	5 mL	50 ± 10 mL (babies)
≥2 to <3	5 – 10 mL	8 mL	80 ± 20 mL (younger children)
≥3 to <9	5 – 10 mL	10 mL	100 ± 20 mL (older children)
≥9	5 – 10 mL	13 mL	130 ± 30 mL (adults)

Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; N Engl J Med. 1962 Dec 20; 267:1273-8

Of Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Intrathecal cytarabine mixed in NS, lactated Ringer's injection, or Elliot's B solution is stable for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

Supplier:
Commercially available from various manufacturers. See package insert for further information.

9.3 Fludarabine (01/10/18)

(Fludara®, fludarabine phosphate, 2-fluoro-ara-AMP) NSC# 312887

Source and Pharmacology:
Fludarabine phosphate is a synthetic purine nucleoside. It differs from the physiologic nucleosides, adenosine, in that the sugar moiety is arabinose instead of ribose, and by the addition of a fluorine atom to the purine base adenine. Fludarabine is also a fluorinated nucleotide analog the antiviral agent vidarabine, (ara-A). The addition of fluorine results in increased aqueous solubility and resistance to enzymatic degradation by adenosine deaminase. Fludarabine (2-fluoro-ara-A) is commercially available as the monophosphate salt (2-fluoro-ara-AMP). The monophosphorylation increases the drug's aqueous solubility while maintaining pharmacologic activity. The chemical name for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-0-phosphono β-D-arabino-furanosyl) (2-fluoro-ara-AMP) and the molecular weight is 365.2.

Fludarabine is a purine antagonist antimetabolite. *In vivo*, fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A and then it is phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP. This metabolite appears to act by inhibiting DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis. The mechanism of action of this antimetabolite is not completely characterized and may be multi-faceted.

Phase I studies in humans have demonstrated that within several minutes after intravenous infusion, fludarabine phosphate is converted to the active metabolite, 2-fluoro-ara-A and becomes undetectable. Therefore, pharmacokinetics studies have focused on 2-fluoro-ara-A. Fludarabine phosphate 25 mg/m^2 infused intravenously over 30 minutes to adult cancer patients, showed a moderate accumulation of 2-fluoro-ara-A. During a 5-day treatment schedule, 2-fluoro-ara-A plasma trough levels increased by a factor of about 2.

Fludarabine is widely distributed. The volume of distribution at steady state (V_{ss}) reported after daily administration of 25 mg/m^2 for 5 days to adults averaged at 96-98 L/m^2. Tissue distribution studies in animals indicate that the highest concentrations of the drug are in liver, kidney, and spleen. Although the extent to which fludarabine and/or its metabolites distribute into the CNS in humans has not been determined to date, severe neurologic toxicity (e.g., blindness, coma) has been reported in patients receiving the drug, particularly in high dosages. There is evidence from animal studies that fludarabine distributes into the CNS and that a toxic metabolite (2-fluoroadenine, possibly formed by bacteria in the GI tract), can be absorbed systematically via enterohepatic circulation and distributed into CSF. According to *in vitro* data, about 19-29% of fludarabine is bound to plasma proteins.

Following IV administration, fludarabine phosphate is dephosphorylated rapidly to fludarabine. Plasma concentrations of fludarabine decline in a linear, dose-independent manner. The elimination profile of fludarabine also has been reported to be either biphasic or triphasic; however, reported terminal elimination half-lives have been similar. In adult cancer patients receiving fludarabine 25 mg/m^2 as a 30-minute IV infusion daily for 5 days, a terminal half-life of about 20 hours was reported. In a limited number of pediatric patients, the plasma concentration profile of fludarabine exhibited both monoexponential and biexponential decay, with a mean $t_{1/2}$ of 10.5 hours in

patients with monoexponential elimination and a $t_{1/2}$ of 1.2-1.4 and 12.4-19 hours, respectively, in patients with biexponential elimination.

Renal clearance accounts for about 40% of the total body clearance of fludarabine. Renal elimination appears to become more important at high dosages of the drug. The dose of fludarabine needs to be adjusted in patients with moderate renal impairment.

The use of fludarabine in combination with pentostatin is not recommended due to the risk of severe pulmonary toxicity.

Table 13 – Fludarabine Toxicity:

	Common Happens to 21-100 subjects out of every 100	**Occasional** Happens to 5-20 subjects out of every 100	**Rare** Happens to < 5 subjects out of every 100
Immediate: Within 1-2 days of receiving drug	Fever, fatigue, weakness, pain, nausea, vomiting, anorexia, cough, dyspnea	Edema including peripheral edema, chills, rash, diarrhea, rhinitis, diaphoresis, malaise, abdominal pain, headache, back pain, myalgia, stomatitis, flu-like syndrome	Anaphylaxis, tumor lysis syndrome, dehydration*
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression (anemia, neutropenia, thrombocytopenia), infection (urinary tract infection, herpes simplex infection, pneumonia, upper respiratory)	Weight loss, gastrointestinal bleeding, hemoptysis, paresthesia, allergic pneumonitis, bronchitis, pharyngitis, visual disturbance, hearing loss, hyperglycemia	Sinusitis, dysuria, opportunistic infections and reactivation of latent viral infections like Epstein-Barr virus (EBV), herpes zoster and John Cunningham (JC) virus (progressive multifocal leukoencephalopathy [PML])[L], EBV associated lymphoproliferative disorder, panycytopenia (can be prolonged), pulmonary hypersensitivity[a] (dyspnea, cough, hypoxia, interstitial pulmonary infiltrate), pulmonary toxicity (acute respiratory distress syndrome [ARDS], pulmonary fibrosis, pulmonary hemorrhage, respiratory distress, respiratory failure), pericardial effusion, skin toxicity (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigus), liver failure, renal failure, hemorrhage, transfusion-associated graft-versus-host disease has occurred following transfusion of nonirradiated blood products, phlebitis*, sleep disorder*, cerebellar syndrome*, depression*, mentation impaired*, alopecia*, pruritus*, seborrhea*, esophagitis*, constipation*, mucositis*, dysphagia*, hesitancy*, cholelithiasis*, abnormal liver function tests*, osteoporosis*, arthralgia*, abnormal renal function test*, proteinuria*, epistaxis*, hemorrhagic cystitis*, eosinophilia*
Delayed:			Neurotoxicity (increased with high doses): seizures, agitation, confusion, weakness, visual

Any time later during therapy, excluding the above conditions			disturbances, optic neuritis, optic neuropathy, photophobia, blindness, paralysis, coma, death, peripheral neuropathy[a]; autoimmune phenomena: thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, hemolytic anemia, acquired hemophilia
Late: Any time after completion of treatment			Myelodysplastic syndrome/acute myeloid leukemia (mainly associated with prior or concomitant or subsequent treatment with other anticancer treatments), skin cancer (new onset or exacerbation)
Unknown Frequency and Timing:	**Pregnancy Category D** Based on its mechanism of action, fludarabine phosphate can cause fetal harm when administered to a pregnant woman. Fludarabine phosphate was embryolethal and teratogenic in both rats and rabbits.		

(L) Toxicity may also occur later.
* Reported in ≤ 3% of subjects. Since these are not considered life threatening they are not included in the consent.
[a] These effects were not reported in children.

Formulation and Stability:
Fludarabine phosphate injection is available as sterile lyophilized powder and in solution. Each single-dose vial of powder contains 50 mg of the active ingredient fludarabine phosphate, 50 mg of mannitol, and sodium hydroxide to adjust the pH to 7.7. After reconstitution, the pH range for the final product is 7.2-8.2. The single-dose solution vial contains 25 mg/mL, 2 mL of fludarabine phosphate. It may contain mannitol and is preservative-free.

Fludarabine phosphate vials should be stored refrigerated at 2-8ºC (36-46ºF).

Guidelines for Administration:
See Treatment and Dose Modification sections of the protocol.

Fludarabine phosphate powder should be reconstituted with 2 mL of Sterile Water for Injection. The solid cake should fully dissolve in 15 seconds or less. The resulting concentration is 25 mg/mL. When reconstituted to a final concentration of 25 mg/mL, the drug is stable for at least 16 days at room temperature and normal light conditions. The manufacturer recommends that the solution be used within 8 hours after reconstitution.

Prior to administration, fludarabine 25 mg/mL solution or the reconstituted 25 mg/mL solution should be further diluted in 100 mL or 125 mL of D5W or NS. Concentrations of 0.25 to 1 mg/mL have been used in clinical trials. When diluted to a final concentration of 1 mg/mL, fludarabine is stable for at least 16 days at room temperature and normal light conditions. The manufacturer recommends that the diluted solution be used within 8 hours after preparation. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Supplier:
Commercially available from various manufacturers. See package insert for further information.

9.4 Intrathecal Triples (08/03/21)

(Methotrexate/Hydrocortisone/Cytarabine, IT-3)

Source and Pharmacology:

The intrathecal route of administration of a drug produces more consistent CSF drug concentrations at relatively smaller doses because of the volume difference between the CSF and blood compartments (140 mL vs. 3500 mL in an adult). (The CSF volume of children after the first 3 years is equivalent to that of an adult). Drug half-lives are longer as well because clearance is related to flow rather than metabolism or protein binding. Intrathecal methotrexate has a biphasic elimination curve from the CSF with a $t_{½}$ of 4.5 and 14 hours respectively. Following IT injection of cytarabine the elimination of the drug from the CSF is biphasic with a $t_{½}$ of 1 and 3.4 hours respectively which is 8-fold longer than the clearance from plasma. The elimination of hydrocortisone is similarly prolonged.

Table 14 - Intrathecal Triple Therapy (Methotrexate/Hydrocortisone/Cytarabine) Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, headache	Arachnoditis: (headache, fever, vomiting, meningismus and pleocytosis)	Rash, anaphylaxis (L), paresis, bleeding into subarachnoid or subdural space (risk > with platelet counts <20,000), confusion, fatigue, disorientation, seizures
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, somnolence, ataxia, cranial nerve palsy, transient and rarely permanent paraplegia (L), speech disorders
Delayed: Any time later during therapy, excluding the above condition		Cognitive disturbances (L), learning disabilities (L)	Demyelating leukoencephalopathy[1] (L), blindness[1]
Late: Any time after the completion of treatment			Progressive CNS deterioration[1]

[1] *May be enhanced by systemic therapy such as high dose methotrexate or cytarabine and/or cranial irradiation.*
(L) Toxicity may also occur later.

Formulation and Stability:

Methotrexate 25 mg/mL **preservative free** 2 mL vial or methotrexate 20 mg preservative free sterile powder for injection vial. Cytarabine 100 mg preservative free sterile powder for injection. Hydrocortisone sodium succinate 100 mg vial sterile powder for injection.

Guidelines for Administration:

See Treatment and Dose Modification sections of the protocol.

For intrathecal administration, dilute each agent with 5-10 mL preservative free NS, lactated ringers or Elliot's B solution or as per institutional standard of practice. The volume of CSF removed should be equal to at least half the volume delivered.

Table 15 – Methotrexate Dosing Guidelines by Age

Patient Age (years)	Recommended volume	10% CSF volume	CSF Volume *
0 < 1 year	5-10 mL	5 mL	50 ± 10 mL (babies)
≥ 1 to < 2 years	5-10 mL	5 mL	50 ± 10 mL (babies)
≥ 2 to < 3 years	5-10 mL	8 mL	80 ± 20 mL (younger children)
≥ 3 to < 9 years	5-10 mL	10 mL	100 ± 20 mL (older children)
≥ 9 years	5-10 mL	13 mL	130 ± 30 mL (adults)

**Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection. N Engl J Med 1962 Dec 20; 267:1273-8*

Of note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Intrathecal triples are stable in NS for 24 hours at 25ºC but contain no preservative and should be administered as soon as possible after preparation.

Supplier:
Commercially available from various manufacturers. See package insert for further information.

9.5 Leucovorin Calcium **(05/07/19)**
(LCV, Wellcovorin®, citrovorum factor, folinic acid, Calcium folinate) NSC #003590

Source and Pharmacology:
Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)- l-isomer, known as Citrovorum factor or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase. In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Leucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid (an active metabolite of 5-FU) to thymidylate synthase and thereby enhances the inhibition of this enzyme. Peak serum levels of 5-methyl THF (an active metabolite) were reached at approximately 1.3-1.5 hours (IV/IM) and 2.3 hours for the oral form. The terminal half-life of total reduced folates was approximately 6.2 hours. Following oral administration, leucovorin is rapidly absorbed and expands the serum pool of reduced folates. At a dose of 25 mg, almost 100% of the *l*-isomer (the biologically active form) but only 20% of the *d*-isomer is absorbed. Oral absorption of leucovorin is saturable at doses above 25 mg. The apparent bioavailability of leucovorin was 97% for 25 mg, 75% for 50 mg, and 37% for 100 mg doses. Both oral and parenteral leucovorin raise the CSF folate levels.

Table 16 – Leucovorin Calcium Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug			Anaphylaxis, urticaria, seizure
Unknown Frequency and timing:	Fetal toxicities and teratogenic effects of leucovorin in humans are unknown. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:

Leucovorin calcium for injection is supplied as a sterile ready to use liquid and a sterile powder for injection. The 10 mg/mL preservative free liquid is available in 50 mL vials containing sodium chloride 400 mg/vial. Store preservative free liquid in the refrigerator at 2°-8°C (36°-46°F) protected from light. The powder for injection is available in 50 mg, 100 mg, 200 mg, and 350 mg vials. Store at room temperature 15°-25°C (59°-77°F) protected from light. Reconstitute the sterile powder with sterile water for injection or bacteriostatic water for injection to a concentration of 10 mg/mL leucovorin calcium. **Do not use diluents containing benzyl alcohol for doses > 10 mg/m² or in infants < 2 years of age or patients with allergy to benzyl alcohol.** When Bacteriostatic Water is used, the reconstituted solution is good for 7 days. If reconstituted with SWFI, use solution immediately as it contains no preservative. One milligram of leucovorin calcium contains 0.004 mEq of leucovorin and 0.004 mEq of calcium.

The oral form of leucovorin is available as 5 mg, 10 mg, 15 mg, and 25 mg tablets. Inactive ingredients vary depending on manufacturer but tablet formulations may include: corn starch, dibasic calcium phosphate, magnesium stearate, pregelatinized starch, lactose, microcrystalline cellulose, and sodium starch glycolate.

Guidelines for Administration:
See Treatment and Dose Modifications sections of the protocol.

Injection:
Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute). IV leucovorin and sodium bicarbonate are incompatible.

Oral:
Oral leucovorin should be spaced evenly (e.g., every six hours) throughout the day and may be taken without regard to meals. Doses > 25 mg should be given IV due to the saturation of absorption.

Leucovorin should not be administered < 24 hours after intrathecal injections which contain methotrexate unless there are special circumstances.

Supplier:
Commercially available from various manufacturers. See package insert for further information.

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Treatment failure (See Appendix VIII for definitions).
b) Adverse Events requiring removal from protocol therapy (See Section 6.1, Section 6.2, and Section 6.3.1)
c) Refusal of protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of up to 2 cycles of therapy.
f) Physician determines removal from protocol is in the patient's best interest.
g) Repeat eligibility studies are outside the parameters required for eligibility prior to the start of GMI-1271 (Uproleselan) (See Section 8.1).
h) Study is terminated by Sponsor.
i) Pregnancy
j) Development of secondary malignancy
k) Patient receives concurrent cancer therapy that is not part of protocol therapy (See Section 7.1)

Patients who are removed from protocol therapy during Cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.5 whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent
b) Withdrawal of consent for any required observations or data submission.
c) The patient does not receive protocol treatment after study enrollment.
d) Patient enrollment onto another COG study with therapeutic (anti-cancer) intent.
e) Lost to follow-up
f) Death

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

The study will require a minimum of 4 DLT-evaluable patients and a maximum of 12. Once the MTD or recommended Phase 2 dose has been defined, up to 6 additional patients with recurrent or refractory AML, t-AML, MDS, t-MDS or MPAL without restrictions on heme evaluability may be enrolled to acquire PK data in a representative number of young patients so that the study includes an approximately equal distribution of patients <12 years old and 12-17 years old. Therefore, the expected maximum number of patients required for the entire study will be 22 allowing for 6 evaluable patients at each of two dose levels, 20% inevaluability for DLT or for failure to contribute essential PK samples (for patients with weight ≥ 10 kg: pre-dose, 30 minutes and 2 hrs after the dose on days 1 and 6; for patients with weight <10 kg: pre-dose, 30 minutes and 1.5 hrs after the dose on days 1 and 6), and 6 additional patients for PK analysis at the MTD/RP2D. The absolute maximum will be 36 patients which would occur in the unlikely scenario that both dose levels expand to 12 due to DLTs of different classes (See Section 11.2.2).

The enrollment rate is expected to be about 1 patient per month based on previous COG early phase new agent studies for patients with AML. Therefore, the study may require up to 36 months to complete enrollment but is expected to be completed within about 22 months.

11.2 Definitions

11.2.1 Evaluable for Adverse Events

Any patient who receives at least one dose of the study drugs is considered evaluable for Adverse Events. In addition, for the dose-escalation portion during Cycle 1, patients must receive at least 85% of the prescribed dose per protocol guidelines and must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. Patients in the dose escalation part of the study, who do not have DLT and are not considered evaluable for toxicity will be replaced.

11.2.2 Maximum Tolerated Dose

- The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See Section 5.5) during Cycle 1 of therapy.

- In the unlikely event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (eg, hepatotoxicity and myelosuppression), AND all of the following conditions are met, expansion of the cohort to 12 patients will be considered:

  - One of the DLTs does not appear to be dose-related
  - The Adverse Effects are readily reversible
  - The study chair, PEP-CTN statistician, PEP-CTN committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

- The DLTs observed in the pharmacokinetic (PK) expansion cohort will be counted towards the total number of DLTs observed at the MTD. If ≥ 1/3 of the cohort of patients at the MTD (during the dose evaluation plus the PK expansion) experience DLT then the MTD will be exceeded.

- If the maximum dose level (DL1) is safe (i.e., less than 1/3 of patients experience a Cycle 1 DLT among 6 DLT-evaluable patients), then DL1 will be the RP2D.
- Patients enrolled in the PK expansion cohort will be replaced if unevaluable for PK analysis defined as pre-dose, 30 minutes and 2 hrs after the dose on days 1 and 6 for patients with weight ≥ 10 kg; pre-dose, 30 minutes and 1.5 hrs after the dose on days 1 and 6 for patients with weight <10 kg

11.3 Dose Evaluation and Determination of MTD

Up to six DLT-evaluable patients will be enrolled at DL1 in Part A. If 1 or fewer DLT-evaluable patients experience a Cycle 1 dose limiting toxicity, then DL1 will be the RP2D and up to six additional patients will be enrolled in Part B (PK cohort) at this dose level. If 2 or more patients experience a Cycle 1 DLT at DL1, then the maximum tolerated dose has been exceeded and DL-1 will open for enrollment. Further, if the Part B cohort opens at DL1 and the number of patients in Part A and Part B combined who experience a Cycle 1 dose limiting toxicity exceeds 33%, then the maximum tolerated dose has been exceeded and DL-1 will open for enrollment. Up to six DLT-evaluable patients will be enrolled at DL-1. If 1 or fewer DLT-evaluable patients experience a Cycle 1 dose limiting toxicity at DL-1, then DL-1 will be the MTD/RP2D and up to six additional patients will be enrolled in Part B (PK cohort) at this dose level. If 2 or more patients experience a Cycle 1 DLT at DL-1, then the maximum tolerated dose has been exceeded and the study will close to accrual. Further, if the Part B cohort opens at DL-1 and the number of patients at DL-1 in Part A and Part B combined who experience a Cycle 1 dose limiting toxicity exceeds 33%, then the maximum tolerated dose has been exceeded and the study will close to accrual. See exceptions to rule in Section 11.2.2 for defining the MTD.

11.4 Pharmacokinetic and Correlative Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of uproleselan (GMI-1271) will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

While the primary aim of this study is to evaluate the toxicity of uproleselan (GMI-1271), patients will have disease evaluations performed as indicated in Section 8.1. If the study agent is too toxic and no MTD/RP2D is determined, then no patients will be enrolled in the PK expansion cohort.

All these analyses will be descriptive and exploratory and hypothesis-generating in nature.

11.5 Gender and Minority Accrual Estimates

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past COG early phase studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Efforts will be made to extend the accrual to a representative population, but in a Phase 1 trial which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

The gender and minority distribution of the study population is expected to be:

Table 17 – Planned Enrollment Report

	PLANNED ENROLLMENT REPORT				
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian / Alaska Native	0	0	0	0	0
Asian	1	2	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	2	0	0	4
White	10	14	3	2	29
More Than One Race	0	0	0	0	0
Total	**13**	**18**	**3**	**2**	**36**

This distribution was derived from the patients enrolled in previous early phase COG trials.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v.5.0' is understood to represent the most current version of CTCAE v.5.0 as referenced on the CTEP website.

12.2 COG Response Assessment

12.2.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started) after up to 2 cycles of therapy. The patient's best response assignment will be assessed according to the specific criteria defined in Appendix VIII.

12.2.2 Response Criteria

For patients who are enrolled onto this study with <5% blasts complete remission will be defined only as the attainment of a MRD negative complete remission as determined by central flow cytometry. Definitions of response criteria for leukemia are described in Appendix VIII.

12.3 CNS Leukemia at Diagnosis

CNS1 Disease

CNS1 (negative) at diagnosis of relapsed/refractory disease is defined as no blasts in cytospin CSF regardless of CSF WBC or RBC counts **AND** no clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome) **AND** no radiographic evidence of intracranial or intradural mass.

CNS2 Disease

CNS2 disease at diagnosis of relapsed/refractory disease is defined as blasts present in cytospin CSF with CSF WBC < 5/μL.

CNS3 Disease

CNS3 disease at diagnosis of relapsed/refractory disease is defined as blasts present in cytospin CSF with CSF WBC ≥ 5/uL **AND/OR** clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome) **OR** radiographic evidence of an intracranial or intradural mass consistent with a chloroma. Retinal hemorrhage and extra-ocular orbital masses are not considered CNS leukemia.

12.4 Extramedullary Disease

The same modality (CT, MRI, and/or FDG PET) used for pre-treatment evaluation should preferably be performed for follow-up imaging. Patients will be considered in complete remission if there has been complete radiographic resolution of disease. If radiographic imaging demonstrates residual extramedullary disease, tissue biopsy should be used to determine response, if considered to be in the best interest of the patient. If tissue biopsy is not obtained, then radiographic studies should be used to determine extramedullary disease response. The differentiation between residual disease and residual scar tissue on radiographic studies may be difficult and the final determination of radiographic disease status should be made by the treating clinician in consultation with the local radiologist.

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. Please follow directions for routine reporting provided in the Case Report Forms for this protocol. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

During follow up, routine reporting will include all toxicities reported via CTEP-AERS (See footnote 1 in Table A) and all Grade 5 events regardless of attribution.

When a patient is Off Study, the following events must be reported:

- Any Death that can be attributed (possibly, probably, or definitely) to protocol therapy and is not due to cancer recurrence must be reported via CTEP-AERS.
- Any Secondary Malignancy that can be attributed (possibly, probably, or definitely) to protocol therapy must be reported via CTEP-AERS.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) whether the adverse event is considered serious; 3) the adverse (severity); and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

13.1 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the NCI CTCAE version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Step 2: Grade the adverse event using the NCI CTCAE v.5.0.

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions in the table below. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Table A: Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6)

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported via CTEP-AERS with full follow-up reports submitted within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Expectations to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

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- The NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the AE and should ONLY be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events (i.e., a hospital visit where a patient is admitted for observation or minor treatment such as

hydration and released in less than 24 hours). Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP or non-CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Early Phase Trials Utilizing an Agent under a CTEP-IND or Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.

- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased
BLOOD/LYMPHATICS DISORDERS	Anemia

- See also the Specific Protocol Exceptions to Expedited Reporting (SPEER) in Section 9.1.10 of the protocol. Additional protocol-specific exceptions to expedited reporting of serious adverse events are the toxicities in bold font listed under the drug information section of the protocol (Section 9.1).

- As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

13.2 When to Report an Event in an Expedited Manner

- Some adverse events require notification **within 24 hours** (refer to Table A for timing requirements) to NCI via the web at http://ctep.cancer.gov and by telephone call to the Study Chair.

- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A for timing requirements).

- Expedited AE reporting for this study must only use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page https://ctepcore.nci.nih.gov/ctepaers/pages/task.

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

To report adverse events in an expedited fashion use the NCI's Adverse Event Expedited Reporting System (CTEP-AERS). A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at https://ctepcore.nci.nih.gov/ctepaers/pages/task. If prompted to enter a sponsor email address, please type in: COGAERS@childrensoncologygroup.org.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Email supporting documentation to the PEP-CTN Study Assigned Research Coordinator (See Study Committee section for contact information). **ALWAYS include the ticket number on all documents. Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to (301) 897-7497. In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

Any medical documentation supporting an expedited report (eg, H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: (301) 897-7404.

13.4 Specific Examples for Expedited Reporting

13.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting table in this protocol.

13.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI, COG, or industry sponsor IND/IDE since these are considered serious AEs.

13.4.3 Reportable Categories of Death

- Death attributable to a CTCAE v5.0 term.
- Death Neonatal: Newborn death occurring during the first 28 days after birth.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 "Disease Progression" in the system organ class (SOC). "General disorder and administration site conditions". Evidence that the death was a manifestation of underlying disease (eg, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring **within 30 days** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring **greater than 30 days** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

13.4.4 Secondary Malignancy

A **secondary malignancy** is a cancer caused by treatment for a previous malignancy (eg, treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (eg, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment related secondary malignancy.

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms in the following section.

13.4.4.1 Reporting Secondary AML/MDS

All cases of AML and MDS that occur in patients following their chemotherapy for cancer must be reported via CTEP-AERS and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the completed CTEP-AERS report within 14 days of an AML/MDS diagnosis occurring after protocol treatment for cancer.

13.4.5 Second Malignancy

A **second malignancy** is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

13.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

Note: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Death Neonatal", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, should be completed and emailed to the PEP-CTN Study Assigned Research Coordinator along with any additional medical information along with any additional medical information. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

13.4.6.1 Pregnancy

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the **"Pregnancy, puerperium and perinatal conditions"** SOC.

Pregnancy needs to be followed until the outcome is known if the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

13.4.6.2 Pregnancy Loss (Fetal Death)

Pregnancy loss is defined in CTCAE as "Death in utero" Any pregnancy loss should be reported expeditiously, as **Grade 4 "Pregnancy, loss"** under the **"Pregnancy, puerperium and perinatal conditions"** SOC. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

13.4.6.3 Death Neonatal

Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days after birth"* should be reported expeditiously, as **Grade 4 "Death neonatal" under the "General disorders and administration" SOC, when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

13.4.7 Syndrome Reporting

Unless otherwise specified in this protocol, syndromes should be reported as a single event using the CTCAE term for the composite syndrome, and not as the individual events that make up the syndrome. For example, Tumor Lysis Syndrome should be reported under the composite definition rather than reporting the component events (hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia) separately.

13.4.8 Reporting Sepsis and Infectious Toxicities
Refer to the detailed guidance on reporting sepsis and infectious toxicities located on the COG website at https://cogmembers.org/uploadedFiles/Site/Disc/CRA/InfectionFlowchart_12042020.pdf.

13.5 Definition of Onset and Resolution of Adverse Events

Note: These guidelines below are for reporting adverse events on the COG PEP-CTN case report forms and do not alter the guidelines for CTEP-AERS reporting.

13.5.1 If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

13.5.2 If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

13.5.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.5.4 The resolution date of the AE is defined as the date at which the AE returns to baseline or less than or equal to Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing".

13.5.5 An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.6 Other Recipients of Adverse Event Reports

13.6.1 Events that do not meet the criteria for CTEP-AERS reporting in Section 13.3 should be reported at the end of each cycle using the forms provided in the CRF packet.

13.6.2 Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories:

1. Non-computerized Information: Therapy Delivery Maps (TDMs), Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.

2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the PEP-CTN Operations and Data/Statistics Center.

3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 Reporting

Data Mapping Utility (DMU) Reporting Complete
Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Complete reporting consists of Patient Demographics, Baseline Abnormalities, On/Off Treatment/Study Status, Treatment/Course/Dosing information, Adverse Events, Late Adverse Events, and Response data as applicable. More information on the DMU is available on the CTEP Website: https://ctep.cancer.gov/protocolDevelopment/dmu.htm. **DMU reporting is not a responsibility of institutions participating in this trial.**

14.3 CRADA/CTA/CSA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

14.4 Monitoring

On-site, retrospective source data verification is completed by Theradex on an annual basis for 100% of COG PEP-CTN patients enrolled in early phase clinical trials.

This study will additionally include central monitoring as part of data review. Source documents will be uploaded via CTSU's Source Document Portal (see Appendix II for details).

14.5 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the Data and Safety Monitoring Committee.

14.5.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group PEP-CTN policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG PEP-CTN Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the PEP-CTN scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the PEP-CTN Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG member's Web site.

14.5.2 Monitoring by the Study Chair and the Steering Committee

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the PEP-CTN Chair, Vice Chair and Statistician on a weekly conference call.

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APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

U.S. sites participating in the PEP-CTN network are required to use the NCI CIRB as of March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Active status at the site(s) on the IRB/REB approval and on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the FDA Form 1572 in the Registration and Credential Repository (RCR) profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the FDA Form 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- And active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

Submitting Regulatory Documents
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Checking Your Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Requirements For PEPN2113 Site Registration:
IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification, and/or Protocol Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

Delegation of Tasks Log
Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. The DTL application is located on the CTSU members' website at http://www.ctsu.org.

To maintain an approved site registration status, the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available

in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

Data Submission / Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.
Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Rave CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require

expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave.**

Pre-treatment AEs: AEs that occur after informed consent is signed and prior to start of treatment are collected in Medidata Rave using the Pre-treatment Adverse Event form.

Pre-existing medical conditions (formerly referred to as baseline AEs) identified during baseline assessment are not considered AEs and therefore should not be reported on the Pre-treatment Adverse Event form. If these pre-existing conditions worsen in severity, the investigator must reassess the event to determine if an expedited report is required. Whether or not an expedited report is required, the worsened event should be reported as a routine AE.

Treatment-emergent AEs:All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period, and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 Days after the Last Administration of the Investigational Agent/Intervention are collected using the Late Adverse Events form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Rave, the Rave CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form in Rave. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence, that internet connectivity is lost; a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered electronically into CTEP-AERS using the direct link from Medidata Rave..

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: Protocols > Documents>Protocol Related Documents> Adverse Event Reporting; and
- Additional resources: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

Central Monitoring

Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients' charts (i.e., source data verification).

Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP). This application is available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with the CRA or Investigator roles in Rave can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional information on the SDP is available on the CTSU members' website under Auditing & Monitoring > Source Document Portal in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

APPENDIX II: PROTOCOL CENTRAL MONITORING

Central monitoring will be required for all patients enrolled at each site. All documents must be uploaded with 2 weeks of the corresponding time point or cycle.

Monitored Data	Protocol Section	CRF Question/ Data Element	Monitoring Conditionality	Source document	CTSU Document Type	Time point
Eligibility						
Confirmation of eligible diagnosis	4.1.3	*Does patient have the required diagnosis to be eligible for this study?*	**Required**	E.g., clinical note, laboratory test report, pathology report, etc.	Clinical Note, Laboratory Report or Pathology report	Enrollment
Performance Level	4.1.6	*ECOG performance status*	**Required**	E.g., clinical note, eligibility checklist	Clinical Note, Eligibility Determination Checklist	
Adequate Bone Marrow function	4.1.8.1	*Does patient have adequate bone marrow function?*	**Required**	Laboratory test report	Laboratory Report	
Adequate Renal Function	4.1.8.2	*Does patient have adequate renal function?*	**Required**	Laboratory test report	Laboratory Report	
Adequate Cardiac Function	4.1.8.4	*Does patient have adequate cardiac function?*	**Required**	E.g., Echocardiogram, Scan Report	Clinical Note, Echocardiogram Report, or Scan Report(s)	
Date of Informed Consent	3.5	*Date of Informed Consent*	**Required**	Signed and Dated Informed Consent Document with redacted signatures	Informed Consent	
Drug Administration Elements						
Total **Uproleselan (GMI-1271)** dose	5.1	*Total Dose:*	**Required**	Medication administration record	Treatment Administration Document	Cycle 1 Cycle 2
Disease Evaluation Elements						
Bone Marrow Aspirate or Biopsy	8.1	*Was the patient's disease status evaluated during this reporting period?*	**Required**	E.g., Bone Marrow Biopsy and Aspirate Report, Radiology Report	Bone Marrow Biopsy and Aspirate Report, Radiology Report	Cycle 1 Cycle 2
Adverse Event Capture						
Labs/reports documenting protocol specific CTEP-AERS reportable events	13.0	*Has an Adverse Event Expedited report been filed?*	**Conditional:** If response is YES, CM is required	E.g., hospital admission report, laboratory reports, etc.	Relevant Document	Cycle 1 Cycle 2

Addressing Monitoring Findings

In the event that this monitoring identifies unacceptable procedures or significant deviations from protocol procedures, then the site will need to submit a corrective action plan to COGRegComp@childrensoncologygroup.org within two weeks.

In the event of significant repeated major deviations from the protocol, COGQA, in consultation with the study chair, may recommend that COG leadership suspend accrual at the site.

APPENDIX III: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	> ULN- ≤ 1.5 x ULN
Grade 2:	> 1.5 x ULN - 3.0 x ULN
Grade 3:	> 3.0 x ULN -10.0 x ULN
Grade 4:	> 10.0 x ULN

ALT: Use institutional ULN for ALT and CTCAE v 5 criteria for grading.
AST: For the purpose of this study, the ULN for AST is 50 U/L regardless of baseline.

Grade 1:	> 50 U/L - ≤ 150 U/L
Grade 2:	151 U/L -250 U/L
Grade 3:	251 U/L -1000 U/L
Grade 4:	> 1000 U/L

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN - 5.0 x ULN
Grade 3:	> 5.0 x ULN -20.0 x ULN
Grade 4:	> 20.0 x ULN

APPENDIX IV: YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY PEPN2113
(for children from 7 through 12 years of age)

We want to tell you all about this study. You and your family can decide if you want to be in it. Ask questions if you don't understand.

1. What is the name of the study? **A study to find the safe dose of uproleselan (GMI-1271) in combination with fludarabine and cytarabine for patients with AML that has come back or does not respond to therapy and that expresses E-selectin ligan on the cell membrane.**

2. Who is in charge of the study? The study is being done by PEP-CTN and is being done at other hospitals.

3. What is the study about? We are asking you to take part in a research study because you have AML that has either come back or does not respond to therapy. A research study is when doctors work together to try out new ways to help people who are sick. We are testing a new drug call uproleselan (GMI-1271) in combination with fludarabine and cytarabine. By doing this study, we are hoping we can find the safe dose we can give of uproleselan (GMI-1271) in combination with fludarabine and cytarabine safely.

4. What will happen to me in the study? Children who are part of this study will be treated with cancer fighting medicine called fludarabine and cytarabine as well as the new drug uproleselan (GMI-1271). You will have some tests and check-ups done more often than if you weren't part of this study. Some of these tests will require extra needle sticks for blood collection. The doctors want to see if the combination of uproleselan (GMI-1271), cytarabine and fludarabine will make children with your type of cancer get better. We don't know if this combination will work well to get rid of your cancer. That is why we are doing this study.

   Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is better chance at getting rid of the AML but we don't know for sure if there is any benefit of being part of this study.

   Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are infection, low blood counts, feeling tired, and feeling sick. Other things may happen to you that we don't yet know about.

5. Do I have to be in the study? You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. The doctors and nurses will still take care of you. There may be other treatments for your illness that your doctor can tell you about. If you have any questions or don't like what is happening, please tell your parent, the doctor or nurse.

INFORMATION SHEET REGARDING RESEARCH STUDY PEPN2113
(for teens from 13 through 17 years of age)

We want to tell you all about this study. You and your family can decide if you want to be in it. Ask questions if you don't understand.

1. What is the name of the study? **A study to find the safe dose of uproleselan (GMI-1271) in combination with fludarabine and cytarabine for patients with AML that has come back or does not respond to therapy and that expresses E-selectin ligan on the cell membrane.**

2. Who is in charge of the study? The study is being done by PEP-CTN and is being done at other hospitals.

3. What is the study about? We are asking you to take part in a research study because you have AML that has either come back or does not respond to therapy. A research study is when doctors work together to try out new ways to help people who are sick. We are trying to learn more about how to treat the kind of cancer that you have. We will do this by trying a new medicine called uproleselan (GMI-1271) in combination with fludarabine and cytarabine. By doing this study, we are hoping we can find the safe dose we can give of uproleselan (GMI-1271) in combination with fludarabine and cytarabine safely.

4. What will happen to me in the study? Children who are part of this study will be treated with cancer fighting medicine called fludarabine and cytarabine as well as the new drug uproleselan (GMI-1271). You will have some tests and check-ups done more often than if you weren't part of this study. Some of these tests will require extra needle sticks for blood collection. The doctors want to see if the combination of uproleselan (GMI-1271), cytarabine and fludarabine will make children with your type of cancer get better. We don't know if this combination will work well to get rid of your cancer. That is why we are doing this study.

   Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is better chance at getting rid of the AML, but we don't know for sure if there is any benefit of being part of this study.

   Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are infection, low blood counts, feeling tired, and feeling sick. Other things may happen to you that we don't yet know about.

5. Will I be paid to be in this study? You will not be paid for being in this study.

6. Do I have to be in the study? You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. The doctors and nurses will still take care of you. There may be other treatments for your illness that your doctor can tell you about. If you have any questions or don't like what is happening, please tell your parent, the doctor or nurse

APPENDIX V: BIOMARKER STUDIES

Schedule for patients ≥ 10kg:

Time Point	Specimen and Quantity	Send Specimens to:
Cycle 1 Day 1, Pre-dose		
	• *1-2 mL blood in sodium citrate tube for PK (required)* [1]	*Pyxant Labs*
Cycle 1 Day 1, 30 minutes after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required)* [1]	*Pyxant Labs*
Cycle 1 Day 1, 1 hour after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required)* [1]	*Pyxant Labs*
Cycle 1 Day 1, 2 hours after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required)* [1]	*Pyxant Labs*
Cycle 1 Day 1, 4 hours after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required)* [1]	*Pyxant Labs*
Cycle 1 Day 6, Pre-dose		
	• *1-2 mL blood in sodium citrate tube for PK (required)* [1]	*Pyxant Labs*
Cycle 1 Day 6, 30 minutes after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required)* [1]	*Pyxant Labs*
Cycle 1 Day 6, 1 hour after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required)* [1]	*Pyxant Labs*
Cycle 1 Day 6, 2 hours after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required)* [1]	*Pyxant Labs*
Cycle 1 Day 6, 4 hours after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required)* [1]	*Pyxant Labs*
End of Cycle 1		
	• *2-4 mL bone marrow in sodium heparin (green top) tube for MRD*	*Hematologics*
End of Cycle 2		

	• *2-4 mL bone marrow in sodium heparin (green top) tube for MRD*	*Hematologics*

[1]Time from start of first infusion of uproleselan (GMI-1271) for the day. Collect 1 mL per time point for patients < 6 years old, and 2 mL per time point for patients ≥ 6 years old.

Schedule for patients < 10kg:

Time Point	Specimen and Quantity	Send Specimens to:
Cycle 1 Day 1, Pre-dose		
	• *1-2 mL blood in sodium citrate tube for PK (required) [1]*	*Pyxant Labs*
Cycle 1 Day 1, 30 minutes after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required) [1]*	*Pyxant Labs*
Cycle 1 Day 1, 1.5 hour after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required) [1]*	*Pyxant Labs*
Cycle 1 Day 1, 4 hours after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required) [1]*	*Pyxant Labs*
Cycle 1 Day 6, Pre-dose		
	• *1-2 mL blood in sodium citrate tube for PK (required) [1]*	*Pyxant Labs*
Cycle 1 Day 6, 30 minutes after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required) [1]*	*Pyxant Labs*
Cycle 1 Day 6, 1.5 hour after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required) [1]*	*Pyxant Labs*
Cycle 1 Day 6, 4 hours after start of infusion		
	• *1-2 mL blood in sodium citrate tube for PK (required) [1]*	*Pyxant Labs*
End of Cycle 1		
	• *2-4 mL bone marrow in sodium heparin (green top) tube for MRD (required)*	*Hematologics*
End of Cycle 2		
	• *2-4 mL bone marrow in sodium heparin (green top) tube for MRD (required)*	*Hematologics*

[1]Time from start of first infusion of uproleselan (GMI-1271) for the day. Collect 1 mL per time point for patients < 6 years old, and 2 mL per time point for patients ≥ 6 years old.

APPENDIX VI: CORRELATIVE STUDIES GUIDE

Correlative Study	Appx.	Volume per Sample (ml)	Total Volume (ml)
End of Cycle Bone Marrow for MRD	2	2-4 mL	4-8 mL
Blood for Pharmacokinetics Analysis	8-10	1-2 mL	8-20 mL
Total Blood + Bone Marrow Volume =			12-28 mL

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI [c]
Tissue							
1	MRD	Multi-parameter flow cytometry CLIA: Y	End of cycle disease assessment	Bone marrow or peripheral blood	End of cycles 1-2	M	L. Brodersen, PhD Hematologics, Inc 3161 Elliot Ave, Suite 200 Seattle, WA 98121
Blood							
1	Pharmaco-kinetics	Multiple CLIA: N	To evaluate the C_{max}, T_{max}, elimination half-life, clearance and volume of distribution of GMI-1271	Plasma	See Specimen Collection Table in Section 8.3	M	GlycoMimetics, Inc 9708 Medical Center Drive Rockville, MD 20850

APPENDIX VII-A: PHARMACOKINETIC (PK) WORKSHEET (≥ 10KG)

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg
Uproleselan (GMI-1271) Dose: _____ mg/kg Uproleselan (GMI-1271) Total Dose: _____ mg IV infusion

Blood samples will be collected in consenting patients in sodium citrate tubes at the following time points: Pre-dose, 30 minutes, 1, 2, and 4 hours after start of infusion of Cycle 1 Day 1 and Cycle 1 Day 6 for patients ≥10kg.

Peripheral blood samples for PK analysis should be obtained as follows: For patients ≥ 6 years old, collect 2 mL of blood into a sodium citrate tube per timepoint. For patients < 6 years old, collect 1 mL of blood into a sodium citrate tube per timepoint.

Schedule for patients ≥ 10kg:
Record the exact date and time the sample is drawn.

Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected
Cycle 1, Day 1	Immediately Pre-dose	___/___/___	|__|__| : |__|__|
Cycle 1, Day 1	30 minutes after start of infusion (±5 minutes)	___/___/___	|__|__| : |__|__|
Cycle 1, Day 1	1 hour after start of infusion (±20 minutes)	___/___/___	|__|__| : |__|__|
Cycle 1, Day 1	2 hours after start of infusion (±20 minutes)	___/___/___	|__|__| : |__|__|
Cycle 1, Day 1	4 hours after start of infusion (±20 minutes)	___/___/___	|__|__| : |__|__|
Uproleselan (GMI-1271) Dose on Cycle 1, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|

Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected
Cycle 1, Day 6	Immediately Pre-dose	___/___/___	|__|__| : |__|__|
Cycle 1, Day 6	30 minutes after start of infusion (±5 minutes)	___/___/___	|__|__| : |__|__|
Cycle 1, Day 6	1 hour after start of infusion (±20 minutes)	___/___/___	|__|__| : |__|__|
Cycle 1, Day 6	2 hours after start of infusion (±20 minutes)	___/___/___	|__|__| : |__|__|
Cycle 1, Day 6	4 hours after start of infusion (±20 minutes)	___/___/___	|__|__| : |__|__|
Uproleselan (GMI-1271) Dose on Cycle 1, Day 6	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__| |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__| |__|__| : |__|__|

One copy of this PK Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.3, in addition to detailed guidelines for packaging and shipping PK samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX VII-B: PHARMACOKINETIC (PK) WORKSHEET (< 10 KG)

COG Pt ID # _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg
Uproleselan (GMI-1271) Dose: _____ mg/kg Uproleselan (GMI-1271) Total Dose: _____ mg IV infusion

Blood samples will be collected in consenting patients in sodium citrate tubes at the following time points: Pre-dose, 30 minutes, 1.5, and 4 hours after start of infusion of Cycle 1 Day 1 and Cycle 1 Day 6 for patients <10kg

Peripheral blood samples for PK analysis should be obtained as follows: For patients ≥ 6 years old, collect 2 mL of blood into a sodium citrate tube per timepoint. For patients < 6 years old, collect 1 mL of blood into a sodium citrate tube per timepoint.

Schedule for patients < 10 kg:
Record the exact date and time the sample is drawn.

Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected
Cycle 1, Day 1	Immediately Pre-dose	___/___/___	|__|__| : |__|__|
Cycle 1, Day 1	30 minutes after start of infusion (±5 minutes)	___/___/___	|__|__| : |__|__|
Cycle 1, Day 1	1.5 hour after start of infusion (±20 minutes)	___/___/___	|__|__| : |__|__|
Cycle 1, Day 1	4 hours after start of infusion (±20 minutes)	___/___/___	|__|__| : |__|__|
Uproleselan (GMI-1271) Dose on Cycle 1, Day 1	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__|

Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected
Cycle 1, Day 6	Immediately Pre-dose	___/___/___	|__|__| : |__|__|
Cycle 1, Day 6	30 minutes after start of infusion (±5 minutes)	___/___/___	|__|__| : |__|__|
Cycle 1, Day 6	1.5 hour after start of infusion (±20 minutes)	___/___/___	|__|__| : |__|__|
Cycle 1, Day 6	4 hours after start of infusion (±20 minutes)	___/___/___	|__|__| : |__|__|
Uproleselan (GMI-1271) Dose on Cycle 1, Day 6	**Date:**___/___/___	**Infusion Start Time:** |__|__| : |__|__| |__|__| : |__|__|	**Infusion Stop Time:** |__|__| : |__|__| |__|__| : |__|__|

One copy of this PK Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.3, in addition to detailed guidelines for packaging and shipping PK samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX VIII: RESPONSE CRITERIA FOR LEUKEMIA

Response Criteria:
For patients who are enrolled onto this study with <5% blasts, complete remission will be defined only as the attainment of a MRD negative complete remission as determined by central flow cytometry. For patients enrolled onto this study with ≥5% blasts, definitions of complete, partial or incomplete count recovery will be assessed using COG-specific criteria for pediatric patients.

COG Response Criteria:

COG Complete Remission (COG-CR):
Attainment of < 5% leukemic blasts in the bone marrow as determined by central flow cytometry with no evidence of circulating leukemic blasts or extramedullary disease and with recovery of peripheral blood counts (ANC ≥ 500/µL and platelet count ≥ 50,000/µL). The qualifying CBC must be drawn on the day of the marrow or up to 7 days after bone marrow. There is no requirement for bone marrow cellularity.

COG CR With Partial Recovery of Platelet Count (COG-CRp):
Attainment of < 5% leukemic blasts in the bone marrow as determined by central flow cytometry and no evidence of circulating leukemic blasts or extramedullary disease and with recovery of ANC ≥ 500/µL without platelet recovery to 50,000/µL. The qualifying CBC must be drawn on the day of the marrow or up to 7 days after bone marrow.

COG CR with incomplete blood count recovery (COG-CRi):
Attainment of < 5% leukemic blasts in the bone marrow as determined by flow cytometry and no evidence of circulating leukemic blasts or extramedullary disease and with ANC > 200/µL and platelet count > 20,000/µL without dependence on platelet transfusions (defined as: platelet count > 20,000/µL AND no platelet transfusions x 5 days). The qualifying CBC must be drawn on the day of the marrow or up to 7 days after bone marrow.

Aplasia:
If a patient has a hypoplastic bone marrow for ≥ 60 days and failure to recover a peripheral ANC > 200/µL and a non-transfusion dependent platelet count > 20,000/µL not due to malignant infiltration or severe infection (defined as ≥ Grade 3).

MRD negative:
Presence of < 0.05% of leukemic blasts by flow cytometry.

Extramedullary disease:
The same modality (CT, MRI, and/or FDG PET) used for pre-treatment evaluation should preferably be performed for follow-up imaging. Patients will be considered in complete remission if there has been complete radiographic resolution of disease. If radiographic imaging demonstrates residual extramedullary disease, tissue biopsy should be used to determine response, if clinically feasible. If tissue biopsy is not clinically appropriate, then radiographic studies should be used to determine extramedullary disease response. The differentiation between residual disease and residual scar tissue on radiographic studies may be difficult and the final determination of radiographic disease status should be made by the treating clinician in consultation with the local radiologist.

COG Treatment Failure (COG-TF):
Failure to achieve COG-CR, COG-CRp or COG-CRi as defined above after up to 2 cycles of therapy. Persistence of circulating leukemia blasts confirmed by flow cytometry or of extramedullary disease will also constitute treatment failure. Patients who do not have a marrow at diagnosis are not evaluable for response/TF. For patients who enroll with fewer than 5% of blasts, TF is defined as failure to achieve MRD negative COG-CR, MRD negative COG-CRp or MRD negative COG-CR_i.

Bone Marrow Relapse:
(Patients must meet one of the following criteria to be defined as having relapse disease)

I. A single bone marrow sample showing ≥1% leukemic blasts by flow cytometry performed at the central laboratory.
II. In cases where a bone marrow aspirate cannot be obtained because of extensive fibrosis, blast count can be obtained from touch imprints or estimated from an adequate bone marrow core biopsy; blast count must be ≥5% to be eligible. A complete blood count documenting the presence of at least 1,000/ µL (i.e., a WBC count ≥ 10,000/µL with ≥ 10% blasts or a WBC count of ≥ 5,000/µL with ≥ 20% blasts) circulating leukemic cells (blasts) can also be used if a bone marrow aspirate or biopsy cannot be performed.

Extramedullary Relapse
Extramedullary relapse is defined as biopsy proven extramedullary disease after documented CR or evidence of CNS recurrence

CNS Relapse
CNS relapse is defined as a patient having one of more of the following:

1. A single CSF sample with CNS3 status (see Section 4.3) after a previous status of CNS 1.
2. Clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome (Rel-CNS3).

Equivocal CNS Relapse
Patient has a single CSF sample with CNS2 status.

1. In the case of equivocal relapse, CSF evaluation should be repeated at least 1 week and at most 4 weeks later; for repeat CSF, flow cytometric testing and FISH (if a diagnostic FISH marker is available) should be sent.

2. To convert to definitive relapse, the repeat CSF or clinical status must:
   - Meet criteria for CNS relapsed as defined in Section 4.3. **OR**
   - Re-demonstrate CNS2 status, but with blasts confirmed by flow cytometry and/or FISH (Rel-CNS2) on CSF samples from consecutive lumbar punctures.

APPENDIX IX: PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

Patient Name:	**Diagnosis:**	**Trial #:**	PEPN2113
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	Uproleselan (GMI-1271)

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:

CYP isoenzymes	Uproleselan does not cause direct or time-dependent inhibition of CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4.
Protein transporters	Uproleselan is a substrate for the efflux transporters P-gp and MRP2, may be a weak substrate for BCRP, and is not a substrate of the efflux transporter BSEP. These transport proteins may affect how much or how fast uproleselan is moved in and out of cells/organs. Uproleselan is not an inhibitor of the efflux transporters P-gp, BCRP, or BSEP. Uproleselan is not a substrate for or inhibitor of the following uptake transporters: OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2.

These are the things that you need to know:
The study drug uproleselan, may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered transport proteins.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

(Next page: Patient Drug Interaction Wallet Card)

NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE
EMERGENCY INFORMATION		**DRUG INTERACTIONS**	
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before you start or stop any medicines.** **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** Uproleselan interacts with P-gp, MRP2, and BCRP and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** PEPN2113 **Study Drug(S):** Uproleselan	**Use caution and avoid the following drugs if possible:** N/A	Your healthcare providers should be aware of any medicines that are interact with P-gp, MRP2, and BCRP **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference for a list of drugs to avoid** or contact your study doctor. Version Jun/2021	
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov