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APPLICATION NUMBER:

21-877

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA: 21-877
GENERIC NAME: Nelarabine
BRAND NAME: ARRANON
DOSAGE FORM/STRENGTH 5 mg/ml Sterile Solution for Injection
INDICATION: Refractory/Relapsed T-ALL and T-LBL
SUBMISSION TYPE: NDA-NME
SUBMISSION DATES: 29-Apr-, 13-Jul-, 22-Jul-, 27-Jul-, 2-Aug-2005
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ON ORIGINAL

I. EXECUTIVE SUMMARY

The Applicant seeks approval for NDA 21-877 for the use of ARRANON (nelarabine) Injection in the treatment of adults and pediatric patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens, respectively. The proposed **adult** dose is 1500 mg/m² administered intravenously (IV) over 2 hours on Days 1, 3, and 5, repeated every 21 days. The proposed **pediatric** dose is 650 mg/m² administered IV over 1 hour once daily for 5 consecutive days, repeated every 21 days.

In support of the NDA indications, the Applicant submitted two pivotal Phase 2 studies (Study PGAA2001 in **pediatric** patients and Study PGAA2002 in **adult** patients). Study PGAA2001 was a single-arm, Phase 2 study in 85 pediatric patients (≤ 21 years of age) with relapsed/refractory T-ALL and T-cell non-Hodgkin's lymphoma (T-NHL). The maximum tolerated dose (MTD) of 1200 mg/m² IV over 1 hour once daily for 5 consecutive days then repeated every 21 days (determined in Phase 1 studies) was administered to pediatric patients in Phase 2 Study PGAA2001. This dose was reduced to 900 mg/m² and then to 650 mg/m² due to severe neurotoxicity. Study PGAA2002 was also a single-arm, Phase 2 study in 39 adult patients (> 21 years of age) with relapsed/refractory T-ALL or T-LBL. The MTD of 2200 mg/m² IV over 2 hours on Days 1, 3, and 5 then repeated every 21 days (determined in Phase 1 studies) was administered to adult patients in Phase 2 Study PGAA2002. This dose was then reduced to 1500 mg/m² due to severe neurotoxicity. The primary clinical endpoint in both studies was complete response rate.

Exposure (AUC) to ara-GTP correlates with therapeutic response. Data from Phase 1 and Phase 2 studies in adult and pediatric patients suggests that nelarabine AUC correlates with neurotoxicity. Despite achieving statistical significance, there is no useful predictor to individualize dosing, for guarding against irreversible toxicity. It has been hypothesized that the variability may be explained by metabolic enzyme genotype. There is merit in obtaining the genotype information from these patients using the already available blood samples collected by the sponsor.

The Applicant has not evaluated the effect of renal impairment on the pharmacokinetics of nelarabine or ara-G. Both nelarabine and ara-G are partially eliminated by the kidneys; mean % dose excreted in urine is 5.8% for nelarabine and 32% for ara-G. ARRANON label should mention that patients with severe renal impairment (creatinine clearance < 30 ml/min) should be closely monitored for neurotoxicity.

The Applicant has not evaluated the effect of hepatic impairment on the pharmacokinetics of nelarabine or ara-G. ARRANON label should mention that patients with severe hepatic impairment (serum bilirubin > 3.0 mg/dl) should be closely monitored for neurotoxicity.

Recommendation

NDA 21-877 filed for ARRANON (Nelarabine) Injection is acceptable from the Clinical Pharmacology and Biopharmaceutics perspectives. Please forward the Clinical Pharmacology Labeling Recommendations (Pages 53-58 of this review) and the following Comment to the Applicant.

Comment to be sent to the Applicant

Adenosine deaminase (ADA) activity is required for the formation of the active species of nelarabine. — of adenosine deaminase may reduce the effectiveness of this drug in some patients. Please correlate the pharmacokinetic results of the phase 1 studies with the results of the ADA genetic screening and submit this report to the FDA.

II. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Nelarabine is a pro-drug of deoxyguanosine analogue, 9- β -D-arabinofurosylguanine (ara-G). Nelarabine is rapidly demethylated by adenosine deaminase to ara-G. Ara-G is then phosphorylated intracellularly by deoxyguanosine kinase and deoxycytidine kinase to its 5'-monophosphate. The monophosphate is subsequently converted intracellularly to the active arabinosylguanine 5'-triphosphate (ara-GTP). The accumulation of ara-GTP in leukemia blasts allows for its incorporation into deoxyribonucleic acid (DNA) leading to inhibition of DNA synthesis and eventually to cell death.

In support of this NDA, four Phase 1 pharmacokinetic and pharmacodynamic studies (Studies PGAA1001, PGAA1002, PGAA1003, and PGAA1005) were submitted. In addition, several *in vitro* study reports to characterize *in vitro* protein binding, metabolism, enzyme inhibition, and transport of nelarabine and ara-G were submitted.

Pharmacokinetics

Pharmacokinetic data are available for nelarabine, ara-G, and intracellular ara-GTP in 101 adult patients and 25 pediatric patients with refractory hematologic malignancies who participated in the Phase 1 studies at nelarabine IV doses of 104-2900 mg/m². Following nelarabine infusion, plasma concentrations of nelarabine and ara-G declined rapidly in a mono-exponential fashion with an elimination half-life of 0.3 and 3.5 hours, respectively. At the proposed **adult** dose of 1500 mg/m², a mean peak plasma concentration (C_{max}) of 4.1±4.7 µg/ml appeared at the end of the 2-hour infusion on Day 1 in six adult patients. The corresponding value for ara-G is 32.9±6.5 µg/ml, which also appeared at the end of the 2-hour nelarabine infusion (Median ara-G T_{max}=2.1 hours), suggesting that most of nelarabine dose has already been converted to ara-G. Exposure to ara-G was 25 times higher than that for nelarabine on Day 1 after nelarabine infusion (AUC=172±66 µg.h/ml versus 6.9±4.2 µg.h/ml, respectively).

Comparable C_{max} and AUC values were obtained for nelarabine between Days 1 and 5 at the proposed nelarabine adult dose of 1500 mg/m², indicating that the PK of nelarabine after multiple-dosing are predictable from single-dosing. There were not enough data for ara-G to make a comparison between Day 1 and Day 5. Nelarabine has much higher clearance and volume of distribution than ara-G (346±273 L/h/m² and 404±336 L/m² versus 13±3.3 L/h/m² and 42±8.6 L/m², respectively) after the 1500 mg/m² nelarabine dose in adult patients. The PK of both nelarabine and ara-G are linear over the nelarabine dosing range of 104-2900 mg/m² in both pediatric and adult patients from the combined Phase 1 PK data.

At the **adult** proposed nelarabine dose of 1500 mg/m², a mean intracellular C_{max} of ara-GTP appeared within 3-25 hours after nelarabine infusion on Day 1. Exposure to intracellular ara-GTP was 127 times higher than that for nelarabine and 5 times higher than that for ara-G (AUC=890±827 µg.h/ml versus 6.9±4.2 µg.h/ml and 172±66 µg.h/ml, respectively). Because the intracellular levels of ara-GTP were so prolonged, its elimination half-life could not be estimated. There were no multiple-dose data for ara-GTP in adult or pediatric patients.

There were no single- or multiple-dose PK data available for **pediatric** patients at the proposed 650 mg/m² dose given once daily for 5 consecutive days. The analyses of combined Phase 1 PK data at nelarabine of doses of 104-2900 mg/m² indicate that the mean clearance (CL) of nelarabine was 30% higher in pediatric patients (n=25) than in adult patients (n=101) (CL=237±397 L/h/m² versus 182±277 L/h/m², respectively) on Day 1 after nelarabine administration (p > 0.05). The apparent clearance of Ara-G (CL/F) was comparable between the two groups (CL/F=7.8±6.0 L/m² in adult patients and 7.9±6.2 L/m² in pediatric patients) on Day 1 after nelarabine administration (p > 0.05). The mean elimination half-lives of nelarabine and ara-G were 0.3±0.12 hour and 3.5±1.4 hours, respectively, in adult patients and 0.26±0.13 hour and 2.2±0.86 hours, respectively, in pediatric patients on Day 1 after nelarabine administration.

Exposure-Response Relationships:

Analyses of combined PK data from Phase 1 studies indicate that the mean dose-normalized C_{max} and AUC values for intracellular ara-GTP were 8-fold and 13-fold higher, respectively, in adult responders than in adult non-responders (p<0.05). There were not enough ara-GTP data in pediatric patients to make a comparison between responders and non-responders. Comparable mean dose-normalized C_{max} and AUC values were obtained for ara-G in responders and non-responders whether in adult or pediatric patients. Comparable mean dose-normalized C_{max} and AUC values were obtained for nelarabine in adult responders and adult non-responders. However, pediatric patients who responded to nelarabine therapy had 7- to 8- fold higher mean dose-normalized C_{max} and AUC values for nelarabine than those who did not (p<0.05).

Both mean dose-normalized C_{max} and AUC of ara-GTP were 2.3-fold higher (p>0.05) in patients who experienced neurotoxicity than in those who did not. There were not

enough ara-GTP data to make a comparison of neurotoxicity in pediatric patients. Comparable mean dose-normalized C_{max} and AUC values were obtained for ara-G in adult and pediatric patients who experienced neurotoxicity and those who did not. Exposure to nelarabine tends to be higher (1.2- to 1.7-fold higher dose-normalized C_{max} and AUC) in adult patients who experienced neurotoxicity than those who did not ($p > 0.05$).

This indicates that the efficacy of ARRANON is related to the accumulation of intracellular ara-GTP in **adult** patients and to the exposure to nelarabine in **pediatric** patients. The incidence of neurotoxicity is related to the accumulation of intracellular ara-GTP in **adult** patients.

Distribution

The combined Phase 1 PK data at nelarabine doses of 104 to 2900 mg/m² indicate that the mean steady state volume of distribution (V_{ss}) of nelarabine was 10% higher in pediatric patients ($n=25$) than in adult patients ($n=101$) ($V_{ss}=195\pm 347$ L/m² versus 176 ± 281 L/m², respectively) on Day 1 ($p > 0.05$). The apparent steady state volume of distribution (V_{ss}/F) of ara-G was 38% lower in pediatric patients than in adult patients ($V_{ss}=23\pm 17$ L/m² versus 37 ± 29 L/m², respectively) on Day 1 after nelarabine IV infusion ($p=0.001$). The *in vitro* plasma protein binding of both nelarabine (<20%) and ara-G is low (<25%) over the concentration range of 1.8 to 178 μ g/ml.

Metabolism

In vitro studies with fresh and cryopreserved human hepatocytes indicate that the major metabolic pathway for nelarabine is its O-demethylation by adenosine deaminase to form ara-G. Ara-G undergoes hydrolysis to form guanine. In addition, some nelarabine is hydrolyzed to form methylguanine, which is O-demethylated to form guanine. Guanine is N-deaminated to form xanthine, which is further oxidized to yield uric acid. Ring opening of uric acid followed by further oxidation results in the formation of allantoin. Adenosine deaminase (ADA), the primary enzyme involved in nelarabine metabolism, exhibits genetic polymorphism. Three phenotypes were recognized on electrophoresis: ADA1, ADA2 and ADA2/1. Therefore, patients who are ADA deficient will not respond to nelarabine therapy.

Excretion

The Applicant has not conducted a mass balance study for nelarabine. Urinary excretion data from Study PGAA1002 indicate that nelarabine and ara-G are partially eliminated by the kidneys. Urinary excretion of nelarabine and ara-G averaged $5.8\pm 4.5\%$ and $32.3\pm 18.9\%$ of the administered dose, respectively, in 12 adult patients over the 24 hours after nelarabine infusion on Day 1. In pediatric patients, urinary excretion of nelarabine and ara-G averaged $12.7\pm 13\%$ and $27.4\pm 9.8\%$ of the administered dose, respectively, over the 24 hours after nelarabine infusion on Day 1.

(n=3). Renal clearance averaged 20 ± 17 ml/min for nelarabine and 75 ± 40 ml/min for ara-G in 12 adult patients. The renal clearance values obtained from 2 pediatric patients were 17 ml/min and 56 ml/min for nelarabine and ara-G, respectively.

Special Populations

Effect of Age: Age has no effect on the pharmacokinetics of nelarabine, ara-G, or intracellular ara-GTP ($P > 0.05$). No dosing adjustment is required for ARRANON in elderly patients with T-ALL and T-LBL.

Effect of Gender: Gender has no effect on the pharmacokinetics of nelarabine or ara-G in both **adult** and **pediatric** patients ($P > 0.05$). Dose-normalized C_{\max} and AUC_{0-24} for ara-GTP were 2.5-fold and 3.7-fold higher, respectively, in **adult** females (n=15) than in **adult** males (n=51) ($p < 0.05$). No data for ara-GTP are available in pediatric patients to make a comparison (only one male patient of 8 years). Although mean dose-normalized C_{\max} and AUC_{0-24} for ara-GTP tend to be higher in adult Female Responders than adult Male Responders, the differences were not statistically significant ($p > 0.05$). The same applies to adult female and male patients who experienced neurotoxicity than those who did not.

Effect of Race: Adult African Americans (n=17) had lower mean clearance and volume of distribution of nelarabine than Adult Caucasians (n=74) (by 33% for both values). The opposite is true for ara-G; mean apparent clearance and volume of distribution values had higher in adult African Americans than in adult Caucasians (by about 40% and 33%, respectively). These differences were not statistically significant ($p > 0.05$) except for the difference in the mean clearance for ara-G between the two race groups ($p=0.031$). In **pediatric** patients, nelarabine mean clearance and volume of distribution values were 35% and 22% lower, respectively, in African Americans than in Caucasians ($p>0.05$). Mean apparent clearance and volume of distribution of ara-G were 57% and 18% higher, respectively, in pediatric African Americans than in pediatric Caucasians ($p > 0.05$).

In **adult** patients, mean dose-normalized C_{\max} and AUC_{0-24} for ara-GTP were 2.5-fold and 3.7-fold higher, respectively, in African Americans (n=7) than in Caucasians (n=38) ($p < 0.05$). No data are available in pediatric patients to make a comparison (only one Caucasian male patient of 8 years). Although mean dose-normalized C_{\max} and AUC_{0-24} for ara-GTP were higher in adult African American Responders than adult Caucasian Responders, the differences were not statistically significant ($p > 0.05$). The same applies to adult African Americans and Caucasians who experienced neurotoxicity.

Effect of Renal Impairment: The combined data from the Phase 1 studies were analyzed for **adult** patients who ranged in creatinine clearance (CrCL) from 31-200 mL/min. These adults patients were categorized into three groups: normal with CrCl of > 80 mL/min (n=68), mild with CrCl=50-80 mL/min (n=27), and moderate with CrCl < 50 mL/min (n=3). No trend is observed for the change in nelarabine mean clearance and

volume of distribution with the degree of renal impairment. However, ara-G mean apparent clearance (CL/F) was about 35% and 55% lower in patients with mild and moderate renal impairment, respectively, than in adult patients with normal renal function ($p < 0.05$). The mean dose-normalized C_{max} and AUC_{0-24} values for ara-GTP were 2.4-fold and 3.4-fold higher, respectively, in adult patients with mild renal impairment than in adult patients with normal renal function ($p < 0.05$). Patients with moderate renal impairment had 2.3-fold and 2.6-fold higher mean dose normalized C_{max} and AUC_{0-24} values, respectively, than patients with normal renal function ($p > 0.05$). No comparison could be made for nelarabine, ara-G, or ara-GTP in **pediatric** patients as most of patients had a normal renal function with CrCL values ranging from 88-363 ml/min. Patients with renal impairment should be closely monitored for neurotoxicity.

Effect of Hepatic Impairment: The Applicant has not evaluated the effect of hepatic impairment on the pharmacokinetics of nelarabine or ara-G. Patients enrolled in the Phase 1 studies and the pivotal Phase 2 studies had adequate baseline hepatic function as demonstrated by hepatic transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] of 3 x upper limit of normal and bilirubin of 1.5 mg/dL. Patients with hepatic impairment should be closely monitored for neurotoxicity.

Drug-Drug Interactions

Nelarabine and ara-G are not substrates of CYP P450 enzymes. Nelarabine and ara-G did not significantly inhibit the activities of the major CYP P450 enzymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4) at *in vitro* concentrations of nelarabine and ara-G of $> 100 \mu\text{M}$ (IC_{50} of $> 30 \mu\text{g/ml}$ versus C_{max} of $5.4 \mu\text{g/ml}$ for nelarabine and $32 \mu\text{g/ml}$ for ara-G at the proposed adult nelarabine dose of 1500 mgm^2). The potential for drug-drug interactions between nelarabine and substrates of these enzymes are unlikely.

Administration of fludarabine (30 mg/m^2) as 30-minute infusion 4 hours before nelarabine (1200 mg/m^2) infusion did not affect the pharmacokinetics of either nelarabine or ara-G in 12 adult patients. However, exposure to intracellular ara-GTP was greatly increased when nelarabine was administered in combination with fludarabine. Mean C_{max} and AUC_{0-24} of Ara-GTP increased by about 60% and 50%, respectively, when nelarabine was administered in combination with fludarabine. As ara-GTP is the active cytotoxic moiety, this increase may result in an increased response and/or neurotoxicity to nelarabine when is given in combination with fludarabine. The package insert for ARRANON

Nelarabine and ara-G are not substrates or inhibitors of the efflux transporter, P-glycoprotein (ABCB1).

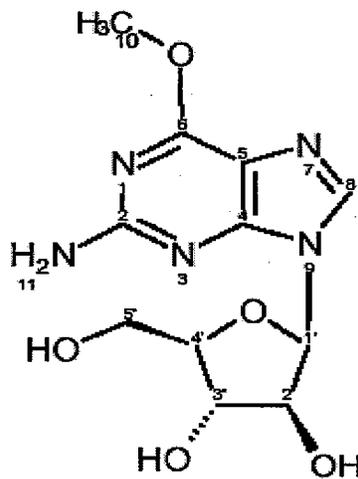
III. QUESTION-BASED REVIEW

A. General Attributes

1. What are the highlights of the chemistry and physicochemical properties of the drug substance and drug product?

ARRANON (nelarabine, 506U78) is a pro-drug for the cytotoxic deoxyguanosine analogue, 9- β -*D*-arabinofurosanylguanine (ara-G). The chemical name for nelarabine is 2-amino-9- β -*D*-arabinofuranosyl-6-methoxy-9*H*-purine. Nelarabine has the following structural formula (Fig. 1):

Fig. 1



Molecular Formula: $C_{11}H_{15}N_5O_5$ (Nelarabine), $C_{10}H_{13}N_5O_5$ (Ara-G)
Molecular Weight: 297 (Nelarabine), 283 (Ara-G)

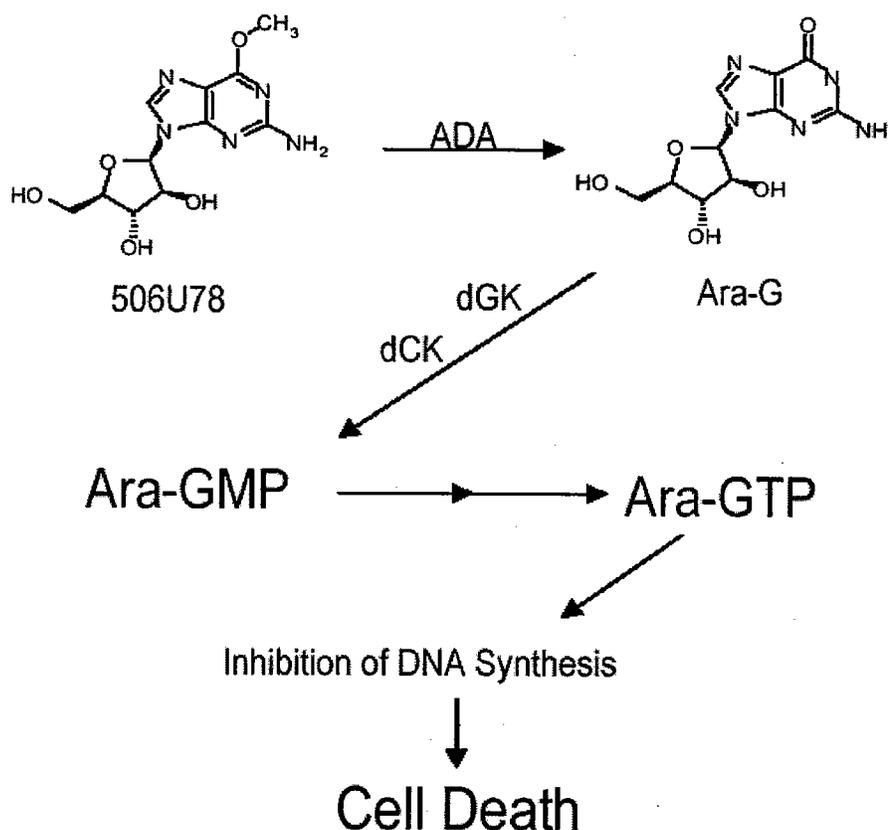
Nelarabine contains four adjacent chiral atoms (C1-C4) in the sugar moiety. Nelarabine is an ampholyte (weak acid/weak base) with an aqueous solubility of 8 mg/mL at 25° C over the pH range of 4-10. Nelarabine is \sim more water soluble than ara-G. The octanol/water partition coefficient is \sim ° C. Nelarabine has two pK_a values, $pK_{a1}=2.5$ and $pK_{a2}=12$. Nelarabine is supplied as a sterile solution in 0.45% normal saline. Each 250-mg vial contained 50 mL of a 5 mg/mL nelarabine solution.

2. What is the proposed mechanism of action?

Nelarabine is rapidly demethylated by adenosine deaminase (ADA) to ara-G (MW=283) (Fig. 2). Ara-G is then phosphorylated intracellularly by deoxyguanosine kinase and deoxycytidine kinase to its 5'-monophosphate. The mono-phosphate is subsequently converted intracellularly to the active arabinosylguanine 5'-triphosphate (ara-GTP),

MW=361). The accumulation of ara-GTP in leukemia blasts will allow for its incorporation into deoxyribonucleic acid (DNA) leading to inhibition of DNA synthesis and eventually to cell death. The T-cells are more sensitive than the B-cells to the cytotoxic effects of nelarabine and ara-G. *In vitro* studies with human leukemia cell lines demonstrated that nelarabine and ara-G inhibit human T-cell lines at IC₅₀ values ranging from 0.31- 4.4 μM (0.09-1.3 μg/ml) and from 0.31- 5.0 μM (0.09-1.5 μg/ml), respectively. The IC₅₀ values in B-cells for nelarabine and ara-G were at least 20-fold higher [>200 μM (>56.6 μg/ml) and >100 μM (>28.3 μg/ml), respectively].

Fig. 2 Mechanism of action of Nelarabine



3. What is the proposed indication?

The proposed indication is the use of nelarabine in the treatment of pediatric and adults patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL), whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

Two drugs have been approved for use in patients with relapsed or refractory ALL, teniposide and clofarabine. Teniposide was approved for treatment of refractory childhood acute lymphoblastic leukemia in combination with other approved anticancer agents. Clofarabine is a purine nucleoside analog that recently was granted an accelerated approval by the FDA for the treatment of relapsed or refractory childhood ALL after two prior regimens.

4. What are the proposed dose and dosing regimens?

The proposed dose of nelarabine in adult patients is 1500 mg/m² administered intravenously (IV) over two hours on Days 1, 3, and 5, then repeated every 21 days. The proposed dose of nelarabine in the pediatric patients is 650 mg/m² IV daily for 5 consecutive days, then repeated every 21 days.

B. GENERAL CLINICAL PHARMACOLOGY

5. What are the design features of the pivotal clinical studies?

In support of the NDA indications (relapsed/refractory T-ALL and T-LBL), the Applicant submitted two pivotal Phase 2 studies: Study PGAA2001 in pediatric patients and Study PGAA2002 in adult patients. The summary of these studies are as follows:

Study PGAA2001 (Pediatrics):

The study was conducted in pediatric with relapsed or refractory T-ALL or T-cell non-Hodgkin's lymphoma (T-NHL) by Children's Oncology Group (COG). The study was an open label, multi-center, single-arm, Phase 2 study in 151 pediatric patients with relapsed/refractory T-ALL and T-NHL. Patients were entered into the study according to the following four strata:

Stratum 01 (n=37): T-ALL or T-NHL in first relapse (>25% bone marrow blasts, with or without concomitant extramedullary relapse – other than central nervous system (CNS).

Stratum 02 (n=48): T-ALL or T-NHL in second or later relapse (>25% bone marrow blasts, with or without concomitant extramedullary relapse – other than central nervous system (CNS).

Stratum 03 (n=32): T-ALL or T-NHL with positive bone marrow and CSF (>5% bone marrow blasts and CNS 2 or 3 involvement); CNS 2: subjects with <5 white blood cells (WBC)/mm³ and positive cytology; CNS 3: subjects with 5 WBC/mm³ and positive cytology.

Stratum 04 (n=34): Extramedullary relapse and <25% bone marrow blasts in the bone marrow (excluding isolated CNS relapse).

The study started at the recommended Phase 2 dose of 1200 mg/m² given daily as a one-hour IV infusion for 5 consecutive days of a 21-day cycle (MTD from Phase 1 studies). After the first patient at this dose experienced grade 3/4 neurotoxicity, the 1200 mg/m² daily for 5 days was reduced to a 900 mg/m² daily for 5 days. The dose was then reduced further to 650 mg/m²/day x 5 days for all patients due to grade 3/4 neurotoxicity. A summary of the strata, number of patient/stratum, dose, and age groups for the 151 patients are as follows:

Table 1. Strata, Number of Patients, Dose, and Age Groups

Stratum	Dose (mg/m ²)	Number of Patients/Dose	Age Group			
			2mo-2yrs	3-12yrs	13-16yrs	17-21yrs
01 (N=37)	650	31	0	18	9	4
	900	6	1	3	1	1
02 (N=48)	650	39	2	21	10	6
	900	9	1	5	1	2
03 (N=32)	400	24	2	14	5	3
	650	6	0	3	1	2
	900	2	0	2	0	0
04 (N=34)	400	25	2	8	9	6
	650	8	0	2	4	2
	900	1	0	1	0	0

No response data were available for Strata 03 and 04. The majority of patients in both Strata 03 and 04 withdrew from the study due to progressive disease and/or no response (Stratum 03: 50%; Stratum 04: 74%). Three patients in Stratum 03 withdrew due to toxicity and four due to death (due to cerebral hemorrhage, bacterial sepsis, bacterial sepsis, neutropenic infection, hemorrhage and pulmonary hemorrhage, and pneumonitis). One patient in Stratum 04 withdrew due to toxicity and two due to death (due to tumor and status epilepticus). A summary of results of the response rate for the 85 patients in Strata 01 and 02 are shown in Table 2.

Table 2. Summary of Response Rates by Strata

	Number (%) of Subjects					
	Stratum 01 (1 st Relapse)			Stratum 02 (2 nd or later Relapse)		
	650 mg/m ² (n=31)	900 mg/m ² (n=6)	Total (n=37)	650 mg/m ² (n=39)	900 mg/m ² (n=9)	Total (n=48)
*Complete Response	13 (42%)	1 (17%)	14 (38%)	5 (13%)	2 (22%)	7 (15%)
95% CI	[25, 61]	[0, 64]	[22, 55]	[4, 27]	[3, 60]	[6, 28]
Less Than Complete Response (<CR)	18 (58%)	5 (83%)	23 (62%)	34 (87%)	7 (78%)	41 (85%)

* (defined below in response to Question #6)

For the Stratum 01 at the 650 mg/m² dose, 42% (13/31) of patients achieved a CR. At the 900 mg/m² dose, 17% (1/6) of patients achieved a CR.

For the Stratum 02 at the 650 mg/m² dose, 13% (5/39) of patients achieved a CR. At the 900 mg/m² dose, 22% (2/9) of patients achieved a CR.

No obvious dose-response relationship was found. For Stratum 01, response rate was higher after the 650 mg/m² dose than after the 900 mg/m² dose; the reverse is found for Stratum 02.

Study PGAA2002 (Adults):

The study was conducted in adults with relapsed or refractory T-ALL or LBL by Cancer and Leukemia Group B (CALGB). The study was an open-label, multi-center, single-arm, Phase 2 study in 39 adult patients with relapsed/refractory T-ALL (n=26) or T-LBL (n=13). Patients ranged in age between 16 to 66 years. Most patients were male (n=32) and most were Caucasians (n=27). The study started at the recommended Phase 2 dose of 2200 mg/m² given as an intravenous (IV) infusion over 2 hours on Days 1, 3 and 5 of a 21-day cycle (MTD from Phase 1 studies). This dose was then reduced to 1500 mg/m² on Days 1, 3 and 5 of a 21-day cycle because of the risk of neurologic toxicity. Only 3 out of 39 patients received the 2200 mg/m² dose. All 39 patients received at least one cycle of treatment, 25 of 39 patients received two cycles, 8 received three cycles, 3 received four cycles, 3 received five cycles, and only 1 patient received six cycles. The primary clinical endpoints were complete and partial response rates (defined below in response to Question #6). A summary of the results is shown in Tables 3 and 4.

Table 3. Summary of Response Rates by Number of Patients (%) for All Patients

	1 Prior Induction (N=11)	2 Prior Inductions (N=28)	Total (N=39)
Response Rate (CR + PR)	6 (55%)	10 (36%)	16 (41%)
[95% CI]	[23, 83]	[19, 56]	[26, 58]
Complete Response	4 (36%)	7 (25%)	11 (28%)
[95% CI]	[11, 69]	[11, 45]	[15, 45]
Partial Response	2 (18%)	3 (11%)	5 (13%)
Less than Partial Response	5 (45%)	18 (64%)	23 (59%)

According to the Applicant, 41% (16/39) of patients experienced a CP+PR responses. Eleven patients (28%) had CR and 5 had PR (13%). Four of the 11 patients (36%) with CR had only 1 prior induction therapy, while 7 of the 28 patients (25%) with CR had 2 prior inductions.

Table 4. Summary of Response Rates by Number of Patients (%) by Disease Type

	ALL (N=26)	LBL (N=13)	Total (N=39)
Response Rate (CR + PR)	11 (42%)	5 (38%)	16 (41%)
[95% CI]	[23, 63]	[14, 68]	[26, 58]
Complete Response (CR)	8 (31%)	3 (23%)	11 (28%)
[95% CI]	[14, 52]	[5, 54]	[15, 45]
Partial Response (PR)	3 (12%)	2 (15%)	5 (13%)
Less than a Partial Response	15 (58%)	8 (62%)	23 (59%)

Eleven of 26 patients with ALL (42%) and 5 of 13 patients with LBL (38%) experienced responses (CR + PR).

6. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmaco-dynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The primary endpoint used in the pivotal Phase 2 Study PGAA2001 in pediatric patients was complete response rate defined as:

Complete Response (CR): Bone marrow blast counts $\leq 5\%$, no other evidence of disease, and full recovery of peripheral blood counts (i.e., ANC $>1500/\mu\text{l}$, platelets $>100,000/\mu\text{l}$, Hemoglobin ≥ 10 g/dl for patients less than 2 years of age, Hemoglobin ≥ 11 g/dl for patients >2 years of age).

The primary clinical endpoint used in the pivotal Phase 2 Study PGAA2002 in adult patients was complete and partial response rates defined as follows:

Complete Response (CR):

ALL: absolute neutrophil count (segs and bands) $>1500/\mu\text{L}$, no circulating blasts, platelets $>100,000/\mu\text{L}$, bone marrow cellularity $>20\%$ with trilineage hematopoiesis, and $<5\%$ marrow blast cells, none of which appear neoplastic. All previous extramedullary manifestations of disease were to be absent (e.g., lymphadenopathy, splenomegaly, skin or gum infiltration, testicular masses, or CNS involvement). Because chemotherapy can produce prolonged cytopenias, subjects who did not recover normal peripheral blood counts but also did not relapse within 6 months of their final chemotherapy treatment could be considered retrospectively to have achieved a CR starting one month after their last transfusion.

LBL: disappearance of all measurable disease, signs, symptoms, and biochemical changes related to the tumor and appearance of no new lesions.

Partial Response (PR):

ALL: required all of the CR criteria except that the marrow may still contain 5-25% leukemia blast cells. Even if $<5\%$ blasts were present, the response was a PR if Auer rods or blast cells with obvious leukemia morphology (e.g., malignant promyelocytes) were present.

LBL: when compared with pre-treatment measurements, a reduction of 50% in the sum of the products of the perpendicular diameters of all measurable lesions. No new lesions could appear and no existing lesion could enlarge. A $<50\%$

reduction and 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and no new lesions was present.

The above clinical endpoints were selected after consultation with the FDA at the two End-Of-Phase 2 meetings on 18-Jun-1997 and 24-Nov-2003.

7. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess the pharmacokinetic parameters and exposure-response relationships?

In Phase 1 studies, plasma and urine samples were analyzed for nelarabine and ara-G using a validated high performance liquid chromatography (HPLC) method. Intracellular ara-GTP was measured in leukemia blasts using a validated HPLC assay method at 100 nm. Validations of these methods are discussed in Section III.F of this review. The cytotoxic activity is attributed to intracellular Ara-GTP.

Exposure-Response Evaluations

8. What are the characteristics of the exposure-response relationship for efficacy?

Plasma concentrations of nelarabine, ara-G, or ara-GTP were not measured in the pivotal Phase 2 clinical studies (Studies PGAA2001 and PGAA2002). The Applicant performed exploratory pharmacokinetic/pharmacodynamic analyses on the combined data from Phase 1, dose-escalation Studies PGAA1001, PGAA1002, and PGAA1003 to determine the relationships between exposure (C_{max} , AUC) to intracellular ara-GTP and response rate (Complete and partial) (see the Pharmacometric review for details).

The analyses of combined Phase 1 PK data indicate that the mean dose-normalized C_{max} and AUC values for intracellular ara-GTP were 8-fold and 13-fold higher, respectively, in adult responders than in adult non-responders ($p < 0.05$) (Tables below). There are not enough ara-GTP data in pediatric patients to make a comparison between responders and non-responders. Comparable mean dose-normalized C_{max} and AUC values were obtained for ara-G in responders and non-responders whether in adult or pediatric patients. Comparable mean dose-normalized C_{max} and AUC values for nelarabine were obtained in adult responders and adult non-responders. However, pediatric patients who responded to nelarabine therapy had 7- to 8- fold higher mean dose-normalized C_{max} and AUC values for nelarabine than those who did not. This indicates that the cytotoxic activity of ARRANON can be attributed to the exposure to intracellular ara-GTP in adult patients and to the exposure to nelarabine in pediatric patients.

Table 5a. Relationship between Exposure and Response Rate for Nelarabine

Parameter	Response (CR/PR)	No Response
Adult Patients		
	(n=26)	(n=72)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	8.1±6.5	9.5±9.8
AUC/Dose (ng.h/ml/1mg/m ²)	8.2±8.6	10.4±10.2
Pediatric Patients		
	(n=9)	(n=15)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	90±167	13.4±17.6
AUC/Dose (ng.h/ml/1mg/m ²)	64±116	10.4±10.2

Table 5b. Relationship between Exposure and Response Rate for Ara-G

Parameter	Response (CR/PR)	No Response
Adult Patients		
	(n=28)	(n=63)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	23±6.1	28±8.5
AUC/Dose (ng.h/ml/1mg/m ²)	91±34	85±27.6
Pediatric Patients		
	(n= 10)	(n=15)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	30±11.7	28±8.5
AUC/Dose (ng.h/ml/1mg/m ²)	85±37	85±27

Table 5c. Relationship between Exposure and Response Rate for Ara-GTP

Parameter	Response (CR/PR)	No Response
Adult Patients		
	(n=15)	(n=34)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	133±139	16±8.9
AUC ₀₋₂₄ /Dose (ng.h/ml/1mg/m ²)	4134±4749	315±321
Pediatric Patients		
	(n=0)	(n=1)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	--	6.3
AUC ₀₋₂₄ /Dose (ng.h/ml/1mg/m ²)	--	42.5

9. What are the characteristics of the exposure-response relationship for safety?

The dose-limiting toxicity observed in Phase 1 and 2 studies was Grade 3 and Grade 4 neurotoxicity affecting both the central (e.g., somnolence, seizures, dizziness, confusion, and ataxia) and peripheral (e.g., hypoesthesia, paresthesia, pain in extremities, peripheral neuropathy) nervous system (CNS).

The Applicant performed exploratory pharmacokinetic/pharmacodynamic analyses on the combined data from Phase 1, dose-escalation Studies PGAA1001, PGAA1002, and PGAA1003 to determine the relationships between exposure (C_{max} , AUC) to each of nelarabine, ara-G, and ara-GTP and neurotoxicity (see the Pharmacometric review for details).

The analyses of combined Phase 1 PK data indicate that both mean dose-normalized C_{max} and AUC of ara-GTP were 2.3-fold higher ($p > 0.05$) in patients who experienced neurotoxicity than in those who did not. There are not enough ara-GTP data to make a comparison of neurotoxicity in pediatric patients. Comparable mean dose-normalized C_{max} and AUC values were obtained for ara-G in adult and pediatric patients who experienced neurotoxicity and those who did not. Exposure to nelarabine was higher (1.2- to 1.7-fold higher dose-normalized C_{max} and AUC) in adult patients who experienced neurotoxicity than those who did not ($p > 0.05$). This indicates that the neurotoxicity of ARRANON can be attributed to the exposure to both intracellular ara-GTP and nelarabine in adult patients.

Table 6a. Relationship between Exposure and Neurotoxicity for Nelarabine

Parameter	Incidence of Neurotoxicity	No Neurotoxicity
Adult Patients		
	(n=32)	(n=69)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	10.2±8.0	8.4±9.3
AUC/Dose (ng.h/ml/1mg/m ²)	14.3±26	8.6±9.3
Pediatric Patients		
	(n=4)	(n=21)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	16±13	50±119
AUC/Dose (ng.h/ml/1mg/m ²)	14±7	35±82

Table 6b. Relationship between Exposure and Neurotoxicity for Ara-G

Parameter	Incidence of Neurotoxicity	No Neurotoxicity
Adult Patients		
	(n=27)	(n=68)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	20±6.3	22±5.6
AUC/Dose (ng.h/ml/1mg/m ²)	81±29	95±35
Pediatric Patients		
	(n=3)	(n=22)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	27±9.3	29±9.7
AUC/Dose (ng.h/ml/1mg/m ²)	91±36	86±31

Table 6c. Relationship between Exposure and Neurotoxicity for Ara-GTP

Parameter	Incidence of Neurotoxicity	No Neurotoxicity
Adult Patients		
	(n=19)	(n=32)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	77±116	34±71
AUC ₀₋₂₄ /Dose (ng.h/ml/1mg/m ²)	2217±3481	995±2809
Pediatric Patients		
	(n=1)	(n=0)
$C_{max}/Dose$ (ng/ml/1mg/m ²)	6.3	--
AUC ₀₋₂₄ /Dose (ng.h/ml/1mg/m ²)	42.5	--

10. Does this drug prolong the QT_c interval?

A thorough QT_c study has not been performed. According to the Medical Reviewer (HFD-150), no evidence from clinical data suggests that nelarabine prolongs QT_c.

11. Are the dose and dosing regimen of the drug consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The selection of the dose for the pivotal Phase 2 clinical studies was based on the maximum tolerated dose (MTD) determined in the Phase 1, dose-escalation studies (Studies PGAA1001, PGAA1002, and PGAA1003) in adult patients and pediatric patients with refractory hematologic malignancies.

- **Study PGAA1001:** This was an open-label, dose-escalation, Phase 1 study in 93 patients (65 adults, 28 pediatric patients) with Refractory Hematologic Malignancies. Nelarabine was administered to **adult** patients at doses of 205 mg/m² (n=4), 411 mg/m² (n=4), 822 mg/m² (n=5), 1000 mg/m² (n=1), 1200 mg/m² (n=16), 1644 mg/m² (n=30), and 2466 mg/m² (n=5) by intravenous (IV) infusion over 1 hour once daily for 5 consecutive days, repeated every 21 to 28 days. Nelarabine was administered to **pediatric** patients at doses of 104 mg/m² (n=5), 208 mg/m² (n=1), 416 mg/m² (n=4), 833 mg/m² (n=3), 1200 mg/m² (n=4), 1250 mg/m² (n=10), and 1562 mg/m² (n=1) as a 1-hour intravenous (IV) infusion once daily for 5 consecutive days, repeated every 21 to 28 days.

The MTD of nelarabine determined in this study was 1200 mg/m² for both adult and pediatric patients. This dose was evaluated in the pivotal Phase 2 Study PGAA2001 in pediatric patients and was subsequently reduced to 900 mg/m² and then 650 mg/m² based on the observed neurologic adverse events.

- **Study PGAA1002:** This was an open-label, dose-escalation, Phase 1 study in 27 patients (17 adult and 10 pediatric patients) with refractory hematologic malignancies. Nelarabine was administered at doses of 900 mg/m² (n=9 adults, n=3 pediatrics), 1200 mg/m² (n=7 adults, n=4 pediatrics), or 1500 mg/m² (n=1 adult, n=3 pediatrics) as a 2-hour IV infusion once daily for 3 consecutive days, repeated every 21 to 28 days.

The MTD of nelarabine determined in this study was 900 mg/m² for adult patients. No MTD was determined for pediatric patients. The dosing schedule used in this study has not been evaluated in the Phase 2 program.

- **Study PGAA1003:** This was an open-label, dose-escalation, Phase 1 study in 48 patients (46 adult and 2 pediatric patients) with refractory hematologic malignancies. Nelarabine was administered at doses of 1200 mg/m² (n=4 adults, n=1 pediatric), 1500 mg/m² (n=5 adults, n=1 pediatric), 1800 mg/m² (n=4 adults), 2200 mg/m² (n=20 adults), 2500 mg/m² (n=11 adults), and 2900 mg/m² (n=2 adults) as a 2-hour intravenous infusion on a Day 1, 3, and 5, repeated every 21 to 28 days.

The MTD of nelarabine determined in this study was 2200 mg/m² for adult patients. No MTD was determined for pediatric patients in this study. The 2200 mg/m² was evaluated in the pivotal Phase 2 Study PGAA2002 in adult patients and was subsequently reduced to 1500 mg/m² based on the observed neurologic adverse events.

Pharmacokinetic (PK) Characteristics

12. What are the single- and multiple-dose PK parameters?

Single-Dose Administration:

The following tables report the single-dose pharmacokinetics (PK) parameters determined on Day 1 for nelarabine and ara-G in adult patients (Studies PGAA1002 and PGAA1003) and pediatric patients (Study PGAA1002) after administration of nelarabine.

Table 7. Arithmetic Mean±SD (%CV) Non-Compartmental PK Parameters for Nelarabine on Day 1

Dose (mg/m ²)	N	C _{max} (µg/ml)	AUC _{0-∞} (µg.h/ml)	CL (L/h/m ²)	V _{ss} (L/m ²)	t _{1/2} (h)
Adult Patients (n=44)						
900	7	3.9±3.2 (82%)	5.1±3.8 (75%)	316±230 (73%)	432±370 (86%)	0.33±0.14 (42%)
1200	15	5.6±5.1 (90%)	8.2±3.1 (38%)	176±133 (75%)	198±162 (82%)	0.27±0.09 (34%)
1500	6	4.1±4.7 (115%)	6.9±4.2 (61%)	346±273 (79%)	404±336 (83%)	0.27±0.11 (42%)
1800	3	11.2±6.6 (59%)	32.7 (n=1)	59 (n=1)	86 (n=1)	0.53 (n=1)
2200	5	11.3±6.8 (60%)	12.2, 30.9 (n=2)	86, 212 (n=2)	28, 628 (n=2)	0.35, 0.44 (n=2)
2500	6	10.3±2.7 (26%)	17.8 (n=1)	155 (n=1)	181 (n=1)	0.33 (n=1)
2900	2	17.4, 11.2	25.3 (n=1)	176 (n=1)	157 (n=1)	0.39, 0.39
Pediatric Patients (N=6)						
1200	4	6.9±2.4 (34%)	9.04±3.5 (39%)	123±20 (16%)	131± 20 (15%)	0.275±0.16 (57%)
1500	2	10.8, 8.2	12.6, 11.0	120, 105	139, 108	0.24, 0.15

Table 8. Arithmetic Mean±SD (%CV) Non-Compartmental PK Parameters for Ara-G on Day 1 after Nelarabine IV Infusion

Dose (mg/m ²)	N	C _{max} (µg/ml)	*T _{max} (h)	AUC _{0-∞} (µg.h/ml)	CL/F (L/h/m ²)	V _{ss} /F (L/m ²)	t _{1/2} (h)
Adult Patients (N=29)							
900	8	13.4±5.1 (38%)	2.3 (2.0-2.7)	65.6±26.0 (39%)	18±10.6 (58%)	95±60 (63%)	3.3±0.84 (25%)
1200	11	22.7±4.7 (21%)	2.1 (1.8-4.0)	117±47.3 (40%)	11±3.2 (29%)	47±16 (34%)	2.9±1.3 (44%)
1500	3	32.9±6.5 (20%)	2.1 (2.0-2.2)	172±66 (39%)	13±3.3 (25%)	42±8.6 (20%)	1.9±0.68 (34%)
1800	2	24.3, 33.3	2.1, 2.1	105, 191	7.9, 17.5	56, 63.5	2.3, 5.4
2200	3	37.4±9.2 (25%)	2.1 (2.0-2.3)	197±39.8 (20%)	12±3.5 (28%)	62±17 (27%)	3.8±0.4 (11%)
2500	0	--	--	--	--	--	--
2900	2	58.5, 60.8	2.0, 2.0	283, 294	10.3, 11.1	48.4, 61.7	3.5, 4.2
Pediatric Patients (N=6)							
1200	4	23.8±4.5 (19%)	2.0 (1.75-2.2)	112±47.7 (43%)	10.1±3.3 (33%)	34±5.6 (17%)	2.4±0.78 (32%)
1500	2	26.5, 31.4	2.0, 2.1	78.4, 94.6	5.7, 12.5	35, 38	1.1, 3.9

*Median (Range)

After the end of nelarabine infusion, both plasma concentrations of nelarabine and ara-G declined in a monoexponential fashion. Nelarabine is rapidly eliminated from the plasma ($t_{1/2} \sim 0.3$ hour). Plasma concentrations of nelarabine were not detectable 2 hours after the end of the infusion. Nelarabine has much higher clearance and volume of distribution than ara-G. Peak plasma concentrations of ara-G appeared within 2 hours of nelarabine infusion, suggesting that most of nelarabine dose was converted to ara-G. Ara-G is eliminated at a slower rate than nelarabine ($t_{1/2} \sim 3$ hours). Plasma concentrations of ara-G were detectable up to 23 hours after the end of nelarabine infusion.

The combined data from the Phase 1 Studies PGAA1001, PGAA1002, and PGAA1003 indicate that mean clearance (CL) of nelarabine is about 30% higher in pediatric patients than in adult patients, 237 ± 397 L/h/m² versus 182 ± 277 L/h/m², respectively, on Day 1 after nelarabine doses of 104-2900 mg/m² (n=101 adults, n=25 pediatric patients). The apparent clearance of Ara-G (CL/F) is comparable between the two groups. The mean CL/F of ara-G is 7.8 ± 6.0 L/m² in adult patients and 7.9 ± 6.2 L/m² in pediatric patients on Day 1 after nelarabine administration. The mean elimination half-lives of nelarabine and ara-G are 0.30 ± 0.12 hour and 3.5 ± 1.4 hours, respectively, in adult patients and 0.26 ± 0.13 hour and 2.2 ± 0.86 hours, respectively, in pediatric patients on Day 1 after nelarabine administration.

The following are the pharmacokinetic parameters for intracellular ara-GTP assessed in 21 adult patients after IV infusion of nelarabine on Day 1 (Study PGAA1003) and 1 pediatric patient (Study PGAA1002):

Table 9. Arithmetic Mean \pm SD (%CV) Non-Compartmental PK Parameters for Intracellular Ara-GTP on Day 1 after Nelarabine IV Infusion

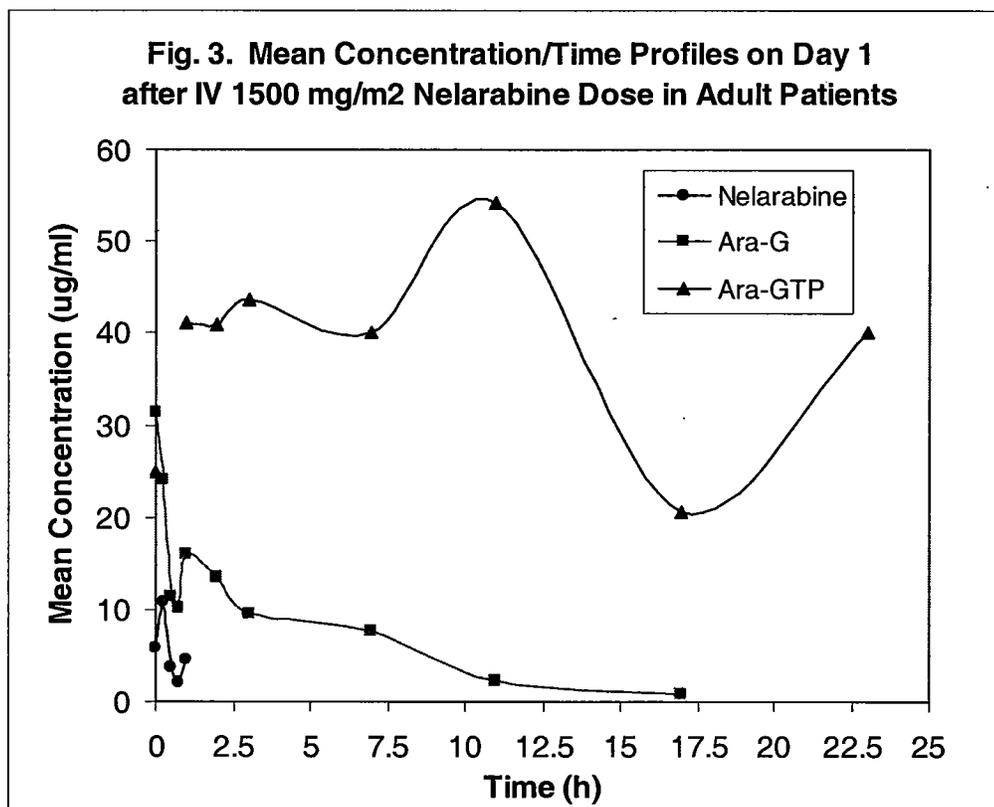
Dose (mg/m ²)	N	C _{max} (µg/ml)	*T _{max} (h)	AUC ₀₋₂₄ (µg.h/ml)
Adult Patients (N=21)				
1200	3	13.9 \pm 3.4 (25%)	2.4 (2.1-48.4)	219 \pm 38 (17%)
1500	5	50.1\pm43.9 (87%)	7.9 (3.0-25.2)	890\pm827 (93%)
1800	3	53.2 \pm 37.9 (71%)	5.3 (3.7-47.2)	768 \pm 507 (66%)
2200	4	50.8 \pm 15.9 (31%)	2.6 (2.0-45.5)	867 \pm 265 (31%)
2500	4	43.2 \pm 19.3 (45%)	3.7 (2.0-22.5)	702 \pm 279 (40%)
2900	2	43.3, 58.8	2.1, 3.3	621, 935
Pediatric Patients (N=1)				
1500	1	9.4	1.0	65.7

*Median (Range)

At the proposed IV 1500 mg/m² nelarabine dose, a mean C_{max} for intracellular ara-GTP appeared within 3-25 hours after nelarabine infusion. Exposure (AUC) to intracellular

ara-GTP is 127 times higher than that for nelarabine and 5 times higher than that for ara-G. Because the intracellular levels of ara-GTP were so prolonged, the elimination half-life could not be estimated.

Mean concentration/time profiles in adult patients for nelarabine, ara-G, and ara-GTP on Day 1 following nelarabine IV infusion of 1500 mg/m² dose are shown in the Figure below:



Multiple-dose Administration:

The following tables report the multiple-dose pharmacokinetics (PK) parameters determined on Days 3 and 5 for nelarabine and ara-G in adult patients after nelarabine IV infusion (Study PGAA1003). There are no adequate multiple-dose PK data available for pediatric patients at the proposed 650 mg/m² dose and schedule of daily doses for 5 consecutive days. There no multiple-dose data for ara-GTP in adult or pediatric patients.

Table 10. Arithmetic Mean±SD (%CV) Multiple-Dose Non-Compartmental PK Parameters for Nelarabine

Dose (mg/m ²)	N	C _{max} (µg/ml)	AUC _{0-∞} (µg.h/ml)	CL (L/h/m ²)	V _{ss} (L/m ²)	t _{1/2} (h)
Day 3						
1200	4	6.01±5.4 (90%)	19.1 (n=1)	50.1 (n=1)	56.3 (n=1)	0.41 (N=1)
1500	4	5.4±2.9 (54%)	ND	ND	ND	ND
1800	2	7.4, 16.5	ND	ND	ND	ND
2200	3	7.7±7.6 (99%)	ND	ND	ND	ND
2500	2	4.9, 13.4	6.8 (n=1)	390	181	0.26
2900	1	7.75	ND	ND	ND	ND
Day 5						
1200	2	2.2, 4.3	2.9, 6.0	202, 467	243, 543	0.31, 0.35
1500	3	5.7±2.1 (36%)	7.6±2.1 (28%)	228±39 (17%)	275±82 (30%)	0.42±0.17 (40%)
1800	3	13.1±5.2 (39%)	16.2, 29.6 (n=2)	65.3, 109 (n=2)	77, 173 (n=2)	0.31, 0.66 (n=2)
2200	1	20.3	ND	ND	ND	ND
2500	0	ND	ND	ND	ND	ND
2900	1	14.8	20.4	49.6	189	0.39

ND=Not Determined

Table 11. Arithmetic Mean±SD (%CV) Non-Compartmental PK Parameters for Ara-G after Nelarabine IV Infusion

Dose (mg/m ²)	N	C _{max} (µg/ml)	AUC _{0-∞} (µg.h/ml)	CL/F (L/h/m ²)	V _{ss} /F (L/m ²)	t _{1/2} (h)
Day 3						
1200	1	32.3	135	6.7	24	2.3
1500	0	ND	ND	ND	ND	ND
1800	0	ND	ND	ND	ND	ND
2200	0	ND	ND	ND	ND	ND
2500	1	54.3	163	15.5	41	1.7
2900	0	ND	ND	ND	ND	ND
Day 5						
1200	3	25.3±0.64 (3%)	112±16.0 (14%)	11.7±2.8 (24%)	45.6±7.7 (17%)	2.8±0.54 (19%)
1500	2	24.0, 29.4	86.4, 120	12.4, 17.2	79.5, 53.8	2.0, 2.9
1800	1	26.6	70.1	26.3	51.2	1.1
2200	0	ND	ND	ND	ND	ND
2500	0	ND	ND	ND	ND	ND
2900	1	43.6	215	15.1	73.5	3.5

Comparable C_{max} and AUC were obtained for nelarabine between Days 1 and 5 at the proposed nelarabine adult dose of 1500 mg/m², indicating that the PK of nelarabine after multiple-dosing of nelarabine are predictable from single-dosing. There were not enough data for ara-G to make a comparison between Day 1 and Day 5.

13. How do the pharmacokinetics of the drug in healthy volunteers compare to that in patients?

Nelarabine is a cytotoxic agent and has never been administered to healthy volunteers.

14. What are the characteristics of drug absorption?

Nelarabine is administered by an intravenous infusion and has not been given orally to humans.

15. What are the characteristics of drug distribution?

Both nelarabine and ara-G are extensively distributed throughout the body. Steady state volume of distribution (V_{ss}) for nelarabine averaged 176 ± 281 L/m² in adult patients and 195 ± 347 L/m² in pediatric patients on Day 1 following nelarabine IV doses of 104-2900 mg/m² (n=101 adults, n=25 pediatrics). Apparent steady state volume of distribution (V_{ss}/F) of ara-G averaged 37 ± 29 L/m² in adult patients and 23 ± 17 L/m² in pediatric patients on Day 1 following nelarabine IV doses of 104-2900 mg/m² (n=101 adults, n=25 pediatrics).

The *in vitro* plasma protein binding of both nelarabine and ara-G is low (<25%) over the concentration range of 1.78-178 µg/ml (Table 11). Plasma protein binding is independent on nelarabine concentrations. Plasma protein binding increased as ara-G concentrations increased.

Table 12. Mean±SD % protein bound to human plasma

<i>In vitro</i> Concentration (µg/ml)	Nelarabine	Ara-G
1.78	10.25±5.0%	6.5±6.7%
17.8	19.6±15.5%	10.6±7.5%
178	7.02±4.0%	24.4±16.9%

16. Does the mass-balance study suggest renal or hepatic as the major route of drug elimination?

The Applicant has not conducted a mass-balance study for nelarabine. Urinary excretion data from Phase 1 Studies PGAA1002 and PGAA1003 indicate that nelarabine and ara-G are partially eliminated by the kidney; the mean % of dose excreted in urine over 24 hours was $5.8 \pm 4.5\%$ and $32.3 \pm 18.9\%$, respectively, in 12 adult patients. Patients enrolled in the Phase 1 Studies PGAA1001, PGAA1002, and PGAA1003 had creatinine clearance (CrCL) values ranging from 31-363 mL/min. The combined PK data from these studies indicate that ara-G apparent clearance (CL/F) is highly correlated with CrCL (p=0.0032), while nelarabine clearance (CL) is not correlated with CrCL (p=0.787).

Fig. 4

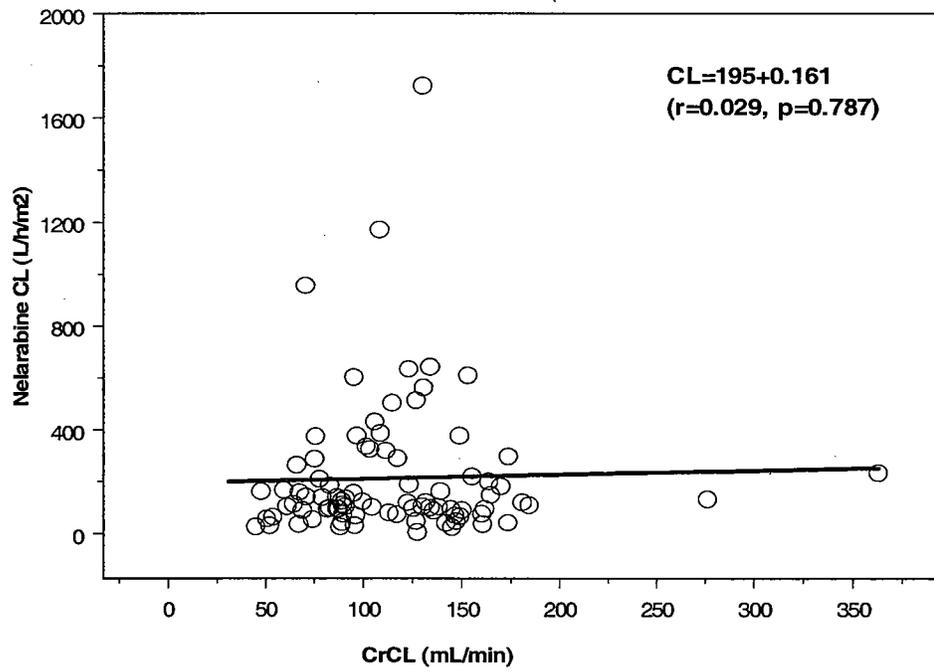
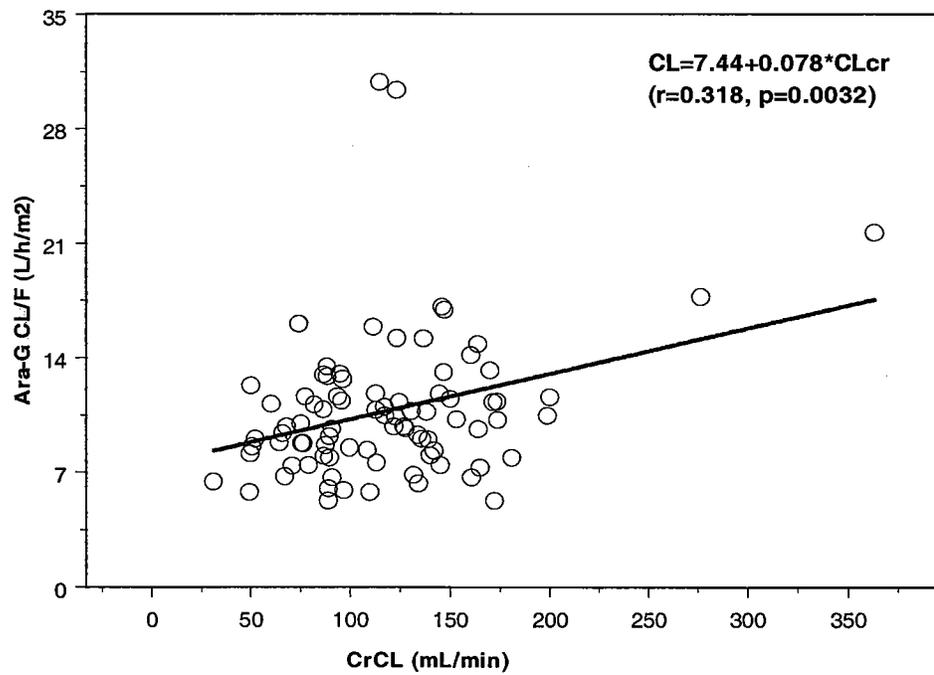


Fig. 5



Patients enrolled in the pivotal Phase 2 Studies PGAA2001 and PGAA 2002 had adequate baseline renal and hepatic function as demonstrated by calculated creatinine clearance of ≥ 50 ml/min and hepatic transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] of 3 x upper limit of normal and bilirubin of 1.5 mg/dL.

17. What are the characteristics of drug metabolism?

The extent of *in vitro* metabolism of [^{14}C]-nelarabine (506U78) and [^{14}C]-ara-G in cryopreserved hepatocytes from mouse, rabbit, and monkey and cryopreserved and fresh hepatocytes from humans was determined over 24-hour incubations (Report RD2004/00449/00). Results are shown below:

Table 13 . Percentage of Each Metabolite of [^{14}C]-Nelarabine (506U78) (150 μM) in Radiochromatograms of Mouse, Rabbit, Monkey and Human Hepatocyte Samples

Peak ID	RT (min)	Percent of Total ^{14}C (%) in Chromatogram				
		Fresh Human	Cryo Human	Cryo Monkey	Cryo Rabbit	Cryo Mouse
Allantoin	3.4	<0.5%	ND*	<0.5%	1.22%	7.78%
Uric acid	5.8	12.1%	2.20%	ND	ND	ND
Xanthine	8.6	<0.5%	0.77%	ND	0.98%	ND
ara-G	10.7	44.4%	43.7%	11.8%	37.2%	26.1%
506U78	19.3	41.5%	52.3%	87.2%	58.5%	64.7%
Total		98%	99%	99%	97.9%	98.6%

*ND=Not Detected

In fresh human hepatocytes, allantoin, uric acid, xanthine, ara-G, and 506U78 represented <0.5%, 12.1%, <0.5%, 44.4%, and 41.5% of the total nelarabine radioactivity, respectively.

In cryopreserved human hepatocytes, uric acid, xanthine, ara-G and 506U78 represented 2.2%, 0.77%, 43.7%, and 52.3% of the total nelarabine radioactivity, respectively. Allantoin was not detected in cryopreserved human hepatocytes incubations.

Table 14. Percentage of Each Metabolite of [^{14}C]-Ara-G (150 μM) in Radiochromatograms of Mouse, Rabbit, Monkey and Human Hepatocyte Samples

Peak ID	RT (min)	Percent of Total ^{14}C (%) in Chromatogram				
		Fresh Human	Cryo Human	Cryo Monkey	Cryo Rabbit	Cryo Mouse
Allantoin	3.3	<0.5%	ND	1.4%	9.4%	87.5%
Uric acid	5.8	27.4%	5.1%	0.57%	<0.5%	ND
Xanthine	8.6	<0.5%	0.61%	ND*	1.8%	ND
ara-G	10.7	70.4%	93.5%	96.1%	85.2%	10.8%
Total		97.8%	99.2%	98.1%	96.4%	98.3%

*ND=Not Detected

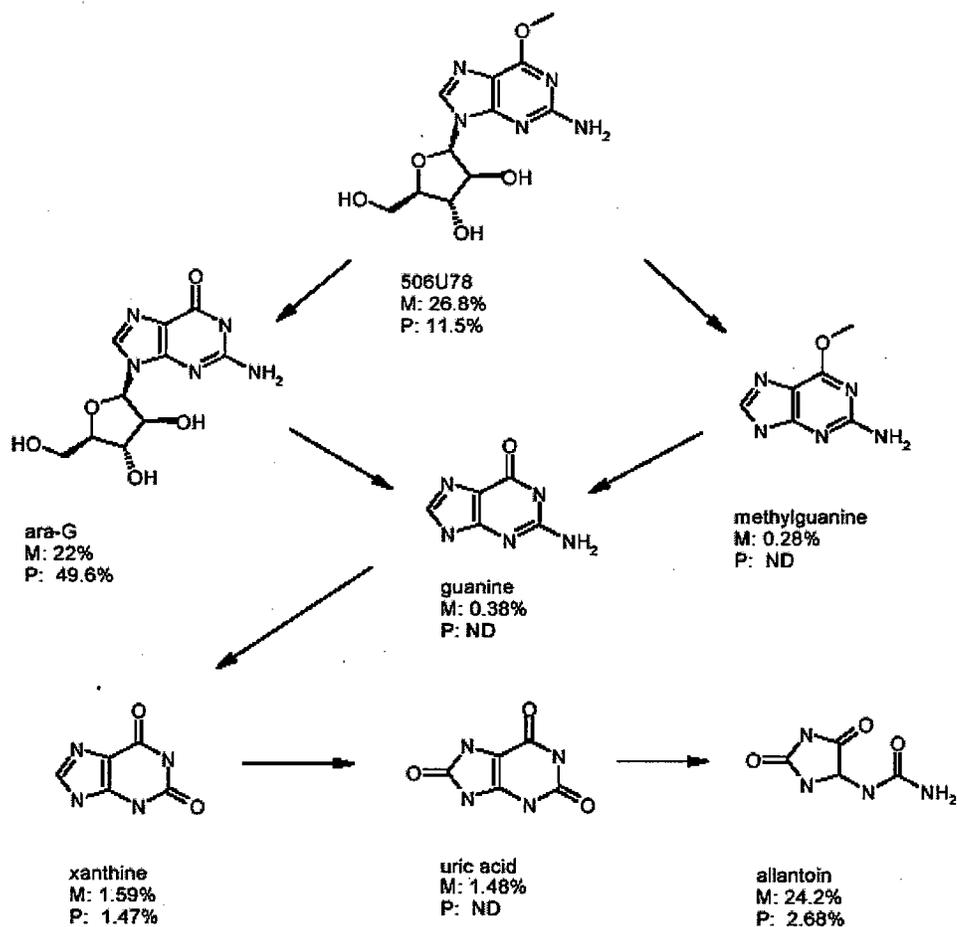
Based on these data, the Applicant proposes the following metabolic pathway of nelarabine (506U78) (Fig. 6). The major metabolic pathway for nelarabine is its O-demethylation by adenosine deaminase to form ara-G. Ara-G then undergoes hydrolysis to form guanine. In addition, some nelarabine is hydrolyzed to form methylguanine, which is O-demethylated to form guanine. Guanine is N-deaminated to form xanthine, which is further oxidized to yield uric acid. Ring opening of uric acid followed by further oxidation results in the formation of allantoin.

Adenosine deaminase (ADA), the primary enzyme involved in nelarabine metabolism, is a genetically polymorphic enzyme in the normal population. Three phenotypes were recognized on electrophoresis: ADA1, ADA2 and ADA2/1. ADA deficiency has been identified as the metabolic basis for 20-30% of cases with recessively inherited Severe Combined Immunodeficiency (SCID) which is caused by the mutations of ADA. The structural gene for ADA is encoded as a single 32 kb locus containing 12 exons on the long arm of chromosome 20 (20q13.2-qter) [Markert *et al.*, 1989, Hirshorn *et al.*, 1989].

- Markert M L, Norby-Slycord C, Ward F E 1989 A high proportion of ADA point mutations associated with a specific alanine-to-valine substitution. *American Journal of Human Genetics* 45:354-361.
- Hirshorn R, Tzall S, Ellenbogen A, Orkin S H 1989 Identification of a point mutation resulting in a heat-labile adenosine deaminase (ADA) in two unrelated children with partial ADA deficiency. *Journal of Clinical Investigation* 83:497-501.

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Fig. 6 Proposed metabolic pathways



M – Mouse (intact male)

P – Cynomolgus monkey (intact male)

ND – not detected

Values shown represent total amount of metabolite recovered (represented as % of administered dose) in urine and feces combined of intact male animals only. There was no marked gender-related difference in the metabolic profiles

18. What are the characteristics of drug excretion?

The Applicant has not conducted a mass balance study for nelarabine. Urine data collected up to 24 hours after nelarabine infusion on Day 1 in Studies PGAA1002 and PGAA1003 indicate that nelarabine and ara-G are partially eliminated by the kidneys. A summary of the results are shown in the Tables 15 and 16.

Table 15. Urinary Excretion Data Over 24 Hours on Day 1 (Study PGAA1002)

Age Group	Dose (mg/m ²)	n	Arithmetic Mean	SD
Nelarabine				
Adult Patients	900	5	4.02%	2.5%
	1200	6	7.9%	4.6%
	1500	1	2.24%	--
	Overall	12	5.8%	4.15%
Pediatric Patients	900	1	3.5%	--
	1200	1	6.9%	--
	1500	1	27.6%	--
	Overall	3	12.7%	13.04%
Ara-G				
Adult Patients	900	4	24.6%	12.3%
	1200	6	37.5%	21.8%
	Overall	10	32.35%	18.9%
Pediatric Patients	900	1	16.4%	--
	1200	1	30.5%	--
	1500	1	35.2%	--
	Overall	3	27.4%	9.7

Table 16. Mean±SD Urinary Excretion and Renal Clearance Data Over 24 Hours on Day 1 in Adult Patients (PGAA1003)

Dose (mg/m ²)	n	Nelarabine		Ara-G	
		% Dose Excreted	CLr (mL/min)	% Dose Excreted	CLr (mL/min)
1200	3	7.1±4.5%	22.4, 48.6 (n=2)	34.7±9.5%	111±32.3
1500	5	6.35±2.6%	30.5, 40.6 (n=2)	18.3±6.1%	55.1±22.3
1800	2	15.9%, 19.0%	2.85, 14.0	27.0%, 29.0%	69.8, 133.9
2200	3	7.25±2.5	19.3 (n=1)	20.3±2.6%	89.3 (n=1)
2500	1	3.6%	--	5.3%, 27.7%	12.5
2900	1	0.57%	1.3	15.4%	49.3
Overall	15	7.1±5.2%	19.9±17.5	22.8±9.5%	75.75±39.7

In Study PGAA1002, urinary excretion of nelarabine and ara-G averaged 5.8±4.1% and 32.3±18.9% of the administered dose, respectively in 12 adult patients over the 24 hours after nelarabine infusion on Day 1.

In Study PGAA1003, urinary excretion of nelarabine and ara-G averaged 7.1±5.2% and 22.8±9.5%, respectively in 16 adult patients over 24 hours after nelarabine infusion on Day 1. Renal clearance averaged 19.9±17.5 ml/min for nelarabine and 75.7±39.7 ml/min for ara-G in 12 adult patients.

19. Based on pharmacokinetic (PK) parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The pharmacokinetics of nelarabine and ara-G are linear over the nelarabine dosing range of 104-2900 mg/m² on Day 1 (Combined data from the Phase 3 Studies PGAA1001, PGAA1002, and PGAA1003). Except for the AUC of nelarabine (p>0.05), significant linear relationships are found between C_{max} and AUC and administered nelarabine dose (p < 0.05). No significant relationships were found between nelarabine dose and either of C_{max} or AUC for ara-GTP.

Fig. 7

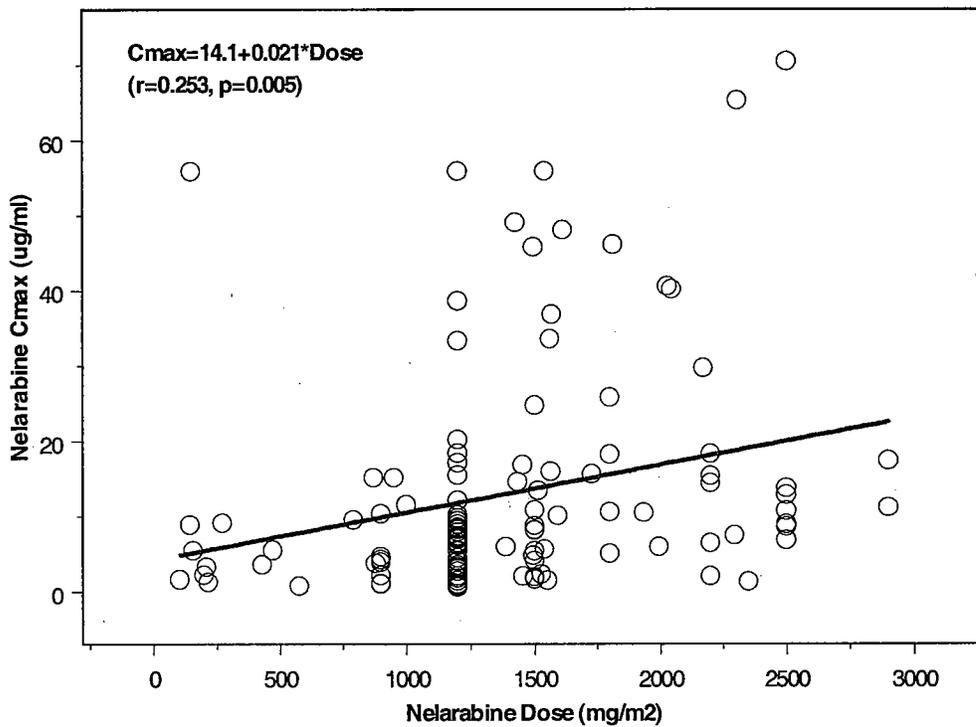


Fig. 8

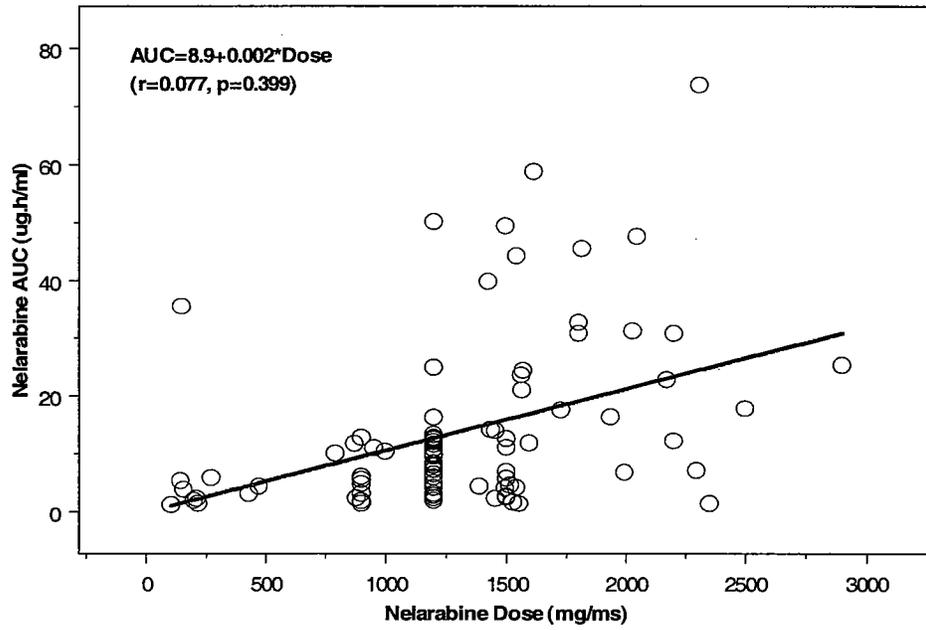


Fig. 9

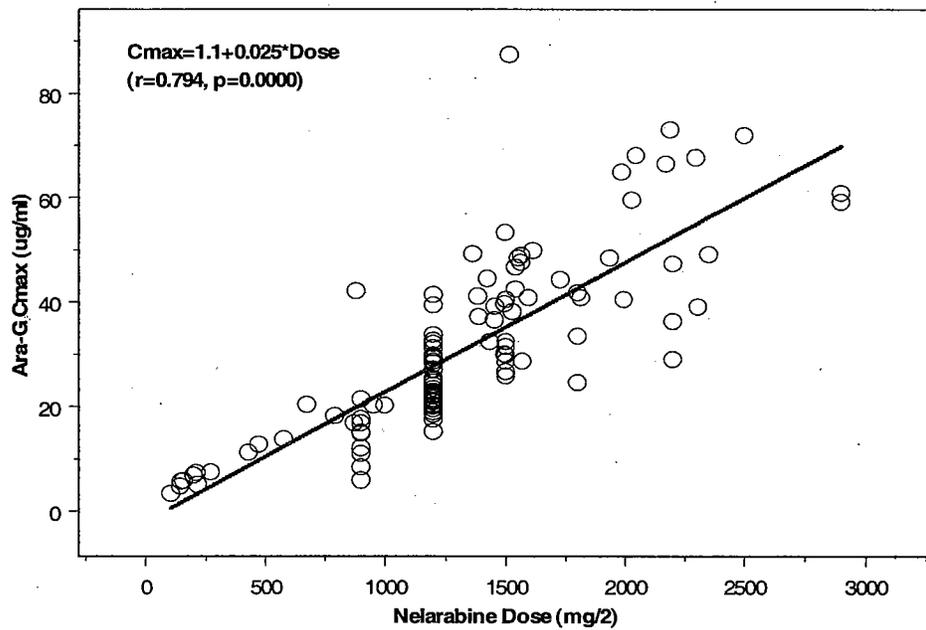


Fig. 10

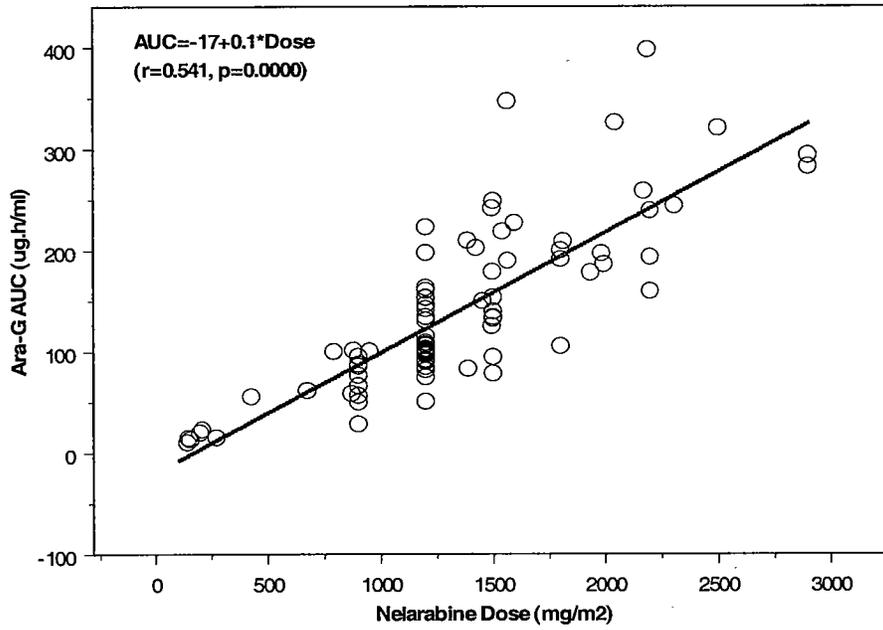


Fig. 11

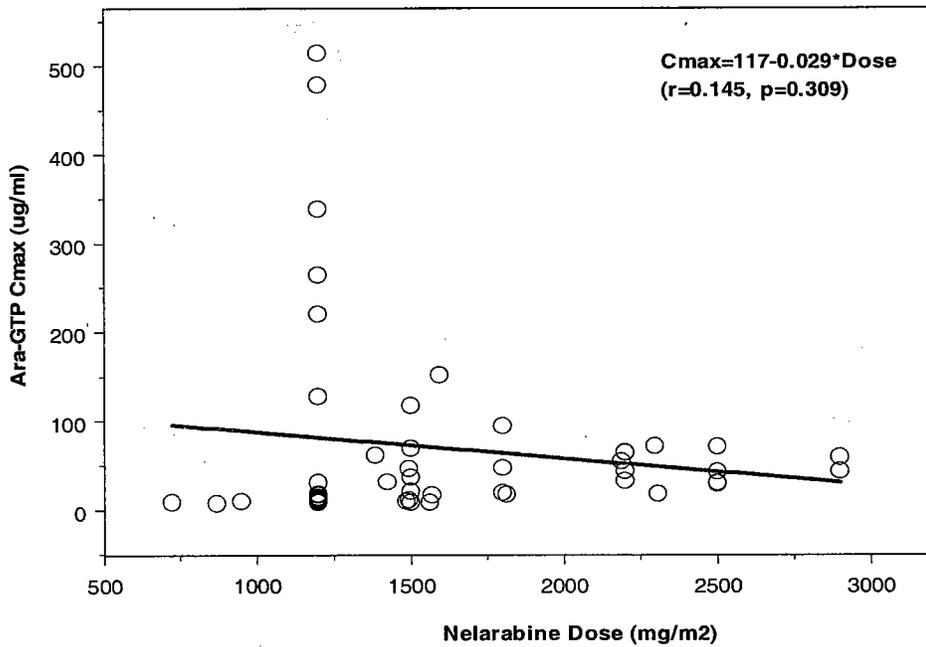
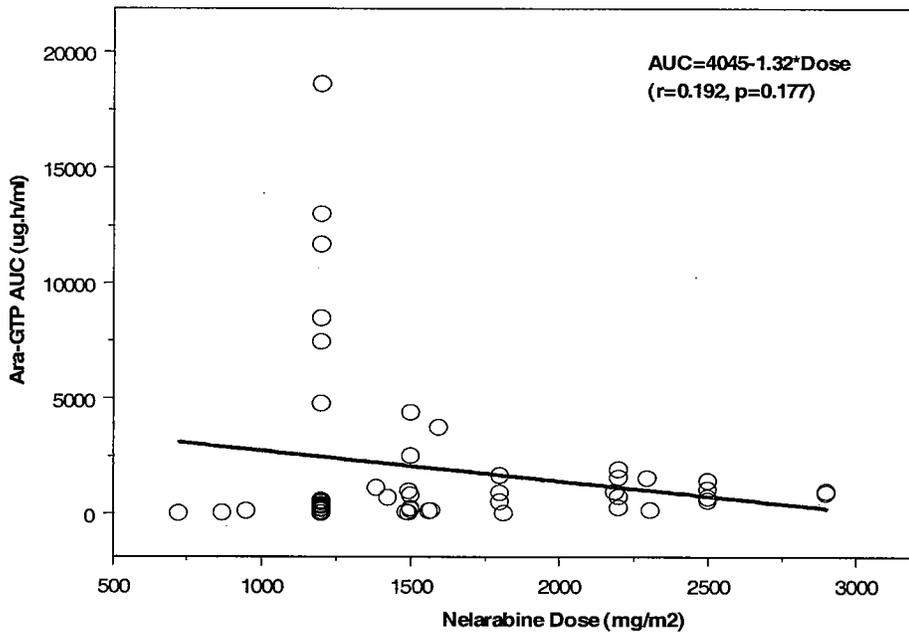


Fig. 12



20. How do the pharmacokinetic (PK) parameters change with time following chronic dosing?

The mean C_{max} and AUC for each of Nelarabine and ara-G were similar on Days 1, 3, and 5 following IV administration of nelarabine (Study PGAA1003). In addition, the mean elimination half-life of nelarabine and ara-G is 0.29 ± 0.12 hour and 3.0 ± 1.3 hours, respectively. Thus, accumulation of these drugs is not expected upon chronic dosing of nelarabine.

21. What is the intra- and inter-subject variability of pharmacokinetic parameters in patients, and what are the major causes of variability.

A large inter-patient variability is noted in the PK parameters for nelarabine and intracellular ara-GTP. At the proposed adult nelarabine dose of 1500 mg/m^2 , the coefficients of variation (%CV) ranged from 42-115% for nelarabine, from 20-39% for ara-G, and from 87-93% for ara-GTP. The within individual patients PK parameters were comparable from Days 1, 3, to 5 in most patients for both nelarabine and ara-G. The PK parameters for intracellular ara-GTP were determined only on Day 1.

C. INTRINSIC FACTORS

22. What intrinsic factors influence exposure or response to the drug? What is the impact of these factors on exposure and response?

The combined data from the Phase 1 Studies following IV infusion of nelarabine at dose levels ranging from 104-2900 mg/m² were analyzed (by the reviewer) to determine the effect of intrinsic factors such as body surface area (BSA), height (HT), weight (WT), age, gender, race, and renal categories on clearance and steady state volume of distribution for nelarabine and ara-G and dose-normalized C_{max} and AUC₀₋₂₄ for Intracellular ara-GTP (normalized to nelarabine dose). The database includes 101 adult patients (68 males and 33 females) and 25 pediatric patients (16 males and 9 females). Patients ranged in age from 3.0-83 years. There were 90 Caucasians, 22 African Americans, 5 Hispanics, 1 Asian, and 8 Others. Patients had calculated creatinine clearance (CrCL) values ranging from 31-363 mL/min and an adequate baseline hepatic function as demonstrated by hepatic transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] of 3 x upper limit of normal and bilirubin of 1.5 mg/dL.

Effect of BSA, HT, and WT:

Ara-G apparent clearance (CL/F) and steady state volume of distribution (V_{SS}/F) are strongly correlated with BSA, HT, and WT (p < 0.05); while nelarabine clearance (CL) and steady state volume of distribution (V_{SS}) are not correlated with these intrinsic factors (p > 0.05) as shown from the equations below:

Nelarabine CL=195+97.12*BSA	[r=0.062, p=0.529]
Nelarabine CL= -281+3.88*HT	[r=0.142, P=0.143]
Nelarabine CL= 239+2.52*WT	[r=0.075, p=0.428]
Nelarabine V _{SS} =91.8+146.3*BSA	[r=0.093, p=0.337]
Nelarabine V _{SS} =-490+5.04*HT	[r=0.187, p=0.054]
Nelarabine V _{SS} =227+2.15*WT	[r=0.074, p=0.436]
Ara-G CL/F =0.352 + 10.6*BSA	[r= 0.467, p=0.0000]
Ara-G CL/F =-12.2 + 0.186 HT	[r=0.454, p=0.0000]
Ara-G CL/F=7.7+0.164*WT	[r=0.430, p=0.0000]
Ara-G V _{SS} /F=-40.5+69.5*BSA	[r=0.568, p=0.0000]
Ara-G V _{SS} /F=-127+1.25*HT	[r=0.565, p=0.0000]
Ara-G V _{SS} /F=7.5+1.1*WT	[r=0.523, p=0.0000]

Dose-normalized C_{max} and AUC₀₋₂₄ of ara-GTP are not related to BSA, HT, or WT (P > 0.05):

Ara-GTP C_{max} /nelarabine Dose=157-47.4*BSA [r=0.122, P=0.392]
Ara-GTP AUC_{0-24} /nelarabine Dose=5786-2073*BSA [r=0.159, p=0.265]

Ara-GTP C_{max} /nelarabine Dose=284-1.25*HT [r=0.136, P=0.341]
Ara-GTP AUC_{0-24} /nelarabine Dose=11220-54*HT [r=0.175, p=0.221]

Ara-GTP C_{max} /nelarabine Dose=115-0.63*WT [r=0.115, P=0.414]
Ara-GTP AUC_{0-24} /nelarabine Dose=3894-26.8*WT [r=0.147, p=0.299]

Effect of Age:

In the adult patients, age has no effect on the mean clearance or volume of distribution values for both nelarabine and ara-G ($p > 0.05$). Age has no effect on dose-normalized C_{max} and AUC_{0-24} values for ara-GTP ($p > 0.05$).

Fig. 13

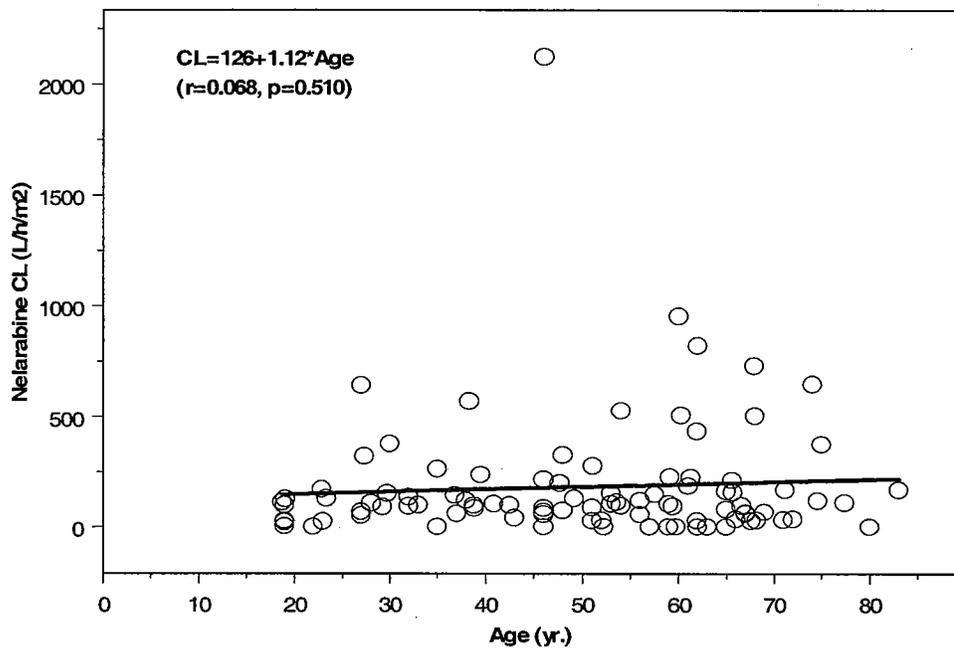


Fig. 14

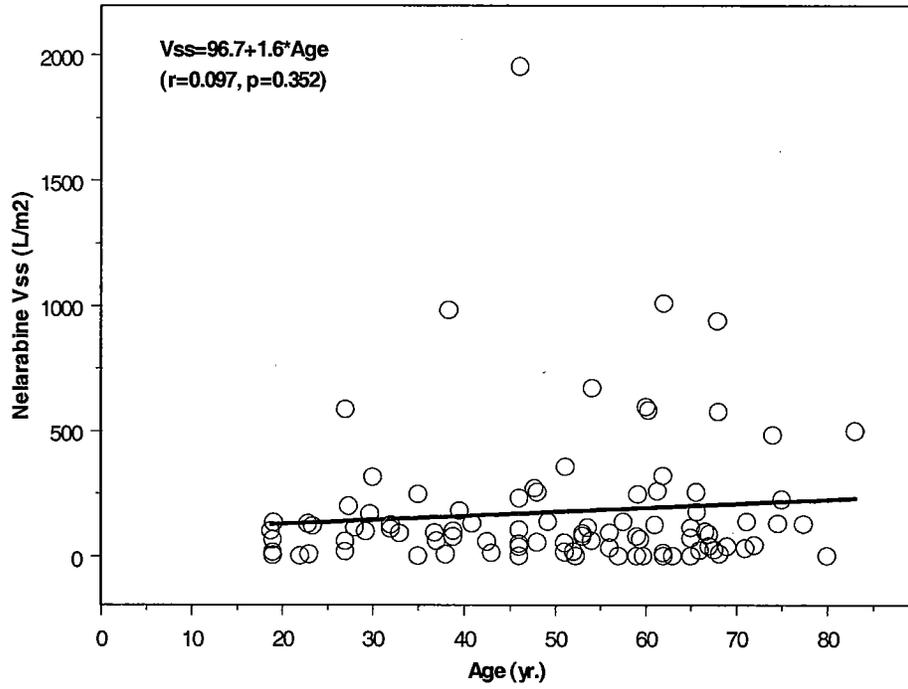


Fig. 14

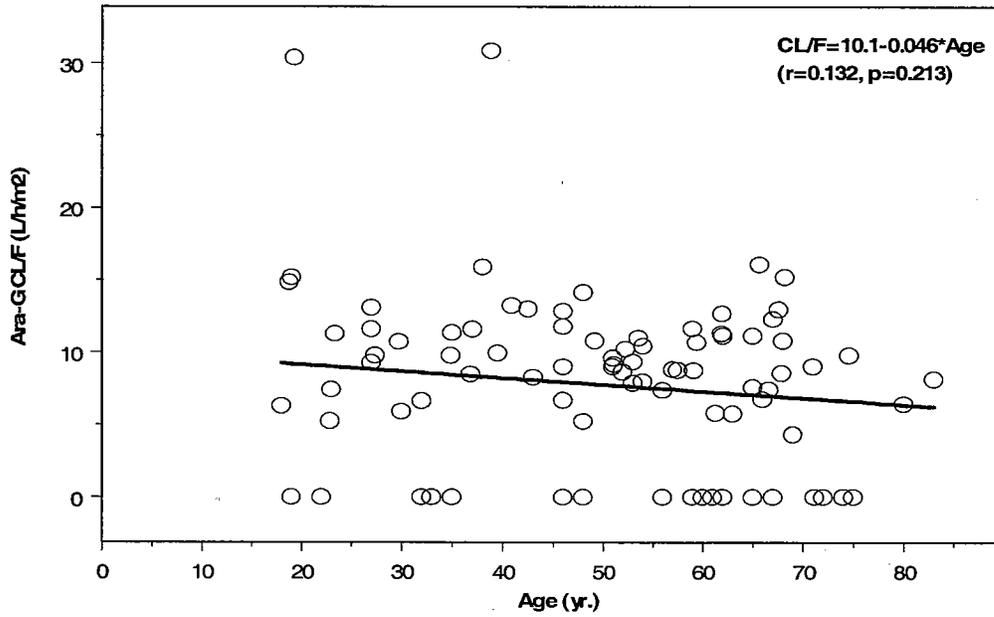


Fig. 15

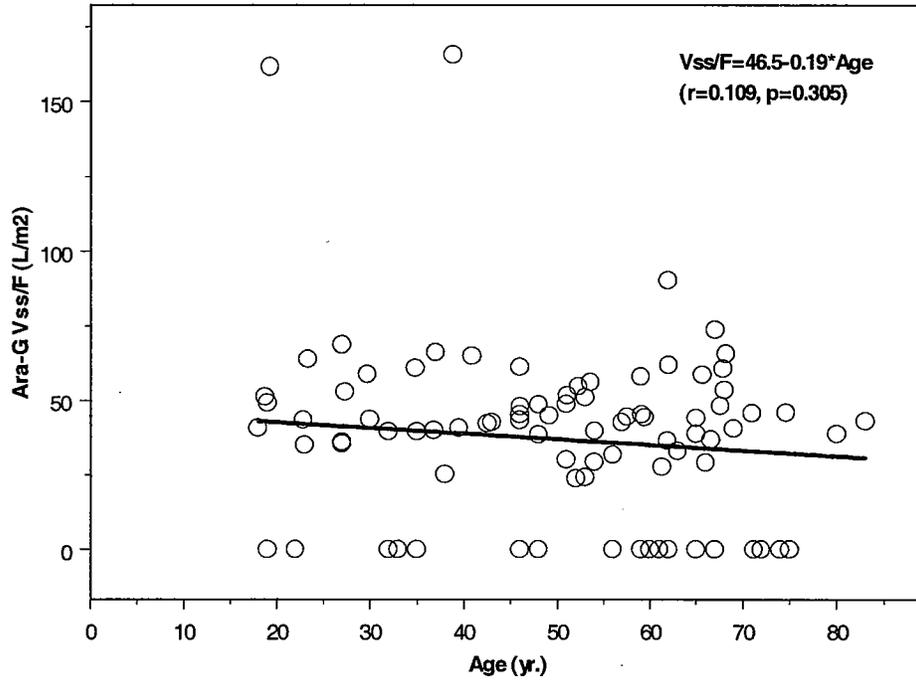


Fig. 16

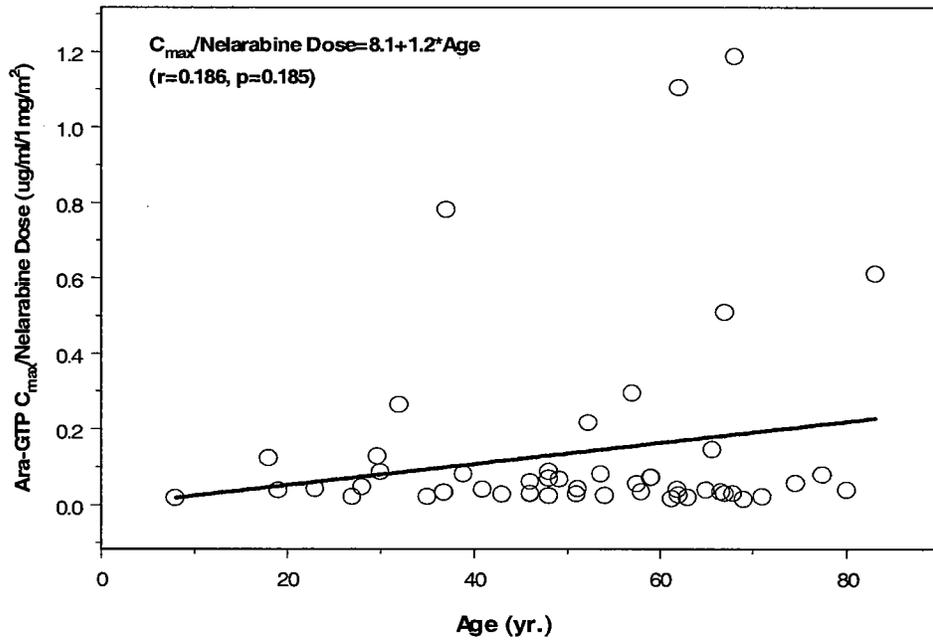
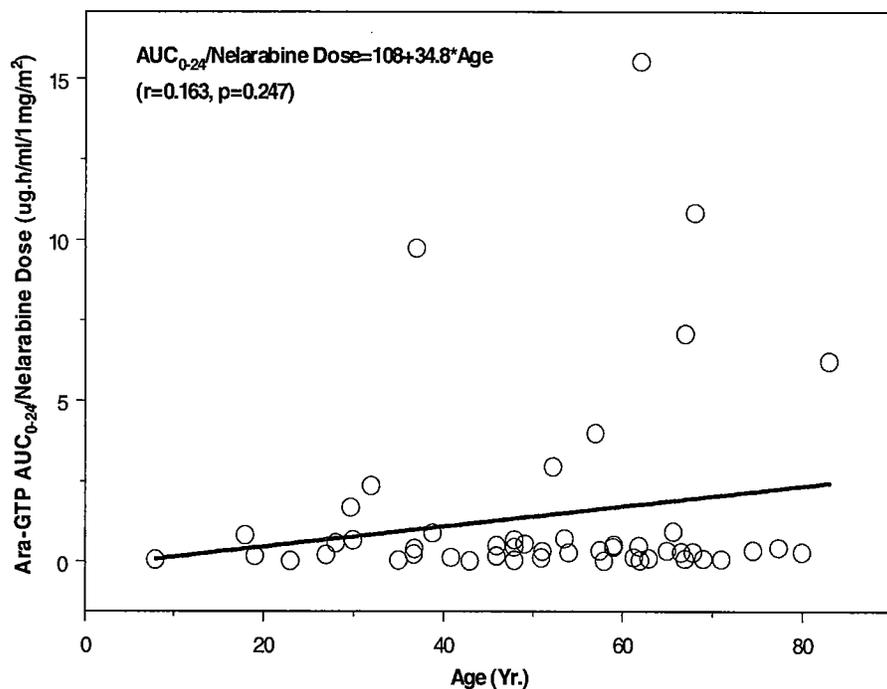


Fig. 17



Effect of Gender:

Gender has no effect on the mean clearance or volume of distribution values for both nelarabine and ara-G whether in all patients (adult or in pediatrics) ($P > 0.05$).

Table 17. Mean±SD CL and V_{SS} Versus Gender for Nelarabine

Parameter	Females	Males	p-value
All Patients (n=42 Females and 84 Males)			
CL (L/h/ m ²)	189±354	194±278	0.450
V _{SS} (L/ m ²)	169±338	185±272	0.374
Adult Patients (n=33 Females and 68 Males)			
CL (L/h/ m ²)	201±390	172±199	0.316
V _{SS} (L/ m ²)	192±373	168±223	0.349
Pediatric Patients (n=9 Females and 16 Males)			
CL (L/h/ m ²)	145±150	284±474	0.193
V _{SS} (L/ m ²)	78±85	253±413	0.111

*(Student's t-test, 1-tailed distribution, and 2 samples of equal variance)

Table 18. Mean±SD CL/F and V_{ss}/F Versus Gender for Ara-G

Parameter	Females	Males	p-value
All Patients (n=42 Females and 84 Males)			
CL/F (L/h/ m ²)	7.7±5.4	7.9±6.4	0.445
V _{ss} /F (L/ m ²)	31±21	34±29	0.341
Adult Patients (n=33 Females and 68 Males)			
CL/F (L/h/ m ²)	7.2±4.3	7.6±7.1	0.252
V _{ss} /F (L/ m ²)	35±22	38±33	0.318
Pediatric Patients (n=9 Females and 16 Males)			
CL/F (L/h/ m ²)	8.8±6.9	8.1±6.6	0.269
V _{ss} /F (L/ m ²)	23±16	23±17	0.465

*(Student's t-test, 1-tailed distribution, and 2 samples of equal variance)

Dose normalized C_{max} and AUC₀₋₂₄ for ara-GTP were 2.5-fold and 3.7-fold higher, respectively, in adult female than in adult male patient (p < 0.05). No data are available in pediatric patients to make a comparison.

Table 18. Mean±SD Dose-Normalized C_{max} and AUC₀₋₂₄ Versus Gender for Ara-GTP

Parameter	Females	Males	p-value
Adult Patients (n=15 Females, n=35 Males)			
C _{max} /Dose (ng/ml/mg/m ²)	86±116	35±76	0.033
AUC ₀₋₂₄ /Dose (ng.h/ml/mg/m ²)	2979±4493	807±2006	0.009
Pediatric Patients (n=1)			
C _{max} /Dose (ng/ml/mg/m ²)	--	6.3	█
AUC ₀₋₂₄ /Dose (ng.h/ml/mg/m ²)	--	42.5	█

*(Student's t-test, 1-tailed distribution, and 2 samples of equal variance)

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Table 18. Mean±SD Dose-Normalized C_{max} and AUC₀₋₂₄ Versus Gender for Ara-GTP

Parameter	Females	Males	p-value
Adult Responders (n=6/15 Females and 9/35 Males)			
C _{max} /Dose (ng/ml/mg/m ²)	190±126	95±140	0:075
AUC ₀₋₂₄ /Dose (ng.h/ml/mg/m ²)	3185±5041	2278±3729	0:060
Incidence of Neurotoxicity (of any grade) in Adult Patients (n=5/15 Females and 15/35 Males)			
C _{max} /Dose (ng/ml/mg/m ²)	117±113	63±118	0:171
AUC ₀₋₂₄ /Dose (ng.h/ml/mg/m ²)	4135±4125	1532±3103	0:065

*(Student's t-test, 1-tailed distribution, and 2 samples of equal variance)

Although adult Female Responders had 2.0-fold and 1.4-fold higher C_{max}/dose and AUC₀₋₂₄/dose for ara-GTP, respectively, than adult Male Responders, the differences were not statistically significant (p > 0.05).

Although adult females who experienced neurotoxicity had also 2.0-fold and 2.7-fold higher C_{max}/dose and AUC₀₋₂₄/dose for ara-GTP, respectively, than adult males who experienced neurotoxicity, the differences were not statistically significant (p > 0.05).

Effect of Race

The followings are the results of the analyses of the combined PK data from the Phase 1 studies versus race:

Table 19. Mean±SD CL and V_{ss} Versus Race for Nelarabine

Parameter	Race Groups				
	Whites	Blacks	Hispanics	Asians	Others
All Patients					
	(n=90)	(n=22)	(n=5)	(n=1)	(n=8)
CL (L/h/ m ²)	218±343	147±185	110±77	60.3	88±103
V _{ss} (L/ m ²)	202±325	141±222	118±97	59.8	77±101
Adult Patients					
	(n=74)	(n=17)	(n=4)	(n=1)	(n=5)
CL (L/h/ m ²)	202±305	136±195	114±88	60.3	95±145
p-value		0:202			
V _{ss} (L/ m ²)	196±303	132 239	123±111	59.8	84±139
p-value		0:210			

Pediatric Patients					
	(n=16)	(n=5)	(n=1)	(n=0)	(n=3)
CL (L/h/m ²)	288±477	188±150	93	--	80±72
p-value		0.296			
V _{ss} (L/m ²)	229±418	178±141	95	--	70±78
p-value		0.359			

Table 20. Mean±SD CL/F and V_{ss}/F Versus Race for Ara-G

Parameter	Race Groups				
	Caucasians	African Americans	Hispanics	Asians	Others
All Patients					
	(n=90)	(n=22)	(n=5)	(n=1)	(n=8)
CL/F (L/h/m ²)	7.1±5.5	10.3±7.5	10.0±3.1	11.5	8.3±7.2
V _{ss} /F (L/m ²)	29±22	38±35	39±5.6	66	34±37
Adult Patients					
	(n=74)	(n=17)	(n=4)	(n=1)	(n=5)
CL/F (L/h/m ²)	7.0±5.0	9.8±7.4	8.2±4.1	11.5	10.8±11.6
p-value		0.031			
V _{ss} /F (L/m ²)	33±23	44±39	44±0.42	66	55±62
p-value		0.075			
Pediatric Patients					
	(n=16)	(n=5)	(n=1)	(n=0)	(n=3)
CL/F (L/h/m ²)	7.2±6.3	11.3±8.2	11.7	--	7.1±3.9
p-value		0.149			
V _{ss} /F (L/m ²)	22±18	26±18	34.1	--	23.5±12.5
p-value		0.344			

Because most patients were Caucasians and because there is a high variability in the database; it was hard to compare between the Caucasian group and other race groups.

In adult patients, nelarabine mean clearance and volume of distribution values were lower in African Americans than in Caucasians (by 33% for both values). The opposite is true for are-G; mean apparent clearance and volume of distribution values were higher in African Americans than in Caucasians (by about 40% and 33%, respectively).

In pediatric patients, nelarabine mean clearance and volume of distribution values were 35% and 22% lower, respectively, in African Americans than in Caucasians. Are-G; mean apparent clearance and volume of distribution are 57% and 18% higher, respectively, in African Americans than in Caucasians.

Table 20. Mean±SD CL/F and V_{ss}/F Versus Race for Ara-GTP

Parameter	Race Groups				
	Caucasians	African Americans	Hispanics	Asians	Others
Adult Patients					
	(n=38)	(n=7)	(n=1)	(n=1)	(n=4)
C _{max} /Dose (ng/ml/mg/m ²)	39±75	102±146	13.6	282	14.7±7.4
p-value		0.049			
AUC ₀₋₂₄ /Dose (ng.h/ml/mg/m ²)	997±2054	3651±5805	320	9719	117±208
p-value		0.016			
Pediatric Patients					
	(n=1)	(n=0)	(n=0)	(n=0)	(n=0)
C _{max} /Dose (ng/ml/mg/m ²)	6.3	--	--	--	--
AUC ₀₋₂₄ /Dose (ng.h/ml/mg/m ²)	42.5	--	--	--	--

Mean dose-normalized C_{max} and AUC₀₋₂₄ for ara-GTP were 2.5-fold and 3.7-fold higher, respectively, in African Americans than in Caucasians (p < 0.05).

Table 18. Mean±SD Dose-Normalized C_{max} and AUC₀₋₂₄ Versus Race for Ara-GTP

Parameter	African Americans	Caucasian	p-value
Adult Responders (n=3/7 African Americans and 8/38 Caucasian)			
C _{max} /Dose (ng/ml/mg/m ²)	225±156	123±137	0.159
AUC ₀₋₂₄ /Dose (ng.h/ml/mg/m ²)	4697±6667	3368±3613	0.069
Incidence of Neurotoxicity (of any grade) in Adult Patients (n=2/7 and 17/38 Males)			
C _{max} /Dose (ng/ml/mg/m ²)	97±121	69±117	0.342
AUC ₀₋₂₄ /Dose (ng.h/ml/mg/m ²)	3639±4833	1762±3083	0.189

African Americans who responded to nelarabine therapy had 1.8-fold and 1.4-fold higher mean dose-normalized C_{max} and AUC₀₋₂₄ for ara-GTP, respectively, than Caucasians who responded to nelarabine therapy (p > 0.05).

Mean dose-normalized C_{max} and AUC₀₋₂₄ were 1.4-fold and 2.1-fold higher, respectively, in adult African Americans who experienced neurotoxicity than adult Caucasians who also experienced neurotoxicity (p > 0.05).

Effect of Renal Impairment

The Applicant has not evaluated the effect of renal impairment on the pharmacokinetics of nelarabine or ara-G. The following results are obtained from the analyses of

combined data from the Phase 1 studies in adult patients who ranged in creatinine clearance (CrCL) from 31-200 mL/min. Adult Patients were categorized into three groups: normal with CrCl of > 80 mL/min (n=68), mild with CrCl=50-80 mL/min (n=27), and moderate with CrCl < 50 mL/min (n=3). Pediatric patients ranged in CrCL from 69-363 ml/min).

Table 21. Mean±SD CL and V_{SS} for Nelarabine in Adult Patients

Parameter	Renal Groups		
	Normal (n=68)	Mild (n=27)	Moderate (n=3)
*CrCL (mL/min)	115 (82-200)	67 (50-79)	47 (31-49)
CL (L/h/ m ²)	169±288	215±265	195±264
p-value		0.127	0.323
V _{SS} (L/ m ²)	157±276	221±308	218±251
p-value		0.118	0.210

*Median (Range)

Table 22. Mean±SD CL/F and V_{SS}/F for Ara-G in Adult Patients

Parameter	Renal Groups		
	Normal (n=68)	Mild (n=27)	Moderate (n=3)
*CrCL (mL/min)	115 (82-200)	67 (50-79)	47 (31-49)
CL/F (L/h/ m ²)	9.0±6.2	5.8±5.1	4.05±3.8
p-value		0.013	0.042
V _{SS} /F (L/ m ²)	42±31	29±26	23±21
p-value		0.045	0.099

*Median (Range)

In adult patients, no trend is observed for the change in nelarabine mean clearance and volume of distribution with the degree of renal impairment. The mean apparent clearance of ara-G (CL/F) decreased by 35% and 55% in adult patients with mild and moderate renal impairment, respectively, compared to adult patients with normal renal function. The mean volume of distribution of ara-G (V_{SS}/F) was 30% and 45% lower in patients with mild and moderate renal impairment, respectively, than in patients with normal renal function.

Table 21. Mean±SD CL and V_{ss} for Nelarabine in Pediatric Patients

Parameter	Renal Groups	
	Normal (n=21)	Mild (n=1)
*CrCL (mL/min)	146 (88-363)	69
CL (L/h/ m ²)	267±417	89.4
V _{ss} (L/ m ²)	220±365	52.2

Table 22. Mean±SD CL/F and V_{ss}/F for Ara-G in Pediatric Patients

Parameter	Renal Groups	
	Normal (n=21)	Mild (n=0)
*CrCL (mL/min)	146 (88-363)	--
CL/F (L/h/ m ²)	8.3±6.2	--
V _{ss} /F (L/ m ²)	31.3±11.6	--

*Median (Range)

No comparison could be made in pediatric patients as most of patients had normal renal function with CrCL values ranging from 88-363 ml/min. Only one patient had mild renal impairment with a CrCL value of 69 ml/min.

Table 22. Mean±SD CL/F and V_{ss}/F for Ara-GTP in Adult Patients

Parameter	Renal Groups		
	Normal (n=32)	Mild (n=15)	Moderate (n=3)
*CrCL (mL/min)	115 (82-200)	67 (50-79)	47 (31-49)
C _{max} /Dose (ng/ml/mg/m ²)	97±206	230±336	222±335
p-value		0.047	0.164
AUC ₀₋₂₄ /Dose (ng.h/ml/mg/m ²)	839±1934	2818±4728	2189±3477
p-value		0.021	0.135

*Median (Range)

The mean dose-normalized C_{max} and AUC₀₋₂₄ values for ara-GTP were 2.3-fold and 3.4-fold higher, respectively, in patients with mild renal impairment than in patients with normal renal function (p < 0.05). Patients with moderate renal impairment had 2.3-fold and 2.6-fold higher mean dose-normalized C_{max} and AUC₀₋₂₄ values than patients with normal renal function (p > 0.05). No data available were available for ara-GTP in pediatric patients (only one male, Caucasian, pediatric patient of 8 years with normal renal function (CrCL= 173.25 ml/min).

Effect of Hepatic Impairment

The Applicant has not evaluated the effect of hepatic impairment on the pharmacokinetics of nelarabine or ara-G. Patients enrolled in the Phase 1 studies and pivotal Phase 2 studies had adequate baseline hepatic function as demonstrated by hepatic transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] of 3 x upper limit of normal and bilirubin of 1.5 mg/dL.

23. Based on what is known about exposure-response relationships, what dosage regimen adjustments, if any, are recommended for each subgroup listed below?

Geriatrics

Age has no effect on the clearance of nelarabine or ara-G; no dosing adjustment is required for ARRANON in elderly patients with T-ALL and T-LBL.

Pediatrics

Pediatric patients tend to have higher nelarabine clearance (by 30%) and higher volume of distribution (by 10%) than adult patients; however, these differences are not statistically significant ($p=0.212$ and $p=0.391$, respectively). The apparent clearance of ara-G is comparable between the two groups ($p=0.428$) and its apparent steady state of distribution is significantly lower (by 38%) in pediatric patients than in adult patients ($p=0.001$).

Table 23. Comparison of Clearance and Volume of Distribution Values in Pediatric and adult Patients (Mean±SD)

Parameter	Pediatric Patients (n=25)	Adult Patients (101)	p-value
Nelarabine			
CL (L/h/ m ²)	237±397	182±277	0.212
V _{SS} (L/ m ²)	195±347	176± 281	0.391
Ara-G			
CL/F (L/h/ m ²)	7.9±6.3	7.8±6.0	0.428
V _{SS} /F (L/ m ²)	23±17	37±30	0.001
Ara-GTP			
C _{max} /Dose (ng/ml/mg/m ²)	6.3 (n=1)	51±92 (n=50)	■
AUC ₀₋₂₄ /Dose (ng.h/ml/mg/m ²)	42.5 (n=1)	1459±3105 (n=50)	■

*(Student's t-test, 1-tailed distribution, and 2 samples of equal variance)

Patients with Renal Impairment

The mean apparent clearance of ara-G is 35% and 55% lower in adult patients with mild and moderate renal impairment, respectively, than in adult patients with normal renal

function. At the present time, no dosage adjustment recommendation can be made for patients with mild to moderate renal impairment (creatinine clearance > 30 mL/min). Patients with severe renal impairment (creatinine clearance < 30 mL/min) were excluded from the Phase 1 studies and from the pivotal Phase 2 studies. We recommend that patients with severe renal impairment (creatinine clearance < 30 mL/min) should be closely monitored for neurotoxicity.

Patients with Hepatic Impairment

The Applicant has not evaluated the pharmacokinetics of nelarabine or ara-G in patients with hepatic impairment. We recommend that patients with severe hepatic impairment (serum bilirubin > 3.0 mg/dl) should be closely monitored for neurotoxicity.

24. What pregnancy and lactation use information is there in the application?

There are no clinical studies of ARRANON in pregnant women. In rabbits, nelarabine caused increased incidences of fetal malformations, anomalies, and variations when given as 8-hour infusion at doses of 354 mg/ m²/day (approximately 24% of the adult dose on a mg/m² basis) during days 7-19 of gestation. The package insert mentions that women of child-bearing potential should be advised to avoid becoming pregnant while receiving treatment with ARRANON.

D. EXTRINSIC FACTORS

Drug-drug interactions

25. Is the drug a substrate of CYP enzyme(s)?

Nelarabine and ara-G are not substrates for cytochrome (CYP) P450 enzymes.

26. Is the drug an inhibitor and/or an inducer of CYP enzymes?

In vitro studies with human liver microsomes produced IC₅₀ values for both nelarabine and ara-G of > 100 µM (> 30 µg/ml), indicating that nelarabine or ara-G have no inhibition activity on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 enzymes (Report CD2004/01142/00). Thus, the potential for drug-drug interactions between nelarabine or ara-G and drugs that are substrates of these enzymes is unlikely. Results are shown in Table 24.

Table 24; Metabolism-Dependent Inhibition of CYP Activities by Nelarabine

CYP Enzyme	Substrate	Nelarabine		Positive Control Inhibitor	Positive Control	
		IC ₅₀ (μ M)			IC ₅₀ (μ M)	
		Control Pre-inc ¹	NADPH Pre-inc ²		Control Pre-inc ¹	NADPH Pre-inc ²
1A2	Phenacetin	>100	>100	Furafylline	2.8	0.16
2A6	Coumarin	>100	>100	None	ND	ND
2B6	Bupropion	>100	>100	None	ND	ND
2C8	Paclitaxel	>100	>100	None	ND	ND
2C9	Diclofenac	>100	>100	Tienilic Acid	2.4	0.35
2C19	S-mephenytoin	>100	>100	Ticlopidine	1.2	0.50
2D6	Bufuralol	>100	>100	Paroxetine	2.5	0.38
3A4	Atorvastatin	>100	>100	Troleandomycin	33	2.9
3A4	Midazolam	>100	>100	Troleandomycin	14	1.2
3A4	Nifedipine	>100	>100	Troleandomycin	29	5.0

1. Microsomes, buffer and nelarabine were pre-incubated for 20 minutes with probe substrate prior to initiation of reaction by addition of NADPH

2. Microsomes, buffer and nelarabine were pre-incubated for 20 minutes with NADPH prior to initiation of reaction by addition of probe substrate

ND – Not Determined

Table 25; Metabolism-Dependent Inhibition of CYP Activities by Ara-G

CYP Enzyme	Substrate	Ara-G		Positive Control Inhibitor	Positive Control	
		IC ₅₀ (μ M)			IC ₅₀ (μ M)	
		Control Pre-inc ¹	NADPH Pre-inc ²		Control Pre-inc ¹	NADPH Pre-inc ²
1A2	Phenacetin	>100	>100	Furafylline	2.8	0.16
2A6	Coumarin	>100	>100	None	ND	ND
2B6	Bupropion	>100	>100	None	ND	ND
2C8	Paclitaxel	>100	>100	None	ND	ND
2C9	Diclofenac	>100	>100	Tienilic Acid	2.4	0.35
2C19	S-mephenytoin	>100	>100	Ticlopidine	1.2	0.50
2D6	Bufuralol	>100	>100	Paroxetine	2.5	0.38
3A4	Atorvastatin	>100	>100	Troleandomycin	33	2.9
3A4	Midazolam	>100	>100	Troleandomycin	14	1.2
3A4	Nifedipine	>100	>100	Troleandomycin	29	5.0

1. Microsomes, buffer and ara-G were pre-incubated for 20 minutes with probe substrate prior to initiation of reaction by addition of NADPH

2. Microsomes, buffer and ara-G were pre-incubated for 20 minutes with NADPH prior to initiation of reaction by addition of probe substrate

ND – Not Determined

27. Is the drug a substrate and/or inhibitor of P-glycoprotein (P-gp) transporter processes?

Nelarabine and ara-G are neither substrates nor inhibitors of the human P-gp efflux transporter.

P-gp Substrate Studies: *In vitro* transport studies with MDCKII-MDR1 cell monolayers were conducted to determine if [¹⁴C]-nelarabine and [¹⁴C]-ara-G are substrates of P-gp

efflux transporter in the presence and absence of a potent inhibitor of P-gp, GF120918A, and using [³H]-amprenavir as a positive control (Report RD2004/00140/00). Efflux rates and efflux ratios of [¹⁴C]-nelarabine, [¹⁴C]-ara-G and [³H]-amprenavir in the presence and absence of GF120918A are shown in the table below:

Table 26. Results of P-glycoprotein Transport Studies for [¹⁴C]-Nelarabine and [¹⁴C]-ara-G

Compound	Rate A→B ¹	Rate B→A	Apical efflux ratio ²
[¹⁴ C]-Nelarabine (3 μM)	0.34 ± 0.02	0.34 ± 0.01	1.0
[¹⁴ C]-Nelarabine (3 μM)+ GF120918A (2 μM)	0.18±0.04	0.15±0.02	0.8
[¹⁴ C]-ara-G (3 μM)	0.21 ± 0.04	0.19 ± 0.02	0.9
[¹⁴ C]-ara-G (3 μM)+GF120918A (2 μM)	0.15±0.03	0.17±0.07	1.1
[³ H]-Amprenavir ⁴ (3 μM)	0.45 ± 0.01	7.82± 0.94	17
[³ H]-Amprenavir (3 μM)+ GF120918A (2 μM)	3.4±0.4	3.9±0.1	1.2

1. Data is the mean ± standard deviation from 3 monolayers. Rates are in pmol/min/cm².

2. Defined as B→A / A→B. Compounds classified as a Pgp substrate if apical efflux ratio ≥ 2.0.

3. Amprenavir was used as positive control (apical efflux ratio for amprenavir >15).

P-gp Inhibition Studies: *In vitro* transport studies with MDCKII-MDR1 cell monolayers were conducted to assess the ability of nelarabine and ara-G to inhibit P-gp by determining the basolateral to apical [B→A] transport of [³H]-digoxin (27 nM) in the absence or presence of either drug (0.3-100 μM) and using GF120918A (2 μM), as the positive control for Pgp inhibition (RD2004/00254/00). Results are shown below:

Table 27. Effect of Nelarabine on P-gp-Mediated Transport of [³H]-Digoxin

Compound	Conc (μM)	Digoxin Transport Rate (pmol/hr/cm ²) ¹	SD	Transport Rate (%control)	SD
	0	1.64	0.03	100	1.9
Nelarabine	0.3	1.50	0.09	91.7	5.4
	0.5	1.67	0.18	102	11
	1	1.62	0.30	99.0	18.6
	3	1.52	0.15	93.0	9.0
	5	1.54	0.18	94.0	10.8
	10	1.62	0.06	98.9	3.4
	30	1.64	0.23	100	14
	50	1.58	0.04	96.3	2.3
	100	1.58	0.03	95.1	1.5
GF120918A ²	2	0.41	0.02	24.7	1.3

1. Mean ± standard deviation from 3 monolayers.

2. Positive control

Table 28. Effect of Ara-G on P-gp-Mediated Transport of [³H]-Digoxin

Compound	Conc (μM)	Digoxin Transport Rate (pmol/hr/cm ²) ¹	SD	Transport Rate (%control)	SD
	0	1.64	0.03	100	1.9
Ara-G	0.3	1.70	0.04	104	2.6
	0.5	1.52	0.19	92.7	11.6
	1	1.55	0.07	94.6	4.1
	3	1.70	0.12	104	7.4
	5	1.54	0.04	93.9	2.5
	10	1.53	0.15	93.0	9.0
	30	1.64	0.06	100	3.4
	50	1.68	0.13	102	1.8
	100	1.63	0.20	99.4	12.4
GF120918A ²	2	0.41	0.02	24.7	1.3

1. Mean ±SD from 3 monolayers

2. Positive control

28. Are there other metabolic/transporter pathways that may be important?

No data are available indicating that other metabolic/transporter pathways may be important for nelarabine and ara-G.

29. Does the product's label specify co-administration of another drug, and, if so, has the interaction potential between these drugs been evaluated?

The effect of fludarabine on the pharmacokinetics of nelarabine, ara-G, and ara-GTP was evaluated in 12 patients with refractory leukemia (Study PGAA1005). Patients received nelarabine 1200 mg/m² IV over 2 hours on Days 1, 3, and 5. Fludarabine 30 mg/m² was administered 4 hours before nelarabine infusion over 30 minutes on Days 3 and 5 in course 1 and on Days 1, 3, and 5 on the second course. The results of this study are summarized below:

Table 29. Mean±SD (%CV) Non-Compartmental PK Parameters after Nelarabine Infusion

Parameter	Day 1 (Nelarabine Alone)	Day 3 (Nelarabine+ Fludarabine)
Nelarabine (n=12)		
C _{max} (μg/ml)	5.5±3.2	5.3±2.4
AUC _{0-∞} (μg.h/ml)	10.9, 12.7 (n=2)	ND
CL (L/h/m ²)	104, 116 (n=2)	ND
V _{ss} (L/m ²)	125, 140 (n=2)	ND
t _{1/2} (h)	0.36, 0.57 (n=2)	ND
Ara-G (n=8)		
C _{max} (μg/ml)	22.5 ±5.0	25.5±5.5
*T _{max} (h)	2.0 (1.0-2.5)	2.1 (2.0-2.4)
AUC _{0-∞} (μg.h/ml)	117±24	125±16
CL/F (L/h/m ²)	11.6±3.2	10.7±2.8
V _{ss} /F (L/m ²)	72±25	60±12
t _{1/2} (h)	5.0±1.8	4.8±2.1

Ara-GTP (n=12)		
C _{max} (µg/ml)	169±190	269±315
*T _{max} (h)	9.1 (2.0-25)	5.7 (2.2-26)
AUC ₀₋₂₄ (µg.h/ml)	3157±3591	4724±6375

*Median (Range) ND=Not determined

Nelarabine C_{max} was comparable whether is given alone or in combination with fludarabine. Other nelarabine PK parameters could not be compared because of inadequate number of patients either alone or in the presence of fludarabine.

Ara-G PK parameters were comparable whether nelarabine is administered alone or in combination with fludarabine.

Fludarabine affects the intracellular accumulation of ara-GTP. Mean C_{max} and AUC₀₋₂₄ of Ara-GTP increased by about 60% and 50%, respectively, when nelarabine was administered in combination with fludarabine.

The package insert indicate

As ara-GTP is the active moiety, this increase may result in an increase in the response and neurotoxicity to nelarabine when is given in combination with fludarabine.

30. What other co-medications are likely to be administered to the target patients population? What drug-drug interaction information is available for these comedications?

In the pivotal Phase 2 studies (Studies PGAA2001 and PGAA2002), patients were permitted to receive supportive care therapy, including transfusions of blood and blood products, antibiotics and anti-emetics. No records in the study reports were found on which drugs were given concomitantly with nelarabine during these studies.

31. Are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are coadministered?

None

32. Are there any medications that should be contraindicated in patients receiving the drug?

Undetermined

33. Are there other drugs that may have a significant pharmacokinetic interaction when coadministered with the drug?

Undetermined

34. Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or plasma protein binding?

None

35. What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?

None

E. GENERAL BIOPHARMACEUTICS

36. Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

NOT APPLICABLE

37. What is the composition of the to-be-marketed formulation?

The drug product, Nelarabine Injection, 5 mg/mL is a clear, colorless injection solution containing 5 mg of nelarabine per milliliter filled into a Type I, clear glass vial with a gray rubber stopper and aluminum seal. The components and quantitative composition of Nelarabine Injection, 5 mg/mL, is shown below:

Table 30. Qualitative/quantitative composition of Nelarabine Injection

Component	Quantity (mg/mL)	Function
Nelarabine	5	Active
Sodium Chloride	4.5	-
Water for Injection (WFI)	q.s.	Solvent/vehicle
Total unit dose	1.0 mL	-

38. What is the *in vivo* relationship of the proposed commercial formulation to the pivotal trial formulation in terms of comparative exposure?

NOT APPLICABLE

39. What is the effect of food on the bioavailability of the drug and what dosing recommendations should be made regarding administration in relation to meals?

NOT APPLICABLE

40. Has the Applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?

NOT APPLICABLE

F. ANALYTICAL SECTION

41. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Nelarabine and ara-G in plasma and urine samples and ara-GTP in leukemia blast cells were the drug-related moieties that were measured in the Phase 1 studies.

42. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Nelarabine and ara-G are not highly bound to human plasma proteins (<25%). Total drug concentrations (free+unbound) for both nelarabine and ara-G were measured in human plasma and urine samples.

43. What bioanalytical methods are used to assess drug concentrations?

Nelarabine and Ara-G:

Plasma and urine samples were analyzed for nelarabine and ara-G using a validated high performance liquid chromatography (HPLC) assay method. Blood samples were collected into EDTA Vacutainer tubes containing [redacted] to prevent further conversion of nelarabine to ara-G after blood sample collection. Blood samples were extracted [redacted] to precipitate the proteins. The tubes were then centrifuged and plasma extracts were [redacted] to measure nelarabine and ara-G. Urine samples were analyzed directly (i.e., without extraction) for nelarabine and ara-G using HPLC at [redacted] nm.

Intracellular Ara-GTP:

Intracellular ara-GTP in leukemia cells were analyzed using a validated HPLC assay method _____ at _____ nm. Briefly, after removal of plasma from the blood samples, the cell pellets were suspended in phosphate-buffered saline. The mononuclear cells were then isolated by _____ centrifugation and then extracted by _____ and extracts _____ for HPLC analyses.

44. What is the range of the standard curve? How does it relate to the requirements for clinical studies?

Plasma calibration curves were linear over the concentration range of _____ µg/ml for both nelarabine and ara-G (regression coefficients (r^2) not reported). Urine calibration curves were linear over the concentration range of _____ µg/ml for both nelarabine and ara-G (r^2 not reported).

In leukemia cell samples, calibration curves for ara-GTP were linear over the concentration range of _____ µg/ml ($r^2 =$ _____).

45. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The LLOQ was _____ µg/ml for both nelarabine and ara-G. The LLOQ was _____ µg/ml for ara-GTP.

46. What are the accuracy, precision, and selectivity at these limits?

The intra- and inter-day precisions (%CV) of quality control samples are shown below:

Table 31. Inter-Assay Precision and Inter-Assay Bias in Quality Controls Samples (Plasma)

Quality Controls (µg/ml)	Study No.	Inter-Assay Precision (%CV)	Inter-Assay Bias (%Bias)
Nelarabine			
/	PGAA1001	/	/
	PGAA1002	/	/
	PGAA1003	/	/
	PGAA1005	/	/
Ara-G			
/	PGAA1001	/	/
	PGAA1002	/	/
	PGAA1003	/	/
	PGAA1005	/	/

Table 32. Inter-Assay Precision and Inter-Assay Bias in Quality Controls Samples (Urine)

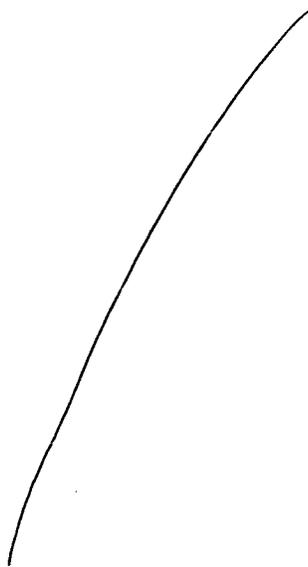
Quality Controls ($\mu\text{g/ml}$)	Study No.	Inter-Assay Precision (%CV)	Inter-Assay Bias (%Bias)
Nelarabine			
	PGAA1002		
	PGAA1003		
Ara-G			
	PGAA1002		
	PGAA1003		

No assay report was found for the analysis of intracellular ara-GTP in leukemia cells. The Applicant claims that the inter-day precision (%CV) and accuracy (% difference from nominal) of the assay was _____ respectively. An article by Rodriguez et al. [High-performance liquid chromatography method for the determination and quantitation of arabinosylguanine triphosphate (ara-GTP) and fludarabine triphosphate in human cells, J Chromatg B 745:421-430, 2000] reports that the intra-day precision in ara-GTP quality controls samples of 90 and 902 $\mu\text{g/ml}$ was 0.7 and 0.4%, respectively, and inter-day precision was 2% and 1%, respectively.

G. CLINICAL PHARMACOLOGY LABELING RECOMMENDATIONS

[SENTENCES ADDED ARE IN ITALIC AND IN BOLD, SENTENCES DELETED ARE DOUBLE-STRIKED]

CLINICAL PHARMACOLOGY



5 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

APPENDIX 1

Office of Clinical Pharmacology and Biopharmaceutics Pharmacometrics Review

NDA:	21-877
Compound:	Arranon® (nelarabine or 506U78) injection
Submission Dates:	4/29/05, 7/13/05, 7/22/05, 7/27/05, 8/2/05
Sponsor:	Glaxo Smith Kline
Pharmacometrics Reviewer:	Leslie Kenna, Ph.D.
Pharmacometrics Team Leader:	Joga Gobburu, Ph.D.

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EXECUTIVE SUMMARY

This review describes an exposure-response analysis performed to identify the predictor(s) of therapeutic and adverse responses to nelarabine. The analysis dataset includes pharmacokinetic, demographic, safety and efficacy data from Phase 1 and Phase 2 studies in adult and pediatric patients. The analysis suggests that exposure (AUC) to ara-GTP correlates with therapeutic response, while exposure (AUC) to nelarabine correlates with neurotoxicity. The analysis did not identify any useful predictor to individualize dosing for guarding against irreversible toxicity. It has been hypothesized that the wide variability in ara-GTP and nelarabine AUC may be explained by metabolic enzyme genotype. Therefore, there is merit in obtaining genotype information using the already available blood samples collected by the Sponsor.

RECOMMENDATION

It is recommended that the Sponsor evaluate whether any genotype data collected is predictive of nelarabine and/or ara-GTP exposure, and, consequently, safety and/or efficacy (see Comment, Page #3).

INTRODUCTION

Nelarabine is proposed as a treatment of adult and pediatric patients with T cell acute lymphoblastic leukemia (T-ALL) or T cell lymphoblastic lymphoma (T-LBL) who have relapsed following treatment with two chemotherapies. This is an orphan indication.

Nelarabine, a prodrug of the active compound ara-GTP, is demethylated to ara-G, which is then phosphorylated to ara-GTP. Ara-GTP is a deoxyguanosine analog; it leads to cell death by inhibiting DNA synthesis.

The primary endpoint for efficacy was Response Rate, where success (Complete Response) was defined with respect to bone marrow blast counts and peripheral blood counts. Survival and duration of response were also determined.

The Sponsor collected PK and safety data in four Phase 1 studies and evaluated efficacy in two Phase 2 studies (designs outlined below). Plasma concentrations of nelarabine and ara-G in adult and pediatric patients were determined primarily on Day 1 during the first course of therapy. Patients with circulating leukocyte blast counts $>10,000/\mu\text{L}$ had blood samples collected for the quantification of intracellular concentrations of ara-GTP.

Design of Phase 1 and Phase 2 Studies

PGAA1001: Phase 1 study

Nelarabine was administered as a 1-hour intravenous infusion at 5 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, 60 mg/kg, 75 mg/kg, 1000 mg/m², or 1200 mg/m² once daily for 5 consecutive days in adult and pediatric patients. A second course of therapy, 21 days after initiation of the first course of nelarabine therapy, was optional.

PGAA1002: Phase 1 study

Nelarabine was administered as a 2-hour intravenous infusion at 900, 1200, or 1500 mg/m² once daily for 3 consecutive days in adult patients. The regimen was repeated every 21 days.

PGAA1003: Phase 1 study

Nelarabine was administered as a 2-hour intravenous infusion at 1200, 1500, 1800, 2200, 2500, and 2900 mg/m² on a Day 1, 3, and 5 schedule in adult patients. The dosing schedule was repeated every 21 to 28 days.

PGAA1005: Phase 1 study

Nelarabine was administered as a 2-hour intravenous infusion at 1200 mg/m² on Days 1, 3, and 5. Fludarabine was administered 4 hours before the nelarabine infusion at a

dose of 30 mg/m² infused over 30 minutes on Days 3 and 5 in Course 1 and on Days 1, 3, and 5 on second and subsequent courses. The 5-day course was repeated every 21 to 28 days.

PGAA 2001: Phase 2 study

This Phase 2 study was conducted in pediatric patients with refractory or relapsed T-ALL or T-cell non-Hodgkin's lymphoma (TNHL). Nelarabine was administered as a 1 hour infusion once daily for 5 days on 21 day cycles. Doses of 400, 650, 900, 1200 mg/m² were administered.

PGAA 2002: Phase 2 study

This Phase 2 study was conducted in adults with refractory or relapsed T-ALL or T-LBL. Nelarabine was administered as a 2 hour infusion on 21 day cycles. Doses of 1500 mg/m² were administered on days 1, 3 and 5.

Dose Selection

Table 1 shows the percent of responders and percent of subjects reporting any neurotoxicity as a function of the dose administered during the Phase 1 studies. In this dataset, there is no evidence of a relationship between dose and therapeutic response, however, there is evidence suggesting that the incidence of neurotoxicity increases with dose. Note that the Sponsor selected the dose for the Phase 2 studies based on an analysis of the response and adverse event data collected in Phase 1.

Figure 1 shows the results in Table 1 graphically.

Dose	Response (CR or PR)	Neurotoxicity
Missing	5/10 (50%)	5/6 (83%)
0 - ≤500	3/9 (33%)	4/10 (40%)
>500 - ≤900	0	4/9 (44%)
>900 - ≤1000	9/24 (38%)	4/5 (80%)
>1000 - ≤1200	6/21 (29%)	14/25 (56%)
>1200 - ≤1500	5/23 (22%)	12/22 (55%)
>1500 - ≤2000	5/16 (31%)	20/23 (87%)
>2000 - ≤2500	0	15/17 (88%)
>2500	33/113 (29%)	5/5 (100%)

Table 1. Percent Response and Percent of Subjects with Neurotoxicity in Phase 1 Studies. Note that the data for Study PGAA1005 was not included in the analysis of

response or adverse events since responses would be confounded by Fludarabine exposure.

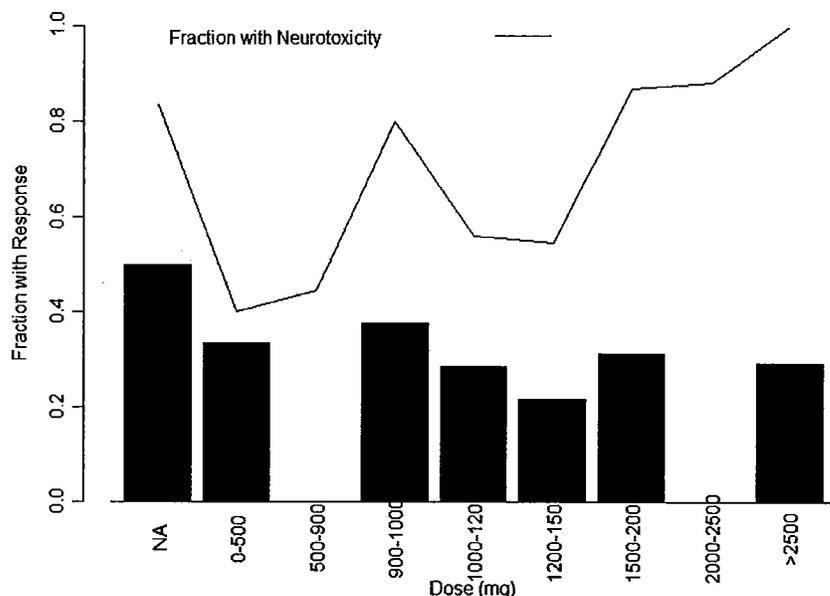


Figure 1. Dose-Response: Efficacy and All-Cause Neurotoxicity as a Function of Nelarabine Dose.

Table 2 summarizes the efficacy data collected during the Phase 2 studies. Note that both Phase 2 studies were uncontrolled. During the course of the trial, the dose was reduced downward from 1200 mg/m² to 650 mg/m² for pediatric patients and from 2200 mg/m² to 1500 mg/m² for adult patients due to neurotoxicity.

	Adults (N=28)	Peds (N=39)
Dose	1500 mg/m ²	650 mg/m ²
Duration of Infusion	2 hrs	1 hr
Days Dosing	1, 3, 5	1-5
Cycle length	21 days	21 days
Complete Response	18% [6%,37%]	13% [4%,27%]
Duration of CR	15-195 wks	4.7-36.4 wks

One year Survival (Kaplan-Meier)	29% [12%, 45%]	14% [3%,26%]
Median Survival (wks)	20.6 [10.4, 36.4]	13.1 [8.7,17.4]

Table 2. Efficacy in Phase 2 Studies.

METHODS

The goal of this analysis is to evaluate the relation between drug exposure and: (1) therapeutic response, and (2) adverse events. There is a focus on neurotoxicity since neurotoxic adverse events were dose limiting and, in some cases, irreversible.

Specific Aims

- Model the exposure - response relationship
- Model the exposure - adverse event relationship
- Identify any predictors of exposure

Note that exposure data consists of nelarabine, ara-G or ara-GTP AUC.

Data

The data contributing to the analysis are described in Table 3. The data were collected in three Phase 1 studies and two Phase 2 studies. One Phase 2 study was conducted in adult patients and one was conducted in pediatric patients. The Sponsor measured the concentration of nelarabine and ara-G in the Phase 1 studies only. Concentrations of ara-GTP were measured in a subset of adult patients in the Phase 1 studies—patients with circulating leukocyte blast counts >10,000/ μ L.

Demographic variables include age, weight, sex, body surface area, height, creatinine clearance and race.

Note that the data from the Phase 1 study Study 1005 was not included in the analysis since the presence of Fludarabine may confound outcomes.

Study	Group	Dose (iv)	Dosing	Concentration measured?
Phase 1 1001	Adults Pediatrics	\leq 1200 mg/m ² 1 hr infusion	Days 1-5	Yes
Phase 1 1002	Adults	\leq 1500 mg/m ² 2 hr infusion	Days 1,3,5	Yes
Phase 1 1003	Adults	\leq 2900 mg/m ² 2 hr infusion	Days 1,3,5	Yes

Phase 2 2001	Pediatrics	650 mg/m ² (↓ from 1200) 1 hr infusion	Days 1-5 2-21 day cycles Stop: After 2 yrs, AE or disease→	No
Phase 2 2002	Adults	1500 mg/m ² (↓ from 2200) 2 hr infusion	Days 1,3,5 2-21 day cycles If respond in cycle 1 or 2: up to 4-21 day cycles	No

Table 3. Design of Studies Used in the Reviewer's Analysis.

Analysis

Pharmacokinetics

Nonlinear modeling was performed in Splus using the nlme() function to evaluate the statistical significance of demographic variables as predictors of: (1) nelarabine AUC_{inf}, (2) ara-G AUC_{inf} and (3) ara-GTP AUC_t. All covariates listed in the **Data** section of this review were tested for inclusion during each round of the analysis. During each round of covariate selection, the covariate yielding the largest drop in the likelihood was added to the base model for the next round of covariate selection. The covariate selection process ceased when the addition of any covariate did not lead to a change in the likelihood of more than 4 points.

Pharmacodynamics

Given the lack of concentration measurements in Phase 2 studies, two separate analyses were performed: (1) for a dataset with pooled Phase 1 and Phase 2 data, and (2) for a dataset with only Phase 1 data. When the dataset with Phase 2 responses was analyzed, AUC of nelarabine, ara-G and ara-GTP were not evaluated as predictors of response.

1. Exposure – Therapeutic Response

A logistic regression analysis was performed in SAS using the PROC LOGISTIC routine to evaluate the statistical significance of demographic and exposure variables as predictors of therapeutic response. The response variable is a binary outcome; subjects who achieved a “Complete Response” or “Partial Response” were categorized as “Responders” in this analysis. The covariate search procedure consisted of a 0.15 significance level for forward inclusion in the model and a 0.05 significance level for backward elimination.

2. Exposure – All-Cause Neurotoxicity

A logistic regression analysis was performed in SAS using the PROC LOGISTIC routine to evaluate the statistical significance of the demographic and exposure variables as predictors of all-cause, any grade neurotoxicity. This adverse event response variable is a binary outcome and corresponds to the “conero” variable in the Sponsor’s dataset. The covariate search procedure consisted of a 0.15 significance level for forward inclusion in the model and a 0.05 significance level for backward elimination.

3. Exposure – Severity of Specific Neurotoxicities

A logistic regression analysis was performed in SAS using the PROC LOGISTIC routine to evaluate the statistical significance of the demographic and exposure variables as predictors of the severity of the following adverse events: ataxia, seizure, pain in extremity, dizziness, peripheral neuropathy and neutropenia. This adverse event response variable is a categorical variable and corresponds to the “attox”, “sztox”, “petox”, “dztox”, “pntox” and “nptox” variables in the Sponsor’s dataset, respectively. The covariate search procedure consisted of a 0.15 significance level for forward inclusion in the model and a 0.05 significance level for backward elimination.

RESULTS

Pharmacokinetics

Figure 2, Figure 3 and Figure 4 are plots of the predicted versus measured values of nelarabine AUCinf, ara-G AUCinf and ara-GTP AUCt data for the best fitting model. Body surface area (BSA) was the only significant predictor of nelarabine exposure. BSA and creatinine clearance were significant predictors of ara-G exposure. Dose, BSA, sex and race were significant predictors of ara-GTP exposure. Note that considerable unexplained variability in ara-GTP and nelarabine exposure remains after inclusion of these covariates.

$$\text{AUC Nelarabine} = 9.68 + 0.0151 \cdot \text{DOSE} - 32.9 \cdot (\text{BSA} - 1.75)$$

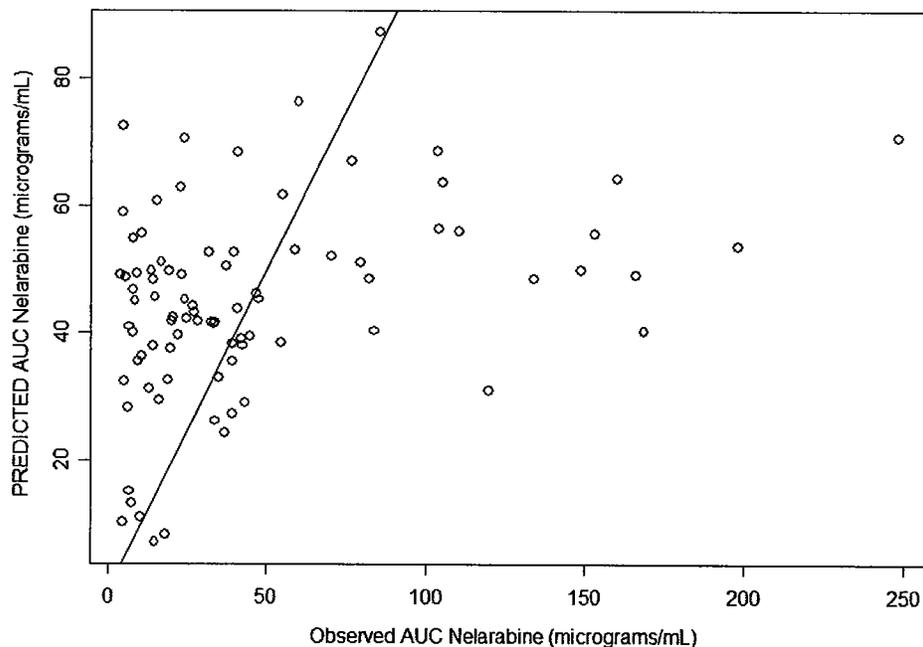


Figure 2. Predicted versus measured values of nelarabine for the best fitting model to the nelarabine AUCinf data.

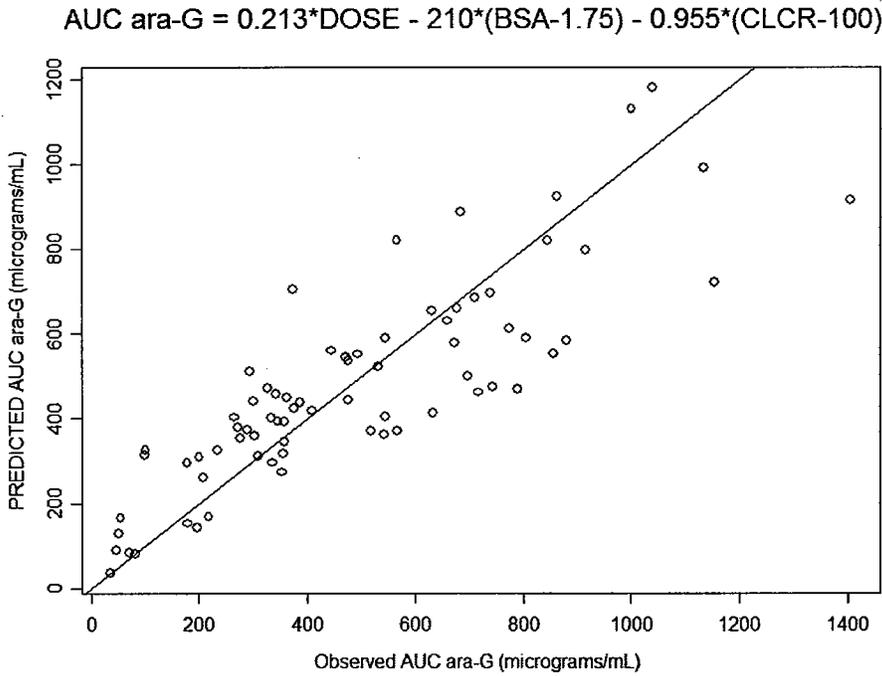


Figure 3. Predicted versus measured values of ara-G for the best fitting model to the ara-G AUCinf data.

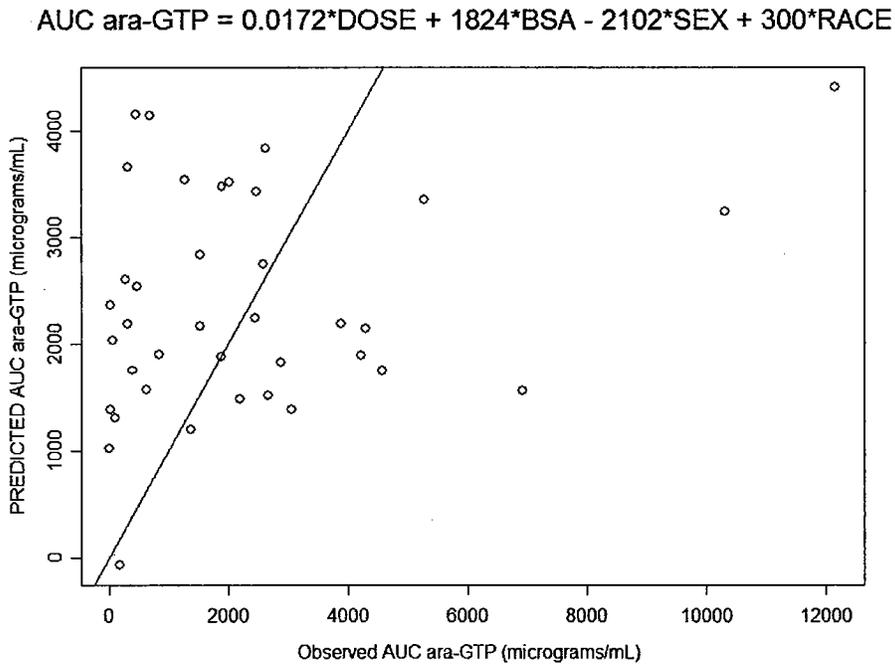


Figure 4. Predicted versus measured values of ara-GTP for the best fitting model to the ara-GTP AUCt data.

One use of a model for ara-GTP AUCt is to augment the dataset used for exposure (ara-GTP) – response analysis by permitting one to impute ara-GTP exposure in subjects that do not have a measurement. (Recall that measurements of ara-GTP concentration were sparse; ara-GTP concentration was measured in a limited number of subjects in the Phase 1 studies and no concentration data were collected during Phase 2 studies.) Figure 4 suggests that the model fails to predict ara-GTP exposure well; high values of ara-GTP are especially underpredicted. Consequently, missing ara-GTP levels in the subjects for whom ara-GTP was not measured were not imputed.

Pharmacodynamics

1. Exposure-Therapeutic Response

Exposure (AUCt) to ara-GTP and race (Caucasian / Other) were significant predictors of therapeutic response ($p=0.006$). Figure 5, a boxplot of ara-GTP exposure for Responders (response=1) vs. Non-Responders (response=0), illustrates the impact of exposure graphically – there is a greater response in patients with greater AUC ara-GTP. Note that there are nine responders and 30 nonresponders in this dataset.

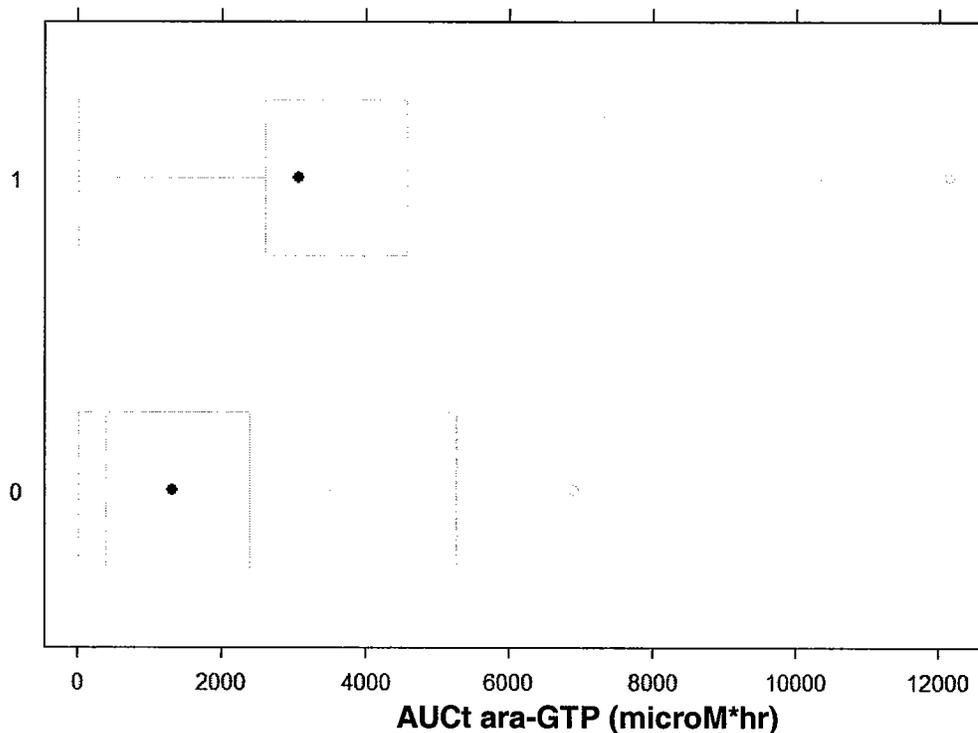


Figure 5. Boxplot of ara-GTP Exposure for Responders (y-axis category = 1) Versus Non-Responders (y-axis category = 0).

There were 33 Caucasian subjects and 6 Non-Caucasian subjects in this dataset. The response rate was 15% in Caucasian subjects and 67% in Non-Caucasian subjects.

Are there any useful predictors of ara-GTP AUCt?

Recall that the pharmacokinetic analysis identified Sex and Race as significant predictors of ara-GTP AUCt (Figure 3). Figure 6 shows the relation between these covariates and the distribution of AUCt ara-GTP. This figure shows that there is only 1 non-caucasian female in the dataset and that her value of ara-GTP AUC is very high. The median AUC ara-GTP is similar in Caucasian males and females. There are 5 caucasian females in the dataset, 23 caucasian males in the dataset and 10 non-caucasian males in the dataset. Based on the limited data in non-caucasian females, it cannot be determined whether race is a real predictor of AUC ara-GTP or if this is an outlying point that has a strong influence on the analysis.

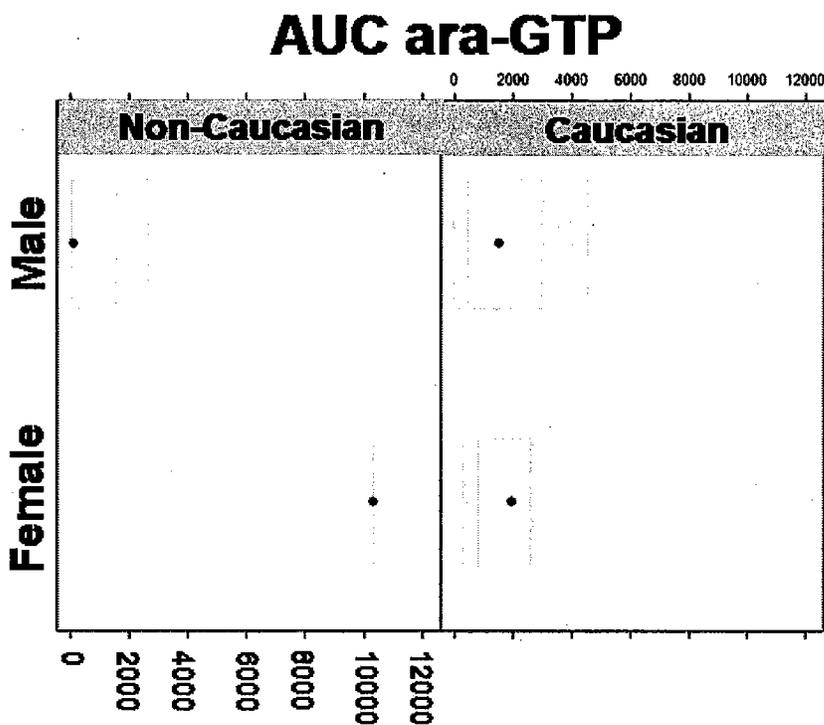


Figure 6. Distribution of AUC ara-GTP as a function of race and sex. There are 5 caucasian females, 23 caucasian males, 10 non-caucasian males and 1 non-caucasian female in the dataset.

Figure 7 and Figure 8 illustrate the individual influence of the factors race and sex on exposure to ara-GTP. Figure 7 shows a boxplot of AUC ara-GTP for caucasian versus non-caucasian subjects. Figure 8 shows a boxplot of AUC ara-GTP for male versus female subjects. The median of the distributions show clear separation, however, there is considerable overlap in the distributions.

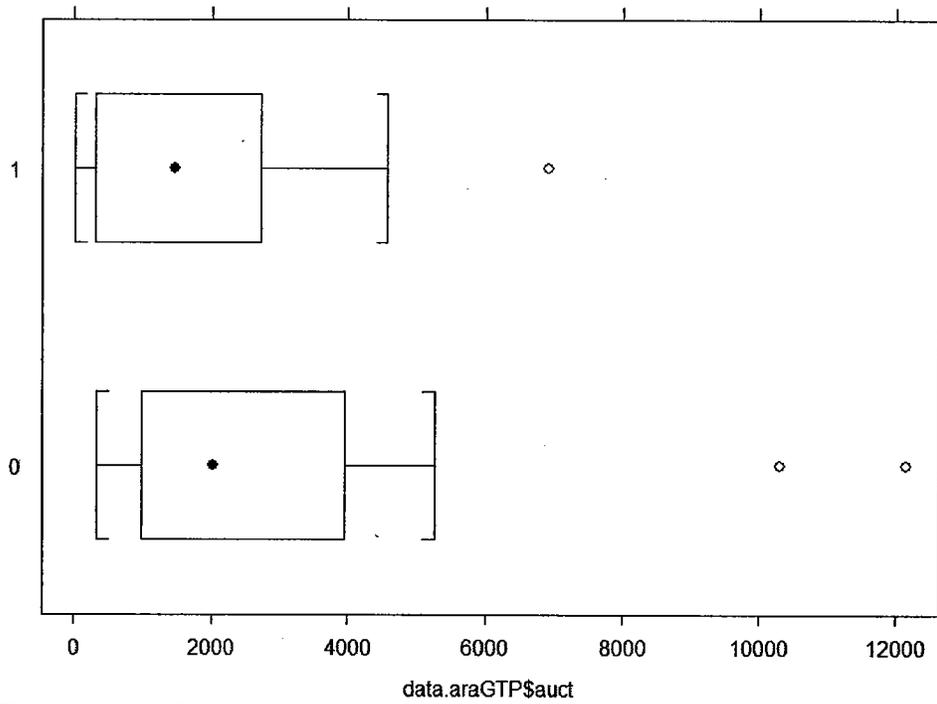


Figure 7. AUCt ara-GTP for Males (y-axis variable = 1) and Females (y-axis variable = 0). There are 28 males and 11 females in this dataset.

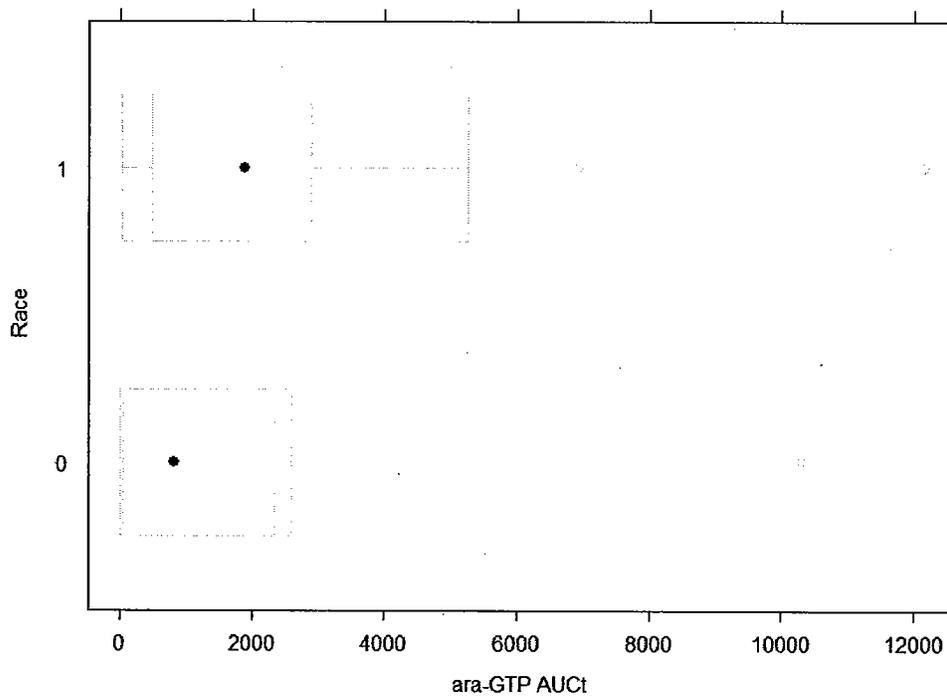


Figure 8. AUCt ara-GTP for Caucasian (y-axis variable = 1) and Non-Caucasian (y-axis variable = 0) Patients.

2. Exposure – All-Cause Neurotoxicity

AUC nelarabine was identified as a significant predictor of all-cause, any grade neurotoxicity ($p < 0.05$). Figure 9 illustrates this graphically; the percent of subjects experiencing neurotoxicity increases with increasing AUC nelarabine. However, the percent of responders does not increase with increasing AUC nelarabine.

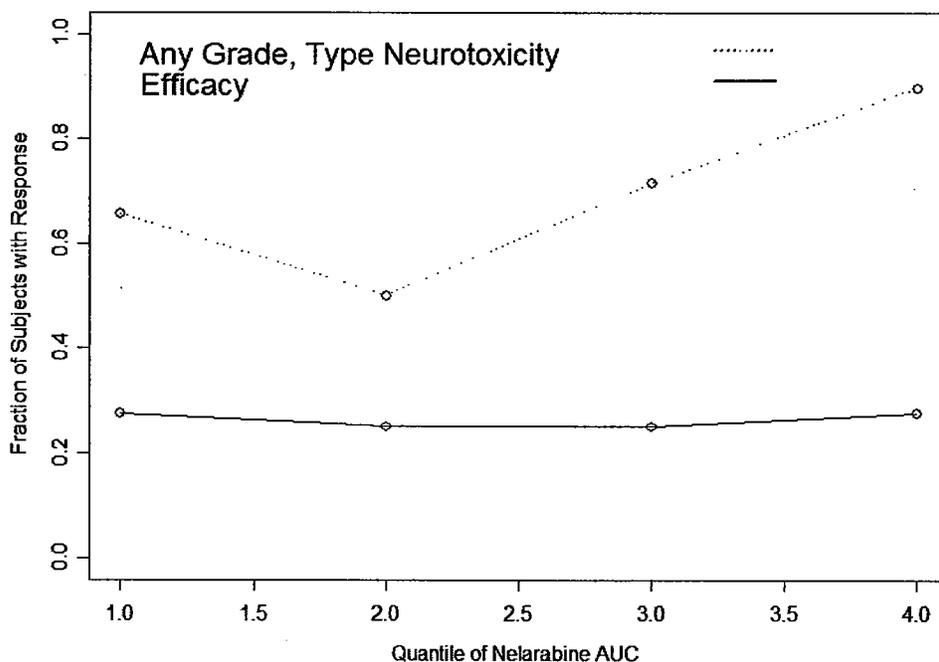


Figure 9. All-Grade, Any Type Neurotoxicity Depends on Nelarabine AUC, but Efficacy Does Not Depend on Nelarabine AUC. Note that the quantiles of AUC are as follows: Quantile #1: 2-12.675 microM*hr; Quantile #2: 12.675-29 microM*hr; Quantile #3: 29-51.925 microM*hr; Quantile #4: 51.925-2146.1 microM*hr.

3. Exposure – Severity of Specific Neurotoxicities

Table 4 summarizes the results of the analysis. AUCnelarabine was a statistically significant predictor of the severity of ataxia, seizure and pain in extremity. Dose was a statistically significant predictor of peripheral neuropathy and dizziness. None of the predictors tested were significantly correlated with neutropenia or Guillain-Barre syndrome.

Adverse Event	Predictor	P
Ataxia	AUC Nelarabine	0.0330
Seizure	AUC Nelarabine	0.0038
Pain in Extremity	AUC Nelarabine	0.0467

Peripheral Neuropathy	Dose	0.0009
Dizziness	Dose	0.0002
Neutropenia	NONE	NA
Guillain-Barre	NONE (only 1 event)	NA

Table 4. Predictors of Severity of Adverse Events Evaluated.

Figures 10, 11 and 12 show the model predicted and observed fraction of subjects having a severe adverse event as a function of nelarabine exposure (AUC). The line on each plot shows the logistic model predicted probability of having a severe adverse event. The points on each plot indicates the observed fraction of subjects having a severe (grade ≥ 3) level of toxicity for each of 4 quantiles of nelarabine AUC. The x-coordinate of the point is located at the midpoint of the AUC in the particular quantile. The categories of exposure are based on grouping the data for the four quantiles of nelarabine AUC. The categories of exposure were: 2-13 microM*hr, 13-29 microM*hr, 29-52 microM*hr and 52-2100 microM*hr. Note that 25% of the AUC data ranged from 52 microM*hr to 2100 microM*hr.

Adverse Event: Seizure

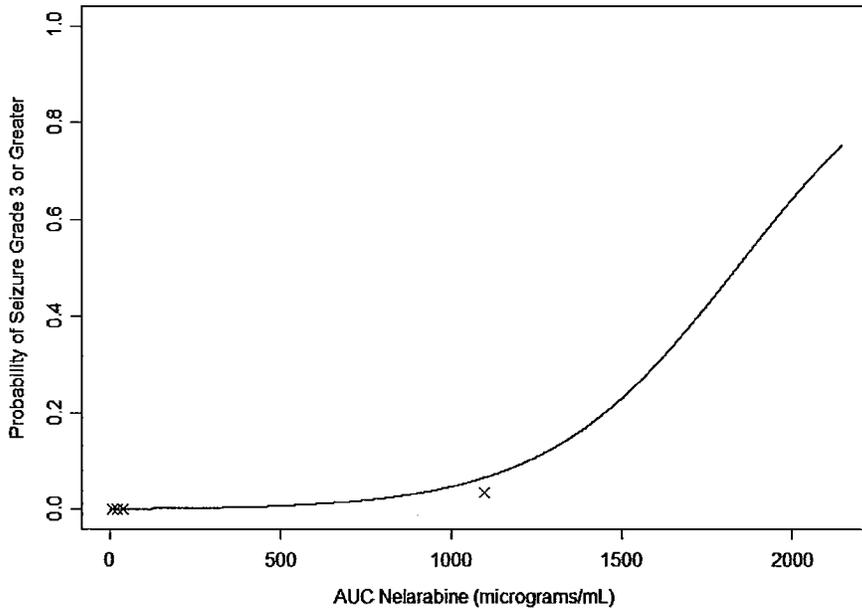


Figure 10. Probability of Severe Seizure as a Function of AUC Nelarabine. The line shows the logistic model predicted probability of having a seizure of grade ≥ 3 . The points indicate the observed fraction of subjects having a severe (grade ≥ 3) seizure for each of 4 categories of exposure.

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Adverse Event: Ataxia

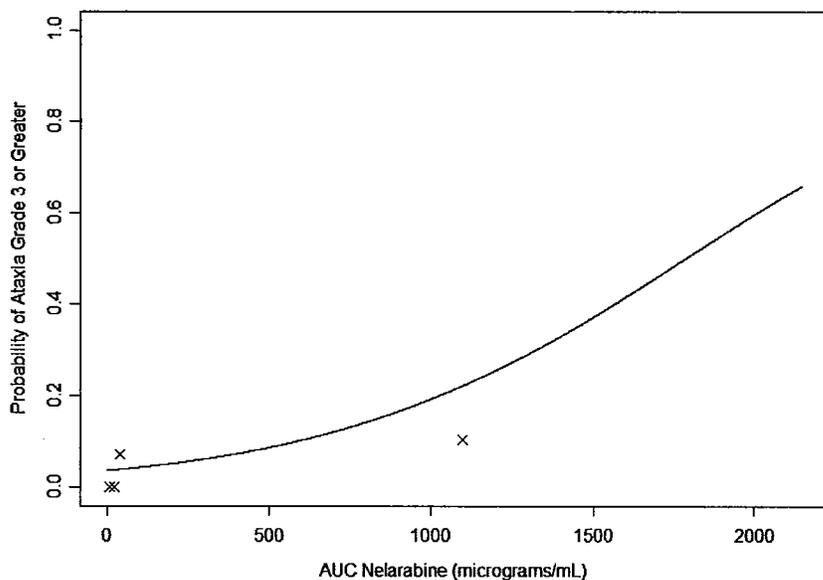


Figure 11. Probability of Severe Ataxia as a Function of AUC Nelarabine. The line shows the logistic model predicted probability of having ataxia of grade ≥ 3 . The points indicate the observed fraction of subjects having severe (grade ≥ 3) ataxia for each of 4 categories of exposure.

Adverse Event: Pain in Extremity

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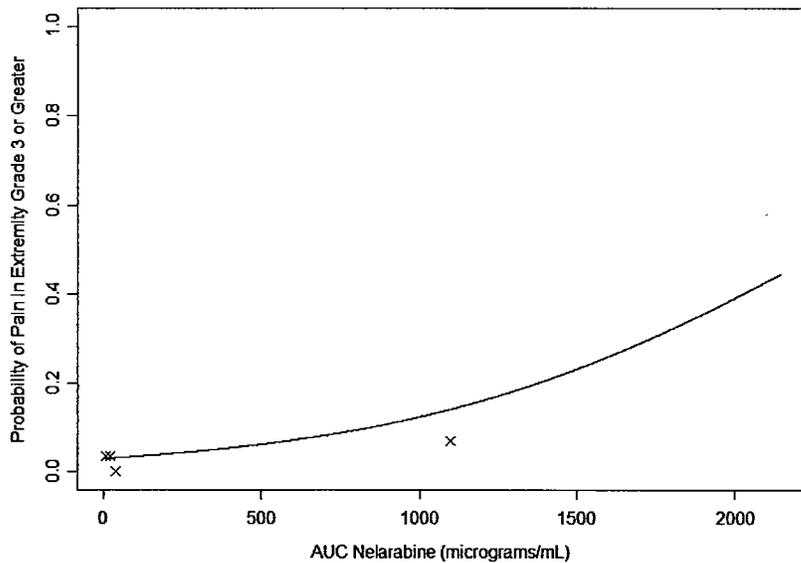


Figure 12. Probability of Severe Pain in Extremity as a Function of AUC Nelarabine. The line shows the logistic model predicted probability of having pain in extremity of grade ≥ 3 . The points indicate the observed fraction of subjects having severe (grade ≥ 3) ataxia for each of 4 categories of exposure.

When reviewing these figures, note that the mean AUC nelarabine in subjects who received 1500 mg/m² (the proposed dose in adults) was 32 microM*hr and the mean AUC nelarabine in patients who receive 650 mg/m² is expected to be less than 17 microM*hr.

Are there any useful predictors of nelarabine AUC?

Since nelarabine exposure correlates with neurotoxicity, it would be useful to adjust the dose a priori to mitigate adverse events. However, the pharmacokinetic analysis did not yield any useful predictors for dose individualization (Figure 2).

DISCUSSION / CONCLUSIONS

What is the relationship between exposure and toxicity/effectiveness?

In summary, a logistic regression analysis of the PK/PD and demographic data from Phase 1 studies in adult patients suggest that exposure (AUC) to ara-GTP correlates with therapeutic response. Data from Phase 1 and Phase 2 studies in adult and pediatric patients suggests that exposure (AUC) to nelarabine correlates with all grade neurotoxicity, as well as with the severity of ataxia, pain in extremity or seizure.

It is sensible that ara-GTP was identified as a significant predictor of therapeutic response given that it is measured at the drug's site of action. Furthermore, correlation between nelarabine exposure and neurotoxicity is consistent with preclinical data (based on a comment from an attendee at the nelarabine briefing held on September 19, 2005).

Is there a need for dose adjustment in any special populations?

At this time, there is no recommended strategy for a priori dose individualization.

Body surface area was the only significant predictor of nelarabine AUC while body surface area, sex and race were significant predictors of ara-GTP AUC. It is unclear whether race and sex are true predictors of ara-GTP AUC or if the result was influenced by the extreme value of AUC ara-GTP measured in the single Non-Caucasian Female in the dataset. Regardless, despite achieving statistical significance as predictors of nelarabine and ara-GTP AUC, considerable unexplained variability in exposure remained.

It has been hypothesized that the variability in AUC nelarabine and AUC ara-GTP may be explained by adenosine deaminase genotype – the enzyme involved the conversion of nelarabine to ara-G. It would be useful to evaluate whether adenosine deaminase genotype may aid dose individualization.

APPENDIX

Assays for concentration measures

Plasma, cerebrospinal fluid, and urine nelarabine and ara-G concentrations and blast cell ara-GTP concentrations were determined using validated high-performance liquid chromatography methods. Serial blood samples were collected after the first and last dose of administration during the initial course of treatment with nelarabine for the determination of plasma concentrations of nelarabine and ara-G. Patients with circulating leukocyte blast counts $>10,000/\mu\text{L}$ had blood samples collected for the quantification of intracellular concentrations of ara-GTP. Twenty-four-hour urine collections were obtained after the first dose for measurement of nelarabine and ara-G recovery.

Additional Figures

Figures 13-20 summarize the effect of exposure to nelarabine on neurotoxicity as observed in the Phase 1 and Phase 2 data. To produce the plots, subjects are grouped by quantiles of dose or AUC nelarabine and the probability of neurotoxicity is computed for each exposure category. The categories for dose of nelarabine are: 60-875 mg, 875-2195 mg, 2195-3000 mg, and 3000-6400 mg. The categories for AUC of nelarabine are 2-12.675 microM*hr, 12.675-29 microM*hr, 29-52 microM*hr, and 52-2146 microM*hr. Note that the first bar for the dose plots (range: 60-875 mg) would cover the average value in a pediatric patient expected with the Sponsor's proposed dose (dose: 650 mg/m²; mean BSA observed in pediatric patients= 1.3 m²; expected dose in mg: 845 mg). The third bar for the dose plots (range: 2195-3000 mg) would cover the average value in an adult patient expected with the Sponsor's proposed dose (dose: 1500 mg/m²; mean BSA observed in adults = 1.9 m²; expected dose in mg: 2723 mg). Recall that the mean AUC in subjects who received 1500 mg/m² (the proposed dose in adults) was 32 microM*hr and the mean AUC in patients who receive 650 mg/m² is expected to be less than 17 microM*hr. For the plots relating AUC to neurotoxicity, the second bar

includes within its range the exposure expected in pediatric patients (12.675-29 microM*hr). The third bar includes within its range the exposure expected in adult patients (29-52 micrograms/m²: AUC = 32).

Figures 13 and 14, analogous to the Sponsor's analysis, show adverse events according to a simple metric that lumps all nervous system toxicity into a single YES/NO binary variable. According to this metric, there is a dose-related increase in neurotoxicity with 40% and 70% of subjects in the lowest and second highest dose categories, respectively, (dose categories expected for pediatric patients and adult patients) experiencing some type of neurotoxicity.

Figures 15-20 show the breakdown for the types of neurotoxicity that were specifically shown to have AUC- dependent severity in a logistic regression analysis.

Figure 16 shows that there is no severe ataxia expected for patients with an AUC of nelarabine expected for the pediatric dose. There is a 7% probability of severe ataxia for patients with an AUC of nelarabine expected for the adult dose.

Figure 18 shows that there is less than a 3% probability of severe pain in extremity expected for patients with an AUC of nelarabine expected with the pediatric and adult doses.

Figure 20 shows that there is less than a 3% probability of severe seizure expected for patients with an AUC of nelarabine expected with the pediatric and adult doses.

These results suggest that the level of severe ataxia, pain in extremity or seizure is much lower than predicted based on the binary YES/NO metric of neurotoxicity. Ataxia is observed with the greatest incidence – 7% of subjects with the mean AUC nelarabine equivalent to the value expected with the adult dose had a severe incident of ataxia.

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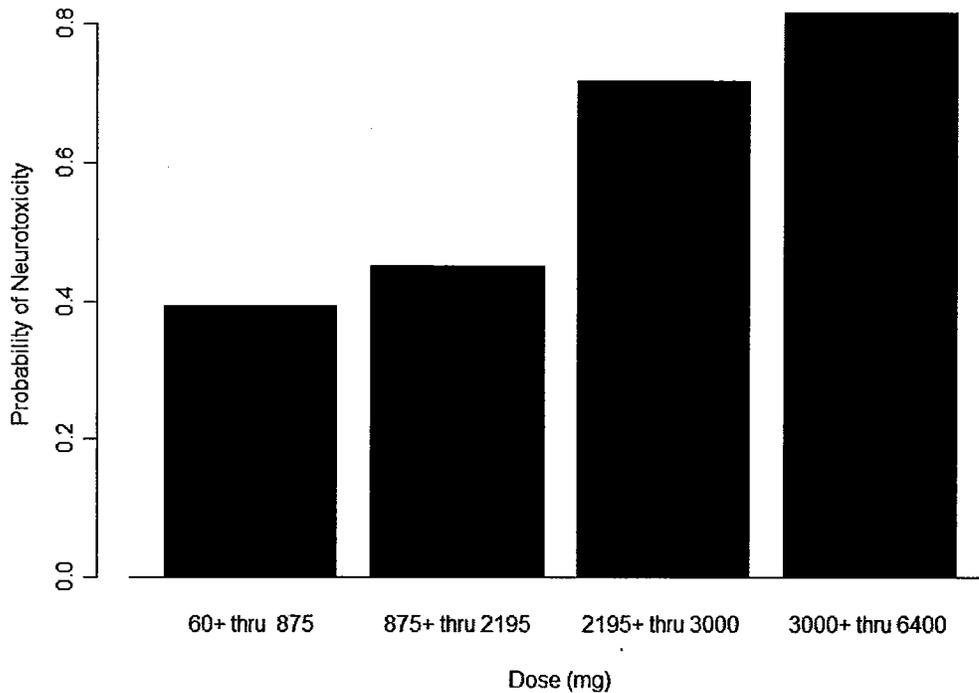


Figure 13. Probability of Any Neurotoxicity (Binary Variable) in Phase 1 and 2 Studies By Quantiles of Dose. Subjects are grouped by quantiles of dose and the probability of neurotoxicity is computed for each exposure category. The categories for dose of nelarabine are: 60-875 mg, 875-2195 mg, 2195-3000 mg, and 3000-6400 mg. Note that the first bar for the dose plots (range: 60-875 mg) would cover the average value in a pediatric patient expected with the Sponsor's proposed dose (dose: 650 mg/m²; mean BSA observed in pediatric patients= 1.3 m²; expected dose in mg: 845 mg). The third bar for the dose plots (range: 2195-3000 mg) would cover the average value in an adult patient expected with the Sponsor's proposed dose (dose: 1500 mg/m²; mean BSA observed in adults = 1.9 m²; expected dose in mg: 2723 mg).

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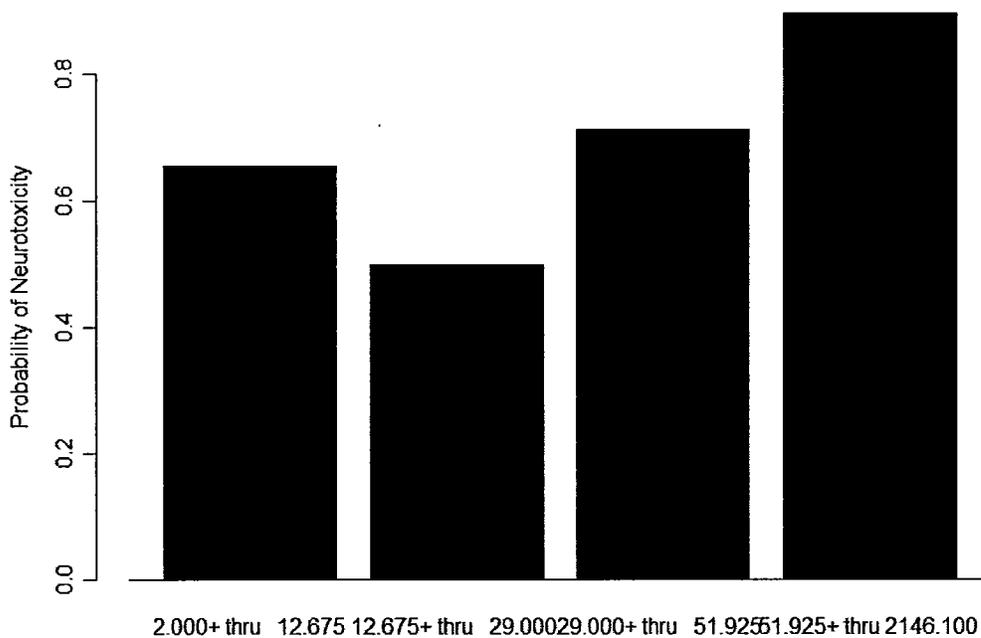


Figure 14.

Probability of Any Neurotoxicity (Binary Variable) in Phase 1 Studies By Quantiles of AUC. Subjects are grouped by quantiles of AUC nelarabine and the probability of neurotoxicity is computed for each exposure category. The mean AUC in subjects who received 1500 mg/m² (the proposed dose in adults) was 32 microM*hr and the mean AUC in patients who receive 650 mg/m² is expected to be less than 17 microM*hr. For the plots relating AUC to neurotoxicity, the second bar includes within its range the exposure expected in pediatric patients (12.675-29 microM*hr). The third bar includes within its range the exposure expected in adult patients (29-52 micrograms/m²: AUC = 32).

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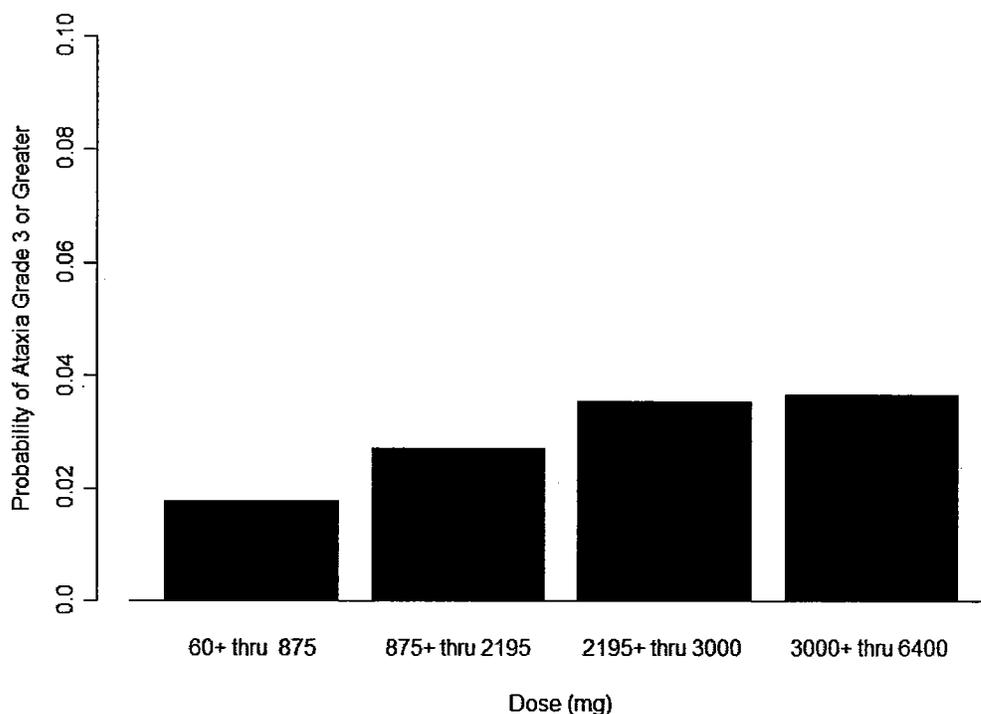


Figure 15. Probability of Ataxia of Grade ≥ 3 in Phase 1 and 2 Studies By Quantiles of Dose. Subjects are grouped by quantiles of dose and the probability of neurotoxicity is computed for each exposure category. The categories for dose of nelarabine are: 60-875 mg, 875-2195 mg, 2195-3000 mg, and 3000-6400 mg. Note that the first bar for the dose plots (range: 60-875 mg) would cover the average value in a pediatric patient expected with the Sponsor's proposed dose (dose: 650 mg/m²; mean BSA observed in pediatric patients= 1.3 m²; expected dose in mg: 845 mg). The third bar for the dose plots (range: 2195-3000 mg) would cover the average value in an adult patient expected with the Sponsor's proposed dose (dose: 1500 mg/m²; mean BSA observed in adults = 1.9 m²; expected dose in mg: 2723 mg).

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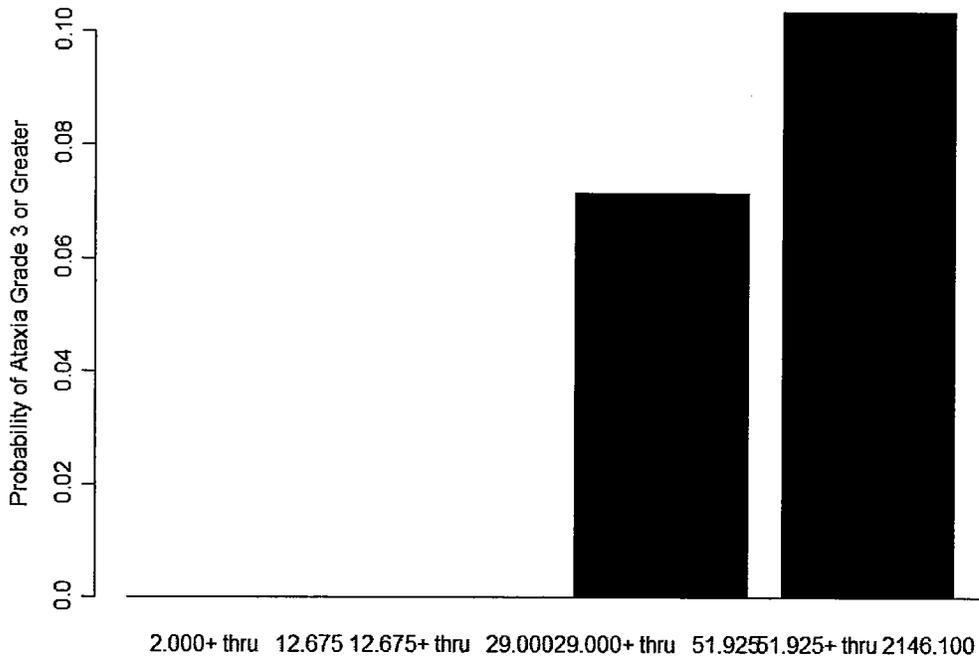


Figure 16. Probability of Ataxia of Grade ≥ 3 in Phase 1 Studies By Quantiles of AUC. Subjects are grouped by quantiles of AUC nelarabine and the probability of neurotoxicity is computed for each exposure category. The mean AUC in subjects who received 1500 mg/m² (the proposed dose in adults) was 32 microM*hr and the mean AUC in patients who receive 650 mg/m² is expected to be less than 17 microM*hr. For the plots relating AUC to neurotoxicity, the second bar includes within its range the exposure expected in pediatric patients (12.675-29 micrograms*hr/mL). The third bar includes within its range the exposure expected in adult patients (29-52 micrograms/m²: AUC = 32).

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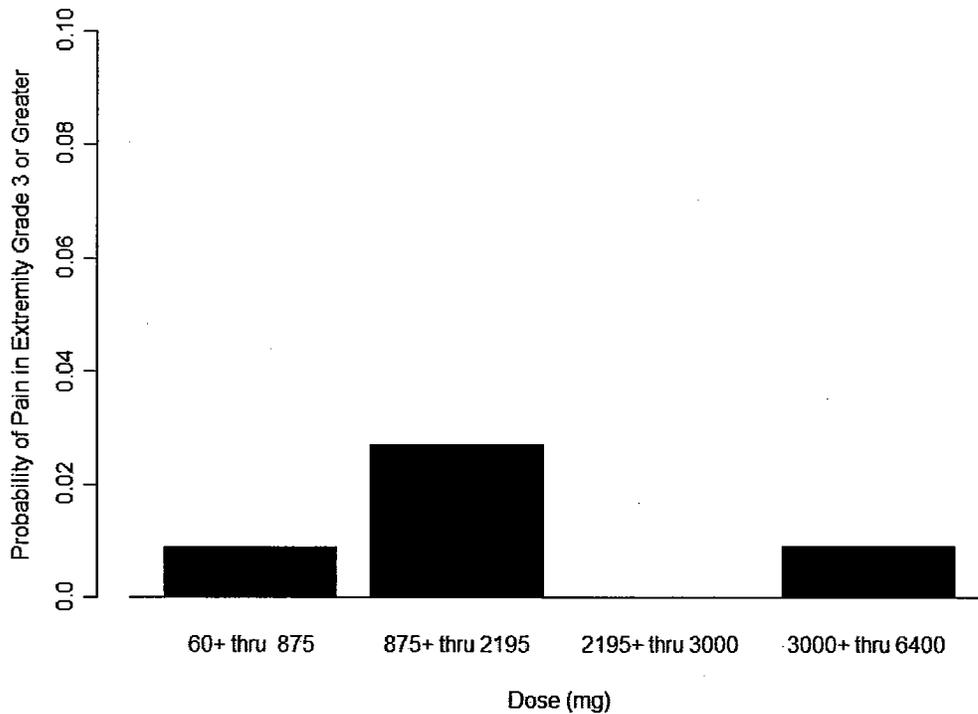


Figure 17. Probability of Pain in Extremity of Grade ≥ 3 in Phase 1 and 2 Studies By Quantiles of Dose. Subjects are grouped by quantiles of dose and the probability of neurotoxicity is computed for each exposure category. The categories for dose of nelarabine are: 60-875 mg, 875-2195 mg, 2195-3000 mg, and 3000-6400 mg. Note that the first bar for the dose plots (range: 60-875 mg) would cover the average value in a pediatric patient expected with the Sponsor's proposed dose (dose: 650 mg/m²; mean BSA observed in pediatric patients= 1.3 m²; expected dose in mg: 845 mg). The third bar for the dose plots (range: 2195-3000 mg) would cover the average value in an adult patient expected with the Sponsor's proposed dose (dose: 1500 mg/m²; mean BSA observed in adults = 1.9 m²; expected dose in mg: 2723 mg).

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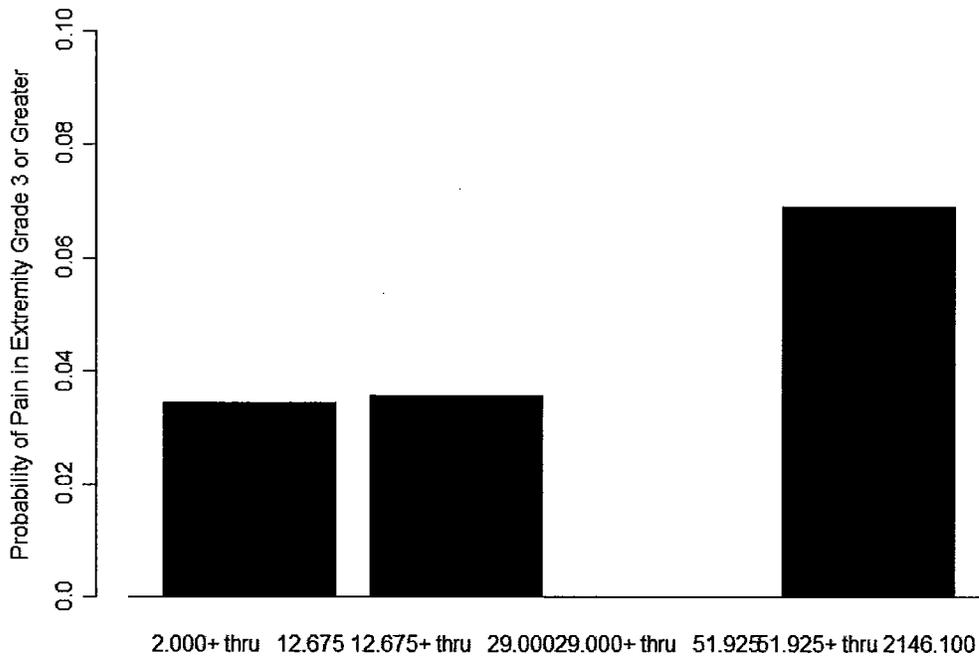


Figure 18. Probability of Pain in Extremity of Grade ≥ 3 in Phase 1 Studies By Quantiles of AUC. Subjects are grouped by quantiles of AUC nelarabine and the probability of neurotoxicity is computed for each exposure category. The mean AUC in subjects who received 1500 mg/m² (the proposed dose in adults) was 32 microM*hr and the mean AUC in patients who receive 650 mg/m² is expected to be less than 17 microM*hr. For the plots relating AUC to neurotoxicity, the second bar includes within its range the exposure expected in pediatric patients (12.675-29 micrograms*hr/mL). The third bar includes within its range the exposure expected in adult patients (29-52 micrograms/m²: AUC = 32).

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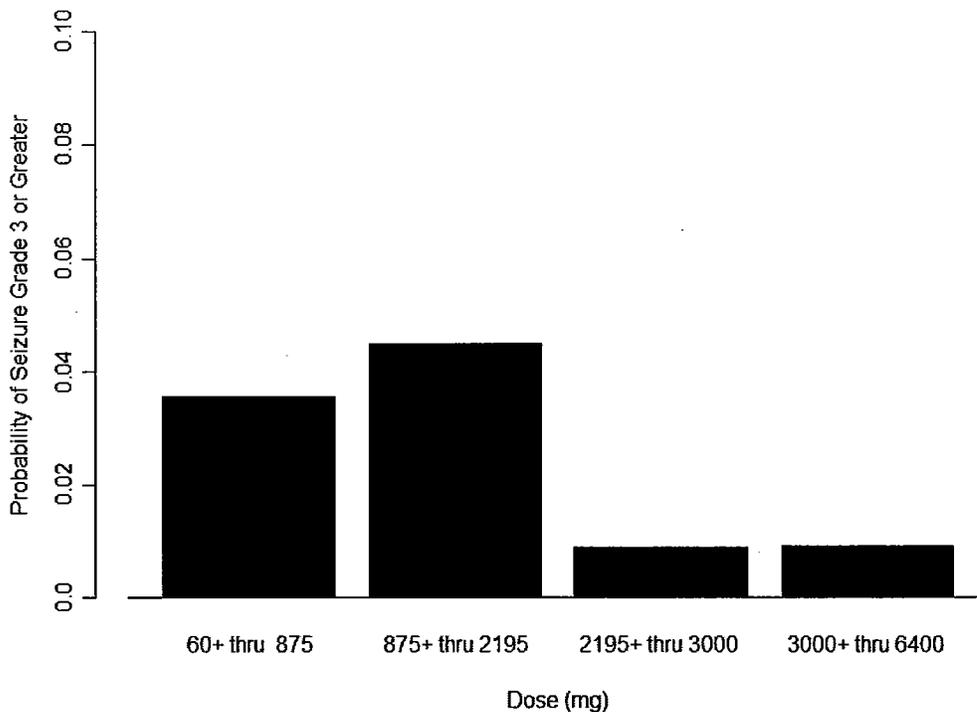


Figure 19. Probability of Seizure of Grade ≥ 3 in Phase 1 and 2 Studies By Quantiles of Dose. Subjects are grouped by quantiles of dose and the probability of neurotoxicity is computed for each exposure category. The categories for dose of nelarabine are: 60-875 mg, 875-2195 mg, 2195-3000 mg, and 3000-6400 mg. Note that the first bar for the dose plots (range: 60-875 mg) would cover the average value in a pediatric patient expected with the Sponsor's proposed dose (dose: 650 mg/m²; mean BSA observed in pediatric patients= 1.3 m²; expected dose in mg: 845 mg). The third bar for the dose plots (range: 2195-3000 mg) would cover the average value in an adult patient expected with the Sponsor's proposed dose (dose: 1500 mg/m²; mean BSA observed in adults = 1.9 m²; expected dose in mg: 2723 mg).

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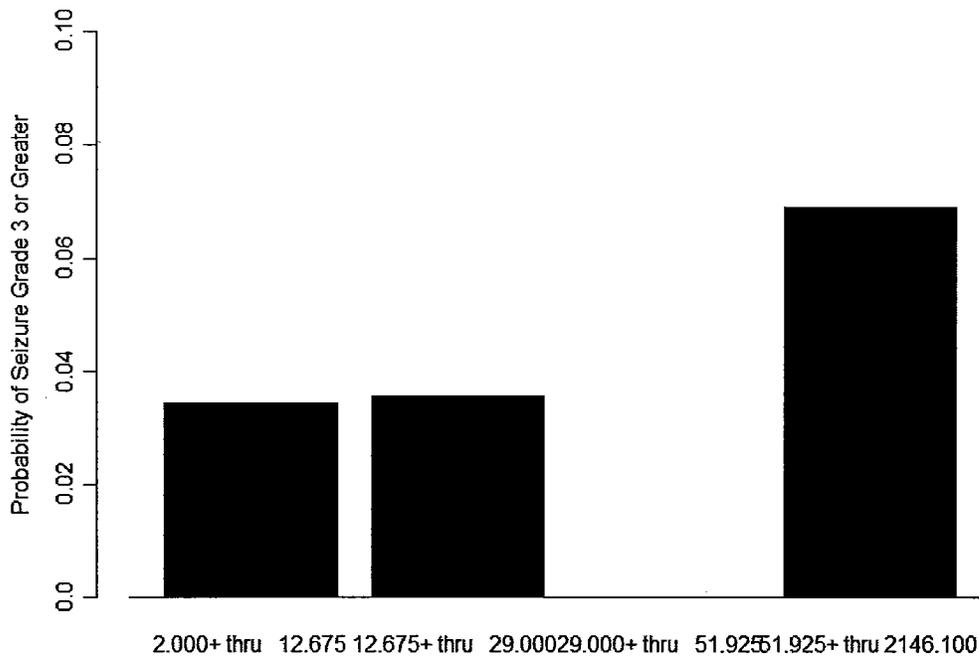


Figure 20. Probability of Seizure of Grade ≥ 3 in Phase 1 Studies By Quantiles of AUC. Subjects are grouped by quantiles of AUC nelarabine and the probability of neurotoxicity is computed for each exposure category. The mean AUC in subjects who received 1500 mg/m^2 (the proposed dose in adults) was 32 microM*hr and the mean AUC in patients who receive 650 mg/m^2 is expected to be less than 17 microM*hr . For the plots relating AUC to neurotoxicity, the second bar includes within its range the exposure expected in pediatric patients ($12.675\text{-}29 \text{ micrograms*hr/mL}$). The third bar includes within its range the exposure expected in adult patients ($29\text{-}52 \text{ micrograms/m}^2$: $\text{AUC} = 32$).

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APPENDIX 3

I. Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-877	Brand Name	ARRANON®	
OCPB Division (I, II, III)	Dpe1	Generic Name	Nelarabine	
Medical Division	HFD-150	Drug Class	A prodrug of ara-G (deoxy-guanosine analogue)	
OCPB Reviewer	Sophia Abraham	Indication(s)	Relapsed T-ALL & T-LBL	
OCPB Team Leader	Brian Booth	Dosage Form	5 mg/ml solution in glass vial	
		Dosing Regimen	Adult: 1,500 mg/m ² IV over 2 hours on days 1, 3, and 5 repeated every 21 days. Pediatric: 650 mg/m ² IV over 1 hour daily for 5 days repeated every 21 days.	
Date of Submission	29-Apr-2005	Route of Administration	IV	
Estimated Due Date of OCPB Review		Sponsor	GlaxoSmithKline	
PDUFA Due Date	29-Sep-2005	Priority Classification		
Division Due Date	10-Oct-2005			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling				
Reference Bioanalytical and Analytical Methods	X	4		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X	1		
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
II. Patients-				
single dose:				
multiple dose:	X	3		

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies				
-				
In-vivo effects on primary drug:	X	1		
In-vivo effects of primary drug:				
In-vitro:	X	1		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	1		
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X	3		
Literature References				
Total Number of Studies		14		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-877, HFD-150 (SRyan), HFD-860 (Booth, Rahman, Mehta), CDR (Biopham)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sophia Abraham
9/26/2005 01:07:37 PM
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