

**Adverse Events (any grade) Occurring in  $\geq$ 5% of 40 Patients with APL who Received  
TRISENOX™ at a dose of 0.15 mg/kg/day**

System organ class / Adverse Event	All Adverse Events, Any Grade		Grade 3 & 4 Events	
	n	%	n	%
Erythema- non-specific	5	10		
Increased sweating	5	10		
Facial edema	3	8		
Night sweats	3	8		
Petechiae	3	8		
Hyperpigmentation	3	8		
Non specific skin lesions	3	8		
Urticaria	3	8		
Local exfoliation	2	5		
Eyelid edema	2	5		
<b>Cardiac disorders</b>				
Tachycardia	22	55		
ECG QT corrected interval prolonged > 500msec	16	38		
Palpitations	4	10		
ECG abnormal other than QT interval prolongation	3	7		
<b>Infections and infestations</b>				
Sinusitis	8	20		
Herpes simplex	5	13		
Upper respiratory tract infection	5	13	1	3
Bacterial infection- non-specific	3	8	1	3
Herpes zoster	3	8		
Nasopharyngitis	2	5		
Oral candidiasis	2	5		
Sepsis	2	5	2	5
<b>Musculoskeletal, connective tissue and bone disorders</b>				
Arthralgia	13	33	3	8
Myalgia	10	25	2	5
Bone pain	9	23	4	10
Back pain	7	18	1	3
Neck Pain	5	13		
Pain in limb	5	13	2	5
<b>Hematologic Disorders</b>				
Anemia	8	14	2	5
Thrombocytopenia	7	19	5	12
<i>Febrile neutropenia</i>	5	13	3	8
<i>Leukocytosis</i>	4	10	1	3
<i>Neutropenia</i>	4	10	4	10

**Adverse Events (any grade) Occurring in ≥5% of 40 Patients with APL who Received  
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System organ class / Adverse Event	All Adverse Events, Any Grade		Grade 3 & 4 Events	
	n	%	n	%
<b>Disseminated Intravascular Coagulation</b>	3	8	3	8
<b>Lymphadenopathy</b>	3	8		
<b>Vascular disorders</b>				
Hypotension	10	25	2	5
<b>Flushing</b>	4	10		
<b>Hypertension</b>	4	10		
<b>Pallor</b>	4	10		
<b>Psychiatric Disorders</b>				
<b>Anxiety</b>	12	30		
<b>Depression</b>	8	20		
<b>Agitation</b>	2	5		
<b>Confusion</b>	2	5		
<b>Ocular Disorders</b>				
Eye irritation	4	10		
Blurred vision	4	10		
Dry eye	3	8		
Painful red eye	2	5		
<b>Renal and Urinary Disorders</b>				
<b>Renal Failure</b>	3	8	1	3
Renal Impairment	3	8		
<b>Oliguria</b>	2	5		
Incontinence	2	5		
<b>Reproductive System Disorders</b>				
<b>Vaginal Hemorrhage</b>	5	13		
Intramenstrual Bleeding	3	8		
<b>Ear Disorders</b>				
<b>Earache</b>	3	8		
Tinnitus	2	5		

**Table 20-Patients who had study drug discontinued due to adverse events**

Patient ID	Event	Severity	Study Day	Related	Hospitalized?	Outcome	Serious
1020	Peripheral neuropathy	Severe	78	Possibly	No	Recurrent	Yes
1034	Bone pain and marrow necrosis	Sever	42	Possibly	No	Resolved	Yes

Three patients died on study- two from hemorrhage and one from *Aspergillus infection*. These deaths were probably related to disease progression and are unlikely to be due to arsenic trioxide.

**Table 20 Deaths on Study**

Patient ID	Study Day	Cause of Death
1019	39	Disease progression DIC, renal failure, stroke
1036	16	Disease progression Intracranial hemorrhage
1052	86	Pulmonary aspergillus infection

### APL Differentiation Syndrome

A syndrome characterized by a combination of fever, dyspnea, fluid retention, pleural effusions, pericardial effusions or leukocytosis that could be fatal was initially described in conjunction with all trans retinoic acid (ATRA) therapy for APL. It was initially termed retinoic acid or ATRA syndrome. The syndrome has been observed with APL therapies other than ATRA, including arsenic trioxide, and subsequently was determined to be due to the coordinated differentiation of promyelocytes into mature myelocytes. It will be referred to as the APL differentiation syndrome. Therapy consists of supportive care plus high dose corticosteroids until symptoms resolve.

Nine (23%) patients had a constellation of symptoms that were consistent with APL differentiation syndrome, 3 (8%) of which were considered severe. Six patients had leukocytosis, five of which were treated with dexamethasone at a dose of 20 mg/day for 3 to 5 days until symptoms resolved. No patients withdrew from therapy as a result.

### Hyperleukocytosis

A total white cell count in the peripheral blood of greater than 10 000 cells/mm<sup>3</sup> is considered hyperleukocytosis. Therapy is directed to decreasing the WBC using cytotoxic chemotherapy if clinical signs and symptoms warrant. Fourteen patients (35%), six of whom had APL differentiation syndrome, had hyperleukocytosis, ranging from 17.9 to 169.4 x 10<sup>3</sup> cells/mm<sup>3</sup>. There was no correlation between baseline WBC and peak-WBC. No patient was treated with cytotoxic chemotherapy. One patient, 1036, had an

intracranial hemorrhage when the WBC reached  $85.6 \times 10^3$  cells/mm<sup>3</sup> and died 2 days later with a WBC of  $136 \times 10^3$  cells/mm<sup>3</sup>.

### **Neuropathy**

Seventeen (43 %) patients had signs or symptoms of neuropathy that may be associated with arsenic exposure. There were 12 events reported during induction and 13 during consolidation. Most events were peripheral limb numbness, tingling, or paresthesias. Six patients (15%) had more than one episode. One patient, 1020, had peripheral neuropathy that progressed from mild to severe, so stopped arsenic trioxide during consolidation. The neuropathy resolved, but recurred with subsequent arsenic trioxide. In most patients the neuropathy was mild and resolved, but in 5 patients (13%) the neuropathy never resolved including one who had moderate paresthesia with severe muscle weakness.

### **Other Efficacy Data submitted**

#### **7.5.2. Reviewer's Trial # 2      Sponsor's protocol # 97-66**

#### **7.5.3. Objectives**

To quote from the study protocol

- *"To evaluate the safety and potential efficacy of Arsenic Trioxide in patients with relapsed or refractory acute promyelocytic leukemia.*
- *To evaluate the pharmacokinetics of Arsenic trioxide."*

##### **7.5.3.1. Design**

This was an open label, single arm phase I study.

##### **7.5.3.2. Population**

Confirmed diagnosis of acute promyelocytic leukemia by bone marrow morphology, and by conventional cytogenetics for t(15:17) or positive reverse transcriptase polymerase chain reaction (RT-PCR) assay for PML/RAR- $\alpha$ , or fluorescence in situ hybridization (FISH) analysis showing evidence of RAR- $\alpha$  or PML translocations was required.

Relapse from or resistance to standard antileukemic therapy, defined as:

- At least one course of induction chemotherapy using an anthracycline antibiotic; and
- At least one course of induction therapy using either all-trans retinoic acid or 9-cis retinoic acid

Patients should have adequate hepatic (serum bilirubin  $\leq 2.5$  mg/dl), and renal (serum creatinine  $\leq 2.5$  mg/dl) status. Patients should have a negative pregnancy status and a signed informed consent.

Patients with history of grand mal seizures, active serious and uncontrolled infections, concurrent cytotoxic chemotherapy, radiation or investigational agents were not allowed.

### 7.5.3.3. Primary Endpoint

The primary endpoint is complete response (CR) which is defined as cellular bone marrow aspirate with < 5 % blasts; Peripheral blood WBC  $\geq$  3000/mm<sup>3</sup> or ANC  $\geq$  1,500/mm<sup>3</sup> and platelet count  $\geq$  100,000/mm<sup>3</sup>.

### 7.5.3.4. Planned Regimen

Patients would have a *fixed* dose of 10 mg. for the at least the first 5 recipients, given daily for a cumulative maximum of 60 days, diluted in 5% dextrose, infused intravenously over 4 hours. Patients who attain a CR may receive one additional course of therapy beginning not less than 4 weeks after completion of the initial course of therapy. The dose-schedule would be the same as the induction dose, administered for 30 days. *No maintenance therapy was planned.*

The dose would not be escalated for the *first 5 patients*. Amendments could be made after these patients were reviewed if needed.

## Results

The sponsor submitted data from 12 patients in a phase I protocol 96-97 for patients with relapsed or refractory APL; 9 attained a complete response for a response rate of 75%. Two patients received arsenic trioxide at the recommended dose of 0.15 mg/kg, the others received doses ranging from 0.06 mg/kg to 0.20 mg/kg.

### FDA Comments on Efficacy and Safety of ATO in APL studies:

The number of patients in this NDA who received the recommended dose of 0.15 mg/kg is limited (N=42). Using intent to treat analysis, 28 of the 42 (67%) patients had complete responses. Patients were not disqualified in the FDA scoring for not having required studies done unless the studies intended to establish the primary endpoint of complete remission were missing. Including an additional 6 possible responders, the combined response rate for complete and possible responders is 78%. There does not appear to be a site bias in response.

The median duration of response (time between CR and subsequent therapy) was 85 days or 3 months or 12 weeks.

The toxicities were in general consistent with those seen in APL therapy and were generally reversible. The QTc prolongation did not have any evidence of being cumulative.

## 8. Overview of Efficacy

Arsenic trioxide was administered to 52 patients with relapsed or refractory acute promyelocytic leukemia, 42 patients received a dose of 0.15 mg/kg/day. Twenty-eight of the 42 patients were able to attain remission by protocol criteria for a remission rate of (67%).

Another 6 patients were considered possible responders because their records were incomplete. If these patients are included, the remission rate is 81%, which is consistent with the results seen in the Phase 2 study. An additional 8 of 10 patients with refractory or relapsed APL were treated at doses other than the recommended dose of 0.15 mg/kg.

Arsenic trioxide appears to produce durable remissions. However, it is impossible to infer from the current NDA submission, the role of induction and consolidation versus that of maintenance therapy or bone marrow transplant on the durability of responses or length of survival.

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## 9. Overview of Safety

### 9.1. All adverse events

A total of 99 patients from all the studies were analyzed for safety. The results are summarized in the following table.

**Table 21 Summary of Adverse of Events in 99 Patients**

**Table 1 Adverse Events (any grade) Occurring in  $\geq 10\%$  of 99 Patients who Received TRISENOX**

System organ class / Adverse Event	All Adverse Events, Any Grade			Grade 3 & 4 Events		
	APL at recomm ended dose	Non- APL and APL at other doses	Total	APL at recom mende d dose	Non- APL and APL at other doses	Total
<b>General disorders and administration site conditions (any)</b>	<b>42</b>	<b>51</b>	<b>93</b>	<b>6</b>	<b>13</b>	<b>19</b>
Fatigue	36	33	69	5	2	7
Pyrexia	13	33	46	1	2	3
Edema peripheral	14	17	31	2	1	3
Edema lower limb	8	7	15	1	0	1
Edema	10	20	30	1	1	2
Rigors	7	19	26			
Chest pain	4	12	16	0	3	3
Pain	3	9	12	0	4	4
Weight gain	10	8	18			
Weight loss	5	5	10			
Injection site pain	2	9	11			
<b>Gastrointestinal disorders (any)</b>	<b>38</b>	<b>48</b>	<b>86</b>	<b>3</b>	<b>9</b>	<b>12</b>
Nausea	21	38	59			
Anorexia	10	9	19			
Appetite decreased	7	9	16			

Table 1 Adverse Events (any grade) Occurring in ≥10% of 99 Patients who Received TRISENOX

System organ class / Adverse Event	All Adverse Events, Any Grade			Grade 3 & 4 Events		
	APL at recomm ended dose	Non- APL and APL at other doses	Total	APL at recom mende d dose	Non- APL and APL at other doses	Total
Diarrhea	12	28	40	0	1	1
Vomiting	10	29	39	1	0	1
Abdominal pain	8	20	28	1	3	4
Sore throat	10	17	27	1	0	1
Constipation	10	13	23	0	1	1
Abdominal distension	8	5	13			
Abdominal pain upper	2	10	12	0	2	2
<b>Metabolism and nutrition disorders (any)</b>	<b>33</b>	<b>46</b>	<b>79</b>	<b>4</b>	<b>16</b>	<b>20</b>
ALT increased	8	9	17	3	3	6
AST increased	8	6	14	0	2	2
Hyperglycemia	25	30	55	3	8	11
Hypokalemia	5	27	32	2	8	10
Hypomagnesemia	5	17	22	0	1	1
Hypocalcemia	1	10	11	0	1	1
<b>Nervous system disorders (any)</b>	<b>31</b>	<b>47</b>	<b>78</b>	<b>1</b>	<b>7</b>	<b>8</b>
Headache	15	33	48	0	1	1
Insomnia	6	21	27	0	1	1
Dizziness (excluding vertigo)	10	13	23			
Paresthesia	7	16	23	0	2	2
Tremor	4	7	11			
<b>Respiratory, (any)</b>	<b>26</b>	<b>43</b>	<b>69</b>	<b>11</b>	<b>14</b>	<b>25</b>
Cough	11	29	40	0	1	1
Dyspnea	15	20	35	5	6	11
Epistaxis	4	14	18			
Dyspnea exertional	6	8	14	2	0	2
Hypoxia	3	11	14	0	6	6
Crepitations	6	6	12			
Pleural effusion	4	8	12	3	1	4
Rales	6	6	12			
Wheezing	4	7	11			
<b>Skin &amp; subcutaneous tissue disorders (any)</b>	<b>24</b>	<b>45</b>	<b>69</b>	<b>1</b>	<b>3</b>	<b>4</b>
Dermatitis	11	20	31			
Pruritus	10	16	26	1	0	1
Ecchymosis	1	12	13			
Sweating increased	3	7	10	0	1	1
<b>Cardiac disorders (any)</b>	<b>17</b>	<b>36</b>	<b>53</b>	<b>2</b>	<b>5</b>	<b>7</b>
ECG abnormal	3	12	15			
ECG QT prolonged	0	10	10	0	1	1
ECG QT corrected interval prolonged	16	12	28			

Table 1 Adverse Events (any grade) Occurring in ≥10% of 99 Patients who Received TRISENOX

System organ class / Adverse Event	All Adverse Events, Any Grade			Grade 3 & 4 Events		
	APL at recomm ended dose	Non- APL and APL at other doses	Total	APL at recom mende d dose	Non- APL and APL at other doses	Total
Tachycardia	7	29	36	0	1	1
<b>Infections and infestations (any)</b>	<b>18</b>	<b>34</b>	<b>52</b>	<b>1</b>	<b>7</b>	<b>8</b>
Upper respiratory tract infection	7	5	12	0	1	1
<b>Musculoskeletal, connective tissue and bone disorders (any)</b>	<b>19</b>	<b>32</b>	<b>51</b>	<b>1</b>	<b>9</b>	<b>10</b>
Arthralgia	5	17	22	0	5	5
Myalgia	4	13	17	0	2	2
Back pain	6	9	15	0	2	2
Bone pain	3	10	13	1	3	4
Pain in limb	4	8	12	0	3	3
<b>Hematologic disorders (any)</b>	<b>9</b>	<b>28</b>	<b>37</b>	<b>3</b>	<b>17</b>	<b>20</b>
Thrombocytopenia	1	12	13	0	6	6
Anemia	3	8	11	1	2	3
<b>Vascular disorders (any)</b>	<b>12</b>	<b>25</b>	<b>37</b>	<b>3</b>	<b>6</b>	<b>9</b>
Hypotension	6	14	20	2	2	4
<b>Psychiatric disorders (any)</b>	<b>6</b>	<b>26</b>	<b>32</b>	<b>2</b>	<b>1</b>	<b>3</b>
Anxiety	2	17	19			
Depression	0	10	10			
<b>Eye disorders (any)</b>	<b>2</b>	<b>21</b>	<b>23</b>	<b>0</b>	<b>1</b>	<b>1</b>
<b>Renal and urinary disorders (any)</b>	<b>10</b>	<b>12</b>	<b>22</b>	<b>0</b>	<b>4</b>	<b>4</b>
<b>Reproductive system and breast disorders (any)</b>	<b>0</b>	<b>13</b>	<b>13</b>	<b>0</b>	<b>1</b>	<b>1</b>
<b>Ear and labyrinth disorders (any)</b>	<b>2</b>	<b>10</b>	<b>12</b>			

## 9.2. Significant/Potentially Significant Events

### 9.2.1. Deaths within 30 days of arsenic trioxide infusion

The number of patients that died while receiving arsenic trioxide or within 30 days of the last dose were

- 3 patients on the relapsed or refractory APL Phase 2 study
- 3 patients from the Phase 1 study
- 5 patients from the other studies

for a total of 11 of 99 patients (11%).

None of the deaths were attributable to arsenic trioxide.

### **9.2.2. Other Significant/Potentially Significant Events**

QT or QTc prolongation on electrocardiograms was reported in 28 patients. None were symptomatic, and therefore all would be classified as Grade I on the National Cancer Institute Common Toxicity Criteria version 2. One patient who had febrile neutropenia with septic shock on the Phase I study had atrial fibrillation and bundle branch block that may have been related to arsenic trioxide. This patient received amphotericin B as part of his therapy. There is a literature report of a patient who had complete AV block with arsenic trioxide. There was no evidence that the QTc prolongation was cumulative or increased between courses (e.g. induction and consolidation) of arsenic trioxide.

Thirty four patients had non-fatal serious adverse events. The most common was febrile neutropenia which was not considered to be related to arsenic trioxide.

### **9.2.3. Overdose Experience**

There is no data on overdose provided in the submission.

## **9.3. Other Safety Findings**

### **9.3.1. Drug-Demographic Interactions**

No evidence of drug-demographic interactions were presented. Analysis was limited due to the small data set.

### **9.3.2. Drug-Disease Interactions**

ATRA syndrome was described above. There are no other data to describe a drug-disease interaction.

### **9.3.3. Drug-Drug Interactions**

There were no formal drug-drug interaction studies performed. There may be an interaction between Amphotericin B, an antifungal agent known to alter electrolyte levels, and arsenic trioxide that may result in an increased risk for QT prolongation and cardiac dysrhythmia based on the patient who had asymptomatic torsade de pointes with spontaneous resolution.

### **9.3.4. Withdrawal Phenomena/Abuse Potential**

There is no evidence to support abuse potential or withdrawal phenomena.

### **9.3.5. Human Reproduction Data**

One patient who became pregnant during the study period had a spontaneous abortion. Arsenic is associated with birth defects in epidemiological studies.

## 10. Safety Update

A safety update was submitted on June 29, 2000 representing, by prior agreement with the FDA, a 3 month interval rather than the customary 4 month interval. It described experience with an additional 72 patients, 51 with APL. Three patients died within 30 days of the last dose of arsenic trioxide, two from progressive malignancies and one, a patient with APL, from retinoic acid syndrome. Sixteen patients had non-fatal serious adverse events including 2 patients who had Grade 2 peripheral neuropathy that resolved after therapy was discontinued. Two patients had documented prolonged QTc intervals on ECG; both were asymptomatic. The range and severity of adverse events was similar to those reported in the initial cohort of 99 patients.

## 11. Advisory Committee

The Division of Oncology Drug Products made a decision to not present this application to an advisory committee because there were no issues that were perceived as controversial or requiring public discussion.

## 12. Review of Draft Product Label

A review of the proposed package insert for this application is attached as an appendix.

## 13. Conclusions

Arsenic trioxide is safe and effective for the treatment of relapsed or refractory acute promyelocytic leukemia. There are no other available therapies except for retreatment with ATRA and cytotoxic drugs. The dataset was limited, but there were no differences noted in the remission rate based on age, gender, ethnicity, or time since last ATRA dose.

Arsenic trioxide appears to produce durable remissions. However, it is impossible to infer from the current NDA submission, the role of induction and consolidation versus that of maintenance therapy or bone marrow transplant on the durability of responses or length of survival.

The changes in QTc on ECG were asymptomatic and reversible. According to National Cancer Institute Common Toxicity Criteria, version 2.0, changes in the electrocardiogram, and specifically the QT interval that are asymptomatic are considered Grade I toxicity. Further studies, particularly during arsenic trioxide infusion would be required to better understand the potential risks of the observed ECG changes.

## 14. Regulatory Recommendations

The medical reviewers recommend approval of arsenic trioxide for second line therapy for acute promyelocytic leukemia.

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

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[1-289]

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APPROVED THIS WAY  
ON ORIGINAL



Douglas C Throckmorton, M.D.  
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20816  
Tel (301) 594-5383, FAX (301) 594-5494

**MEMORANDUM**

**DATE:** 7.7.00

**FROM:** Douglas C. Throckmorton, M.D., Medical Officer  
Division of Cardio-Renal Drug Products, HFD-110

**THROUGH:** Ray Lipicky, M.D., Ph.D., Division Director  
Division of Cardio-Renal Drug Products, HFD-110

**TO:** Diane Spillman, Project Manager  
Steven Hirschfeld, M.D., Ph.D., and A. Ibrahim, M.D., Medical Officers  
Richard Pasdur, M.D., Director  
Division of Oncology, HFD-150

Handwritten notes in a box: "/S/" and "S.E. 22.0."

**SUBJECT:** Effects of \_\_\_\_\_ on cardiac repolarization (QT-interval prolongation)  
**NAME OF DRUG:** Arsenic Trioxide  
**TRADE NAME:** \_\_\_\_\_  
**FORMULATION:** IV

**RELATED APPLICATIONS:** N/A  
**APPROVED INDICATIONS:** N/A  
**SPONSOR:** Cell Therapeutics, Inc.

**DOCUMENTS USED FOR REVIEW:**

1. Sponsor's summary of \_\_\_\_\_ ECG data (from the ATO Pivotal Study) of 40 patients.
2. Case Report Forms from a subset of the same 40 patients (not including ECGs):  
NDA vols. 1.61-1.63 and 1.68-1.69.
3. Sponsor's summary of reported Adverse Events in NDA 21-248.
4. 'Expert Report on Electrocardiographs' from NDA volume 1.15, section 6.2.4.
5. ECGs from three patients with QT intervals (uncorrected) >500 milliseconds.
6. Integrated Safety Summary, NDA 21-148 \_\_\_\_\_ section 8.8.
7. Approved labels for Moxifloxacin (Avelox) and Bepridil (Vascor).
8. Published literature on the administration of arsenic (in both organic and inorganic forms) to humans.

**DATE CONSULT ASSIGNED:** 5.15.00  
**DATE CONSULT COMPLETED:** 7.6.00

**1.0 BACKGROUND**

The sponsor submitted NDA 21-148 to HFD-150 seeking approval of Arsenic trioxide \_\_\_\_\_ as second-line therapy for Acute Promyelocytic Leukemia in patients who have previously received all-trans-retinoic acid and anthracyclines. One side effect of \_\_\_\_\_ therapy noted was prolongation of the QT interval. Specific advice is being sought from HFD-110 on the following two questions:

- 1) What ought to be included in the labeling regarding the cardiac conduction abnormalities?
- 2) In situations encountering QT prolongation, what suggestions regarding therapy have you made in labeling in the past, and would you have any recommendations for the proposed label for this NDA?

## 2.0 Available Data on the Cardiac Effects of

The available data on the clinical cardiac effects of include the following:

### 1) Cardiac Adverse Events Reported in the NDA

#### Torsade de Pointes

The sponsor notes in their proposed label that 'one patient, being treated concomitantly with amphotericin B, was observed to have had a torsade de points which was asymptomatic and resolved spontaneously.'

#### Deaths and SAEs

**Deaths:** a review of the narratives of the reported deaths revealed no cases of sudden death. Patient died of 'cardiopulmonary arrest' after a protracted clinical course complicated by hypotension, hypokalemia, cardiomyopathy and acidosis. No data on the terminal rhythm are available.

**SAEs:** Patient 1002 developed atrial fibrillation and a right bundle branch block which resolved while continuing to receive. No other SAEs were related to the cardiac conduction system.

### 2 ECGs from three individuals (patients 1008, 1010, and 1023) receiving infusion of

All four of the ECGs (from 3 individuals) demonstrate marked prolongation of the QT interval (>500 msec) without demonstrable U waves. No baseline ECGs are available for comparison in these individuals.

### 3) Summary information from the ECGs performed during the largest trial of arsenic trioxide (ATO Pivotal Study)

In the ATO pivotal trial, 40 subjects with acute promyelocytic leukemia (APML) were treated with. The sponsor summarized the data, derived from ECGs taken at baseline and again following infusion. These infusions were repeated at one to two week intervals for up to 10 weeks. The following table summarizes the occurrence of changes in the QT interval corrected for changes in heart rate (QTc) in this population, as reported by the sponsor. In all cases, the changes in the QTc were not present at baseline.

**Changes in QTc in Pivotal ATO Study<sup>d</sup>**

	# (% of total)
Prolonged QTc <sup>a,b,c</sup>	23/40 (57.5%)
No Effect on QTc	15/40 (37.5%)
Shortened QTc <sup>a</sup>	2/40 (5.0%)

a. Exact definition of 'prolonged' and 'shortened' QTc and the original ECGs are not available.

b. Patients were designated as having an alteration in QT if it was reported in any ECG post-baseline.

c. Correction factor used to determine QTc not available to this reviewer.

d. Data from Sponsor's summary of Atrivex ECG data.

### 4) Summary information adverse events (AEs) reported during the ATO Pivotal Study

This trial exposed 40 individuals with APML to arsenic trioxide, administered as an infusion over 1 to 3 hours, for between one and 9 cycles of therapy. The table below summarizes the reported AEs, taken from the summary prepared by the sponsor. There were no cases of sudden death, malignant ventricular arrhythmias, dizziness or loss of consciousness reported, although there was a high frequency of hypokalemia and hypomagnesemia.

**AEs Reported in ATO Pivotal Study<sup>d</sup>**

	# (% of total)
Prolonged QTc <sup>a,b,c</sup>	21/40 (52.5%)
Hypokalemia	17/40 (42.5%)
Hypomagnesemia	10/40 (25%)
Hypocalcemia	3/40 (7.5%)
CHF <sup>b</sup>	7/40 (17.5%)
Acidosis	2/40 (5.0%)

a. Exact definition of 'prolonged' QTc and the original ECGs are not available.

b. Required groups of adverse events including edema, pleural effusions, shortness of breath and use of O<sub>2</sub>.

c. Correction factor used to determine QTc not available to this reviewer.

d. Data from Sponsor's summary of Atrivex ECG data.

**5) Sponsor's Arsenic ECG Analysis (Cardiologist's Report on ECGs)**

The sponsor had the ECGs from a total of 99 subjects (approximately 1000 ECGs total) analyzed by a single cardiologist, who was blinded to clinical data, who adjusted the machine-read QT intervals as needed. These ECGs came from the pivotal trial described above as well as additional patients who received Atrivex. Some individual ECGs were eliminated at this step due to poor ECG quality. The sponsor then extracted the data on QT and QTc (Bazett's) from the ECGs obtained prior to the first infusion for further analyses. The first table summarizes the subject demographics.

**Demographics from the 99 subjects who received Atrivex**

Demographic	Subjects (%)
<b>Gender</b>	
Female	42 (42.4%)
Male	57 (57.6%)
<b>Ethnicity</b>	
Black	10 (10.1%)
White	80 (80.8%)
Hispanic and Other	9 (9.0%)
<b>Age</b>	
0-17	10 (10.1%)
18-59	60 (60.6%)
60+	29 (29.3%)

a. Data from NDA section 6.2.4, Expert Report on Electrocardiographs.

Next, the sponsor compared the fraction of subjects with prolonged QTc at baseline with the fraction of subjects with prolonged QTc 'during the steady-state phase of infusion.' The sponsor says that this value 'is assumed to have been attained after 10 days of infusion.' Per the sponsor, the estimated serum half-life is approximately 100 hours. The ECGs used for this comparison were obtained at baseline prior to the next cycle of infusion. As such, we have no information about the changes in QT that occurred during the Atrivex infusion.

**QTc Data from Sponsor's ECG Analysis<sup>a</sup>**

	Normal <sup>b</sup>	Borderline <sup>b</sup>	Prolonged <sup>b</sup>
QTc at Baseline	82 (62.1%)	31 (23.5%)	19 (14.4%)
Maximum QTc 'During Steady State of Infusion'	10 (10.8%)	19 (20.4%)	64 (68.8%)

a. Data from NDA section 6.2.4, Expert Report on Electrocardiographs.

b. Values for QTc (male/female):

Normal: ≤430/ ≤450 msec

Borderline: 431-450/451-470

Prolonged: >450/ >470

In data not summarized here, there was no evident difference between men and women in the percentage who developed a prolonged QTc while receiving Atrivex (65%+ for both groups). Similarly, a high percentage of all age groups developed a prolonged QTc, including the group aged 0-17 years (55 to 66%).

Next, the sponsor summarized the change in QTc. Looking only at the ECGs obtained prior to infusion, the sponsor modeled the change in QTc with time from the initial dose to the steady-state. The mean change in QTc from baseline to steady-state was 62±13 msec in males and 35±5 msec in female. The time to half of the steady-state change was 3±2 days in women and 10±4 days in men. The time-courses for the change in QTc, plotted by the sponsor, can be found attached to this memorandum.

Finally, the sponsor summarized the ECG intervals for the 26 patients (26% of total exposed!) who had a QTc >500 msec during the trials. Fifteen of these patients had QTc >550 msec (15% of total exposed). As the sponsor only reported the ECGs obtained just prior to the first infusion, data on the acute effect of later infusions of Atrivex on these QTc's are also not available.

6) Review of the published literature on administration of compounds containing Arsenic to patients with cancer (largely hematological malignancies).

ECG abnormalities are specifically mentioned in one article on the effects of Arsenic Trioxide in patients with APLM (ref. 1). In that study, the only ECG change reported in 15 patients was a sinus tachycardia/1<sup>st</sup>-degree AV block which developed in one patient (6.7%). No other cardiovascular AEs were reported in this trial. Another article, reporting on a trial with 12 patients, did not report any cardiovascular adverse events (ref. 2).

In addition, two cases of Torsade de Pointes following arsenic intoxication has been reported (ref. 3). In both cases, marked prolongation of the QT-U was reported.

### 3.0 ISSUES AND COMMENTS

#### Effects of [redacted] on Cardiac Repolarization

The available data demonstrates that [redacted] has a pronounced effect on cardiac repolarization and its use is likely to be associated with a increased risk for cardiac arrhythmias. First, one individual had TdP detected, out of only 100 subjects administered. Second, the ECG analyses demonstrate an effect of [redacted] to cause an increase in the QTc lasting days after drug infusion. This increase averaged 62±13 msec in males and 35±5 msec in female.

It's important to note, however, that we lack sufficient data to allow us to adequately describe the cardiac effects of [redacted] in the label, including the following:

- 1) Information on the effects of arsenic trioxide on heart rate and other cardiac parameters (e.g., P-R interval, ejection fraction).
- 2) Information on the mean changes in QT and QTc seen during [redacted] infusion, and the duration of these effects following completion of the infusion.
- 3) Information on the metabolism of arsenic trioxide (especially potential accumulation in tissues).
- 4) Information on the effects of arsenic trioxide *in vitro* and pre-clinical models useful for characterize effects on cardiac repolarization.
- 5) Information on the rate of QT prolongation in untreated patients with other hematological malignancies, to assess whether a portion of the reported incidence of prolonged QT may be unrelated to arsenic trioxide infusion.

Given the life-saving potential for this product, and the concurrence between the FDA and sponsor regarding the presumptive effects of [redacted] on the QT, the Division may well determine that this information can be obtained in the post-marketing arena. With the data we have, we can conclude that [redacted] can cause QT prolongation and potentially serious cardiac arrhythmias. Additional data on the cardiac effects of [redacted] should be obtained.

#### Previous Experience with Drugs that Prolong QT Interval

Before making labeling recommendations, two additional points related to previous experience with drugs that prolong the QT need discussing.

##### 1. Significance of QT prolongation

The current view is that any product that causes a prolongation of the QT also has an increased risk of serious ventricular arrhythmias, including Torsade de Pointes (TdP). The degree of risk is thought to vary, depending on the degree to which the QT is prolonged. There is a sense that the drugs we know to produce an increase in the mean QTc of 25 milliseconds or more have a risk of TdP in the 1-5% range. For instance, Bepridil (an anti-anginal) that prolongs the mean QT and QTc by 30 to 40 milliseconds, has an incidence of TdP of around 1%. Sotalol (an antiarrhythmic) also causes marked prolongation of the QT (65 to 130 msec) and is associated with TdP occurring in 5-7% of patients. For these products, the incidence of TdP was evident in relatively small NDA databases (approximately 500 exposed subjects).

On the other hand, drugs such as Terfenadine and Cisapride have smaller effects on the QT interval, and although they are also associated with an increase risk of TdP the estimated rate is <0.1% for both drugs. Avelox (moxifloxacin) causes a 6 msec mean prolongation of the QT, and had no TdP or other serious arrhythmia among 4000 patients in its NDA. This product was approved with a label that notes the prolongation of QT and states that prolonged QT 'may lead to an increased risk for ventricular arrhythmias including torsade de pointes.'

[redacted] falls into the first of these two groups: it causes a marked prolongation of the mean QTc (35-65 msec) and the database has one individual with Torsade de Pointes. Based on our experience with other drugs, then, we can anticipate that the risk of serious cardiac arrhythmias is significant for [redacted], even though the incidence of clinically-significant cardiac events is relatively low (<5%). Since [redacted] is administered by intermittent infusion and has a very long plasma half-life, measures taken to limit the risk of cardiac toxicity will be critical to the safe use of this product.

### 3.0 ISSUES AND COMMENTS (cont)

#### 2) Use of QT prolongation to guide therapy

The second point is the degree of QT prolongation has been used as a guide to modify therapy in at least three antiarrhythmic drugs approved for chronic use, but only for drugs approved for chronic use. The Bepridil label specifically recommends that a QT of greater than 520 msec lead to dose reduction or discontinuation of Bepridil. The Sotalol label warns that it should be used 'with particular caution if the QTc is greater than 500 msec on therapy and serious consideration should be given to reducing the dose or discontinuing therapy when the QTc exceeds 550 msec.' Finally, the Dofetilide label recommends drug discontinuation if the QTc is prolonged to greater than 500 msec. Applying these data to . is not simple, as it is designed for short-term infusion as opposed to chronic use. In addition, the long half-life (100 hours) means that a person who develops a prolonged QT may be at risk of TdP for a significant period of time following the end of the . infusion (which takes place over 1-3 hours).

#### Labeling Recommendations/ Response to Consult Questions

##### 1) What ought to be included in the labeling regarding the cardiac conduction abnormalities?

The label should reflect what is known and unknown about the cardiac effects of arsenic trioxide and then suggest ways of minimizing the potential for the serious adverse effects (*i.e.* sudden death, torsade de pointes). The label should be updated as additional information on the cardiac effects of . are obtained. In this regard, the recent approval of Moxifloxacin serves as an example of a drug approved with the knowledge that it prolonged the QT interval. Inclusion of the following information in labeling is recommended:

**DRAFT LABELING**

**3.0 ISSUES AND COMMENTS (cont)**

2) In situations encountering QT prolongation, what suggestions regarding therapy have you made in labeling in the past, and would you have any recommendations for the proposed label for this NDA?

What to do with patients who develop a prolongation of their QT? We lack sufficient information to know how soon patients will develop a prolonged QT after starting infusion, as well as how long the QT will be prolonged after the infusion is stopped. Without this, we can't really make good recommendations to the physicians about the effect of drug discontinuation on QT interval (although we assume the QT will return to normal as the drug concentration falls). As discussed above, the QT interval used as a boundary for concern has been in the range of 500 msec. Until additional information is available, discontinuation of patients with QT ≥500 msec seems prudent. Patients with prolongation of QT should be monitored until resolution of the QT prolongation in an area where treatment of ventricular arrhythmias can be easily accomplished (e.g., a cardiac step-down unit). Later, as additional information is available that better defines the cardiac risk, this monitoring recommendation can be revisited.

**4.0 CONSULTANT RECOMMENDATIONS**

1. While there is much we do not know about the cardiac effects of the current data suggest that it has an effect to significantly prolong QT interval (30-60 msec mean increase in QTc). In addition, one case of Torsade de Pointes was reported in the small (100 patient) database. Based on our experience with other drugs, these two points suggest that individuals receiving will be at increased risk of serious cardiac events, including polymorphous ventricular tachycardia and sudden death.

2. Specific labeling recommendations are included above. Management of the potential proarrhythmic effects of should aim at the elimination of other know proarrhythmic factors prior to starting its infusion. Cardiac monitoring should be performed for all patients during infusion. Therapy for patients who develop prolonged QT intervals while on should likewise aim to minimize the potential for serious cardiac events, including drug discontinuation for marked prolongation of QT. Patients who develop prolongation of their QT interval should also be monitored until it normalizes.

3. Additional information on the cardiac effects of (listed above) should be obtained following marketing and used to update the labeled information for use by the clinicians and patients. Given the small number of patients anticipated to be in the indicated population, a patients registry may an attractive method of obtaining additional information on the cardiac effects of.

**5.0 REFERENCES**

1. Shen, Z.-X. et al. Use of Arsenic Trioxide (As<sub>2</sub>O<sub>3</sub>) in the treatment of acute promyelocitic leukemia (APL): II. clinical efficacy an pharmacokinetics in relapsed patients. Blood 89:3354-3360 (1997).

2. Soignet,S.L. et al. Complete remission after treatment of acute promyelocitic leukemia with arsenic trioxide. NEJM 339: 1341-1348 (1998).

3. Little, R.E., et al. Torsade de pointes and T-U wave alternans associated with arsenic poisoning. Pacing Clini Electrophysiol 13: 164-170 (1990).

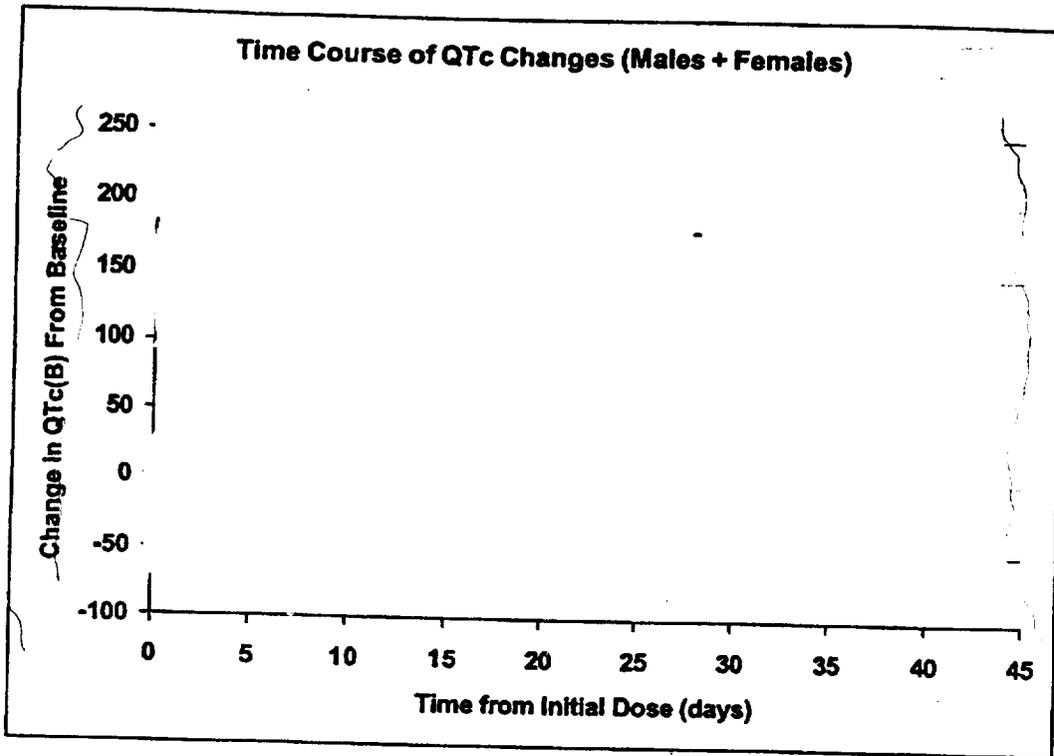
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| ORIG: Division File        |                      |
| HFD-110/Medical Officer    | Douglas Throckmorton |
| HFD-110/PharmTox Reviewer  | John Koerner         |
| HFD-110/Team Leader        | Shaw Chen            |
| HFD-110/ Division Director | Raymond Lipicky      |
| HFD-150/Project Manager    | Diane Spillman       |
| HFD-150/ Medical Officer   | Steven Hirschfeld    |
| HFD-150/ Medical Officer   | Amna Ibrahim         |
| HFD-150/Division Director  | Richard Pasdur       |

NDA No. 21-248

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Figure 1:

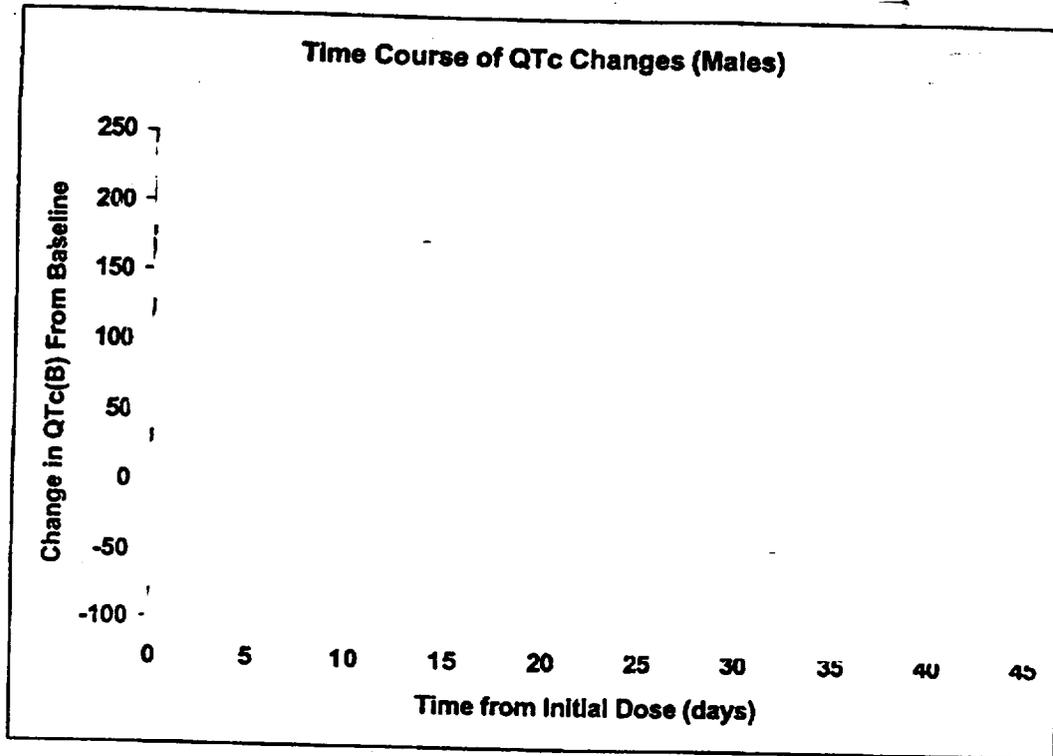


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**Figure 2:**

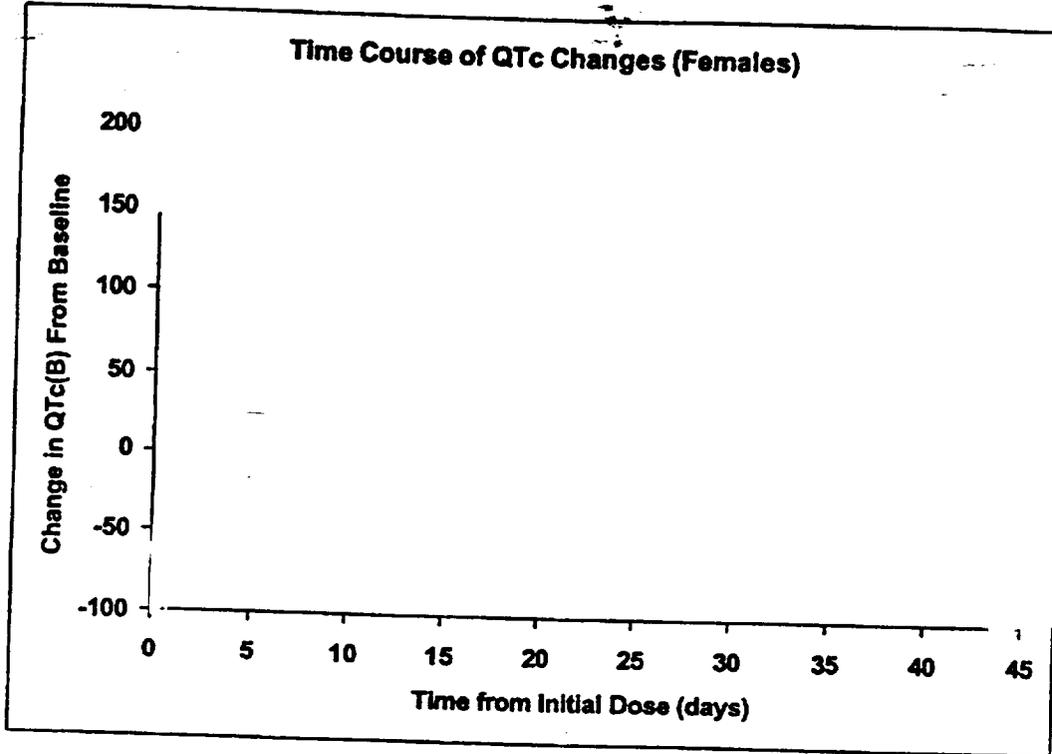


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Section 6.2.4

Figure 3:



SS dQTc =

Half-time =

Corr. Coeff. r =

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