Briefing Document for the Oncologic Drugs Advisory Committee

ODAC Meeting Date: September 1, 2009

NDA: 022-489

Company: Vion, Inc.

Drug: Onrigin™ (laromustine), VNP40101M

Applicant's Proposed Indication: Remission induction in patients 60 years or older with *de novo,* poor risk acute myeloid leukemia (AML)

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1.0 Summary of NDA 022489

Vion has submitted NDA 22-489 for the use of Onrigin™, laromustine, as a single agent, for the indication: remission induction in patients 60 years or older with *de novo*, poor-risk acute myeloid leukemia (AML). The application primarily relies on the findings of a single-arm study and a post-hoc subset of patients from a second single-arm study. The application does not contain definitive results from a completed, well-conducted and randomized controlled trial demonstrating the efficacy or safety of laromustine. However, the application does contain data from a randomized controlled trial which was placed on clinical hold due to excess mortality in the laromustine containing arm.

Several scientific and regulatory issues are pertinent for this ODAC meeting concerning laromustine. The scientific issue is primarily a benefit-risk consideration whether the application contains sufficient efficacy and safety information on laromustine, when used as a single agent, for the treatment of a well-defined patient population. Key to this issue is whether the single-arm studies as designed and conducted isolate the effect of laromustine in order to understand and quantify the benefits and risks associated with laromustine use as a single agent. Additionally, safety concerns have been identified leading to the clinical hold placed of the applicant's phase III trial. The regulatory issues include: (a) pathways for approval and (b) evidentiary standards for the approval of agents for the treatment of acute leukemia.

1.1 Data Submitted for Approval

Two study reports and datasets were submitted in support of the proposed indication: one from a prospective single-arm study in 85 patients (study CLI-043), and one comprised of 55 patients selected post-hoc by Vion from a larger phase 2 single-arm study in a broader patient group (study CLI-033). In addition the application includes a study report and dataset from a third prospective, randomized controlled trial (CLI-037) which compared cytarabine alone to the combination of the same cytarabine plus laromustine in a population of patients age 18 and above with AML in relapse after prior therapy.

Vion has proposed that laromustine be approved for patients who are ≥60 years of age with *de novo*, poor risk AML. Vion defines poor risk patients as those patients who would be considered ineligible for standard induction therapy with daunorubicin/cytarabine (commonly referred to as a "3+7" regimen) because of any one of the following pretreatment baseline “poor risk” characteristics:

a. age ≥70
b. Eastern Cooperative Oncology Group (ECOG) performance status (PS) = 2
c. unfavorable cytogenetics
d. co-morbidities of the heart, lung or liver

This definition of poor risk combines a patient’s medical condition with AML disease characteristics. The validity of the use of this definition of poor risk is not known for several reasons, including the lack of prospective data suggesting that a patient presenting with any of these aforementioned baseline patient or disease characteristics would not be a candidate for standard therapy known to provide clinical benefit. In particular, the use of an arbitrary numeric age to establish a boundary for delineating a treatment option is concerning. "Poor-risk" is much more likely to reflect additional disease variables not yet understood. Several literature reports of randomized controlled studies indicate that, while older patients may have lower rates of remission, there are patients who have durable remissions from regimens such as the 3+7 schedule or a low-dose cytarabine regimen, for example.

The bulk of support for the indication is from the efficacy and safety results of one single-arm phase II trial (CLI-043) in which 85 patients aged 60 or older with previously untreated AML were given at least one intravenous (IV) induction treatment with 600 mg/M^2 of laromustine. Subsequently, all responding patients were to receive cytarabine treatment for consolidation. All patients must have had at least one of the above pretreatment baseline “poor risk” characteristics.

Independent reviewer assessment’s efficacy results demonstrated that 24 of the 85 treated patients (28%, 95% CI: 19%, 39%) achieved CR or CRp. The applicant reported that the median leukemia-free survival was less than 6 months (174 days, 95% CI: 57, 298) with a range from 1 day to 581 days. In almost half (10/24) of the patients whose disease achieved a remission, the leukemia-free survival was less than 90 days. In approximately a third (8/24) of patients who achieved a remission, the leukemia-free survival was less than 60 days. Lastly, for four patients who achieved a remission, the applicant’s reported leukemia-free survival was less than 30 days. However, the calculated leukemia-free survival result from this trial is confounded by the fact that patients who achieved a CR, CRp, or PR with laromustine induction received cytarabine for consolidation. Therefore the result from this trial cannot provide evidence of the durability of remission with single agent laromustine since the responding patients received consolidation therapy with cytarabine.

To provide further support for the NDA application, Vion retrospectively selected a subset of patients from a second single arm phase II trial (CLI-033) which was conducted in patients with AML or myelodysplastic syndrome (MDS). The CLI-033 trial involved the administration of one or two sequential courses of induction therapy with the combination of 3 days of oral hydroxyurea (HU) and a single intravenous (IV) administration of laromustine followed by a single course of laromustine consolidation therapy. For this study, eligible patients were those who were 60 years of age or older and had any one of the following conditions: previously untreated AML, previously untreated high risk MDS, previously untreated Secondary AML, AML in 1st Relapse, or AML or MDS in Relapse. The original study protocol for CLI-033 called for the initiation of hydroxyurea pre-treatment for all patients. The text from the original protocol reads: *Furthermore although short-term administration of hydroxyurea alone is unlikely to induce remissions, its effects on DNA synthesis are predicted to inhibit DNA repair and enhance the anti-tumor activity of VNP40101M.* Thus the initial hypothesis for the trial was that co-administration of HU would enhance the anti-leukemic effect of laromustine over laromustine alone.

In contrast to CLI-043, there was no plan to enroll patients in CLI-033 who were ineligible for standard induction therapy by having any one of the following "poor risk" features: age≥70, PS=2, unfavorable cytogenetics, or organ (heart, lung or liver) dysfunction. In fact, the protocol excluded patients with active cardiac disease.

Efficacy results as judged by independent assessment of response for this subset demonstrated that remission (CR/CRp) was achieved for 16/55 or 29% (95% CI: 17.6%, 42.9%) of the patients. The median leukemia-free survival was slightly over 3 months (111 days, 95% CI: 51, 280). The range was from 11-981 days. However, the applicant's calculated leukemia-free survival result from this trial is confounded by the fact that the patients received concomitant hydroxyurea (HU) which the applicant postulated would enhance the effectiveness of laromustine. Therefore the result from this trial cannot provide evidence for the remission rate or durability of remission, or leukemia-free survival with single agent laromustine since patients received hydroxyurea as well.

Thus, the efficacy conclusions from both studies for laromustine as a single agent are confounded by the additional concomitant or sequential anti-leukemic agents given.

Use of laromustine in these studies was associated with both infusional toxicity (headache, nausea, dizziness, vomiting, hypotension, and dizziness) as well as typical post-infusional toxicity seen with myelosuppressive chemotherapy. However, during the conduct of the phase 2 studies and the phase 3 trial, laromustine use was associated with a unique and sometimes fatal pulmonary toxicity resembling nitrosourea pulmonary toxicity and requiring mechanical ventilation for some patients just achieving leukemia remission. Safety data

review revealed that pulmonary toxicity was in the top 3 causes of Grade 3, 4 and 5 Treatment Emergent Adverse Events (TEAEs) as well as Serious Adverse Events (SAEs).

The ability of the two single arm studies to provide sufficient safety data regarding laromustine's effects is also confounded by the study designs.

Lastly any decision about whether current knowledge about this drug could enable its use must consider the safety results from trial CLI-037 which was placed on hold due to a three-fold increase in deaths in the laromustine arm, in patients who would not be considered poor risk. CLI-037 was a randomized double blind placebo controlled comparison of cytarabine alone versus cytarabine with laromustine for patients above the age of 18 who had experienced a relapse of AML. This trial was placed on hold after 286 patients accrued due to an interim Data Safety Monitoring Board (DSMB) analysis which revealed a three-fold increase in mortality on the laromustine treatment arm. The applicant's results for this trial suggested that although the laromustine arm was associated with a near doubling of response rate (18% for the cytarabine control arm and 35% for the laromustine plus cytarabine arm), the survival appeared inferior for the overall study group and for the responding patients. The applicant's calculations for median overall survival were: 176 days for the cytarabine arm and 128 days for the laromustine plus cytarabine arm. The results from the randomized trial raise the issue of the safe use of laromustine in combination with cytarabine as well as raising a broader question of whether the Agency should be relying on complete response rate or an improvement in complete response rate as a surrogate endpoint for approval in the setting of acute leukemia.

1.2 Regulatory Issues

All drug approvals require evidence of effectiveness and safety from adequate and well controlled studies conducted with a well-defined population for which the therapy is beneficial, and adequate safety for the dose schedule identified so that a favorable benefit-to-risk assessment is clearly demonstrated. Randomized controlled trials provide the best evidence for judging effectiveness and relative safety of a therapy.

The Agency has two pathways for approval of drugs to treat patients with serious and life-threatening illnesses: regular and accelerated approval. The accelerated approval requirements are that (a) a new therapy must show benefit to patients over existing treatments (available therapy) and that (b) confirmatory post-marketing studies should be underway to verify and describe the clinical benefit. The main difference between the two pathways is the endpoint for approval. For regular approval, the approval is based on demonstrating an effect on a clinical benefit endpoint such as overall survival; while for an accelerated approval,

approval is based on a surrogate endpoint which is deemed reasonably likely to predict clinical benefit such as response rate. Applications receiving accelerated approval are required to demonstrate an effect on a clinical benefit endpoint with due diligence.

To consider an application for accelerated approval, the applicant must demonstrate that the drug shows a benefit over available therapies including standard therapies. This demonstration is usually done in the context of a randomized trial. Occasionally if there is no available therapy based on the patient population and disease, the applicant may attempt to demonstrate an effect based on a single agent, single arm study. When an applicant considers development based on a single agent, single-arm study, the applicant must ensure that the patient population does not have available therapy. The Agency's Guidance for Industry: Available Therapy, defines available therapy for drugs considered for accelerated approval. The Guidance states "available therapy (and the terms existing treatments and existing therapy) should be interpreted as therapy that is specified in the approved labeling of regulated products, with only rare exceptions. FDA recognizes that there are cases where a safe and effective therapy for a disease or condition exists but it is not approved for that particular use by FDA. However, for purposes of the regulations and policy statements … only in exceptional cases will a treatment that is not FDA regulated (e.g., surgery) or that is not labeled for use *but is supported by compelling literature evidence (e.g., certain established oncologic treatments) be considered available therapy.*"

Scientific issues arise with developing a drug for the treatment of acute leukemia using a single arm trial and defining a study patient population without available therapy (hence no comparator arm) and include: AML is primarily a disease of the elderly, with median age about 68 years in the U.S., and there is no standard definition of an elderly patient who is not eligible to receive standard induction/consolidation treatment with agents such as cytarabine and daunorubicin. The unproven assumption is that elderly patients with AML, especially those with additional poor-risk features, are assumed not to benefit from standard, available therapy.

In AML, the endpoint for these single-agent, single arm trials has been complete remission rate. Using a single arm study to obtain accelerated approval is not always successful. In 2005, ODAC considered the tipifarnib (Zarnestra®) application, for the treatment of elderly patients with newly diagnosed, poor-risk AML who were stated to be ineligible for standard induction therapy, and the results were based primarily on a single arm trial (CTEP-20). During the ODAC meeting, several issues were raised including the low response rate and whether the patients enrolled on the study could have received standard therapy. In the single-arm study presented for approval, the CR rate was only 11%. The early death rate of 25% exceeded the CR rate raising the question of benefit-risk. Some of the complete responders required additional hospitalization following induction of remission. ODAC members commented that many of the patients

entered on the trial could have tolerated and done well on standard intensive induction therapy. Indeed, some of the patients entered onto the trial eventually received standard intensive induction therapy and went into compete remission. Based on this assessment, ODAC voted against an accelerated approval. A subsequent randomized controlled study showed no survival advantage for Zarnestra® therapy over supportive care.[1]

For acute leukemia trials, the Agency has stated that approval based on data from single agent, single arm studies is possible, based on the demonstration of efficacy, usually the demonstration of durable complete responses, since achieving a complete response for a patient would result in less bleeding, infection, need for blood products and for antibiotics. However, many of the drug approvals for acute leukemia have included evidence from randomized trials. Previous FDA approvals in the treatment of AML in adult patients have been based on Phase III randomized trials (daunorubicin, cytarabine and the combination of iadarubicin and cytarabine). In the controlled trials for cytarabine and anthracyclines, endpoints of survival as well as response rate were used.

One exception is Mylotarg, gemtuzumab ozogamicin, which received accelerated approval for AML in first relapse, based on reasonably consistent findings in three single-arm studies. However, the approval of Mylotarg in 2000 remains a challenge. Please note that Mylotarg received accelerated approval for a different setting than the current application. The Mylotarg indication is for patients with CD33-positive AML in first relapse, who are 60 years of age or older, and who are not considered candidates for other cytotoxic chemotherapy.

2.0 Detailed Consideration of the Application and Submitted Data

The applicant has submitted several datasets during the FDA review. This briefing document and analyses are based on the data available to FDA as of June 30, 2009, unless otherwise indicated. Discussions are continuing with Vion about the format and content of their data submissions.

2.1 AML in the Elderly

The median age of onset of AML is about 68 years. Despite this fact, evidence suggests that only about one third of patients with AML age 60 or above are treated.[6] AML in patients aged ≥60 more frequently presents with antecedent hematological disorders (AHD), unfavorable cytogenetics (monosomy 5 or 6, 5q- or 7q- or complex cytogenetic changes), over expression of p-glycoprotein, and/or other molecular markers of poor prognosis, and is more resistant to usual therapies.[2-5]

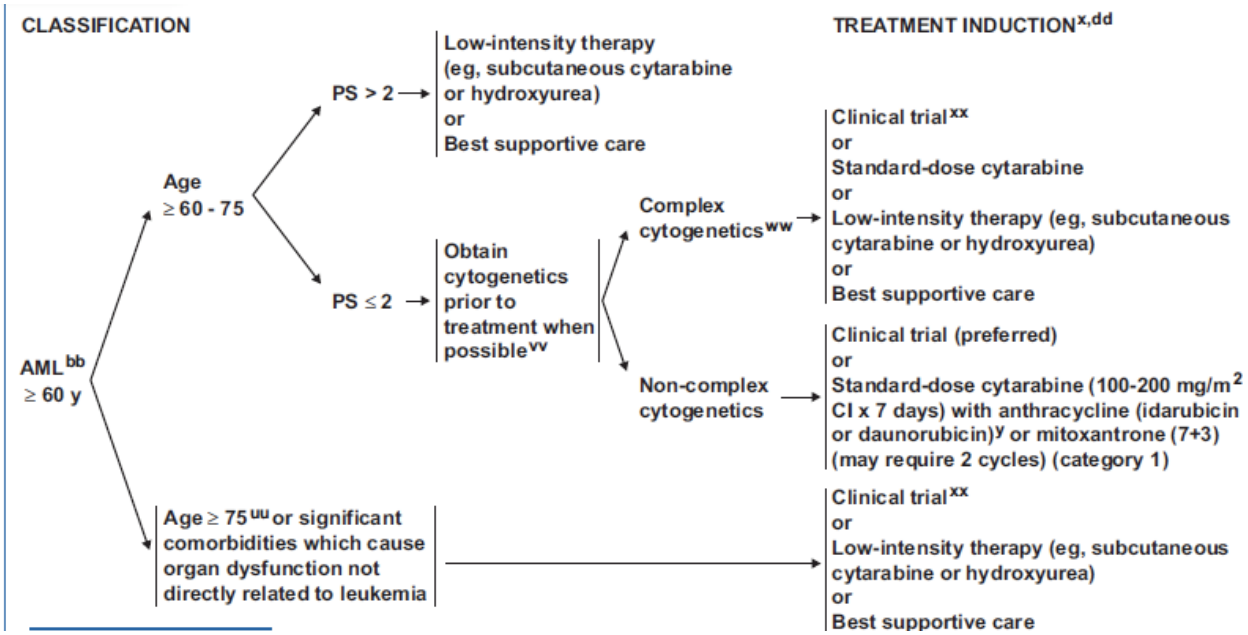
Available Therapy for AML in the Elderly

Patients with AML age 60 years of age and older may be given low intensity treatments such as hydroxyurea (HU) or low dose cytarabine (LDAC), if they are thought to be too frail to tolerate standard therapy, or intensive induction therapy such as "3+7" which describes 3 days of anthracycline administration and 7 days of continuous infusion cytarabine.[3,4] Diversity of opinion exists as to how to characterize patients aged 60 and older who can tolerate and benefit from intensive induction therapy. The percentage of patients who are above 60 who achieve CR/CRp with "3+7" may range from 38% to 60%, based on published data from SWOG[3] and from the Swedish Health Care System[4].

Community Treatment Guidelines for Patients with AML age 60 and older

The outcome of therapy in elderly patients with AML depends on patient characteristics, intensity of the therapy**,** and characteristics of the disease (e.g., age, cytogenetics, ECOG Performance Status (PS), organ dysfunction, initial WBC, and molecular signatures).[2-5] The existing National Comprehensive Cancer Network (NCCN) guidelines for treatment of AML in patients over age 60 arbitrarily divides the patient population into those 60 to 75 years of age and those 75 years and older and is reproduced below in Figure 1. For those patients aged 60-75, the decision about treatment depends on performance status. If the patient's performance status is greater than 2, the NCCN recommends low-intensity therapy or best supportive care. If a patient's performance status is less than or equal to 2, the guideline differentiates treatment choices based on disease characteristics (complex or non-complex cytogenetics). If the patient has complex cytogenetics the recommendations are participation in a clinical trial, low-intensity therapy or best supportive care. If the patient has non-complex cytogenetics the recommendations are participation in a clinical trial or standard dose cytarabine with an anthracycline. Thus, patients age 60-75 with PS 2 and non-complex cytogenetics are considered candidates for standard "3+7" induction therapy.

Figure 1: 2009 NCCN Guidelines for Treatment of AML in the Elderly.



2.2 Regulatory History of Laromustine

IND 61,759 for VNP40101M, cloretazine, was submitted in 2001. Several regulatory meetings were held between the FDA and Vion during the development of laromustine and as regulatory milestones occurred. In summary, FDA expressed concern with the use of laromustine in combination with hydroxyurea or with cytarabine because of the need to demonstrate the treatment contribution of laromustine. FDA recommended that the single agent activity of laromustine alone be characterized, that dose-finding of laromustine in combination with other drugs be evaluated, and that randomized controlled trials be performed against a standard therapy to judge efficacy and safety. FDA also requested that detailed information should be provided to support the reasons that the patients who were enrolled in single-arm studies were not candidates for standard therapies of demonstrated benefit for patients with AML.

2.3 Clinical Trials

2.3.1 Results of Phase I Testing of Laromustine

The results from the Phase I trials of laromustine conducted by Vion as far as the types of toxicities which were found to be dose-limiting are listed here.

Table 1: Phase I Dose Limiting Toxicities (DLTs)

	Laromustine	Laromustine	Toxicity (DLT)
Study	(mg/M^2)	Schedule	
CLI-011	305	Every 4-6 wks	reversible myelosuppression, ↓ platelets
CLI-028	155	Weekly X3	prolonged myelosuppression
CLI-029	708$^+$	Single dose	prolonged myelosuppression/ aplasia
CLI-034	500$^+$+Cytarabine^{++}	Single dose	prolonged myelosuppression, colitis
CLI-036	400$^+$+TMZ^{++}	Single dose	prolonged myelosuppression, ↓ platelet bleeding, colitis

Reviewer's Table

$^+$Laromustine IV as a single dose in relapsed hematopoietic malignancies / AML
$^{++}$ Cytarabine at 1.5g/M^2/d IV X 4 days; TMZ at 300 mg/day PO X 5 days.

2.3.3 Phase II clinical studies

For this NDA, Vion has submitted data from two single-arm studies (CLI-043 and CLI-033) and additional information from a randomized study (CLI-037) of laromustine plus cytarabine versus cytarabine alone. The primary endpoint, leukemia remission, consists of those patients achieving a complete response (CR) and those who would be considered as CR except that platelet recovery did not return to at least 100,000/uL. For the two single-arm studies, remission status was judged by an independent reviewer who examined the bone marrow and blood findings at some time period after the clinical site evaluations. The investigator determination of response guided additional protocol therapy. The independent review determination of response did not guide subsequent therapy. Also, the determination of leukemia recurrence was made by the investigators and not by independent review.

2.3.4 Vion CLI-043 Phase II Trial of Laromustine in 85 Patients with AML age ≥60 years

Eligibility and Trial Design of CLI-043

Vion provided in NDA 022-489 the efficacy and safety results of a single arm phase II trial (CLI-043) in which patients with AML age 60 and older were given at least one IV induction treatment with 600 mg/M^2 of laromustine. To be admitted to this trial, the patients must have previously untreated, *de novo* AML, must be 60 years or older, and must have at least **one** of the following pretreatment baseline "poor risk" characteristics, which Vion considered as disqualifying the patient from standard induction therapy: a. age ≥70, b. ECOG PS=2, c. unfavorable cytogenetics, and d. cardiac, lung or liver co-morbidity.

The protocol treatment in CLI-043 is outlined below:

Induction #1:	Laromustine 600 mg/M^2 IV X 1
Induction #2 for Patients with PR:	Laromustine 600 mg/M^2 IV X 1
Consolidation #1:	Cytarabine 400mg/M^2/day IV X 5 d
A. CR/CRp after Induction #1	
B. PR after Induction #2:	
Consolidation #2:	Cytarabine 400mg/M^2/day IV X 5 d

The primary endpoint for the trial was the response rate defined as CR plus CRp. Secondary endpoints included: overall survival (OS), leukemia-free survival (LFS), toxicities, and other exploratory analyses such as the effect of age, PS, cytogenetics and organ dysfunction on remission rate. The WHO leukemia diagnostic criteria were used.

The definitions of the endpoints are provided below.

CR: Blasts Absent from Peripheral Blood and <5% in Bone Marrow; ANC 1,000/mm^3, Platelet Count≥100,000/mm^3 at any time after start of therapy

CRp: Same as CR except Platelet Count ≥ 20,000/mm^3 Without Transfusions

LFS: Time between date Criteria of CR/CRp first achieved and Recurrence or Death

OS: Time between First Treatment and Death

Unfavorable cytogenetics were defined as including: del (5q)/-5q; del(7q)/ -7; abnormal 3q, 9q, 11q, 20q, 21q or 17p; t(6;9); t(9;22); trisomy 8; and complex karyotypes (>3 unrelated abnormalities).

Baseline pulmonary co-morbidity was defined as values less than 80% for either carbon monoxide diffusing capacity (DLCO) and/or forced expiratory volume in the first second (FEV1), dyspnea at rest or on slight activity, or requiring oxygen.

Cardiac Dysfunction included:

a. Ejection fraction ≤50% or
b. History of significant coronary artery disease (one or more vessel stenosis requiring medical treatment, stent placement or surgical bypass graft) or
c. History of CHF or AMI or
d. Significant arrhythmia including flutter, sick sinus, ventricular arrhythmia or
e. Valvular heart disease (excluding mitral valve prolapse) or
f. Other heart disease.

The table below provides demographics and disease characteristics for the patients enrolled in Vion study CLI-043.

Table 2: CLI -043 Demographics

Number treated (N=85)	Percent
Age≥70	78%
ECOG PS 2	41%
ECOG PS 0-1	32%
Unfavorable Cytogenetics	47%
Cardiac co-morbidity	**73%**
Pulmonary co-morbidity	**77%**
# of Risk Factors	
1	4%
2	21%
3	37%
4	31%
5 or more	8%

Reviewer's Table

Of the 85 patients, 78% were over age 70 and the majority had some evidence of cardiac or pulmonary co-morbidity. However, less than half, 41% were ECOG performance status 2 and 41% had unfavorable cytogenetics.

Of the total, 16% of enrolled patients completed the study. The most frequent reason for study discontinuation was death and the second most frequent was disease progression.

Table 3: Treatment Received by the Responders (based on Investigator Assessment) in CLI-043 Phase II Trial

	n
Induction #1	26
Induction #2	4
Consolidation #1 (cytarabine)	15
With Previous Induction #2	1
Consolidation #2 (cytarabine)	7

Reviewer's Table

Please note: the treatments reported above are only for those patients who were deemed to be responders. By FDA analysis of available data, some patients who received cytarabine consolidation were classified as only partial responders (PR) when they began the cytarabine consolidation.

Thus, all patients received one dose of laromustine 600 mg/m^2 IV as remission induction and 14 of the 85 received two doses of induction therapy. Those achieving a CR or CRp after one or two laromustine induction doses, or those

achieving a PR after 2 laromustine doses, then received cytarabine consolidation, beginning no later than 60 days if in CRp or for any patient, no later than 90 days.

Efficacy Results for CLI-043

The complete remission rate (CR plus CRp) was 24/85, 28% (95% CI: 19%, 39%) based on an independent review of post induction marrows. The applicant's leukemia-free survival (remission duration) was from 1 to 581 days, and 10/24 were less than 90 days. The median overall survival (all patients) was 98 days (95% CI: 42, 497 days) or 3.2 months. FDA judged that, for the responders, the duration of remission and the survival cannot be interpreted as expressing the effect of laromustine alone, but represent the effects of the combination with cytarabine. The study does not isolate or quantify the laromustine contribution to the time in remission. While the role of cytarabine in this study is stated to be limited to a consolidation effect, cytarabine in this dose range may contribute to remission induction also. Considering the timing of the cytarabine treatment, a conservative estimate of the duration of response could include censoring all responses at 60-90 days, to exclude the contribution of cytarabine to the treatment results. In addition, time-to-event endpoints such as leukemia-free survival, progression-free survival, and overall survival outcomes are difficult to interpret in single-arm studies.

Analysis of Safety Results of CLI-043

Attribution of adverse events and toxicity can be difficult to assess in a single arm study of patients with AML. However, patients reported the following side effects during the 30 minute infusion of laromustine: flushing, headache, nausea, vomiting, hypotension, and dizziness.

The following table shows the causes of early toxicities and deaths (≤30 Days) on CLI-043. Of note, pulmonary toxicity caused more early deaths than neutropenia and sepsis.

Table 4: Causes of Early (≤30 Days) Deaths on CLI-043

Patients (N=85)	Early Deaths (n, %)	Total (n, %)
Causes of Death		
Leukemic Progression	**11/31 (34%)**	**11/85 (12.9%)**
Pulmonary Toxicity	**6/31 (19%)**	**6/85 (7.0%)**
Bilateral Infiltrates	1/31 (3%)	1/85 (1.2%)
Acute Respiratory Failure	2/31 (6%)	2/85 (2.4%)
Pneumonia	3/31 (9%)	3/85 (3.5%)
Neutropenia/Sepsis	**5/31 (15%)**	**5/85 (5.9%)**
Acute Renal Failure/Tumor Lysis Syndrome	3/31 (9%)	3/85 (3.5%)
Cardiac Toxicity	2/31 (6%)	2/85 (2.4%)
Cerebral Hemorrhage	1/31 (3%)	1/85 (1.2%)
HSV Meningitis	1/31 (3%)	1/85 (1.2%)
Unknown	2/31 (6%)	2/85 (2.4%)

Reviewer's Table

The Grade 5 adverse events (deaths), irrespective of when they occurred on study, are shown below. Note that pulmonary causes of death were reported in 12%.

Table 5: Causes of Grade 5 Adverse Events on CLI-043

Cause	N	(Per Cent)
• AML	14	(34.0%)
• Infections	13	(31.0%)
• **Pulmonary***	**5**	**(12.0%)**
• Renal	4	(7.3%)
• Cardiac	2	(4.9%)
• General	2	(4.9%)
• Pancytopenia	1	(2.4%)
• GI	1	(2.4%)

Reviewer's Table

*Pulmonary included: Respiratory Failure (3), ARDS (1), Lung Infiltration (1)

The following table lists the causes of Grade 3-4 Adverse Events and therapy-related (based on investigator attribution) Grade 3-4 Adverse Events on CLI-043.

Table 6: Grade 3-4 Adverse Events in ≥ 2% of Patients on CLI-043

Cause	Any	Rx Related
• Blood and Lymphatic	37 (43.6%)	29 (34.1%)
• Infections	18 (21.2%)	7 (8.2%)
• **Pulmonary***	**16 (18.8%)**	**6 (7.1%)**
• Cardiac	12 (14.1%)	0
• GI	11 (13.0%)	0
• General	9 (10.6%)	0
• Metabolic	9 (11.8%)	6 (7.1%)
• Psychiatric	8 (9.4%)	0
• Vascular	7 (8.3%)	0
• Skin	3 (3.5%)	2 (2.4%)
• Renal	3 (3.5%)	0

Reviewer's Table

Pulmonary included: Hypoxia (10), Dyspnea (8), Pleural Effusion (4), Pulmonary Edema (2), and Respiratory Failure (1)

The SAEs which were considered by the investigators to be a direct result of laromustine treatment for patients on CLI-043 and all SAEs on CLI-043 are listed below. Pulmonary toxicity was the third most prevalent SAE overall.

Table 7: Causes of Serious Adverse Events (SAEs) on CLI-043

	Treated-Related SAEs		Any SAEs	
Cause	N	(%)	N	(%)
• Infectious	4	(4.7%)	28	(33.0%)
• ↓PMN, ↓Plts	10	(11.8%)	15	(18.0%)
• **Pulmonary***	**3**	**(3.5%)**	**15**	**(18.0%)**
• AML			14	(17.0%)
• Cardiac			9	(11.0%)
• GI			8	(9.0%)
• Surgery/Trauma	2	(2.4%)	4	(4.7%)
• General			2	(2.4%)
• Renal			2	(2.4%)
• Psychiatric			2	(2.4%)

Reviewer's Table

* Pulmonary: Pleural Effusion (4), Respiratory Failure (2), ARDS (2), Dyspnea (2) and Hypoxia (2)

The CR/CRp remission rate of 28% is in the range of available therapies for AML and does not appear to be superior to either the lower intensity or higher intensity treatment options available for patients with AML 60 years of age and older. The data from CLI-043 does not permit one to conclude that the laromustine plus

cytarabine therapy provides any advantage over that achievable by available therapy, and the contribution of laromustine alone to the outcomes is uncertain. Finally, the finding of pulmonary toxicity is worrisome in view of its prominence in every toxicity listing including: early deaths, Grade 3-5 adverse events, and SAEs, and in view of the population that Vion has proposed for the indication of laromustine, namely, AML ≥ age 60 with baseline heart or lung co-morbidity. While this pulmonary toxicity concern will be discussed further below, overall, laromustine therapy resulted in pulmonary AEs in 80% of patients who had baseline lung co-morbidity as well as in 66% of those without baseline pulmonary impairment.

2.3.5 CLI-033 Phase II Trial for Laromustine

The CLI-033 Phase II single arm trial was designed to gather preliminary data on the safety and effectiveness of the combination of oral hydroxyurea (HU) with laromustine. Treatment consisted of one or two sequential induction courses of 3 days of 30 mg/kg PO q 12 h X6 of oral hydroxyurea and a single intravenous injection of laromustine 600 mg/M^2 on day 2 followed by one consolidation treatment with a single injection of 400 gm/M^2 of IV laromustine. Eligible patients were those who were age ≥60 years with AML or MDS, or patients with relapsed MDS/AML. The trial specifically excluded patients with cardiac co-morbidities. In contrast to CLI-043, there was no attempt to select for patients who were judged as ineligible for standard induction therapy as there was in CLI-043.

The treatment regimen is illustrated in the table below.

Table 8: Therapy Design in the CLI-033 Phase II Trial

Induction Treatment #1:		30 mg/kg HU PO q12h X 6 plus 600 mg/M^2 laromustine IV X 1
Induction Treatment #2	(for patients achieving PR after Induction #1)	30 mg/kg HU PO q12h X 6 plus 600 mg/M^2 laromustine IV X1
Consolidation:		
	CR/CRp after Induction #1 or if PR after Induction #2	400 mg/M^2 laromustine IV once

Reviewer's Table

The primary endpoint of the trial was CR/CRp and the secondary endpoints included the duration of CR/CRp (Leukemia-Free Survival), Progression-Free Survival and Overall Survival.

Study CLI-033 was carried out at 6 centers in the USA and 4 Europe. The enrolled patients were classified by diagnosis into the groups shown below. All patients were ≥60 years of age, PS=0-2, and were ineligible if they had "active cardiac disease." Based on the NCCN guidelines for the treatment of AML, these

enrolled patients could have been considered eligible for standard therapy such as "3+7."

Table 9: CLI-033 Patients grouped by Disease Categories

De Novo AML Previously Untreated	54 Patients
Secondary AML Previously Untreated	51 Patients
Previously Untreated High Risk MDS (>10% Blasts)	26 Patients
1st Relapse of AML or MDS Relapsing from CR as AML	53 Patients

Reviewer's Table

2.3.6 Post hoc selection of patients from CLI-033 to support an indication in patients aged 60 and older with de novo poor-risk AML

Retrospectively, the applicant selected a subgroup of patients from study CLI-033 with de novo AML who were judged to be similar to the patients entered and treated in CLI-043 so that the patients from these two trials could be combined for an efficacy analysis. The assumption was that the patients selected post hoc by the method presented below would be composed of patients who were ineligible for standard induction therapy for AML by virtue of having any one of the pre-treatment baseline clinical features used for eligibility in study CLI-043. The profile of the patients selected from study CLI-033 is shown below to compare the baseline risk characteristics of patients entered on CLI-043 and those retrospectively selected from CLI-033 for a pooled efficacy analysis.

Table 10: Methods Used to Select Patients from CLI-033 for the NDA Efficacy Analysis

- Reclassify From FAB To WHO Criteria to parallel study CLI-043 diagnostic criteria
- Choose patients from CLI-033 who were similar to CLI-043, by virtue of having any one of following:
  - Age ≥70 years of age
  - PS=2
  - Unfavorable cytogenetics
  - Heart, lung, or liver co-morbidities
- 1 De Novo AML patient from CLI-033 was removed and 3 RAEBT-t by FAB were added to the subgroup by changing to the WHO System Classification for AML.

Reviewer's Table

Table 11: Retrospectively Selected Subset of CLI-033 Patients

	CLI-033
Age≥70	71%
ECOG PS 2	29%
ECOG PS 0-1	49%
Unfavorable Cytogenetics	42%
Cardiac Dysfunction	**42%**
Hepatic Dysfunction	**0%**
Pulmonary Dysfunction	**29%**
# of Risk Factors	
– 1	29%
– 2	38%
– 3	25%
– 4	6%
– 5	2%

Reviewer's Table

Thus, Vion identified a subgroup of 55 pts from study CLI-033 for the NDA submission for the analysis of the treatment of laromustine given in combination with HU. While an amendment late in the study allowed for HU use as an investigator option, the patients selected for this analysis had received HU. Of the 55 patients, 71% were age 70 or greater, 29% were ECOG PS 2, 42% had unfavorable cytogenetics, 42% had cardiac co-morbidities and 29% had pulmonary co-morbidities.

The primary efficacy results from this post-hoc subset are shown below. In this subset of patients from CLI-033, 15/25 CR/CRp patients (by investigators) were confirmed by Independent Review. One sample was rated Partial Response by Investigators and Complete Response by Independent Review. Thirty-five percent (19/55) of the investigator-determined response of CR/CRp were not confirmed by Independent Review.

Table 12: Analysis of Efficacy Endpoints From Post Hoc Selected Subset CLI-033

Response Rate (CR/CRp)	CLI-033 N	(%)
Independent Review*	16/55	(**29%**)
Investigator Review	24/55	(44%)
Confirmed by Both Reviews	15/24	
Investigator CR Not Confirmed	9/24	(38%)
No BM Slides Sent for Ind Review	4	
BM Slides of Poor Quality	3	
Inv Rev Challenged by Ind Rev		
Ind Rev Said Blasts >5% in Inv Rev CR	2	
CR by Ind Rev, PR by Inv Rev	1	

Reviewer's Table

Abbreviations: Ind Rev=Independent Review; Inv Rev=Investigator Review, CR=Complete Response; BM=Bone Marrow;

As noted above for study CLI-043, study CLI-033 is also confounded. The FDA interpretation of the use of hydroxyurea in combination for initial treatment is that the response rate, the duration of response, and survival estimates have to be viewed as a result of the laromustine and hydroxyurea in combination. In addition, all protocol treatment decisions were made by the investigators at the sites during the study. The adjudication of response status by independent review occurred after the study was completed and was not planned as part of the study conduct. Therefore, the contribution of laromustine to the outcomes is not isolated and has to be considered as uncertain in this subgroup.

2.3.7 Comparison of patients from CLI-043 and CLI-033

The applicant chose to pool the efficacy and safety data from CLI-043 and the subset of patients from CLI-033. However, the table below suggests that there were differences between the two populations, as well as the differences in study designs and treatments.

Table 13: Baseline Differences between CLI-033 and CLI-043 Patients evaluated for Efficacy Analysis

	CLI-033	CLI-043
• Age≥70	71%	78%
• ECOG PS 2	29%	41%
• ECOG PS 0-1	49%	32%
• Unfavorable Cytogenetics	42%	47%
• **Cardiac Dysfunction**	**42%**	**73%**
• **Pulmonary Dysfunction**	**29%**	**77%**
• **# of Risk Factors**		
– 1	29%	4%
– 2	38%	21%
– 3	25%	37%
– 4	6%	31%
– 5	2%	8%

Reviewer's Table

2.3.8 Summary of Efficacy

The FDA summary of the efficacy analysis for CLI-033 and CLI-043 is provided here.

Table 14: Efficacy Analysis of CLI-043 and CLI-033

	CLI-043	CLI-033
• CR/CRp (by Ind Rev)	28%	29%
• Alive at 2 years without Progression	8%	7%
• Early Deaths (≤30 days)	12%	22%
• Kaplan Meier Median OS	98 days	103 days

Reviewer's Table

Abbreviations: LFS=Leukemia-Free Survival; OS=Overall Survival; Ind Rev=Independent Review

The CR/CRp rates documented by independent review are 28% for CLI-043 and 29% for CLI-033. The percent of the patients who are alive at 2 years or greater from treatment is 7-8% for both protocols; these results are not exceptional. The median overall survival times for CLI-043 and CLI-033 are 98 and 103 days (slightly more than 3 months). These survival results include all patients treated, the same convention that would be applied to a randomized study evaluating an OS outcome.

No new safety signals were identified during the review of the subset of patients from CLI-033.

The applicant submitted an integrated safety analysis from three single arm studies which enrolled patients with hematologic malignancies. However, the issue of pulmonary toxicity remains a concern to be discussed further below.

2.3.9 Integrated Safety Analysis: studies CLI-043, CLI-033 and CLI-029

Patient Population for Integrated Safety Analysis

The patient population for the integrated safety analysis of laromustine consists of all those with hematologic conditions who received one or more doses of laromustine 600 mg/m^2. This total of 277 patients includes 8 patients from another Vion single arm study CLI-029, the 85 patients with poor risk *De Novo* AML greater than 60 years of age (Vion study CLI-043), and 184 patients greater than 60 years of age with previously untreated AML (*De Novo* and secondary), previously untreated high risk MDS, and relapsed AML and MDS (Vion study CLI-033) as outlined here.

Table 15: Patient Population for Integrated Safety Analysis

Patients Who Received Intravenous IV Treatment of Laromustine at 600 mg/M^2

Protocol	Patient diagnosis	Number
– CLI-028	Relapsed AML	8
– CLI-043	De Novo AML≥60	85
– CLI-033	De Novo AML≥60	54
	High Risk MDS≥60	26
	Secondary AML≥60	51
	Relapsed AML/MDS≥60	53
Total		277

Reviewer's Table

Laromustine infusion is associated with flushing, headache, nausea, vomiting, hypotension and dizziness. The 30- and 42-day mortality rates are 15% (42/277) and 25% (69/277) respectively. The causes of <u>early</u> deaths and treatment emergent deaths are listed below.

Table 16: Causes of Early Deaths (Day ≤30 from start of therapy)

	N	(%)
Total number enrolled	277	
Cause:		
Leukemia and Its Complications	20	(7.0%)
Infections	10	(3.6%)
Pulmonary	**7**	**(2.5%)**
Renal	3	(1.0%)
Multi-organ Failure	3	(1.0%)
Unknown	3	(1.0%)
Bleeding	1	(0.4%)

Reviewer's Table

2.3.10 Combined Analysis of Grade 5 Treatment Emergent Adverse Events from the single arm studies

The causes of Grade 5 treatment emergent adverse events (TEAEs) are listed below.

Table 17: Grade 5 TEAEs (Deaths)

Total Patients	N=277	(%)
Infectious	17	(6.1%)
Neoplasms (AML+TLS)	16	(5.4%)
Pulmonary*	**10**	**(3.6%)***
General	8	(2.9%)
Renal Failure	4	(1.4%)
Cardiac	6	(2.2%)
CNS Hemorrhage	2	(0.8%)
Vascular	1	(0.4%)
Blood + Lymphatic	1	(0.4%)
Pancytopenia	1	(0.4%)
GI	1	(0.4%)

Reviewer's Table

*Respiratory: Respiratory failure (4), lung disorder (1), lung infiltration (1), acute respiratory distress syndrome (1), pulmonary edema (1), acute respiratory failure (1), and acute pulmonary edema (1)

2.3.11 Combined Analysis of Grade 3-4 Adverse Events from the single arm studies

The grade 3-4 adverse events seen in greater than 10% of the patients and TEAEs are shown below.

Table 18: Adverse Events in ≥10% of Patients

GI	232 (83.8%)
General	230 (83.0%)
Pulmonary*	**199 (71.8%)**
Infectious	172 (62.1%)
Blood and Lymphatic	179 (64.6%)
Metabolism	162 (58.5%)
Nervous System	145 (52.3%)
Skin	139 (50.2%)
Vascular	126 (45.5%)
Psychiatric	124 (44.8%)
Cardiac	104 (37.5%)
Musculoskeletal	91 (32.9%)
Renal	71 (25.6%)

Reviewer's Table

* Pulmonary: Dyspnea (89), Cough (65), Epistaxis (47), Pleural Effusion (39%), Hypoxia (28); Taken From Table 5.5.1-1 in Module 5.3.5.3.3 of ISS on pp. 107-108

2.3.12 Combined Analysis of SAEs from the single arm studies

Table 19: Serious Adverse Events occurring in Two or More Patients

Total Patients	277
Infectious	73 (26.3%)
Pulmonary*	**52 (18.8%)**
Cardiac	27 (9.7%)
Nervous System	23 (8.3%)
GI	21 (7.6%)
Neoplasms (AML+TLS)	16 (7.6%)
Metabolism	9 (3.2%)
Renal	12 (4.3%)
Vascular	11 (4.0%)
Psychiatric	10 (3.6%)
Hepatic	5 (1.8%)
General	49 (17.7%)

Reviewer's Table

*Pulmonary: Dyspnea (18), Respiratory Failure (9), Pleural Effusion (8), Hypoxia (6), Acute Respiratory Distress Syndrome (3), Lung Disorder (2), Interstitial Lung Disease (2), Lung Infiltration (2), Pulmonary Hypertension (2), Pulmonary Edema (2), Epistaxis (2), Pulmonary Hemorrhage (2).

2.3.13 Conclusions for Integrated Safety Analysis

The percentage of early deaths is 15% at 30 days and 25% at 42 days. These results are not excessive for remission induction therapies currently available. However, pulmonary toxicity is notable in all of the toxicity listings. The pooled safety analyses may underestimate the occurrence of grade 3-5 adverse pulmonary events; also, these events may be higher in patients with pre-treatment cardiac and pulmonary co-morbidities. This is of particular concern because the proposed indicated population for laromustine may have underlying pulmonary and cardiac co-morbidity at baseline.

2.3.14 Additional safety findings from Vion study CLI-037

Vion study CLI-037:

Data from one randomized, placebo-controlled trial is available for additional understanding of the treatment effects of laromustine. In Study CLI-037, patients with relapsed AML, age 18 and older, received cytarabine, given over 3 days as a single agent, or cytarabine given over 3 days in combination with laromustine 600 mg/m^2 given on day 2. A 1:2 randomization was used to allocate patients to cytarabine alone versus the combination. The study had to be placed on clinical hold due to greater mortality on the laromustine-containing arm.

Regarding baseline patient characteristics on the laromustine plus cytarabine arm in study CLI-037, the median patient age was 59 years. The ECOG performance status was reported as PS=0 for 44%, PS=1 for 44%, and PS=2 for 11%.

The CLI-037 study primary endpoint was response rate. Overall survival was a secondary endpoint.

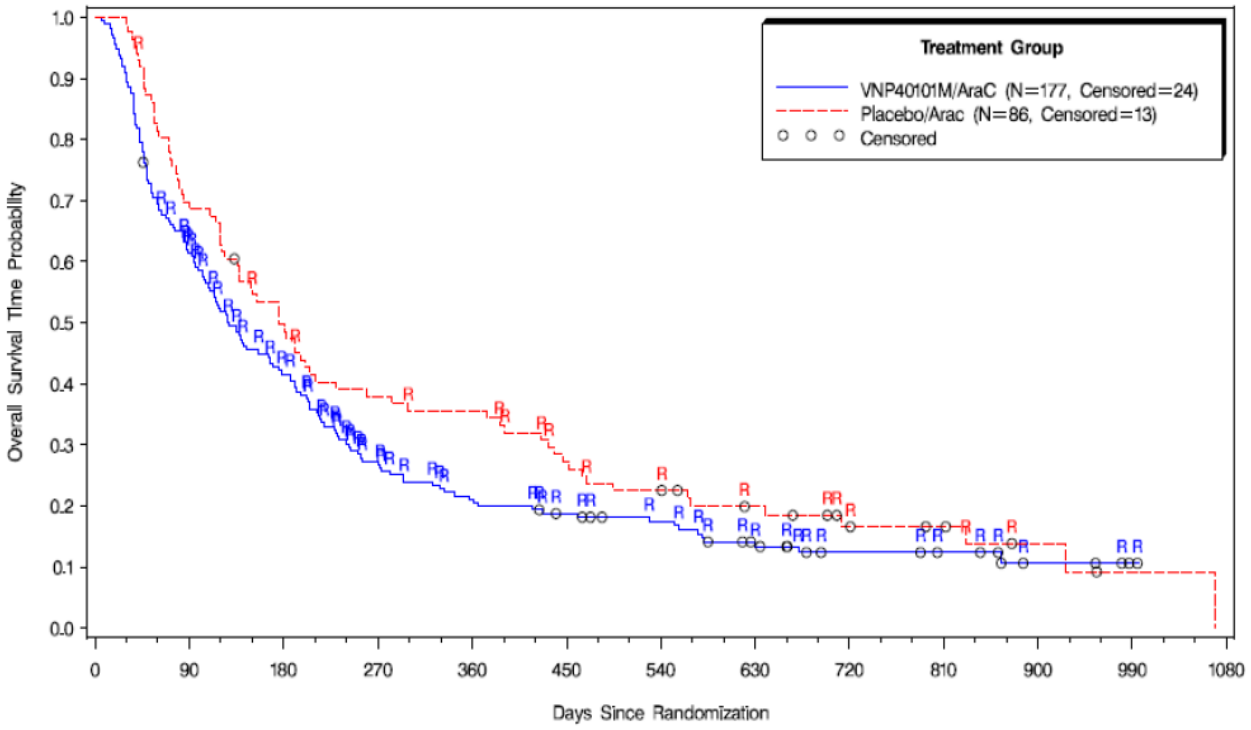
The clinical study report stated that the response rates for study CLI-037 were: 18% for the cytarabine arm and 35% for the laromustine plus cytarabine arm. The clinical study report also stated that the median overall survivals were: 176 days for the cytarabine arm and 128 days for the laromustine plus cytarabine arm.

The following two survival curves are from the Vion CLI-037 clinical study report.

The Kaplan-Meier OS analysis for all patients, as treated, is shown in the applicant's figure number 4, below (our figure number 2). The placebo arm, containing cytarabine alone, is the upper curve, shown in red. The laromustine plus cytarabine curve is the lower curve, shown in blue.

Figure 2: Vion's Figure 4 Cumulative Probability of Overall Survival Time, CLI-037

Figure 4. Cumulative Probability of Overall Survival Time- Kaplan-Meier Graph, AT Analysis Set

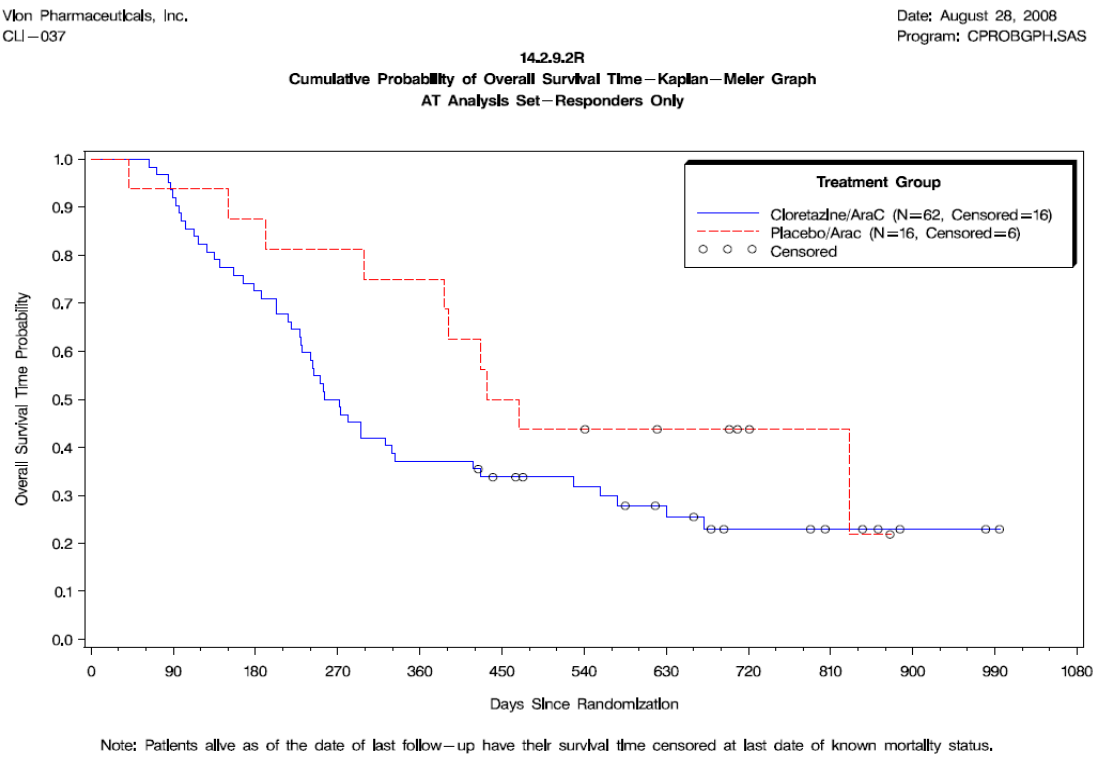


Note: Patients alive as of the date of last follow−up have their survival time censored at last date of known mortality status.
R = patient achieved a CR or CRp.

Source: Figure 14.2.9.2

The figure below shows the applicant's Kaplan-Meier OS results for those patients classified as responding patients in each study arm. The placebo arm, containing cytarabine alone, is the upper curve, shown in red. The laromustine plus cytarabine curve is the lower curve, shown in blue.

Figure 3: Vion's Figure Cumulative Probability of Overall Survival Time-Responders Only, CLI-037



The results of Vion study CLI-037 are presented here without statistical testing for inference since the study was placed on hold for excess toxicity; however, the laromustine-containing treatment is visually inferior for the OS curves for all patients and for the OS limited to the responding patients, despite the fact that the remission rate was higher on the laromustine arm. The treatment-related toxicity, shown below, was judged as unacceptable by the DSMB and the applicant, and the study was placed on hold.

Table 20: Selected Adverse Events with outcome of death from CLI-037

Therapy:	cytarabine+placebo		cytarabine+laromustine	
	N	(%)	N	(%)
	86		177	
Adverse Events with Death	11/86	(13%)	71/177	(46%)
Infectious Deaths	3/86	(3%)	49/177	(28%)
Pulmonary Deaths	0/86	(0%)	15/177	(9%)

Reviewer's Table

Infections, including pneumonia, are frequently encountered with AML, but this pattern of toxicity led Vion to convene a special advisory group to evaluate the pulmonary toxicity observed in study CLI-037 and other laromustine studies.

Report of Vion "Pulmonary Advisory Board" Convened on July 23, 2008: Laromustine Causes Direct Toxicity to the Lung Which Resembles BCNU Toxicity

The applicant, recognizing the excess pulmonary toxicity, convened an advisory board to review the pulmonary toxicity. How the cases were chosen for review has not been described in detail or verified by FDA. The board issued a report which was submitted to the Agency.

The report concluded that some patients on laromustine clinical trials exhibited evidence of a direct toxic effect to the lung: the effects were noted in CLI-043, one of the two phase II single arm trials proposed by Vion to support the request for approval for laromustine, and in Vion study CLI-037, a double blind placebo controlled prospectively randomized Phase III clinical trial to test the efficacy and safety of laromustine when used in combination with cytarabine. The conclusion of the committee, which reviewed toxicity data from the two trials and memoranda, submitted to Vion by medical monitors on the two trials, was that laromustine use is associated with a pulmonary toxicity resembling BCNU or nitrosourea pulmonary toxicity, and has the following clinical features:

- SOB , Cough, Dyspnea, Fever, Rales, Pleural Friction Rub about Day 30;
- Ground Glass Appearance on Chest X-Ray;
- Abnormal Lung CT Scan, Gradual Increase of Hypoxemia;
- Hospitalization about Day 60;
- Intubation about Day 78;
- Death or Improvement on Steroids > Day 80.

Clinical Presentation of Laromustine-Associated Pulmonary Toxicity As Observed in CLI-043 and CLI-037

In the table below, the numbers of patients with each of six different clinical presentations is summarized by the Advisory Committee, which was chaired by Dr. Roy Jones of the UT MD Anderson Cancer Center.

Table 21: Pulmonary Toxicity observed in CLI-043 and CLI-037

Pulmonary Problems on Laromustine	Number of Patients with Problem
1. Acute Pulmonary Infusion Reaction	1 patient
2. Acute Respiratory Failure/ Acute Respiratory Distress Syndrome (ARDS)/ with Bilateral Infiltrates Hours to 30 Days	35 patients
3. Subacute with Infiltrates >30 Days	6 patients
4. Delayed Symptomatic >60 Days	4 patients
5. Non-cardiac Pulmonary Edema	5 patients
6. Pulmonary Hypertension	5 patients

Reviewer's Table

The data indicate that laromustine use, in this regimen, is associated with significant pulmonary toxicity including Grade 3-5 toxicities of acute respiratory failure, ARDS, and hypoxemia.

2.3.15 Vion cross-study comparison analysis of laromustine and the MRC AML14 trial

In the application, Vion provided a cross-study comparison analysis of laromustine treatment as given in the phase 2 studies, with a selected subgroup of patients among those who were enrolled and treated in the MRC AML14 study, conducted in the U.K. over several years and published in 2007. The FDA reviewed the applicant's analysis and concluded that the findings should be interpreted cautiously, as an exploratory comparison, and could not be supportive of the benefit of laromustine. Such an exploratory cross-study comparison could not be a source of substantial evidence for efficacy and safety necessary for a new drug approval. In addition, the results of the low-dose cytarabine in the overall patient population in the AML14 trial appeared similar to those of laromustine used in combination with HU (study CLI-033) or before cytarabine consolidation (study CLI-043).

3.0 Conclusions

All approvals require evidence of effectiveness and safety from adequate and well controlled studies conducted with a well-defined population for which the therapy is beneficial, and adequate safety for the dose schedule identified.

Randomized controlled trials provide the best evidence for judging effectiveness and relative safety of a therapy.

Vion has not provided a randomized, well-controlled study demonstrating the efficacy or safety of laromustine as a single agent or in combination. The results from the two submitted single-arm studies were confounded by the fact that additional therapy was given with laromustine which obscures the treatment effect attributable to laromustine. In study CLI-043, patients achieving remission then received cytarabine consolidation. Thus the contribution of laromustine to the duration of remission cannot be determined. In the subset of patients selected from study CLI-033 who were pooled and analyzed for this NDA as "elderly, poor-risk, de novo AML," all received concurrent hydroxyurea. The applicant had postulated that the addition of hydroxyurea would enhance the effectiveness of laromustine. Given the lack of a comparator arm in this study, we cannot say with certainty whether the applicant's hypothesis is correct. However, we can state that the use of hydroxyurea interfered with the ability of the trial to isolate the contribution of laromustine to the CR rate.

Safety concerns arose when during the conduct of the phase 2 studies and phase 3 trial, laromustine use was noted to be associated with a sometimes fatal pulmonary toxicity resembling BCNU pulmonary toxicity and requiring mechanical ventilation. The toxicity and its management are not well characterized and impose an additional burden on patients. In addition, the phase 3 study of laromustine with cytarabine had to be placed on hold for excess mortality, raising concerns about using laromustine in combination.

The applicant has chosen to submit the results from single arm studies as a pathway to accelerated approval. An accelerated approval requires that the applicant demonstrate that (a) the new therapy must show benefit to patients over existing treatments (available therapy) and that (b) confirmatory post-marketing studies should be underway to verify and describe the clinical benefit.

Issues that arise with developing a drug for the treatment of acute leukemia using a single arm trial and defining a study patient population without available therapy include: AML is primarily a disease of the elderly, with median age about 68 years in the U.S., and currently there is no universally agreed upon standard definition of an elderly patient who is not eligible to receive standard induction/consolidation treatment with agents such as cytarabine and daunorubicin. The unproven assumption is that elderly patients with AML, especially those with additional medical illnesses, are assumed not to benefit from standard, available therapy.

The eligibility criteria in the Vion studies characterize patients as "poor risk" based on age, ECOG performance status of 2, co-morbidities, or unfavorable cytogenetics. Although these characteristics have been used to varying degrees in other studies, these characteristics are vague; they lack newer information

about molecular markers and more specific geriatric assessment tools. There is evidence that some older patients do as well as younger patients with standard available therapy such as induction chemotherapy (3+7) or with low-dose cytarabine schedules. [2, 3]

Previous FDA approvals in the treatment of AML in adult patients have been based on Phase III randomized trials (daunomycin, cytarabine and the combination of iadarubicin and cytarabine). In the controlled trials for cytarabine and anthracyclines, endpoints of survival as well as response rate were used.

Thus far, approvals of agents to treat acute leukemia relying on single arm trial data have been problematic. ODAC reviewed the Zarnestra® application and did not recommend approval. During the ODAC meeting, several issues were raised including the low response rate and whether the patients enrolled on the study could have received standard therapy, since a number of them actually did so subsequently. A subsequent randomized study designed to confirm clinical benefit for regulatory purposes showed no survival advantage for Zarnestra® therapy over supportive care alone.[1]

Evidence for the efficacy and safety of laromustine as a single-agent has not been provided. Studies CLI-033 and CLI-043 are confounded by the additional agents used, HU and cytarabine respectively, so that estimation of the complete remission rate and the durations of remissions resulting from laromustine are confounded and not well characterized. There is evidence also for a unique toxicity involving the lung, which does not occur with the standard agents currently used for AML therapy, and use of laromustine in the patients proposed by the applicant, who have pre-existing cardio-pulmonary co-morbidity, is very concerning.

Evidence from study CLI-037 indicates that laromustine **cannot** be combined safely with concurrent cytarabine induction therapy in the regimen tested. There was an apparent decrease in median overall survival on the laromustine arm: 176 days for the cytarabine arm and 128 days for the laromustine plus cytarabine arm. This detrimental effect on overall survival must be further examined in adequate and well-controlled randomized studies with survival as a primary outcome to assure the safety and efficacy of laromustine. Single arm study results cannot offset the inferior survival observed in the randomized, controlled trial.

4.0 References

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