CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-248

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	21-248
Dates of Submission:	August 18, 2000
Drug Name:	**TRISENOX™ (Arsenic Trioxide Injection)**
Dosage Form:	1 mg/ml Arsenolite in 10-ml Single-Use Ampules For Intravenous Administration
Applicant:	Cell Therapeutics, Inc., Seattle, WA
Reviewer:	Safaa Ibrahim, Ph.D.
Type of Submission:	Review of Responses

This submission is in response to the OCPB's Comments that were forwarded to the sponsor in the letter of August 11, 2000.

Responses are adequate and acceptable (see Attachment 1).

Recommendation

No action is necessary.

/S/ 9/1/00

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

/S/

Reviewer: Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA 21-248
HFD-150/Division file
HFD-150/Spillman, Johnson, Hirschfeld
HFD-860/Mehta, Rahman, Ibrahim
CDR/Biopharm

Attachment 1

AMENDMENT To NEW DRUG APPLICATION: Clinical Pharmacology and Biopharmaceutics

August 18; 2000

Richard Pazdur, M.D., Director
Division of Oncology Drug Products, HFD- 150
Food and Drug Administration
Center for Drag Evaluation and Research
1451 Rockville Pike
(Woodmont II Building)
Rockville. MD 20852

Re: NDA 21-248

Application for Trisenox™ (arsenic trioxide injection) for the treatment of acute promyelocytic leukemia (APL)

Dear Dr. Pazdur:

Reference is made to Cell Therapeutics, Inc.'s original submission of the New Drag Application (NDA) for Trisenox™ (arsenic trioxide injection) on March 28, 2000.

This Amendment is provided in response to the Clinical Pharmacology and Biopharmaceuties (CPB) Information Request # 3, dated August 11, 2000. Each FDA comment, listed below, is followed by the respective cfi response. As requested, we have also provided estimated timeframes for addressing the items; any modification to the timeframes will be reported in an Annual Report post-approval.

Comment 1

[redacted]

cti Response

[redacted]

Comment 2

Conduct an in vitro study to assess the inhibition potential of arsenic trioxide on the major cytochrome P-450 isoenzymes.

cti Response

We will conduct an in-vitro study to assess the inhibition potential of arsenic trioxide on the major cytochrome P450 isoenzymes. We anticipate starting this study by the end of this year (2000).

Comment 3

From the limited pediatric pharmacokinetic information provided in this NDA (n=3), it is possible that the pediatric patients may exhibit higher exposure to arsenic trioxide than the adult population. Since you are seeking approval of the drug for a general patient population, and pharmacokinetics of arsenic trioxide in the pediatric population is unknown, a formal pharmacokinetic study should be conducted in an appropriate number of children to adequately characterize the pharmacokinetics of arsenic trioxide in the pediatric population. Alternatively, this information can also be obtained from a pediatric efficacy trial using a prospectively planned population pharmacokinetic approach. We refer you to our published document titled "Guidance for Industry, Population Pharmacokinetics."

cti Response

When the assay methods for arsenic trioxide are available, we will evaluate the pharmacokinetics of arsenic trioxide in an appropriate number of pediatric patients with cancer for whom arsenic trioxide is an appropriate therapy.

Comment 4

Characterize the pharmacokinetics of arsenic trioxide after administration of 0.15 mg/kg/day of arsenic trioxide in APL patients. Control patients enrolled in the renal and hepatic impaired patient study (see below) may also provide this information.

cti Response

We will characterize the pharmacokinetics of arsenic trioxide after administration of 0.15 mg/kg/day of arsenic trioxide to selected APL patients

Comment 5

Because inorganic and organic arsenic are primarily excreted via the kidneys, patients with renal impairment are likely to have a different disposition pattern that the patients with normal renal function. Please conduct a pharmacokinetic study of arsenic trioxide in patients with varying degrees of renal function. We refer you to our published document titled "Guidance for Industry, Pharmacokinetics in Patients with Impaired Renal Function" for guidance on study design, categories of renal impairment, and data analysis for conducting such study. Please submit your protocol to the Agency for review.

cfi Response

After we have developed the validated assays, we will assess the pharmacokinetics of arsenic trioxide for patients having varying degrees of renal function who are appropriate candidates for treatment with arsenic trioxide. We will submit a protocol for this study, to the Agency for review, close to when the arsenic trioxide assays are available.

Comment 7

Data from all the pharmacokinetic studies conducted as a Phase IV commitment should be analyzed to evaluate the influence of age, gender, and race on the pharmacokinetics of arsenic trioxide.

cti Response

We will stratify patients according to age, gender, and race for whom pharmacokinetic data are available from the studies conducted for the Phase IV commitment in an attempt to evaluate the influence of age, gender, and race on the pharmacokinetics of arsenic trioxide.

We trust that the above responses address your request. Please do not hesitate to call if you have questions or need additional information at (206) 270-8424.

Sincerely yours,

Jennie Allewell
Cell Therapeutics, Inc.
Director, Regulatory Affairs and Compliance

Spillman

JUL 19 2000

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	21-248
Dates of Submission:	March 27, 2000 April 17, 2000 April 26, 2000
Type of Submission:	Original New Drug Application (1P)
Drug Name:	**TRISENOX (Arsenic Trioxide Injection)**
Dosage Form:	1 mg/ml Arsenolite in 10-ml Single-Use Ampules For Intravenous Administration
Indication:	Acute Promyelocytic Leukemia (APL)
Dose:	0.15 mg/kg Infused Daily Over 1-2 Hours For a Maximum of 60 Days
Applicant:	Cell Therapeutics, Inc., Seattle, WA
Reviewer:	Safaa Ibrahim, Ph.D.

I. SYNOPSIS

This New Drug Application (NDA) seeks approval to market TRISENOX (Arsenic Trioxide Injection) for the treatment of patients with relapsed or refractory acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from retinoid and anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. APL is a rare type of blood cancer specifically associated with a chromosome translocation that creates an oncogenic abnormal protein, PML/RARα, resulting from fusion between two genes: promyelocytic leukemia gene (PML) and retinoic acid receptor-α gene (RARα). TRISENOX was designated fast track product for the treatment of APL on February 25, 2000 and was granted orphan drug designation for the treatment of APL on March 10, 2000.

TRISENOX (Arsenic Trioxide Injection) is an aqueous sterile injection of the essential nutrient arsenic in the form arsenic trioxide (As_2O_3). In solution, arsenic trioxide exists in the tri-acid form, or arsenous acid [$As(OH)_3$] with a molecular weight of 125.9 g. The molecular formula of the drug substance in the solid state is As_2O_3 with a molecular weight of 197.8 g. Arsenous acid, the active ingredient, is present at a concentration of 1 mg/ml in 10-ml single-use ampules for intravenous administration.

The mechanism of action is not completely understood. It was found that arsenic trioxide causes apoptosis in a cell line APL model, NB4 cells, which can account for the induction of remission in APL patients. NB4 cells showed morphological changes and DNA fragmentation characteristic of apoptosis after incubation with arsenic trioxide at concentrations of 0.5-2.0 μmol/L [Chen et al. 1996, Ref. 1, Appendix I].

One pivotal study and one pilot study were submitted to support the proposed indication in this NDA; study #PLRXAS01 was a multi-center Phase II/III study in patients with APL (n=40) and study #97-66 was a Phase I/II study in patients with APL (n=12). Safety information was provided from studies # PLRXAS01 and 97-66 in patients with APL (n=52) and from the two supporting studies, #98-23 in patients with advanced hematological cancers (n=19) and #98-46 in patients with advanced solid tumors (n=28). Clinical pharmacology information was obtained from pharmacokinetic sampling of some patients during the pilot study #97-66 (n=12/12) and the two supporting safety studies, #98-23 (n=8/19) and #98-46 (n=22/28) and from relevant literatures.

In the three pharmacokinetic studies (#97-66, 98-23, and 98-46), the total arsenic was measured in biological samples using an [redacted] method. This method did not differentiate between trivalent [As(III)] or pentavalent [As(V)] forms of inorganic arsenic or methylated metabolites or any other forms of organic arsenic. The inorganic trivalent arsenic is the active species; pentavalent form and methylated metabolites are less active. The proportion of each species in blood circulation after intravenous administration of arsenic trioxide is not known.

Pharmacokinetics:

The three PK studies conducted by the applicant showed that the daily exposure to total arsenic (as measured by $AUC_{0\text{-}24hr}$) and peak plasma concentration of total arsenic (Cmax) ranged from [redacted] ng.hr/ml and [redacted] ng/ml, respectively, following intravenous doses of 0.06 to 0.35 mg/kg/day. Cmax and $AUC_{0\text{-}24hr}$ increased in proportional to the increase of dose. Steady state was reached in 8-10 days. Dose-normalized $AUC_{0\text{-}24hr}$ is not affected by the duration of infusion (2- or 4-hour). Total arsenic is equally distributed in plasma and RBCs; mean Cmax or AUC ratio is close to unity. Plasma elimination half-life was not accurately estimated (~100 hours) as the 24-hour blood sampling collection was not long enough to adequately characterize the elimination phase of total arsenic.

Since the assay used in this NDA assessed the PK of both the active and inactive species, the PK information is inadequate for the labeling of this drug.

Metabolism:

Arsenic is stored mainly in liver, kidney, heart, lung, hair and nails. The metabolism of inorganic arsenic involves two processes: (1) reduction of pentavalent arsenic [As(V)] to trivalent arsenic [As(III)] by arsenate reductase; and (2) methylation of trivalent arsenic [As(III)] to monomethylarsonic acid (MMA) by arsenite methyltransferase and then methylation of MMA to dimethylarsinic acid (DMA) by MMA methyltransferase. Neither MMA nor DMA are demethylated back to the trivalent arsenic. Pentavalent arsenic [As(V)] does not undergo methylation; it is excreted unchanged in urine or reduced to trivalent arsenic [As(III)]. The main site of methylation reactions appears to be the liver. Trivalent arsenite [As(III)] is the main active species. Methyl derivatives of arsenite (MMA and DMA) are less reactive and less toxic than inorganic arsenic.

Excretion:

Elimination of arsenic trioxide after intravenous administration has not been established. Trivalent forms of arsenic are methylated in humans and mostly excreted in urine.

Special Populations:

The effects of age, gender, and race on the pharmacokinetics of arsenic trioxide have not been studied.

However, the Applicant assessed separately the effect of these factors in the PK studies #79-66, 98-23 and 98-46 (Attachment 1). The Applicant claims that the extent of exposure to arsenic trioxide (as assessed by plasma $AUC_{0\text{-}24hr}$) was similar for males and females and differences in exposure in patients ≥ 60 years of age is not expected to be clinically relevant.

Analysis of combined data from the two PK studies #79-66 and #98-46 (n=34 cancer patients, ranging in age from 9-75 years, 22 males and 12 females, 29 Caucasians, 4 Blacks, and 1 Others) indicates that daily exposure to total arsenic may be higher in pediatric patients and female patients. Dose-normalized $AUC_{0\text{-}24hr}$ values were 2-fold higher in pediatric patients (< 16 years of age, n=3) than in adults (16-60 years of age, n=21) and 35% higher in females (n=12) than in males (n=22). Patients of 60 years of age and above (n=10) had a 20% higher $AUC_{0\text{-}24hr}$ than those between 16-60 years of age (n=21), this effect was not statistically significant (p=0.127). The clinical significance of these findings is unknown since total arsenic and not the reactive inorganic species were assessed in the pharmacokinetic studies. At the present time, dosage recommendations can not be made, but we recommend that caution should be exercised when pediatric APL patients are treated with TRISENOX (see also Phase IV Commitments).

No conclusion could be drawn for the effect of race because of the small sample size for other ethnic groups represented in the studies compared to Caucasians.

The effects of renal impairment and hepatic impairment on arsenic pharmacokinetics have not been formally studied (see Phase IV Commitments).

Drug-Drug Interactions:

No formal pharmacokinetic drug interaction studies have been conducted.

Pharmacokinetic/Pharmacodynamic (PK/PD) Relationships:

One of the most clinically relevant adverse events noted in patients treated with arsenic trioxide is prolongation of the QT/QTc interval. A retrospective regression analysis was performed on the QTc interval data collected during pivotal trials from 99 cancer patients indicates that QTc prolongation tends to reach a higher steady-state value in male patients (dQTc=62±13 msec, n=57) than in female patients (dQTc=35±5 msec, n=42). Steady-state QTc was reached sooner in females than in males (3 days versus 10 days respectively). No significant age differences were observed in the maximum change in steady-state QTc prolongation from baseline. The relationship between plasma arsenic trioxide concentrations and QTc interval has not been examined. However, a regression analysis of arsenic dose versus change in steady state QTc interval from baseline in 99 cancer patients shows that QTc prolongation slightly decreased as dose increased [dQTc=61.2-121.5 • Dose, r=0.107, p=0.099]. However, the 0.15 mg/kg dose has the tightest 95% confidence interval; this may be due to the larger number of patients who were administered the 0.15 mg/kg dose. The selection of the dose proposed in the NDA (0.15 mg/kg) was not based on PK/PD relationship but was derived from the dose-escalation Phase I safety studies (#98-23 and #98-46).

II. PHASE IV COMMITMENTS

We recommend that the applicant commit to the following phase IV commitments.

(1)

(2) Conduct an *in vitro* study to assess the inhibition potential of arsenic trioxide on the major cytochrome P-450 isoenzymes.

(3) From the limited pediatric pharmacokinetic information provided in this NDA (n=3), it is possible that the pediatric patients may exhibit higher exposure to arsenic trioxide than adult population. Since the applicant is seeking an approval of the drug for general patient population and the pharmacokinetics of arsenic trioxide in the pediatric population is unknown, a formal pharmacokinetic study be conducted in an appropriate number of children to adequately characterize the pharmacokinetics of arsenic trioxide in the pediatric population. Alternatively, this information can also be obtained from a pediatric efficacy trial using a prospectively planned population pharmacokinetic approach. We refer you to our published document titled "*Guidance for Industry, Population Pharmacokinetics*".

(4) Characterize the pharmacokinetics of arsenic trioxide after administration of 0.15 mg/kg/day of arsenic trioxide in APL patients. Control patients enrolled in the renal and hepatic impaired patient study (see below) may also provide this information.

(5) Because inorganic and organic arsenic are primarily excreted via the kidneys, patients with renal impairment are likely to have a different disposition pattern than the patients with normal renal function. Please conduct a pharmacokinetic study of arsenic trioxide in patients with varying degrees of renal function. We refer you to our published document titled "*Guidance for Industry, Pharmacokinetics in Patients with Impaired Renal Function*" for guidance on study design, categories of renal impairment, and data analysis for conducting such study. Please submit your protocol to the Agency for review.

(6) Since liver is the major site of methylation (detoxification) reactions for arsenic trioxide, accumulation of arsenic trioxide in hepatically impaired patients may occur upon chronic administration of the drug. Please conduct a pharmacokinetic study in hepatically impaired cancer patients. We refer you to our draft document titled "*Guidance for Industry, Pharmacokinetics in Patients with Impaired Liver Function*" for guidance on study design, categories of renal function, and data analysis for conducting such study. Please submit your protocol to the Agency for review.

(7) Data from the all the pharmacokinetic studies conducted as Phase IV commitment should be analyzed to evaluate the influence of age, gender, and race on the pharmacokinetics of arsenic trioxide.

III. LABELING COMMENTS

Please incorporate the changes made in the CLINICAL PHARMACOLOGY/ PHARMACOKINETICS and PRECAUTIONS sections of the package insert for TRISENOX as outlined below:

2 pages redacted from this section of the approval package consisted of draft labeling

DRAFT

LABELING

IV. RECOMMENDATION

The clinical pharmacology information submitted for NDA 21-248 for TRISENOX (Arsenic Trioxide Injection) was reviewed. The Applicant should address the Phase IV Commitments # 1-7 and the Labeling Comments as outlined on pages 5-8 of this review.

Please forward the Phase IV Commitments # 1-7 and the Labeling Comments (Pages 5-8) to the Applicant.

APPEARS THIS WAY
ON ORIGINAL

/S/

Reviewer: Safaa Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

ClinPharm/Biopharm Briefing on July 11, 2000: (Attendees: Drs.: Mehta, Sahajwalla, Rahman, Ibrahim, Huang, Selen, Collins)

RD/FT /S/ 7/19/00

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA 21-248 (Orig.)
HFD-150/Division file
HFD-150/Spillman, Johnson, Hirschfeld
HFD-850/Lesko
HFD-860/Mehta, Rahman, Ibrahim
HFD-205/FOI
CDR/Biopharm

V. TABLE OF CONTENTS

(Note: The appendices (I and II) were retained in the Office of Clinical Pharmacology and Biopharmaceutics and can be obtained upon request)

VI. List of Abbreviations

APL	Acute Promyelocytic Leukemia
As_2O_3	Arsenic trioxide
$As(OH)_3$	Arsenous acid
As(III)	Trivalent inorganic arsenic
As(V)	Pentavalent inorganic arsenic
AUC	Area under the concentration-time curve
Cmax	Peak plasma concentration
CLs	Systemic clearance
DMA	Dimethylarsinic acid
DNA	Deoxyribonucleic acid
dQTc	Change in QTc prolongation from baseline
ECG	Electrocardiograph
ETAAS	Electrothermal atomic absorption spectrometry
HC	Hematological cancers
HPLC	High performance liquid chromatography
ICP-MS	Inductively coupled plasma-mass spectrometry
LLOQ	Lower limit of quantitation
MMA	Monomethylarsonic acid
NDA	New Drug Application
PK	Pharmacokinetics
PML	Promyelocytic leukemia gene
PD	Pharmacodynamics
RARα	Retinoic acid receptor-α gene
RBCs	Red blood cells
Ref.	Reference
SD	Standard deviation
ST	Solid tumors
$t\alpha_{1/2}$	Half-life of distribution phase
$t\beta_{1/2}$	Half-life of elimination phase
Vc	Distribution volume of central compartment

VII. A Question-Based Review

1. ASSAY METHODOLOY

Arsenic content in plasma, red blood cells (RBCs), and urine samples that were collected from patients during the three pharmacokinetic studies (studies 97-66, 98-23, and 98-46) was determined using [redacted] This method [redacted]

The Applicant mentions that [redacted]

The [redacted] ranged from [redacted] ng/ml for plasma, [redacted] ng/ml for RBCs, and [redacted] ng/ml for urine. The [redacted] was [redacted] for both plasma and RBCs and [redacted] for urine.

[redacted] RBCs or urine have been provided in the NDA (requested from the Applicant).

Since the assay used in this NDA [redacted] the submitted PK information is inadequate and was not considered for labeling.

2. CLINICAL PHARMACOLOGY SUMMARY

2.1. DISTRIBUTION

In Vivo:

Distribution of the drug following intravenous administration has not been studied. However, Benramdane et al. 1999 [Ref. 2, Appendix I] investigated the distribution of arsenic species in human organs following fatal intoxication by arsenic trioxide. A 28-year-old man died 3 days after committing suicide by oral absorption of a massive dose of arsenic trioxide (~ 8 g). The collected autopsy samples of most organs were analyzed for total arsenic by electrothermal atomic absorption spectrometry (ETAAS). The arsenic species - inorganic arsenic, in the form of arsenite [As(III)] and arsenate [As(V)], and its metabolites [monomethyl-arsonic acid (MMA) and dimethylarsinic acid (DMA)] – were analyzed by ETAAS after extraction with methanol/water (1:1) and separation by HPLC.

TABLE 1. Concentration of Arsenic Species in Organs and Blood (μg/g dry weight)

Organ	As(III)	DMA	MMA	As(V)	As(III)/ [Mb[a]+As(V)]	MMA/ DMA	Total Arsenic
Liver	122 (83%)[b]	5.9 (4%)	15 (10%)	2.9 (2%)	5	2.5	147
Kidneys	19.9 (75%)	1.6 (6%)	4.5 (17%)	0.53 (2%)	3	2.8	26.6
Muscle	9.2 (75%)	0.73 (6%)	1.9 (16%)	<LOQ[c]	3	2.7	12.3
Heart	9.05 (77%)	0.64(5%)	1.61 (14%)	<LOQ	4	2.5	11.75
Spleen	9.5 (81%)	0.59 (5%)	1.65 (13%)	<LOQ	4	2.8	11.72
Pancreas	9.2 (82%)	0.45 (4%)	1.3 (10%)	<LOQ	5	3.0	11.2
Lung	9.5 (65%)	0.45 (4%)	1.1 (10%)	<LOQ	6	2.4	11.1
Cerebellum	1.15 (47%)	1.6 (19%)	3.7 (30%)	<LOQ	1	2.4	10.9
Brain	4.4 (53%)	1.1 (18%)	2.6 (27%)	<LOQ	1	2.4	8.3
Skin	1.6 (56%)	0.34 (15%)	0.91 (28%)	<LOQ	1	2.7	2.9
Hemolyzed Blood	0.224 (53%)	0.54 (13%)	0.135 (32%)	<LOQ	1	2.5	0.422

a Mb= DMA + MMA.
b Percentage of total arsenic.
c LOQ lower limit of quantification

The results indicated that the liver and kidney showed the highest concentrations of total arsenic, 147 and 27 μg/g, respectively. The total arsenic concentration in hemolyzed blood (0.442 μg/g) was about 7- to 350-fold less than that in all organs. In all organs, As(III) was the predominant species (47-83%) and MMA was more concentrated than DMA (10-30% versus 4-19%). The percentage of As(III), MMA, and DMA in hemolyzed blood was 53%, 32%, and 13%, respectively. As(V) was found in small quantities in liver, kidneys, and blood (2%) and was not detectable in other organs. The ratio of As(III)/metabolites+As(V) ranged from 1-6 and that of MMA/DMA ranged from 2.4-3.0. These ratios in hemolyzed blood were 1.0 and 2.5, respectively.

In Vitro:

Plasma protein binding of arsenic trioxide has not been determined in healthy subjects. Zhang et al. 1998 [Ref. 3, Appendix I] showed that 5.5% of total arsenic was bound to serum proteins in 14 continuous ambulatory peritoneal dialysis (CAPD) patients. Further identification of the arsenic species and protein molecules in serum was carried out in 3 CAPD patients. It was found that only inorganic arsenic species [As(III) or As(V)] were bound to serum proteins and transferrin was the major binding protein.

2.2. METABOLISM

! **Has the metabolism been adequately characterized to identify metabolic pathways and corresponding isozymes?**

The metabolism of inorganic arsenic is well established in literature.

For example, Vahter 1999 [Ref. 4, Appendix I] reported that there are two processes involving in arsenic metabolism: (1) reduction/oxidation reactions that interconvert arsenate [As(V)] and arsenite [As(III)], and (2) methylation reactions, which convert arsenite to monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). A simplified mechanism for the methylation of arsenic is shown below:

$$As(V) \xrightarrow{2e^-} As(III) \xrightarrow{CH_3^+} CH_3As(III) \xrightarrow{CH_3^+} (CH_3)_2As(III)$$

These reactions appear to be similar whether exposure is by the inhalation, oral, or parental route. Before methylation, about 50-70% of absorbed As(V) is rapidly reduced to As(III) by arsenate reductase; however, the mechanism of oxidation of As(III) to As(V) is unknown. The first methylation reaction is catalyzed by arsenite methyl-transferase. The transfer of the second methyl group to form DMA is catalyzed by another enzyme, MMA methyltransferase. The liver is an important initial site for arsenic methylation, where methyltransferase enzymes transfer methyl groups from the co-substrate, S-adenosylmethionine, to arsenite. The amounts of the metaboiites (Table 1) are lower than As(III) indicating that these species are eliminated rapidly from the blood and bile after methylation because of their weak affinity for tissues. Methylation reactions appear to be saturable at doses of about 0.2-1.0 mg/day (0.003-0.015 mg/kg/ day). Neither MMA nor DMA are demethylated back to the trivalent arsenic. Pentavalent arsenic [As(V)] does not undergo methylation; it is excreted unchanged in urine or reduced to trivalent arsenic [As(III)]. Trivalent arsenite [As(III)] is the main form interacting with tissue SH groups resulting in inhibition of many functional groups in various enzymes and receptors. Pentavalent arsenate [AsV)] may substitute for phosphate and bind to transferrin. The methyl derivatives of arsenite (MMA and DMA) are less reactive with tissue constituents and less toxic than inorganic arsenic. The toxicity of the above arsenic species for humans in decreasing order

is: As(III) > As(V) > MMA > DMA (Ref. 4). There are large inter-individual variations in the methylation process of arsenic. Genetic polymorphism in the expression of arsenic methyltransferases has been suggested to account for differences in the metabolism of arsenic in humans. Studies on people exposed to arsenic via drinking water in northern Argentina indicated a lower degree of methylation of arsenic in children than in adults and in men than in women. Children had a significantly higher percentage of inorganic arsenic and a lower percentage of DMA in urine (49% and 47%, respectively), than adults (25% and 74%, respectively) indicating that children are more sensitive to arsenic than adults [Concha et al. 1998, Ref. 5, Appendix I]. Older persons are better methylators of inorganic arsenic than younger individuals, %DMA excreted in urine was 59%, 67%, and 74% in persons of ≤30, 30-50, and > 50 years of age, respectively [Kurttio et al. 1998, Ref. 6, Appendix I]. Women had about 8% higher DMA and 2% less MMA in the urine than men [Ref. 6).

2.3. EXCRETION

The disposition of radiolabeled arsenic trioxide after intravenous administration has not been studied. However, following oral administration of $^{74}As_2O_3$ (6 μCi, 0.01 μg) to six male subjects (Tam et al. 1979, Ref. 7, Appendix I), it is reported that 58±1.5% of radioactive dose was excreted in urine during the first 5 days.

TABLE 2. Percentage of Dose Excreted and Percentage of Radioactivity as Various Forms of Arsenic in Urine for the First 5 Days Following a Single Oral Dose of ^{74}As.

	Percentage of ^{74}As radioactivity in urine				
Subject	Inorganic arsenic	MMA	Un-identified arsenic	DMA	Percentage of dose excreted in urine
1	24.8	18.7	0.3	53.1	60.2
2	24.3	24.6	1.5	49.5	59.9
3	23.0	19.5	0.9	56.6	59.3
4	35.3	24.6	0.3	39.7	50.9
5	27.2	20.8	1.0	5 I.1	57.1
6	28.5	15.4	0.2	55.9	60.1
	27.2 ± I.8[a]	20.64± 1.5[a]	0.7 ±0.2[a]	51.0± 2.6[a]	57.9 ± 1.5[a]

[a] (Mean-+SE for six subjects)

DMA was the major component present in the urine, accounted for 51±2.6% of the radioactivity in urine followed by inorganic arsenic (27±1.8%) and MMA (20.6±1.5%). Unidentified arsenic accounted for 0.7±0.2% of urine radioactivity.

Figure 1 shows the proportion of $^{74}As_2O_3$ radioactivity in urine as total arsenic, inorganic arsenic, MMA, and DMA for Subject No. 5. The pattern of arsenic excretion was similar in the other subjects.

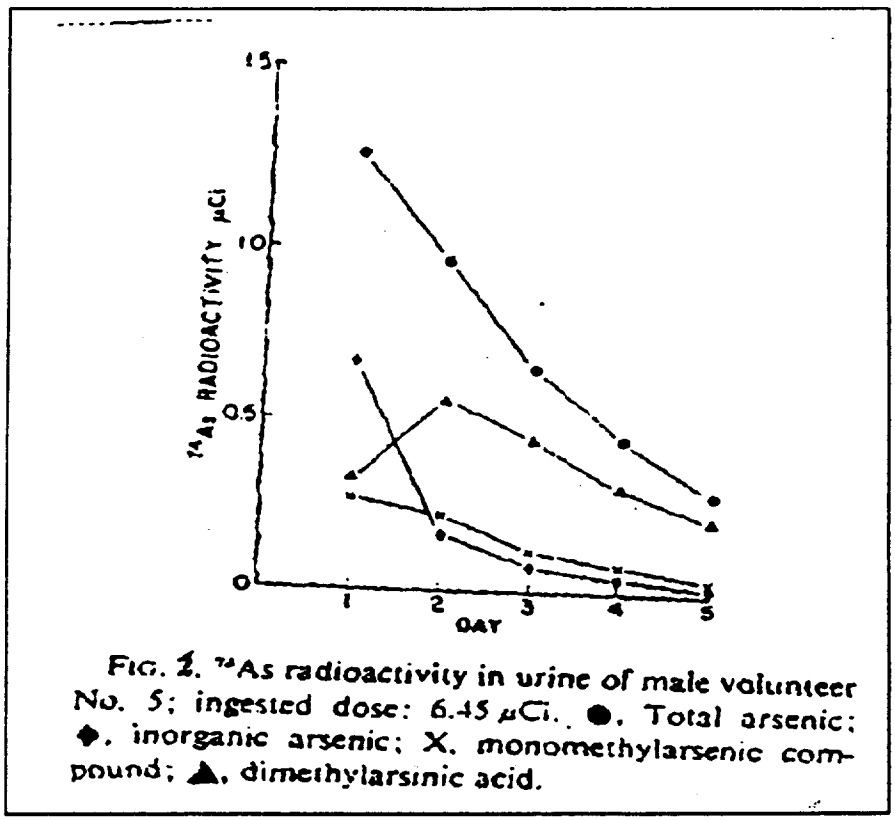


FIG. 1. ^{74}As radioactivity in urine of male volunteer No. 5; ingested dose: 6.45 μCi. ●, Total arsenic; ◆, inorganic arsenic; X, monomethylarsenic compound; ▲, dimethylarsinic acid.

Buchet et al. 1981 (Ref. 8, Appendix I) found that after 4 days the amount excreted in urine was 46%, 78%, and 75% of the ingested dose of 500 μg as trivalent inorganic arsenic (sodium arsenite) (n=3), MMA (n=4) or DMA (n=4), respectively. DMA was excreted unchanged, MMA was slightly (12.6%) methylated into DMA while 75% of the arsenic excreted after ingestion of sodium arsenite was methylated arsenic (about ⅓ as MMA and ⅔ as DMA).

Pomroy et al. 1980 (Ref. 9, Appendix I) reported that following oral doses of ^{74}As (6.4 μCi, 0.06 ng) to six male volunteers in gelatin capsules, 62.3±4.0% of the radioactive dose was recovered in the urine over 7 days and 6.1±2.8% in the feces. Excretion of arsenic in the feces may be due to non-absorption or excretion via the bile.

2.4. PHARMACOKINETICS

! **Have the pharmacokinetics (PK) of arsenic trioxide been adequately characterized?**

--- The pharmacokinetics (PK) of **total arsenic** in plasma and red blood cells (RBCs) were evaluated in three studies, #97-66, #98-23, and #98-46. The outlines of these studies are presented in Appendix II.

In **study #97-66**, twelve patients with acute promyelocytic leukemia were administered arsenic trioxide as 4-hour infusions at daily doses of 0.06 (n=1), 0.10 (n=1), 0.12 (n=1), 0.15 (n=2), 0.16 (n=2), 0.17 (n=1), 0.18 (n=3), and 0.2 (n=1) mg/kg/day. There were 8 males and 4 females, ranged in age from 9-75 years.

In **study 98-23**, twelve patients with advanced hematologic cancers were administered arsenic trioxide as 2-hour infusions at daily doses of 0.1 (n=8), 0.15 (n=3), and 0.3 (n=1) mg/kg/day. There were 9 males, 3 females, aged from 15-75 years.

In **study 98-46**, twenty-two patients with various solid tumors were administered arsenic trioxide as 2-hour infusions at daily doses of 0.15 (n=6), 0.20 (n=3), 0.25 (n=4), 0.30 (n=6), and 0.35 (n=3) mg/kg/day. There were 14 males, 8 females, aged from 11-75 years.

In the above studies, plasma and RBCs samples were analyzed for total arsenic using an
and PK parameters for total arsenic were calculated for each patient using

Tables 1-2, 7-8 and 13-14 (Attachment 1) shows pharmacokinetic parameters for total arsenic on Day 1 in plasma and RBCs for the above three PK studies.

TABLE 3. Effect of the Duration of Infusion*

Mean ± SD (n)	4-Hour Infusion	2-Hour Infusion
Dose-normalized $AUC_{0\text{-}24hr}$ (ng.hr/ml/mg	42 ± 18 (n=12)	40 ± 13 (n=21)

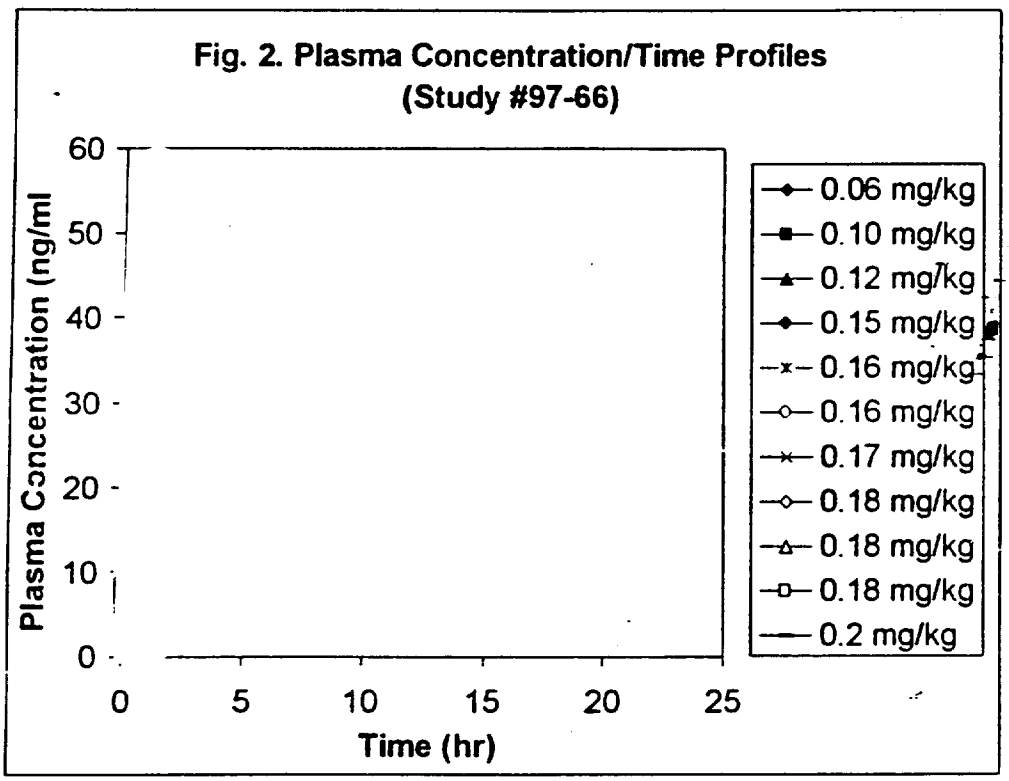
*(Assessed by the Reviewer)

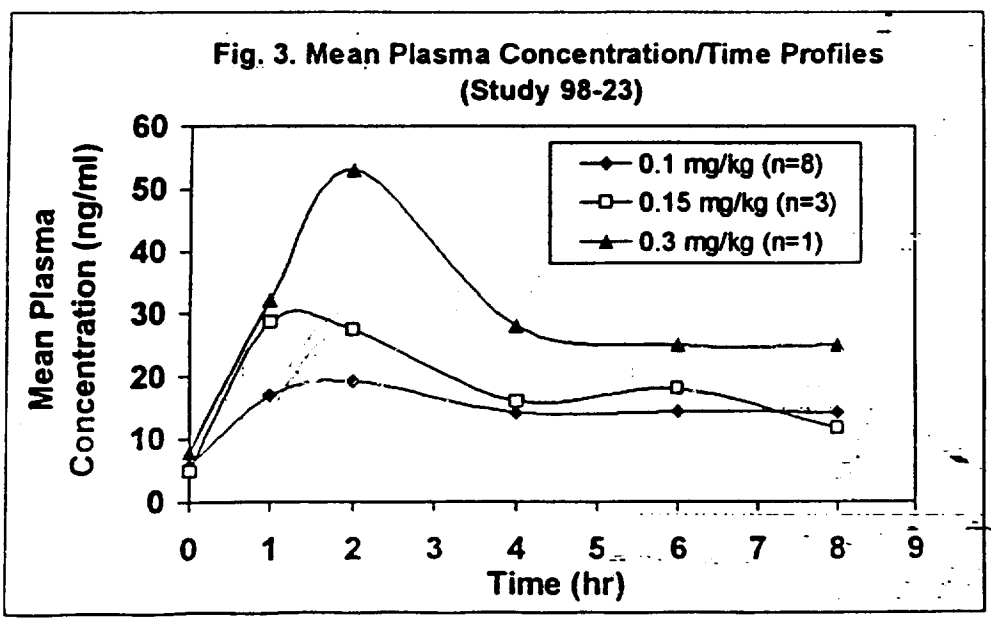
TABLE 4. Plasma/RBCs Ratio (Data pooled from the three PK Studies)*

	Cmax Ratio	$AUC_{0\text{-}24hr}$ Ratio
Mean	0.82	0.92
SD	0.36	0.26
n	46	46

*(Assessed by the Reviewer)

Figure 2 shows the plasma concentration/time profiles for the ALP patients (Study #97-66). **Figure 3 and 4** show mean plasma concentration/time profiles for patients with advanced hematological cancers (Study #98-23) and for patients with solid tumors (Study #98-46), respectively. **Figure 5** shows the trough plasma levels versus time for study #97-66.





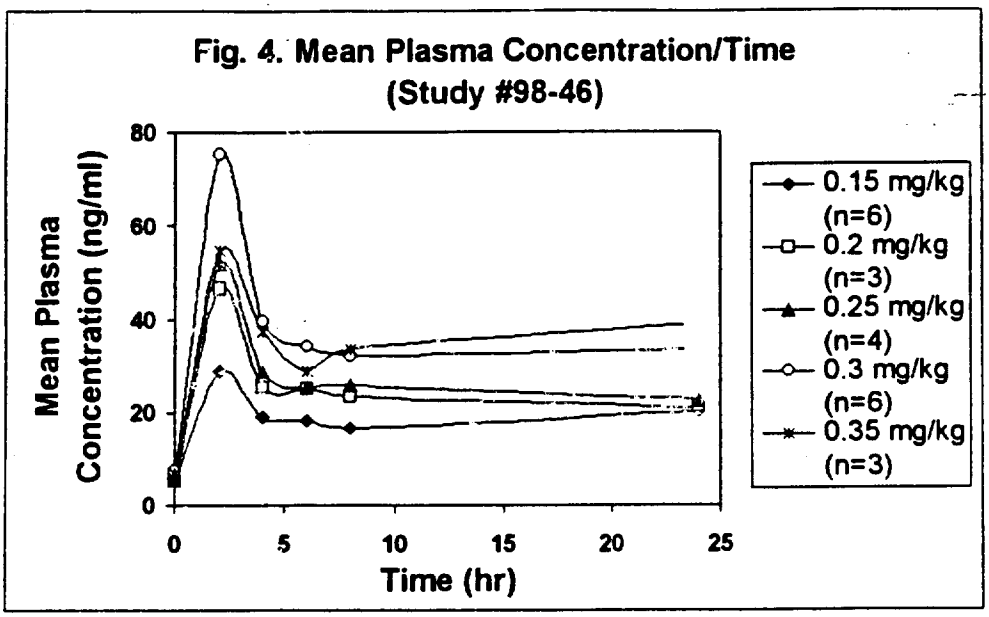


Fig. 4. Mean Plasma Concentration/Time
(Study #98-46)
Mean Plasma Concentration (ng/ml)
80
60
40
20
0
0
5
10
15
20
25
Time (hr)
0.15 mg/kg (n=6)
0.2 mg/kg (n=3)
0.25 mg/kg (n=4)
0.3 mg/kg (n=6)
0.35 mg/kg (n=3)

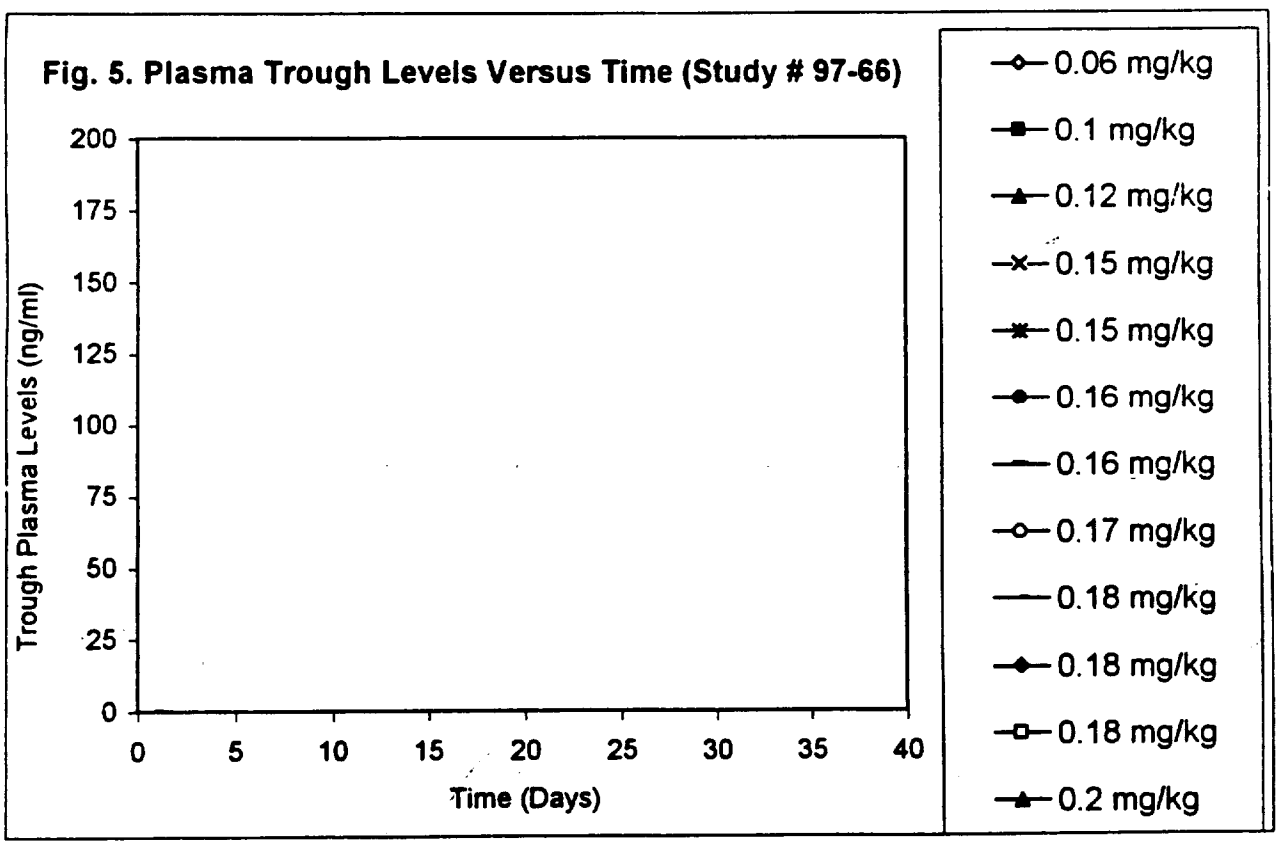


Fig. 5. Plasma Trough Levels Versus Time (Study # 97-66)
Trough Plasma Levels (ng/ml)
200
175
150
125
100
75
50
25
0
0
5
10
15
20
25
30
35
40
Time (Days)
0.06 mg/kg
0.1 mg/kg
0.12 mg/kg
0.15 mg/kg
0.15 mg/kg
0.16 mg/kg
0.16 mg/kg
0.17 mg/kg
0.18 mg/kg
0.18 mg/kg
0.18 mg/kg
0.2 mg/kg

From the above Figures and Tables 3-10, it is concluded that:

- Plasma concentration/time profiles of total arsenic appear to decline in a biexponential pattern. However, these profiles do not represent the inorganic arsenic, the actual active species. It is not known how much inorganic arsenic, methylated metabolites (MMA and DMA), or other forms of organic arsenic appear in blood circulation after intravenous administration of the therapeutic dose of ATRIVEX (0.15 mg/kg).

- The elimination phase was not adequately characterized. The elimination half-life (~ 100 hours) was not accurately estimated and it is considered to be misleading because the 24-hour blood sampling was not long enough to adequately characterize the elimination phase of the drug. At least 300 hours are required to accurately estimate the elimination half-life. In addition, this value was estimated for total arsenic and it does not reflect the true elimination half-life of inorganic arsenic.

- [redacted]

- The duration of infusion (2- or 4- hour) had no effect on dose-normalized area under plasma concentration/time curve ($AUC_{0\text{-}24hr}$) (TABLE 3).

- Total arsenic is equally distributed in plasma and RBCs; mean Cmax or $AUC_{0\text{-}24hr}$ ratio is close to unity (TABLE 4).

In conclusion, this PK information is considered irrelevant since it was obtained for total arsenic and not the active drug moiety, arsenic trioxide. This PK information will not considered for labeling.

2.5. SPECIAL POPULTIONS

! **Have the PK of arsenic trioxide been adequately evaluated in sub-populations of subjects/patients (e.g., disease, renal/hepatic impairment)? In addition, have the effects of certain variables (e.g., age, gender, race) on the PK of arsenic trioxide been adequately addressed to support any dosage adjustment in the package insert?**

The effects of age, gender, and race on the pharmacokinetics of arsenic trioxide have not been studied. The sponsor separately assessed the effect of age, gender, and race in the studies # 97-66, # 98-23 and 98-46. From this analysis, the Applicant claims that the extent of exposure to arsenic trioxide (as assessed by plasma $AUC_{0\text{-}24hr}$ or $AUC_{0\text{-}8hr}$) was similar for males and females and differences in exposure in patients ≥ 60 years of age is not expected to be clinically relevant (see Attachment 1).

The reviewer assessed the effect of these factors and the effect of cancer type using the combined data from the two PK studies #79-66 and #98-46. This database comprised of 34 patients ranging in age from 9-75 years. There were 22 males and 12 females and 29 Caucasians, 4 Blacks, and 1 Others. In these analyses, $AUC_{0\text{-}24hr}$ was normalized to 1-mg dose. $AUC_{0\text{-}8hr}$ values, determined in study #98-23 (n=12), were not included in these analysis.

2.5.1. Effect of Age

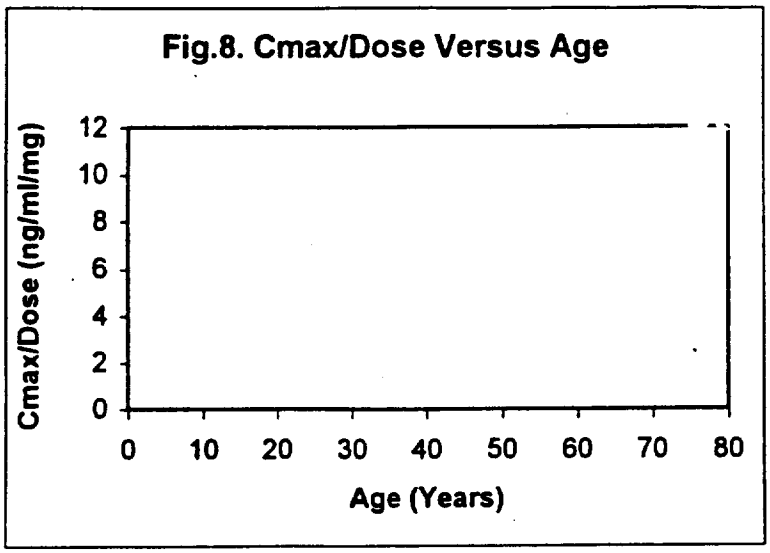
TABLE 6. Mean ± SD (n) Dose-normalized $AUC_{0\text{-}24hr}$ Versus Age

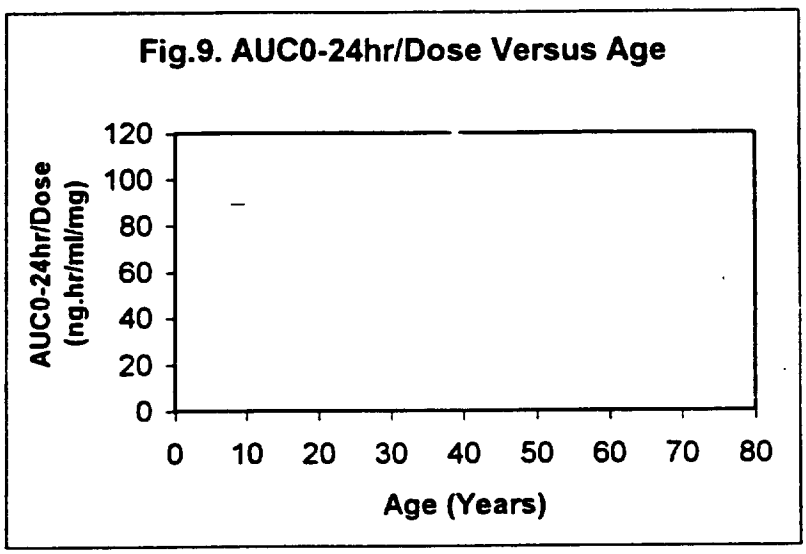
	Age Group (Years)	$AUC_{0\text{-}24hr}$ /Dose (ng.hr/ml/mg)	p-value
I	< 16	79 ± 41 (n=3)	0.00018*
II	16-60	36 ± 12 (n=21)	
III	> 60	43 ± 8 (n=10)	0.127†

* Two-sided T-Test, Group I vs II
† Two-sided T-Test, Group III vs II

From TABLE 6, it appears that age has no effect on dose-normalized $AUC_{0\text{-}24hr}$ values for patients of 16 years of age and above. However, pediatric patients (Age < 16 years) may have higher exposure to total arsenic than adults. Dose-normalized $AUC_{0\text{-}24hr}$ values were about 2-fold higher than those for adults (Age=16-60 years). However, because of the small sample size (n=3) and high variability (CV=50-80%) in the pediatric group, the 2-fold increase in $AUC_{0\text{-}24hr}$/Dose may not be an appropriate estimate. Two patients (9 and 11 years of age) had very high $AUC_{0\text{-}24hr}$/Dose values; 91 ng.hr/ml/mg and 113 ng.hr/ml/mg, respectively, while the third patient (13 years of age) had $AUC_{0\text{-}24hr}$/Dose values in the range of those for adults (see Figures 8 and 9).

Patients of 60 years of age and above had a 20% higher $AUC_{0\text{-}24hr}$ than those of 16-60 years of age; but this effect was not statistically significant (p=0.127). The clinical significant of this age effect is not known as it was assessed for total arsenic and not for the reactive inorganic species. At the present time, dosage recommendations can not be made, however, we recommend that caution should be exercised when pediatric APL patients are treated with TRISENOX.





2.5.2. Effect of Gender

TABLE 7.

Mean± SD (n)	Males	Females	p-value*
$AUC_{0\text{-}24hr}$/Dose (ng.hr/ml/mg)	33±9.05 (22)	45±12.9 (12)	0.02

Two-sided T-Test

Exposure to total arsenic appears to be higher in females than in males (TABLE 7). Dose-normalized $AUC_{0\text{-}24hr}$ values were about 20% and 35%, respectively, higher in females than in males. The clinical significant of this

gender effect can not be assessed as the PK parameters were derived for total arsenic and not for the reactive inorganic species.

2.5.3. Effect of Race

TABLE 8.

Mean ± SD (n)	Caucasians	Blacks	p-value*	Others
$AUC_{0\text{-}24hr}$/Dose (ng.hr/ml/mg)	38±10 (n=29)	24±6.1 (n=4)	0.024	59 (n=1)

*Two-sided T-Test, Caucasians vs Blacks

No definitive conclusion could be drawn because of the small sample size of other ethnic groups compared to Caucasians (TABLE 8).

2.5.4. Renal Impairment

The effect of renal impairment on arsenic pharmacokinetics has not been formally studied.

Because arsenic trioxide is primarily excreted via the kidneys and it accumulates in renally impaired patients upon chronic administration, we recommend that patients with renal impairment should be treated with caution and should be closely monitored for side effects, especially QTc prolongation. We recommend a formal PK study be performed in renally impaired cancer patients. The results of this study will help to provide an adequate dosage recommendations in such patient population.

2.5.5. Hepatic Impairment

The effect of hepatic impairment on arsenic pharmacokinetics has not been formally studied.

However, Buchet et al. 1982 (Ref. 11, Appendix I) reported that following intravenous administration (500 μg), urinary excretion of inorganic arsenic during the first 24 hours was unaffected by hepatic insufficiency; 137±7.4 μg in healthy subjects (n=4) and 143±9.8 μg in patients with hepatic insufficiency (n=12).

because the data

These urinary data are considered preliminary ~~and~~ do not indicate if the systemic clearance of arsenic trioxide did change in hepatic patients. No information was provided on the degree of hepatic insufficiency. As the main site of methylation reactions of arsenic trioxide is the liver, accumulation of arsenic trioxide in hepatically impaired patients may occur upon chronic administration. We recommend that a formal PK study should be conducted in hepatically impaired cancer patients. The results of this study will help to provide an adequate dosage recommendations in such patient population.

We recommend that patients with hepatic impairment be treated with caution and be closely monitored for side effects, especially QTc prolongation.

2.6. DRUG-INTERACTION INTERACTIONS

! **Has any formal drug interaction study been conducted?**

No formal pharmacokinetic drug interaction studies have been conducted.

3. PHARMACOKINETIC/PHARMACODYNAMIC RELTIONSHIPS

! **Was there any attempt to identify any relationship between drug effects or adverse events with plasma arsenic trioxide concentrations?**

One of the most clinically relevant adverse events noted in patients treated with arsenic trioxide is prolongation of the QT/QTc interval. The mechanism by which arsenic prolongs cardiac repolarization has not been established.

Electrocardiographic tracings from 99 cancer patients who participated in studies #PLRXAS01, 97-66, 98-23, and 98-46 were evaluated. The demographics of these patients are presented in Table 2 (Attachment 2).

All QT interval measurements were corrected for heart rate by the method of Basett:

QTc=QT/SQRT(60/HeartRate)

A retrospective regression analysis was performed on the QTc intervals. The steady–state value of QTc change from baseline and the half-time for approaching steady-state were evaluated by fitting the following equation to the QTc interval data using nonlinear least squares regression:

$$dQTc = a \bullet (1 - 0.5^{(t/b)})$$

where "dQTc" is the change in QTc prolongation from baseline, "t" is the time since first infusion for this course of treatment, "a" is the steady state prolongation of QTc, and "b" is the half-time for first-order approach to steady state. The 95% confidence intervals were also computed. Results are shown in Attachment 2.

The results indicate that QTc prolongation tends to reach a higher steady-state value in male patients (dQTc=62±13 msec, n=57) than in female patients (dQTc =35±5 msec, n=42). The steady-state QTc was reached sooner in females than in males, 3 days versus 10 days respectively (Figures 2 and 3, Attachment 2).

No significant age differences were observed in the maximum change in steady-state QTc prolongation from baseline.

The regression analysis of arsenic dose versus change in steady state QTc interval from baseline (Figure 4, Attachment 2) indicates that there is a slight decrease in QTc prolongation as dose increased [dQTc=61.2-121.5 * Dose, r=0.107, p=0.099]. However, at the 0.15 mg/kg dose, the 95% confidence interval was the tightest; this may be due to the large number of patients who were administered this dose. The relationship between plasma arsenic trioxide concentrations and QTc interval has not been examined.

- **Was the proposed labeling dose selected based on the relationship between efficacy and plasma concentrations?**

The proposed labeling dose is 0.15 mg/kg infused daily over 1-2 hours for at least 60 days. The selection of this dose was not based on the relationship between efficacy and plasma concentrations of arsenic trioxide.

Initially, the dose selected (in milligram) was derived from the literature on APL patients who were treated with arsenic trioxide. The supporting dose-escalation safety Phase I studies (#98-23 and #98-46) in patients with other malignancies provided the safe and effective doses for subsequent trials. Later, the dose was modified to a fixed, weight-based dose of 0.15 mg/kg to accommodate pediatric patients. This fixed dose of 0.15 mg/kg was used in the two pivotal studies in APL patients (#97-66 and #PLRXAS01).

Attachment 1

Pharmacokinetic Data for the Three PK Studies

Table 8: Plasma Pharmacokinetic Parameters by Patient after a 4-Hour Intravenous Infusion of Arsenic Trioxide on Day 1

Patient ID	Sex/ Race	Age	Dose		t_{max} (hr)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	$AUC_{0\text{-}last}$ (ng·hr/mL)
			(mg)	(mg/kg)				
1001	F/C	36	10	0.18	4	26	19	473
1002	M/C	45	10	0.12	4	19	175	381
1003	F/C	30	10	0.18	2	31	27	434
1004	M/C	62	10	0.10	2	22	149	495
1005	M/C	25	10	0.06	4	20	NA	430
1006	M/C	75	15	0.20	1	48	39	691
1007	F/B	40	15	0.16	1	26	78	413
1008	F/C	13	10	0.18	2	18	197	337
1009	M/C	9	5	0.17	8	21	133	457
1010	M/C	70	15	0.16	4	40	196	631
1011	M/B	28	14.3	0.15	2	28	70	411
1012	M/B	23	15	0.15	4	30	18	250
		Mean ± SD		0.15 ± 0.04	3.2 ± 1.9	27.4 ± 9	100 ± 72	450 ± 119

NA = not able to determine.

2

Table 6: RBC Pharmacokinetic Parameters by Patient after a 4-Hour Intravenous Infusion of Arsenic Trioxide on Day 1

Patient ID	Sex/ Race	Age	Dose		t_{max} (hr)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	$AUC_{0\text{-}24hr}$ (ng·hr/mL)
			(mg)	(mg/kg)				
1001	F/C	36	10	0.18	4	27	51	374
1002	M/C	45	10	0.12	4	16	29	261
1003	F/C	30	10	0.18	4	27	15	372
1004	M/C	62	10	0.10	4	23	28	376
1005	M/C	25	10	0.06	4	30	18	414
1006	M/C	75	15	0.20	1	64	20	695
1007	F/B	40	15	0.16	1	32	98	547
1008	F/C	13	10	0.18	4	35	18	491
1009	M/C	9	5	0.17	2	24	47	380
1010	M/C	70	15	0.16	4	31	60	520
1011	M/B	28	14.3	0.15	4	26	6	416
1012	M/B	23	15	0.15	4	29	18	239
		Mean ± SD		0.15 ± 0.04	3.3 ± 1.2	30.3 ± 12	34 ± 26	424 ± 125

3

Table 4: Mean ± SD Pharmacokinetic Parameters Grouped According to Dose Level

Pharmacokinetic Parameters	Dose Levels					
	Plasma			Red Blood Cells		
	5 mg (n = 1)	10 mg (n = 6)	15 mg (n = 5)	5 mg (n = 1)	10 mg (n = 6)	15 mg (n = 5)
C_{max} (ng/mL)	21	23 ± 5	34 ± 9	24	26 ± 6	36 ± 16
$AUC_{0\text{-}24hr}$ (ng·hr/mL)	457	425 ± 58	479 ± 180	380	381 ± 74	483 ± 169
normalized to dose of 1 mg						
C_{max} (ng/mL/dose)	4.2	2.3 ± 0.5	2.3 ± 0.6	4.8	2.6 ± 0.6	2.4 ± 1.0
$AUC_{0\text{-}24hr}$ (ng·hr/mL/dose)	91	42 ± 6	32 ± 12	76	38 ± 7	32 ± 11

4
Table 3: Mean ± SD Pharmacokinetic Parameters Grouped According to Age

Pharmacokinetic Parameters	Age Groups in Years					
	Plasma			Red Blood Cells		
	<18 (n = 2)	18-59 (n = 7)	>59 (n = 3)	<18 (n = 2)	18-59 (n = 7)	>59 (n = 3)
C_{max} (ng/mL)	20 ± 2	26 ± 5	37 ± 13	30 ± 8	27 ± 5	41 ± 20
AUC_{0-24hr} (ng·hr/mL)	397 ± 85	399 ± 71	606 ± 101	435 ± 79	375 ± 103	530 ± 160

5
Table 4: Mean ± SD Pharmacokinetic Parameters Grouped According to Gender

Parameter	Plasma		Red Blood Cells	
	Male (n = 8)	Female (n = 4)	Male (n = 8)	Female (n = 4)
C_{max} (ng/mL)	29 ± 11	25 ± 5	30 ± 14	30 ± 4
AUC_{0-24hr} (ng·hr/mL)	468 ± 140	414 ± 57	448 ± 137	446 ± 87

6
Table 5: Mean ± SD Pharmacokinetic Parameters Grouped According to Race

Parameter	Plasma		Red Blood Cells	
	Cauc. (n = 9)	Black (n = 3)	Cauc. (n = 9)	Black (n = 3)
C_{max} (ng/mL)	27 ± 10	28 ± 2	31 ± 14	29 ± 3
AUC_{0-24hr} (ng·hr/mL)	481 ± 113	358 ± 94	431 ± 124	401 ± 155

no effects of age or gender were apparent. Levels of arsenic in plasma and RBCs on the eighth day of treatment were 100% to 400% times those on the first day of treatment. The quantity of arsenic detected in urine over a 24-hour period after a single dose represented approximately 10% of the administered dose.

No clinically significant adverse events in this study were unexpected in this patient population. Therefore, the concentrations of arsenic measured in this study are considered to be within a safe range. The range of arsenic concentrations in this patient population did not correlate with adverse events.

Table 7: Pharmacokinetic Parameters in Plasma after a 2-Hour Intravenous Infusion of Arsenic Trioxide on Day 1

Patient ID	Gender /Race	Age	Dose		t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-last} (ng·hr/mL)
			(mg)	(mg/kg)			
1003	F/C	32	14.9	0.30	2	53	244
1053	M/C	42	6.8	0.10	2	15	100
1054	M/C	67	7.3	0.10	2	16	104
1055	M/C	63	7.7	0.10	2	17	101
1056	M/B	52	6.6	0.10	2	11	70
1057	M/C	54	7	0.10	2	15	105
1058	M/C	62	8.9	0.10	2	14	94
1059	M/C	60	11.9	0.10	1	22	120
1060	M/C	58	8.2	0.10	1	20	93
1061	M/C	52	11.3	0.15	2	24	120
1062	F/O	70	11	0.15	2	27	118
1063	F/C	38	16.5	0.15	1	53	[illegible]
		Mean ± SD		0.13 ± 0.06	1.75 ± 0.5	24 ± 14	120 ± 46

NA = not able to determine.
B = Black
C = Caucasian
O = Other

8

Table 8: Pharmacokinetic Parameters in Red Blood Cells After a 2-Hour Intravenous Infusion of Arsenic Trioxide on Day 1

Patient ID	Gender /Race	Age	Dose		t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-last} (ng·hr/mL)
			(mg)	(mg/kg)			
1003	F/C	32	14.9	0.30	2	74	349
1053	M/C	42	6.8	0.10	2	15	78
1054	M/C	67	7.3	0.10	4	23	131
1055	M/C	63	7.7	0.10	2	29	125
1056	M/B	52	6.6	0.10	2	10	58
1057	M/C	54	7	0.10	4	30	182
1058	M/C	62	8.9	0.10	2	24	119
1059	M/C	60	11.9	0.10	2	39	232
1060	M/C	58	8.2	0.10	2	31	178
1061	M/C	52	11.3	0.15	2	29	163
1062	F/O	70	11	0.15	2	34	156
1063	F/C	38	16.5	0.15	1	42	161
		Mean ± SD		0.13 ± 0.06	2.25 ± 0.9	32 ± 16	161 ± 75

NA = not able to determine.
B = Black
C = Caucasian
O = Other

9

Table 9: Mean Pharmacokinetic Parameters Grouped According to Dose

Dose (mg/kg)	Sample	Mean ± SD		Age (years) Mean ± SD	No. of Males/Females
		C_{max} (ng/mL)	AUC_{0-last} (ng·hr/mL)		
0.10	Plasma	16 ± 3	98 ± 14	57.25 ± 7.3	8/0
	RBC	25 ± 9	138 ± 57		
0.15	Plasma	35 ± 16	135 ± 28	53.3 ± 16	1/2
	RBC	35 ± 7	160 ± 4		
0.30	Plasma	53	244	32	0/1
	RBC	74	349		

10
Table 9: Mean Pharmacokinetic Parameters Grouped According to Age

Age Range (years)	Sample	Mean ± SD		Mean Dose (mg/kg)	No. of Males/Females
		C_{max} (ng/mL)	AUC_{0-hr} (ng hr/mL)		
32 - 59	Plasma	27 ± 18	129 ± 59	0.14	5/2
	RBC	33 ± 21	167 ± 94		
60 - 70	Plasma	19 ± 5	107 ± 11	0.11	4/1
	RBC	30 ± 7	153 ± 47		

11
Table 10: Mean Pharmacokinetic Parameters Grouped According to Gender

Gender	Sample	Mean ± SD		Mean Dose (mg/kg)	Mean ± SD Age (years)
		C_{max} (ng/mL)	AUC_{0-hr} (ng hr/mL)		
Male	Plasma	17 ± 4	101 ± 15	0.11	56.7 ± 7.5
	RBC	26 ± 9	141 ± 54		
Female	Plasma	44 ± 15	177 ± 63	0.20	46.7 ± 20.4
	RBC	50 ± 21	222 ± 110		

12
Table 11: Arsenic Concentration in Plasma and Red Blood Cells on Study Days 1 and 8

Patient ID	Dose (mg/kg)	Plasma Concentration (ng/mL)			RBC Concentration (ng/mL)		
		Day 1	Day 8		Day 1	Day 8	
		2 hr	0 hr	2 hr	2 hr	0 hr	2 hr
1053	0.10	15	28	38	15	NA	25
1058	0.10	14	31	49	24	21	50
1059	0.10	12	21	35	39	22	40
1060	0.10	15	35	57	31	35	68
1061	0.15	24	33	55	29	29	50
1063	0.15	31	24	62	34	14	53

NA = not applicable; sample was not collected.

Table 13: Arsenic Plasma Pharmacokinetic Parameters for 24 Hours after First Intravenous Infusion of Arsenic Trioxide

Patient ID	Gender/ Race	Age	Dose		t_{max} (hr)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	AUC_{0-24hr} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)
			mg	mg/kg					
1072	F/C	68	10.5	0.15	2	29	308	524	10287
1073	M/C	58	13.2	0.15	24	25	NA	485	NA
1074	F/C	54	10.7	0.15	24	29	NA	609	NA
1075	M/C	33	13.6	0.15	2	176	NA	585	NA
1077	M/B	33	10.5	0.15	2	215	197	707	5542
1078	F/C	11	3.5	0.15	2	37	NA	396	NA
1079	M/C	52	18	0.20	2	46	NA	579	NA
1080	M/C	49	26.9	0.20	2	53	242	562	7911
1081	F/O	60	11.7	0.20	2	41	NA	696	NA
1082	F/C	33	30	0.25	2	51	NA	575	NA
1083	M/C	51	16.7	0.25	2	42	25	541	1072
1084	M/C	72	23.9	0.25	2	54	90	753	4374
1085	M/C	47	21	0.25	2	62	58	629	2565
1087	F/C	47	14	0.30	2	34	NA	737	NA
1088	M/C	70	23.4	0.30	2	48	NA	975	NA
1089	M/C	59	25.2	0.30	2	170	43	866	2294
1090	M/C	68	28.2	0.30	2	102	34	1164	2957
1091	M/C	34	29.4	0.30	2	52	NA	655	NA
1092	M/C	75	20.7	0.30	2	45	NA	861	NA
1093	F/C	75	16	0.35	2	59	NA	853	NA
1094	M/C	61	33	0.35	24	50	NA	984	NA
1095	F/C	44	18.2	0.35	2	63	62	746	3950
		Mean ± SD		0.245 ± 0.07	5 ± 7.7	67 ± 52	118 ± 104	704 ± 186	4330 ± 2942

NA = not able to determine.
B = Black
C = Caucasian
O = Other

14

Table 6: Arsenic Red Blood Cell Pharmacokinetic Parameters for 24 Hours after First Intravenous Infusion

Patient ID	Gender /Race	Age	Dose		t_{max} (hr)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	AUC_{0-24hr} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)
			mg	mg/kg					
1072	F/C	68	10.5	0.15	2	40	37	531	1499
1073	M/C	58	13.2	0.15	2	60	NA	667	NA
1074	F/C	54	10.7	0.15	2	58	45	967	3167
1075	M/C	33	13.6	0.15	2	69	44	405	1101
1077	M/B	33	10.5	0.15	2	176	68	753	2826
1078	F/C	11	3.5	0.15	2	34	NA	316	NA
1079	M/C	52	18	0.20	2	74	54	754	2778
1080	M/C	49	26.9	0.20	2	94	27	1034	2229
1081	F/O	60	11.7	0.20	2	46	69	654	3256
1082	F/C	33	30	0.25	6	74	62	1045	4718
1083	M/C	51	16.7	0.25	2	54	13	579	807
1084	M/C	72	23.9	0.25	2	76	38	775	2217
1085	M/C	47	21	0.25	2	111	30	919	2151
1087	F/C	47	14	0.30	2	116	89	1053	5832
1088	M/C	70	23.4	0.30	2	54	114	1000	7419
1089	M/C	59	25.2	0.30	2	183	9	604	1204
1090	M/C	68	28.2	0.30	2	104	51	1106	3829
1091	M/C	34	29.4	0.30	2	78	NA	666	NA
1092	M/C	75	20.7	0.30	2	144	22	1282	3067
1093	F/C	75	16	0.35	2	76	44	1007	3462
1094	M/C	61	33	0.35	4	106	71	1500	8049
1095	F/C	44	18.2	0.35	2	101	19	1167	3018
		Mean ± SD		0.243 ± 0.07	2.3 ± 0.9	88 ± 40	48 ± 27	854 ± 293	3296 ± 1989

NA = not able to determine
B = Black
C = Caucasian
O = Other

Table 15: Mean Pharmacokinetic Parameters for 24 Hours after the First Dose for Regimen A Patients Grouped According to Dose Level

Dose (mg/kg)	Sample	Mean ± SD			
		C_{max} (ng/mL)	$t_{1/2}$ (hr)	AUC_{0-24hr} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)
0.15	Plasma	85 ± 86	253 ± 78	551 ± 108	7915 ± 3355
$n = 6$	RBC	73 ± 52	49 ± 14	607 ± 239	2148 ± 1003
0.20	Plasma	47 ± 6	242	613 ± 73	7911
$n = 3$	RBC	71 ± 24	50 ± 21	814 ± 197	2754 ± 514
0.25	Plasma	52 ± 8	58 ± 33	625 ± 93	2670 ± 1654
$n = 4$	RBC	79 ± 24	36 ± 21	830 ± 200	2473 ± 1631
0.30	Plasma	89 ± 62	38 ± 7	936 ± 181	2626 ± 467
$n = 4$	RBC	114 ± 53	66 ± 46	941 ± 229	4571 ± 2683

Table 16: Mean Pharmacokinetic Parameters of Regimen A Patients (Adults)[1] Grouped According to Age

Age Range in Years	Sample	Mean ± SD				Mean Dose (mg/kg)	No. of Males/Females
		C_{max} (ng/mL)	$t_{1/2}$ (hr)	AUC_{0-24hr} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)		
33 - 47	Plasma	108 ± 82	128 ± 98	647 ± 72	4054 ± 2105	0.22	3/2
	RBC	109 ± 43	59 ± 23	825 ± 269	3326 ± 1923		
49 -59	Plasma	61 ± 54	103 ± 54	607 ± 133	3759 ± 3647	0.21	5/1
	RBC	87 ± 49	30 ± 20	768 ± 192	2037 ± 1009		
60 - 72	Plasma	55 ± 28	144 ± 145	823 ± 250	5873 ± 3888	0.24	3/2
	RBC	64 ± 26	62 ± 32	813 ± 238	3644 ± 2295		

[1] Patient [redacted] age = 11 years) is not included in the summary presented in this table

Table 17: Mean Pharmacokinetic Parameters for Regimen A Patients Grouped According to Gender

Sex	Sample	Mean ± SD				Mean Dose (mg/kg)	Mean ± SD Age (years)
		C_{max} (ng/mL)	$t_{1/2}$ (hr)	AUC_{0-24hr} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)		
Male	Plasma	90 ± 66	99 ± 87	618 ± 204	3816 ± 2317	0.23	54 ± 13
	RBC	96 ± 45	45 ± 31	781 ± 215	2656 ± 1906		
Female	Plasma	37 ± 8	308	590 ± 123	10287	0.20	46 ± 21
	RBC	61 ± 30	61 ± 21	761 ± 307	3694 ± 1651		

Attachment 2

QTc Prolongation Data

Demographics:

The following tables show the breakdown of subjects by Gender, Race, and Age Group:

Table 2: One-way Breakdown of Patient Demographics

	Subjects	% of Total
Gender:		
Female	42	42.4%
Male	57	57.6%
Ethnicity:		
Black	10	10.1%
Caucasian	80	80.8%
Hispanic	4	4.0%
Islander	4	4.0%
Other	1	1.0%
Age Group:	99	100.0%
00-17 yrs	10	10.1%
18-59 yrs	60	60.6%
60+++ yrs	29	29.3%
Total Enrolled Subjects:	99	100.0%

Table 3: Cross-tabulation of Gender by Ethnicity

		Black	Caucasian	Hispanic	Islander	Other	All Races
Female	Count	5	32	3	1	1	42
	% in Gender	11.9%	76.2%	7.1%	2.4%	2.4%	100.0%
	% in Race	50.0%	40.0%	75.0%	25.0%	100.0%	42.4%
Male	Count	5	48	1	3		57
	% in Gender	8.8%	84.2%	1.8%	5.3%		100.0%
	% in Race	50.0%	60.0%	25.0%	75.0%		57.6%
Both	Count	10	80	4	4	1	99
	% in Gender	10.1%	80.8%	4.0%	4.0%	1.0%	100.0%
	% in Race	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 4: Cross-tabulation of Gender by Age Group

		00-17 yrs	18-59 yrs	60+ yrs	All Ages
Female	Count	7	27	8	42
	% in Gender	16.7%	64.3%	19.0%	100.0%
	% in Race	70.0%	45.0%	27.6%	42.4%
Male	Count	3	33	21	57
	% in Gender	5.3%	57.9%	36.8%	100.0%
	% in Race	30.0%	55.0%	72.4%	57.6%
Both	Count	10	60	29	99
	% in Gender	10.1%	60.6%	29.3%	100.0%
	% in Race	100.0%	100.0%	100.0%	100.0%

Table 5: Cross-tabulation of Ethnicity by Age Group

		00-17	18-59	60+++	All Ages
Black	Count		8	2	10
	% in Race		80.0%	20.0%	100.0%
	% in AgeGrp		13.3%	6.9%	10.1%
Caucasian	Count	10	47	23	80
	% in Race	12.5%	58.8%	28.8%	100.0%
	% in AgeGrp	100.0%	78.3%	79.3%	80.8%
Hispanic	Count		3	1	4
	% in Race		75.0%	25.0%	100.0%
	% in AgeGrp		5.0%	3.4%	4.0%
Islander	Count		2	2	4
	% in Race		50.0%	50.0%	100.0%
	% in AgeGrp		3.3%	6.9%	4.0%
Other	Count			1	1
	% in Race			100.0%	100.0%
	% in AgeGrp			3.4%	1.0%
Total	Count	10	60	29	99
	% in Race	10.1%	60.6%	29.3%	100.0%
	% in AgeGrp	100.0%	100.0%	100.0%	100.0%

QTc Analysis:

Comparison of Reproductive-age Females with Others: The following tables contrast women in their reproductive years (designated "Fertile Females" for brevity) from males and non-reproductive-age females. ECG measurements include baseline QTc, the maximum QTc observed during or shortly after the course of therapy or during steady-state, which is assumed to have been attained after 10 days of infusion. Differences between fertile females and others were assessed by means of standard Chi Square contingency table analyses.

Table 6: QTc At Baseline

	Normal	Borderline	Prolonged	Overall
Fertile Females	27 (77.1%)	5 (14.3%)	3 (8.6%)	35 (100.0%)
Others	55 (56.7%)	26 (26.8%)	16 (16.5%)	97 (100.0%)
Overall	82 (62.1%)	31 (23.5%)	19 (14.4%)	132 (100.0%)

Chi Square = 4.57; d.f = 2; p = 0.102
No Significant Difference Detected

Table 7: Maximum QTc Observed During the Period of Infusion

	Normal	Borderline	Prolonged	Overall
Fertile Females	7 (17.9%)	8 (20.5%)	24 (61.5%)	39 (100.0%)
Others	4 (5.7%)	15 (21.4%)	51 (72.9%)	70 (100.0%)
Overall	11 (10.1%)	23 (21.1%)	75 (68.8%)	109 (100.0%)

Chi Square = 4.19; d.f = 2; p = 0.123
No Significant Difference Detected

Table 8: Maximum QTc Observed During the Steady-State Phase of Infusion

	Normal	Borderline	Prolonged	Overall
Fertile Females	7 (20.0%)	6 (17.1%)	22 (62.9%)	35 (100.0%)
Others	3 (5.2%)	13 (22.4%)	42 (72.4%)	58 (100.0%)
Overall	10 (10.8%)	19 (20.4%)	64 (68.8%)	93 (100.0%)

Chi Square = 5.05; d.f = 2; p = 0.080
No Significant Difference Detected

Table 9: Maximum Change in QTc from Baseline Observed during the Steady State Phase of Infusion

	Likely	Unlikely	Clear	Overall
Fertile Females	9 (32.1%)	7 (25.0%)	12 (42.9%)	28 (100.0%)
Others	21 (38.9%)	16 (29.6%)	17 (31.5%)	54 (100.0%)
Overall	30 (36.6%)	23 (28.0%)	29 (35.4%)	82 (100.0%)

Chi Square = 1.04; d.f = 2; p = 0.593
No Significant Difference Detected

Comparison Among Age Groups: The following tables compare pediatric, adult, and elderly patients. ECG measurements include baseline QTc, the maximum QTc observed during or shortly after the course of therapy or during steady-state, which is assumed to have been attained after 10 days of infusion. Differences among age groups were assessed by means of standard Chi Square contingency table analyses.

Table 10: QTc At Baseline

	Normal	Borderline	Prolonged	Overall
Age 0-17 yrs	11 (78.6%)	2 (14.3%)	1 (7.1%)	14 (100.0%)
Age 18-59 yrs	59 (67.8%)	20 (23.0%)	8 (9.2%)	87 (100.0%)
Age 60+ yrs	12 (38.7%)	9 (29.0%)	10 (32.3%)	31 (100.0%)
Overall	82 (62.1%)	31 (23.5%)	19 (14.4%)	132 (100.0%)

Chi Square = 13.74; d.f = 4; p = 0.008
Significant Difference: more borderline and abnormals as age increases.

Table 11: Maximum QTc Observed During the Period of Infusion

	Normal	Borderline	Prolonged	Overall
Age 0-17 yrs	1 (11.1%)	3 (33.3%)	5 (55.6%)	9 (100.0%)
Age 18-59 yrs	8 (12.9%)	13 (21.0%)	41 (66.1%)	62 (100.0%)
Age 60+ yrs		6 (23.1%)	20 (76.9%)	26 (100.0%)
Overall	9 (9.3%)	22 (22.7%)	66 (68.0%)	97 (100.0%)

Chi Square = 4.40; d.f = 4; p = 0.355
No Significant Difference Detected

Table 12: Maximum QTc Observed During the Steady-State Phase of Infusion

	Normal	Borderline	Prolonged	Overall
Age 0-17 yrs	1 (11.1%)	2 (22.2%)	6 (66.7%)	9 (100.0%)
Age 18-59 yrs	9 (14.5%)	14 (22.6%)	39 (62.9%)	62 (100.0%)
Age 60+ yrs		3 (13.6%)	19 (86.4%)	22 (100.0%)
Overall	10 (10.8%)	19 (20.4%)	64 (68.8%)	93 (100.0%)

Chi Square = 5.14; d.f = 4; p = 0.273
No Significant Difference Detected

Table 13: Maximum Change in QTc from Baseline Observed during the Steady State Phase of Infusion

	Likely	Unlikely	Clear	Overall
Age 0-17 yrs	3 (37.5%)	2 (25.0%)	3 (37.5%)	8 (100.0%)
Age 18-59 yrs	22 (39.3%)	22 (39.3%)	12 (21.4%)	56 (100.0%)
Age 60+ yrs	4 (22.2%)	6 (33.3%)	8 (44.4%)	18 (100.0%)
Overall	29 (35.4%)	30 (36.6%)	23 (28.0%)	82 (100.0%)

Chi Square = 4.44; d.f = 4; p = 0.349
No Significant Difference Detected

Pharmacodynamics:

The time-dependent change in QTc (relative to baseline) during the course of therapy w. examined graphically, and by regression analysis. A first-order (exponential) approach to a steady state value of QTc change was postulated. The asymptotic (leveling-off value) for the QTc change, and the half-time for approach to steady-state were evaluated by the fitting the following function to all valid during-treatment measurements, using nonlinear least squares regression:

dQTc = a * (1.0 - 0.5^(t/b)), where:

dQTc is the change in QTc from baseline,

t is the time since first infusion for this course of treatment,

a is the steady-state prolongation of QTc, and

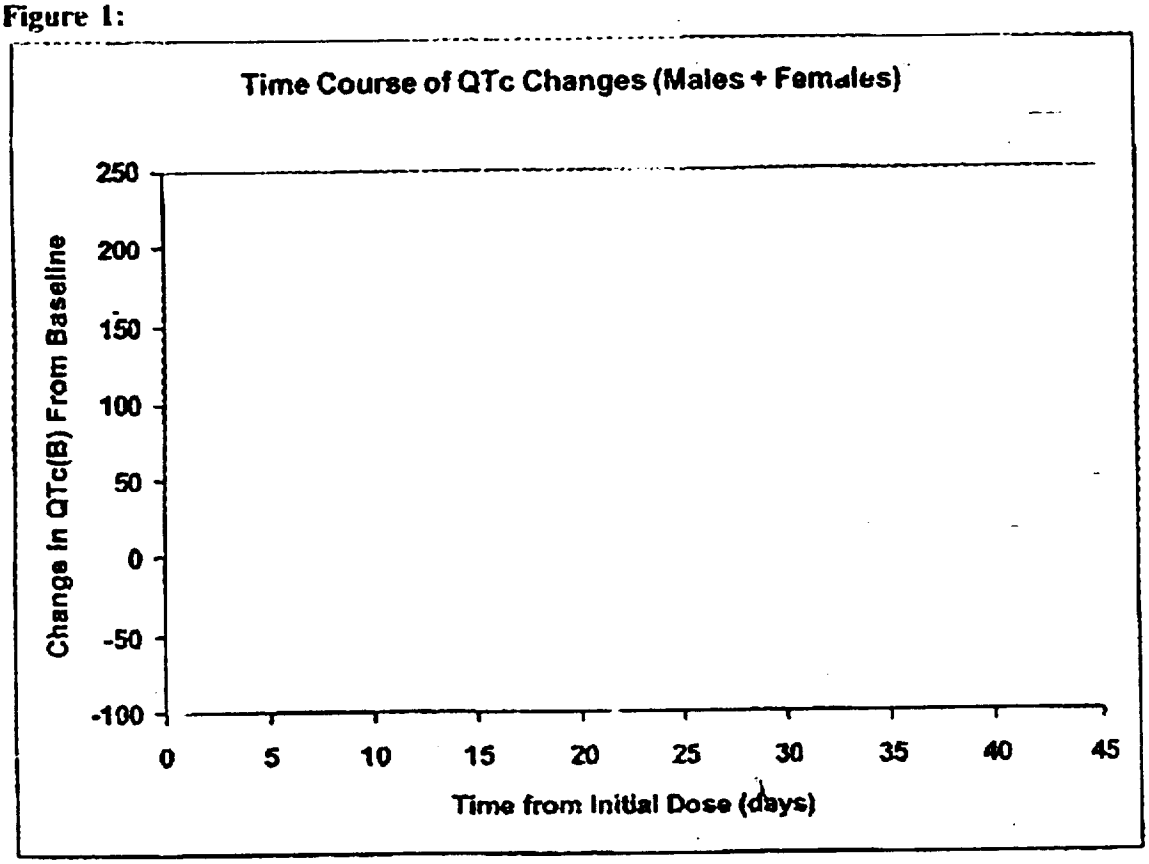
b is the half-time for first-order approach to steady state.

95% confidence bands were also computed and graphed for each curve.

This analysis was carried out for males and females together, and separately, and the results are shown in Figures 1, 2, and 3, below.

It can be seen that the amount of QTc prolongation tends to level off at a higher steady state valued in men (62+/-13 msec) than in women (35+/-5 msec), and that steady-state values are attained sooner (as indicated by half-time) in women (3+/-2 days) than in men (10+/-4 days). These differences are of borderline statistical significance (p approximately equal to 0.05).

Figure 1:

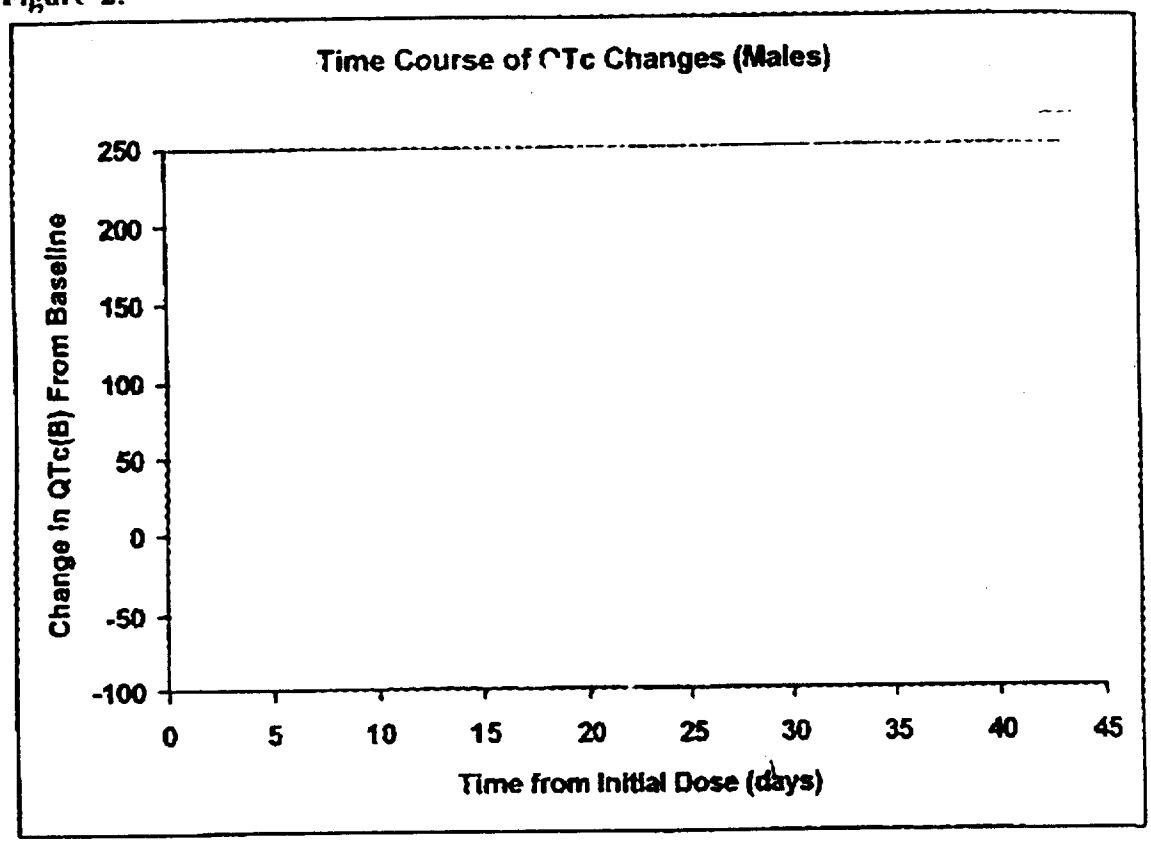


SS dQTc =

Half-time =

Corr. Coeff. r =

Figure 2:

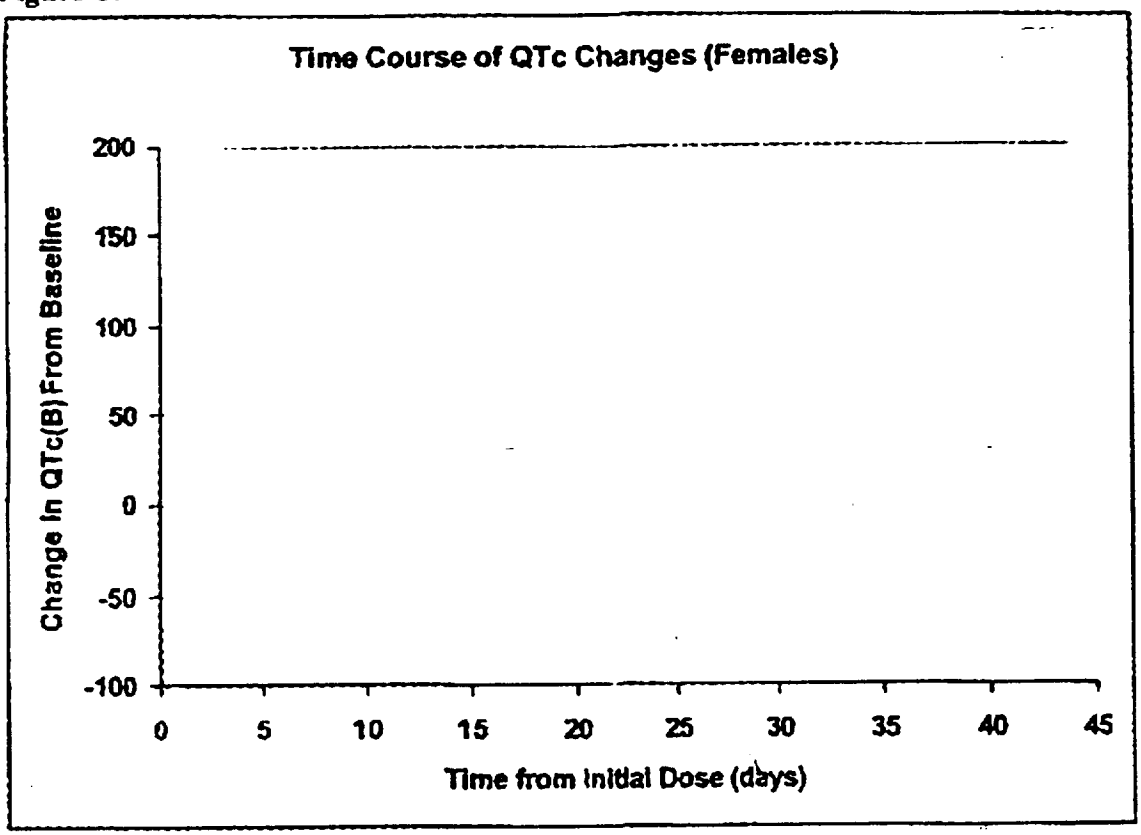


SS dQTc =

Half-time =

Corr. Coeff. r =

Figure 3:



SS dQTc =

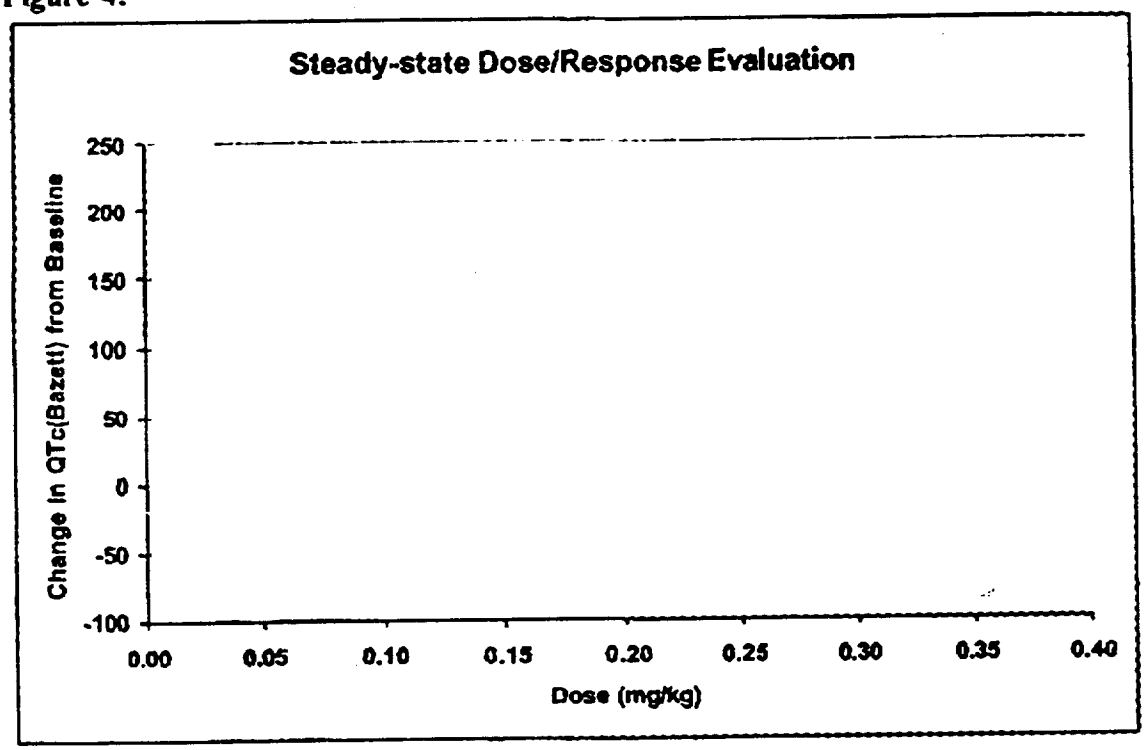
Half-time =

Corr. Coeff. r =

Steady-state Dose-Response Evaluation:

To test for a possible dose-response effect of Arsenic on QT prolongation, a linear regression analysis was carried out using all valid measurements from the steady-state portion of the therapy. The change in QTc from baseline was plotted against the dose, in mg/kg, administered in each infusion. A straight line, with its 95% confidence bands is shown below:

Figure 4:



dQTc = ...

Corr. Coeff. r = ...

It can be seen that there is actually a slight (but statistically not significant) decrease in QT prolongation with increasing dosage. Clearly, the use of administered dose as a rough proxy for actual plasma concentrations renders this analysis very tentative. A much more rigorous pharmacodynamic analysis can be conducted when plasma concentrations become available.

Attachment 3

Proposed Firm's Labeling

18 pages redacted from this section of the approval package consisted of draft labeling