

Clinical Review s NDA 20-038

Drug Name	Fludarabine Phosphate
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Documents reviewed	13 volume sponsor submission

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Clinical Review for NDA 20-038s

1. Executive Summary

The intent of this sNDA is to provide information from clinical trials of fludarabine phosphate (Fludara®) in pediatric cancer patients to fulfill the requirements outlined in the FDA Written Request for obtaining pediatric exclusivity.

Fludarabine phosphate was approved in 1991 for the treatment of patients with B-cell chronic lymphocytic leukemia [CLL] who have not responded to or whose disease has progressed during treatment with at least one standard alkylating agent-containing regimen. Its patent expires on February 23, 2003.

As CLL does not occur in children, (b) (4)

The sponsor has submitted clinical data on pediatric dosing and pharmacokinetic studies derived from two studies [CCG-097 and CCG-0895] conducted by the Children's Cancer Group (CCG), presently known as Children's Oncology Group (COG). Data from these two studies have been reported in the following publications:

CCG-097 - Avramis V., Champagne J., Sato J., Krailo M., Ettinger L., Poplack D., Finklestein J., Reaman G., Hammond D., Holcenberg J. Pharmacology of Fludarabine Phosphate After a Phase I/II Trial by a Loading Bolus and Continuous Infusion in Pediatric Patients. *Cancer Res.* 50: 7226-7231 1990.

CCG-0895 - Avramis V., Wiersma S., Krailo M., Ramilo-Torno L., Sharpe A., Liu-Mares W., Kwock R., Reaman G., Sato J. for the Children's Cancer Group. Pharmacokinetic and Pharmacodynamic Studies of Fludarabine and Cytosine Arabinoside Administered as Loading Boluses followed by Continuous Infusions after a Phase I/II Study in Pediatric Patients With Relapsed Leukemias. *Clin Cancer Res* 4: 45-52 1998.

The first study, CCG-097, was a Phase I dose finding and PK study of a loading bolus followed by continuous infusion of fludarabine in patients with previously treated advanced acute leukemias or solid tumors. Enrollment included 9 patients with acute nonlymphoblastic leukemia (ANLL), 36 patients with ALL and 17 solid tumor patients. The MTD, defined in the above referenced publication in patients with solid tumors, was a loading bolus of 7 mg/m² followed by a continuous infusion of 20.0 mg/m² for 5 days. In patients with acute leukemias, the MTD was not reached. The highest dose administered was a loading bolus of 10.5 mg/m² followed by a continuous infusion of 30.5 mg/m² for 5 days (Dose Level 6).

The difference in the MTDs between the leukemia and solid tumor patients appeared to be related to the way dose-limiting toxicities (DLT) were evaluated. In leukemia patients, hematologic toxicities were not considered in the evaluation of DLTs since marrow ablation

was a goal of therapy. CCG decided to cease escalation beyond the planned highest dose level because of concern for potential irreversible CNS toxicity previously reported in adults. In the solid tumor patients, the DLT was myelosuppression.

An independent retrospective analysis of the MTD could not be conducted, primarily due to missing or incomplete case report forms (CRFs).

An independent retrospective analysis of response in this trial could not be conducted, primarily due to missing or incomplete case report forms (CRFs).

The second study, CCG-0895, was a Phase 1/2 dose-finding, PK, and pharmacodynamic (PD) study of a loading bolus followed by continuous infusion of fludarabine followed by a loading bolus and then continuous infusion of ara-C in children with previously treated advanced acute leukemias. As such it provided no information on the efficacy or safety of fludarabine phosphate alone in pediatric acute leukemia.

1.1 Recommendations

1.1.1 Recommendation on Approvability

The low response rate, especially the low complete response rate, and relatively brief duration of response in pediatric refractory ALL and the absence of response in ANLL and solid tumors do not suggest a role for fludarabine phosphate in the treatment of these malignancies. The combined fludarabine/ara-C trial achieved a modest response rate at the cost of considerable toxicity (see section 8.3).

While the fludarabine/ara-C study cannot provide data on the efficacy of fludarabine alone it does provide efficacy and safety data for the combination. As such it is valuable since it is unlikely that physicians would treat relapsed pediatric ALL with a single agent.

Conclusions:

1. There is no reason to modify the label to include the pediatric data that was presented in this sNDA.
2. By conducting the two studies the sponsor met the requirement for pediatric exclusivity.

1.1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

Not relevant

2. Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

The pediatric clinical development of fludarabine was managed by the CCG (now referred to as the Children's Oncology Group or COG). In February 2001, the sponsor established an agreement with the COG for the use of the CCG-0895 data in support of the pediatric filing. In November 2001, the sponsor received permission from the COG for the use of the CCG-097 data for purposes of the pediatric filing.

Two studies were performed:

1. A Phase 1 study (CCG-097), which characterized the pharmacokinetics and established the maximum tolerated dose (MTD) for fludarabine in children with solid tumors as a 7 Mg/m² bolus dose followed by continuous infusion of 20.0 Mg/m² /day for 5 days.
2. A Phase 1/2 trial (CCG-0895), which was designed to study the pharmacokinetics (PK), pharmacodynamics, safety and efficacy of the fludarabine and ara-C combination regimen in pediatric patients with relapsed acute leukemias.

2.2 Efficacy

Fludarabine monotherapy produced one complete and 3 partial responses (13%) among 36 patients with refractory pediatric ALL. There were no responses among 26 patients with either solid tumors or ANLL. The duration of the complete remission was 55 days. The durations of the partial remissions were 34, 38, and 87 days. Responses could not be independently confirmed due to missing or incomplete case report forms (CRFs).

2.3 Safety

Limited safety data are available for fludarabine monotherapy in pediatric patients. Adverse events occurring at high frequency rates among 58 children with advanced malignancies included fever, pain, and gastrointestinal events such as vomiting, nausea, liver function abnormalities (increased transaminases and bilirubin) and abdominal pain.

In 12 patients with solid tumors, myelosuppression was the dose-limiting toxicity. In dose escalation studies, hematologic toxicities occurred at all dose levels and appeared to increase in severity with ascending doses. Platelet counts appeared to be more sensitive to the effects of fludarabine than hemoglobin and white blood cell counts. In 44 children with acute leukemia the most commonly reported adverse events were fever (91 %) and pain (77%). Vomiting, abdominal pain, and leukopenia were each reported by slightly more than half of patients with leukemia. There were 31 deaths during the study or within 30 days of study completion. The majority of deaths were due to progressive disease.

In 31 pediatric patients with refractory acute leukemias receiving fludarabine followed by ara-C (CCG 0895), profound bone marrow suppression was observed in virtually all patients. The following adverse events (in order of frequency) were reported in >50% of patients: vomiting, fever, pain, thrombocytopenia, anemia, diarrhea, infection, nausea, cough, pneumonia, and rash. There were 12 deaths, primarily from disease progression or infection. Sepsis occurred in 27% of patients. Safety data is summarized in Table

2.4 Dosing

The optimal dose for pediatric patients has not been established. In 12 children with solid tumors, dose-limiting hematological toxicity was observed with a loading dose of 8 mg/m² over 15 minutes followed by 23.5 mg/m²/day by continuous infusion for 5 days. The maximum tolerated dose was established at a loading dose of 7 mg/m² followed by 20 mg/m²/day for 5 days. In 45 children with recurrent leukemia, a loading dose of 10 mg/m² over 15 minutes followed by 30.5 mg/m²/day by continuous infusion for 5 days did not result in dose-limiting toxicity. Higher doses were not studied due to the potential for neurotoxicity. When fludarabine was administered to 31 pediatric patients with relapsed refractory leukemias at a loading dose of 10.5 mg/m² over 15 minutes followed by continuous infusion of 30.5 mg/m²/day for 2 days, the maximum tolerated dose of ara-C that could be administered subsequently was a loading dose of 390 mg/m² over 15 minutes followed by continuous infusion of 101 mg/m²/h over 72 hours.

2.5 Special Populations

The use of fludarabine in children with renal insufficiency has not been studied.

3. Clinical Review

3.1 Introduction and Background

3.1.1 Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Age Groups

Fludarabine phosphate (fludarabine, 2-fluoro-ara-AMP, F-ara-AMP), a purine nucleoside analog, has antitumor activity in human lymphoid malignancies. It was approved for the treatment of patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating agent containing regimen.

Although its mechanism of action has not been fully characterized, fludarabine is known to inhibit DNA synthesis and repair, inhibit ribonucleotide reductase, and induce apoptosis.

The intent of this sNDA is to provide information from clinical trials of fludarabine phosphate in pediatric cancer patients to fulfill the requirements outlined in the FDA Written Request for obtaining pediatric exclusivity.

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There is no proposed indication. Fludarabine demonstrated responses in pediatric patients with ALL. Combined with ara-C, fludarabine demonstrated responses in pediatric ALL and AML.

Pediatric patients less than 21 years of age were eligible for the phase 1 fludarabine study, patients < 19 years of age participated in the combination study.

3.1.2 State of Armamentarium for Indication(s)

Tenoposide (VM-26) is the only approved drug for the treatment of pediatric leukemia.

3.1.3 Important Milestones in Product Development

Fludarabine phosphate was approved in 1991 for the treatment of patients with B-cell chronic lymphocytic leukemia [CLL] who have not responded to or whose disease has progressed during treatment with at least one standard alkylating agent-containing regimen.

3.1.4 Other Relevant Information

None

3.1.5 Important Issues with Pharmacologically Related Agents

None

4. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

None

4.1 Human Pharmacokinetics and Pharmacodynamics

Limited pharmacokinetic data for fludarabine are available from a published study of children (ages 1-21 years) with refractory acute leukemias or solid tumors (Children's Cancer Group Study 0971). When fludarabine was administered as a loading dose over 10 minutes immediately followed by a 5-day continuous infusion, steady-state conditions were reached early. Pharmacokinetic parameters reported supported linear pharmacokinetics.

In vitro and ex vivo studies in leukemic cells have shown that administration of fludarabine prior to cytosine arabinoside (ara-C) increases the intracellular concentration of the ara-C active metabolite, ara-CTP. Thirty-one pediatric patients with relapsed acute leukemias were treated with fludarabine followed by ara-C (Children's Cancer Group Study 0895). When fludarabine was administered at a loading dose of 10.5 mg/m² over 15 minutes followed by

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continuous infusion of 30.5 mg/m²/day for 2 days, the maximum tolerated dose of ara-C administered subsequently was determined to be a loading dose of 390 Mg/m² over 15 minutes followed by continuous infusion of 101 mg/m²/h over 72 hours. The most common non-hematologic dose-limiting toxicity was hyperbilirubinemia.

See also Biopharm review.

5. Description of Clinical Data and Sources

5.1 Overall Data

Two publications:

CCG-097 - Avramis V., Champagne J., Sato J., et al. Pharmacology of Fludarabine Phosphate After a Phase 1/11 Trial by a Loading Bolus and Continuous Infusion in Pediatric Patients. *Cancer Res.* 50: 7226-7231 1990.

CCG-0895 - Avramis V., Wiersma S., Krailo M., et al. for the Children's Cancer Group. Pharmacokinetic and Pharmacodynamic Studies of Fludarabine and Cytosine Arabinoside Administered as Loading Boluses followed by Continuous Infusions after a Phase 1/11 Study in Pediatric Patients With Relapsed Leukemias. *Clin Cancer Res* 4: 45-52 1998.

Thirteen volume sponsor submission.

There was a considerable amount of missing or incomplete data (Table 1).

Table 1. Summary of Patient Numbers

Number of Patients	CCG-097 study	CCG-0895 study
mentioned in the publication	63	31
with complete CRFs available from CCG	29	31
with missing or incomplete CRFs for whom data could be extracted from medical records	33	0
for whom PK or PD data were provided by CCG	23	23
included in the analysis for PK reports	23	23
for whom CRF and extracted data could be subjected to the verification process	50/62 [81%]	28/31 [90%]
included in the analysis for clinical study reports	62	31
subjected to regulatory audit	17	11

Owing to the retrospective nature of the data retrieval and analyses, deficiencies related to documentation, quantity and quality of acquired data imposed limitations on the ability to fully verify data and replicate the published study results through independent analysis

5.2 Tables Listing the Clinical Trials

None

5.3 Postmarketing Experience

Not relevant

5.4. Literature Review

Not relevant

6. Clinical Review Methods

6.1 How the Review was Conducted

Paper submissions were reviewed. It was not possible to independently verify stated results.

6.2. Overview of Materials Consulted in Review

Materials reviewed are listed in section 5.1.

6.3 Overview of Methods Used to Evaluate Data Quality and Integrity

The sponsor engaged the assistance of (b) (4) a contract research organization (CRO), to perform the data verification and audit functions.

Data from the original CRFs, flow sheets, as well as from the Data Collection Forms were entered into the sponsor's database.

Data listings and copies of CRFs were provided to (b) (4) monitors, who reviewed them against available source documents at the study sites. Any discrepancies between the data listings provided by the sponsor and the patient's source documents were noted directly on the data listings. For CCG-0895, these included additional AEs, dates and times of drug administration, dates and times of PK/PD blood or bone marrow sampling information, death, infections, and off-study information. For CCG-097, these were limited to demographics, patient disposition, drug administration, safety profile and pharmacokinetics.

The verified data listings for those patients selected for audit were then forwarded by the (b) (4) monitors to (b) (4), and the data listings for the remainder were sent to the sponsor. Copies of the original listings sent to the regulatory auditors were forwarded to the sponsor for data entry. The original listings were sent later with the site audit reports.

Using by-patient listings generated from the database, (b) (4) monitors performed 100% data verification for specified data for a majority of the patients on both protocols (28 of 31 patients [90%] in Study CCG-0895, and 50 of 62 patients [81 %] in Study CCG-097). Some patients' medical records could not be located for audit. In Study 0895, records for patients F-3 and H-3 were missing. In Study 097, records for patients AA-1, AA-3, H-2, H-5, H-9, H-12, H-20, P-5, P-6 were missing.

6.4 Were Trials Conducted in Accordance with Ethical Standards

Yes

6.5 Evaluation of Financial Disclosure

No financial disclosure information was provided.

7. Integrated Review of Efficacy

7.1 Brief Statement of Conclusions

Studies CCG-097 and CCG-0895 have been conducted in children with malignancies for the purpose of defining the MTD, safety, PK, PD, and efficacy of fludarabine as a single agent or in combination with ara-C.

There was one complete remission (at dose level 2) and 3 partial remissions (1 patient at dose level 2, 2 patients at dose level 6) among 29 patients with ALL. The duration of the complete remission was 55 days. The durations of the partial remissions were 34, 38, and 87 days. There were no responses in patients with ANLL or solid tumors.

The CCG-097 and CCG-0895 studies have shown that plasma F-ara-A (at least 5 μ M) and intracellular F-ara-ATP (75 μ M) concentrations, considered to be synergistic with ara-C, could be achieved. Moreover, fludarabine was able to modulate ara-C metabolism, resulting in increased cellular ara-CTP concentrations, a significant factor for the efficacy of ara-C.

Sponsor analyses demonstrated a lack of correlation between the magnitude of increase in cellular ara-CTP levels and clinical response. Response appeared to correlate with the patient's relapse or refractory status to chemotherapy prior to the fludarabine/ara-C therapy.

In this heavily pre-treated pediatric patient population with poor prognosis, the benefit of a 42% response of modest duration resulting from the combination chemotherapy was achieved at the cost of serious hematologic and gastrointestinal toxicities, requiring substantial supportive therapy.

7.2 General Approach to Review of the Efficacy of the Drug

An independent retrospective analysis of the MTD and efficacy results could not be conducted, primarily due to missing or incomplete case report forms (CRFs).

7.3 Detailed Review of Trials by Indication

Two sequential Phase 1/2 clinical trials involving the use of fludarabine in pediatric patients were conducted by the CCG during 1984-1994.

Collectively, the two clinical trials enrolled 94 patients with advanced malignancies for whom data are available for 93 patients.

The first study, CCG-097, was a Phase 1 dose-finding and PK study of a loading bolus followed by continuous infusion of fludarabine in patients with previously treated advanced acute leukemias or solid tumors.

The second study, CCG-0895, was a Phase 1/2 dose-finding, PK, and pharmacodynamic (PD) study of a loading bolus followed by continuous infusion of fludarabine followed by a loading bolus and then continuous infusion of ara-C in children with previously treated advanced acute leukemias.

The demographic features of the study population enrolled in these studies are summarized in **Table 2**.

Table 2. Summary of demographics

	CCG-097 (fludarabine) N = 62	CCG-0895 (fludarabine/ara-C) N = 31
Acute nonlymphoblastic leukemia (ANLL)	9	18
Acute lymphoblastic leukemia (ALL)	36	13
Solid tumors	17	0
Refractory to last chemotherapy	Not determined	14
In relapse after last chemotherapy	Not determined	10
Unknown refractory or relapse status after last chemotherapy	Not determined	7
Median age (range), years	10(1-21)	8(1-18)
Female	26(42%)	15(48%)
Male	36(58%)	16(52%)
Asian	4(6%)	0
Black	12(19%)	8(26%)
White	28(45%)	14(45%)
Hispanic	17(27%)	8(26%)
Other	1 (2%)	1 (5%)

Study CCG-097: Single-Agent Fludarabine

In this study, the dose schedule (**Table 3**) was designed to achieve estimated (based on adult PK data) plasma concentrations of F-ara-A at time zero (C_0) and at steady state (C_{ss}). If no

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undue toxicity occurred, patients were allowed to receive additional courses (up to a maximum of 4) at 21-day intervals to assess any potential response to therapy.

Table 3. Fludarabine dose-escalation scheme

Dose level	Loading bolus (Mg/m ²)	Continuous infusion (mg/m ² /24 hr x 5 days)	Estimated μ M concentration	
			Co	C _{ss}
1	5.0	13.0	0.70	0.63
2	6.0	16.5	0.85	0.80
3	7.0	20.0	1.0	0.97
4	8.0	23.5	1.1	1.1
5	9.0	27.0	1.3	1.3
6	10.5	30.5	1.5	1.5

Study CCG-0895: Fludarabine/Ara-C Combination

This study evaluated the sequential combination of fludarabine followed by ara-C in pediatric patients with acute leukemia. The MTD of fludarabine derived from the CCG-097 study (Dose Level 6) was administered as a loading bolus of 10.5 mg/m² followed by a continuous infusion of 30.5 Mg/m²/24 hr over 48 hr.

Unlike Dose Level 6 in the CCG-097 study, the duration for the continuous infusion of fludarabine employed in CCG-0895 was shortened from 5 to 2 days because ex vivo and in vitro studies showed that this duration of exposure was sufficient to maximally augment ara-C anabolism.

Following completion of the fludarabine infusion, ara-C was administered as a loading bolus followed by a 72-hour continuous infusion. The dose-escalation scheme for ara-C is summarized in Table 4.

Table 4. Ara-C dose-escalation scheme

Dose level	Loading bolus (15 min)	Continuous infusion (72 hr)
1	250 mg/m ²	65 mg/m ² /hr
2	312 mg/m ²	81 mg/m ² /hr
3	390 mg/m ²	101 mg/m ² /hr
4	487 mg/m ²	126 mg/m ² /hr
5	609 mg/m ²	158 mg/m ² /hr

Study CCG-097: Single-Agent Fludarabine

According to the CCG publication, responses to therapy were defined as follows. A complete remission indicated the absence of symptoms and signs due to the malignancy and radiographic studies showing absence of tumor or a bone marrow with < 5% blasts and normal peripheral blood counts." Partial remission was defined as \geq 50% shrinkage of the

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tumor or a bone marrow with > 5% and ≤ 25% blasts. Among 29 patients with ALL, there was one complete remission (at Dose Level 2) and 3 partial remissions (1 patient at Dose Level 2, 2 patients at Dose Level 6). The duration of the complete remission was 55 days. The durations of the partial remissions were 34, 38, and 87 days. There were no responses in patients with ANLL or solid tumors. The estimated response rate at Dose Level 6 was 13%. The estimated response rate for the entire study population was 15%.

The sponsor was unable to do an independent retrospective analysis of response in this trial. For patients with solid tumors, data on tumor measurements were not recorded on the CRFs. Also, since CRFs were missing or incomplete for 28 patients, the response rate in ALL patients could not be independently derived.

Study CCG-0895: Fludarabine/Ara-C Combination

There was some discordance between the sponsor and CCG estimates of best clinical response. The response data based on the sponsor and CCG assessments for Part 1 are summarized in Table 5.

Table 5. The sponsor and CCG assessments of response - Part 1

	N	CR	PR	MR	SD	PD	NE	Unk
CCG analysis	22	7 (32%)	2 (9%)	3 (14%)	1 (5%)	6 (27%)	2 (9%)	1 (5%)
Sponsor analysis	22	6* (27%)	0	0	5 (23%)	8 (36%)	2 (9%)	1 (5%)

CR = complete response; MR = marginal response (not defined in protocol); NE = not evaluable; PD = progression of disease; PR = partial response; SD = stable disease; Unk = unknown. * One patient (H-8) was technically less than a CR because of persistent platelet counts < 100,000 /mm³.

The duration of responses ranged from 1 to 79 days. With the exception of one patient, responders showed either the same response or a better response to study treatment than they did to their last chemotherapy or ara-C-containing regimen. These results led CCG to expand the study and enroll additional patients with ANLL in Part 2 of the study.

Table 6 summarizes the responses in 11 ANLL patients included in the analysis for Part 2.

Table 6. The sponsor and CCG assessments of response - Part 2

	N	CR	PR	MR	SD	PD	Unk
CCG analysis	11	4 (36%)	1 (9%)	1 (9%)	4 (36%)	1 (9%)	0
Sponsor analysis	11	4* (36%)	0	0	4 (36%)	2 (18%)	1 (9%)

* 2 patients (H-9 and P-2) had only a "marrow CR".

Based on the CCG analysis, there were 4 CRs and 1 PR for a response rate of 45%. The duration of partial and complete responses based on the CCG analysis ranged from 21 to 192 days.

In this population of heavily pretreated pediatric patients with end-stage acute leukemias, study treatment induced clinical responses in 41 % to 45% of patients (CRs > 30%; CCG analysis) with modest response durations. Responders had the same or better response to the study treatment than they did to their last chemotherapy or ara-C-containing regimens. The overall response rate (Parts 1 and 2, sponsor analysis) was 32% (10/31 patients).

Comment: FDA could not independently verify response rate and response duration

Patient responses were also examined for correlations to dose level and to intracellular ara-CTP concentrations (for 12 patients with PD samples available). Response to fludarabine/ara-C did not appear to correlate with either the dose level of ara-C that patients received or with the magnitude of the increase in intracellular ara-CTP concentrations

7.4 Efficacy Conclusions

Published results and the retrospective review of CCG-097 essentially demonstrated that fludarabine given as a loading bolus followed by a continuous infusion was generally well tolerated, and yielded hematologic responses in patients with ALL.

The CCG-097 and CCG-0895 studies demonstrated that plasma F-ara-A (at least 5 μ M) and cellular F-ara-ATP (75 μ M) concentrations considered to be synergistic with ara-C could be achieved. However, sponsor analyses indicated a lack of correlation between the magnitude of increase in cellular ara-CTP levels and clinical response.

In a heavily pre-treated pediatric patient population with poor prognosis, the 41% to 45% (CCG analysis) response rate resulting from the combination chemotherapy was achieved at the cost of serious hematologic and gastrointestinal toxicities, requiring substantial supportive therapy.

8. Integrated Review of Safety

8.1. Brief Statement of Conclusions

Adverse events reported in the pediatric studies are similar to those seen in adults. In solid tumor patients myelosuppression was the dose limiting toxicity. Thrombocytopenia was more common than granulocytopenia or anemia. Nervous system toxicities include nervousness, increased sweating, headache, dizziness, somnolence and depression. Gastrointestinal toxicities included nausea, vomiting, and diarrhea. Pain and fever were also common.

8.2 Description of Patient Exposure

Information on patient exposure for the phase I fludarabine study is not available. For Study CCG-0895: Fludarabine/Ara-C Combination in Part 1 (the dose-finding portion of the study), 14 patients received one course of treatment and 8 received two courses. In Part 2 (ANLL feasibility study at the MTD), 5 patients received one course, 5 patients

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received two courses, and 1 patient received five courses of treatment. Two patients discontinued from Part 1 due to AEs, one due to Grade 4 hyperglycemia and increased amylase levels and the other due to Grade 4 elevated bilirubin and Grade 3 increased SGOT and SGPT. A total of 5 patients discontinued Part 1 due to death. In Part 2, 2 patients were discontinued because of AEs that included persistent elevation of liver transaminases in 1 patient and multiple AEs in another patient (hemorrhagic cystitis, elevated BUN and creatinine, bone marrow aplasia). In both parts of the study, a total of 12 patients died during the study or within 30 days of going off study.

8.3. Methods and Specific Findings of Safety Review

Adverse events are summarized in **Table 7**. For study CCG-097 adverse event (AE) data were available for 58 of 62 patients who received fludarabine. Nearly all patients (98%) experienced an AE.

Table 7 Adverse events. Studies 097 & 0895

Preferred term	CCG-097 Fludarabine alone		CCG-0895 Fludarabine/ara-C combination regimen	
	Solid tumor patients (n=14) (%)	Leukemia patients (n=44) (%)	Part 1 (n=22) (%)	ANLL patients (n=11) (%)
Fever	64	91	82	100
Chills	0	36	14	27
Asthenia	29	43	18	9
Rash	14	30	50	46
Nausea	43	48	55	91
vomiting	50	59	97	91
Nausea and vomiting*	21	18	NA	NA
Diarrhea	14	41	59	46
Infection	21	23	55	91
Leukopenia	14	57	91	91
Thrombocytopenia	14	41	68	73
Anemia	14	25	64	64
Pancytopenia	14	14	27	9

*these adverse events were sometimes reported as one event in the CCG-097 study

Body as a Whole: Fever was the most common event, with 84% of patients overall experiencing this event. Various terms for pain were also common; pain, abdominal pain, back pain, and pain in extremity were each reported by 78%, 47%, 31 %, and 31 % of patients overall, respectively. Also notable was asthenia (40%).

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Digestive System: Vomiting (57%) and nausea (47%) were most common. The event "nausea and vomiting" was also reported in 19% of patients overall. Anorexia and diarrhea were also common, with 45% and 34% of patients experiencing these events, respectively.

Nervous System: The overall incidence of AEs coded to the nervous system (81 %) was higher than reported AEs related to the hematologic system (69%) although the incidence of individual AEs only occasionally exceed 20%. AEs reported in > 20% of patients overall include nervousness (34%), sweating (31%), headache (29%), dizziness (26%), somnolence (24%), and depression (22%).

Hemic and Lymphatic: Leukopenia was reported in 47% of patients overall. Thrombocytopenia (34%), ecchymosis (28%), and petechiae (28%) were also notable.

As expected, some differences in AE profiles were reported in patients with solid tumors compared to those with leukemia. In general, there was a wider spectrum of AEs reported for patients with leukemias. The incidence of fever and vomiting was slightly higher among patients with leukemia, 91 % and 59% respectively, compared to 64% and 50% of patients with solid tumors. Reported hematologic AEs (leukopenia, thrombocytopenia, and anemia), bleeding manifestations (epistaxis, petechiae, ecchymosis, melena and mouth hemorrhage), and infections were more common in patients with leukemia than in patients with solid tumors.

The proportion of patient deaths reported as AEs was higher among patients with solid tumors (43%) compared to patients with leukemia (18%), perhaps reflecting the advanced disease stage of the former group.

Laboratory Toxicities

Laboratory data were incomplete for the majority of patients in this trial. Laboratory toxicities were determined according to the protocol-defined toxicity criteria, and all ≥ 2 grade shifts in laboratory toxicity level from baseline were tabulated. The most dramatic shifts from baseline in toxicity level were observed in the following parameters: WBC, hemoglobin, and platelets. Shifts from baseline in toxicity levels in these parameters among solid tumor patients included an apparent dose-dependent increase in toxicity grade.

Deaths

Information on 53 patient deaths was available from the data collected. These are summarized in **Table 8** by malignancy type.

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Table 8. Patient deaths by malignancy type

Solid tumors N = 17 Dose level					Leukemia N = 45 Dose level							Overall
1	2	3	4	5	1	2	3	4	5	6	Unk	
N=2 n (%)	N=3 n (%)	N = 2 n (%)	N=9 n (%)	N=1 n (%)	N 1 n (%)	N=3 n (%)	N=6 n (%)	N=5 n (%)	N=6 n (%)	N=23 n (%)	N=1	N = 62
Deaths on Study												
	2 (67)	2 (100)	2(22)	--		1 (33)	2 (33)	4 (80)	3 (50)	15 (61)	1 (100)	31(50)
Deaths Overall												
1 (50)	3 (100)	2 (100)	8 (88)	1 (100)	1(100)	2 (67)	3 (50)	4 (80)	6 (100)	21 (91)	1 (100)	53(85)

Deaths that occurred either on study or within 1 month of last fludarabine administration or study completion.

Overall, 53 (85%) of the 62 study patients died. There were 2 (4%), 5 (9%), 5 (9%), 12 (23%), 7 (13%), and 21 (40%) deaths in Dose Levels 1, 2, 3, 4, 5, and 6, respectively. Of the 17 patients with solid tumors, 15 (88%) died. Of the 45 patients with leukemia, 38 (84%) died.

Of the 53 deaths, 31 (58%) occurred either on study or within 1 month of receiving their last dose of fludarabine: 3 (10%), 4 (13%), 6 (19%), 3 (10%), and 14 (45%) patients died in Dose Levels 2, 3, 4, 5, and 6, respectively. One patient whose fludarabine dose level is unknown also died within 1 month of receiving the last dose of fludarabine. Twenty-five (81%) of the patients who died on study were patients with leukemia and 6 (19%) were patients with solid tumors.

The majority of deaths (19, 61 %) that occurred on study were due to progressive disease. Seven (23%) deaths were attributed to "other" causes such as cardiopulmonary or respiratory arrest. The cause of death was unavailable for 5 (16%) patients who died on study.

Study CCG-0895: Fludarabine/Ara-C Combination

Serious adverse events (SAEs) were not defined in the protocol. However, SAEs in 4 patients were reported by the institutions to NCI on Forms 1639 (Adverse Reaction Report). These included Grade 4 liver toxicities, elevated serum amylase and glucose, mucositis, severe skin rash, blisters, and desquamation. These SAEs occurred in Part 1 of the study. No SAEs were reported on Form 1639 during Part 2.

The most frequent AEs were either related to myelosuppression (e.g., leukopenia, thrombocytopenia, anemia, and infection) or gastrointestinal events (e.g., nausea, vomiting, and diarrhea). In the dose-finding phase of the study, AEs reported in > 50% of patients were leukopenia, vomiting, fever, pain, thrombocytopenia, anemia, diarrhea, infection, nausea, cough, pneumonia, and rash. Sepsis occurred in 27% of patients. Hyperbilirubinemia, the DLT at the MTD, was reported in 23% of patients. Although the patient cohorts were small, in general the relative frequency rates for most of the AEs appear to increase with ascending dose levels. The type and frequency of AEs and body systems involved were similar in Part 2 of the study. The most frequent AEs were either related to myelosuppression (e.g., leukopenia, thrombocytopenia, anemia, and infection) or gastrointestinal events (e.g., nausea, vomiting, and diarrhea). Pain was reported in > 70% of patients.

Though the severity of AEs was most often not recorded, most of the reported Grade 4 toxicities were hematologic. The degree of hematologic toxicity is reflected in the large number of red cell and platelet transfusions required to support these patients through the period of myelosuppression. During the dose-finding portion of the study, 20 of the 22 patients required multiple red cell and platelet transfusions. The total number of days each patient received red cell transfusions ranged from 4 to 42 days (mean = 14 days, median = 10 days), and the total number of days for platelet transfusions ranged from 4 to 43 days. Twenty of 22 patients also had Grade 4 neutropenia, with the duration of maximum toxicity

being a median of 16 days and a mean of 21.6 days. Hematologic toxicity was also evident during the second part of the study. The total number of days each ANLL patient in Part 2 received red cell transfusions ranged from 7 to 26 days (mean = 17 days, median = 21 days) and for platelet transfusions ranged from 8 to 29 days (mean = 19, median = 22 days). All 11 patients experienced Grade 4 neutropenia, with median and mean durations of 32.5 days and 42.5 days, respectively.

8.4 Adequacy of Safety Testing

Owing to the retrospective nature of the data retrieval and analyses, deficiencies related to documentation, quantity and quality of acquired data imposed limitations on the ability to fully verify data and replicate the published study results through independent analysis.

8.5 Summary of Critical Safety Findings and Limitations of Data

See section 8.4

9. Dosing, Regimen, and Administration Issues

None

10. Use in Special Populations

10.1 Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Gender effects analyses were not performed. See section 8.4.

10.2 Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

There were insufficient patient numbers to evaluate effects of age, race, or ethnicity on safety or efficacy.

10.3 Evaluation of Pediatric Program

This was a pediatric study.

10.4 Comments on Data Available or Needed in Other Populations

None.

11. Conclusions and Recommendations

11.1 Conclusions

The low response rate, especially the low complete response rate, and relatively brief duration of response for fludarabine phosphate in the treatment of pediatric refractory ALL and the absence of response in ANLL and solid tumors do not suggest a role for fludarabine of these malignancies.

In a heavily pre-treated pediatric patient population with poor prognosis, the combined fludarabine/ara-C response rate was 41% to 45% (CCG analyses). The response duration ranged from 1 to 192 days. Responses were achieved at the cost of serious hematologic and gastrointestinal toxicities, requiring substantial supportive therapy. These results do not suggest a role for fludarabine/ara-C in the treatment of these refractory malignancies.

While the fludarabine/ara-C study cannot provide data on the efficacy of fludarabine alone it does provide efficacy and safety data for the combination. As such it is valuable since it is unlikely that physicians would treat relapsed pediatric ALL with a single agent.

Owing to the retrospective nature of the data retrieval and analyses, deficiencies related to documentation, quantity and quality of acquired data imposed limitations on the ability to fully verify data and replicate the published study results through independent analysis.

11.2 Recommendations

1. By conducting the two studies the sponsor met the requirement for pediatric exclusivity.
2. Proposed labeling change - PRECAUTIONS - Pediatric use section.

Data submitted to the FDA was insufficient to establish efficacy in any childhood malignancy. Fludarabine was evaluated in 62 pediatric patients (median age 10, range 1-21) with refractory acute leukemia (45 patients) or solid tumors (17 patients). The Fludarabine regimen tested for pediatric acute lymphocytic leukemia (ALL) patients was a loading bolus of 8 mg/m² followed by a continuous infusion of 30.5 mg/m²/day for 5 days. Treatment toxicity included profound bone marrow suppression. Platelet counts appeared to be more sensitive to the effects of Fludarabine than hemoglobin and white blood cell counts. Other adverse events included fever, chills, asthenia, rash, nausea, vomiting, diarrhea, and infection. There were no reported occurrences of peripheral neuropathy or pulmonary hypersensitivity reaction.

12. Appendix

12.1 Other Relevant Materials

None.

12.2 Individual More Detailed Study Reviews (If performed)

None.

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/s/

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7/25/03 12:45:38 PM
MEDICAL OFFICER

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