

INTEGRATED SUMMARY of SAFETY

Description of the Safety Population

The sponsor has submitted demographic information on 836 patients enrolled in the 5 clinical efficacy/activity trials and additional experience in expanded access studies. Safety data are provided for 620 patients enrolled in the 5 clinical efficacy/activity trials and interim data from the expanded access experience. FDA has chosen to conduct analyses primarily in the data derived from 229 of the 284 patients enrolled in the clinical studies and to utilize the expanded access data only to supplement targeted analyses of specific toxicities. The primary safety database is derived from the 5 clinical studies. The reasons for exclusion of patients from the database are summarized in the table below.

Protocol	Number of Patients Receiving Study Drug ^a	Number of Patients in Safety Population	Explanation of the Differences in the Number of Patients	Data cutoff	Dates of accrual
RIT-I-000	59	22	Excludes 37 patients who received total body doses other than 65 or 75 cGy	Dec. 1, 2000	4/1990 - 1/1996
RIT-II-001	47	47		Dec. 1, 2000	12/1995 - 11/1996
RIT-II-002	78	61	Excludes 17 patients who only received tositumomab	Jan. 17, 2001	9/1996 - 1/2000
RIT-II-004	60	59	Excludes 1 patient with Mantle Cell NHL	Jan. 31, 2001	11/1996 - 3/1998
CP-97-012	40	40		Dec. 17, 2000	7/1998 -
Total	284	229			
^a Number of patients receiving iodine I 131 tositumomab as of August 31 2000.					

Study population for Integrated Summary of Safety

The baseline entry characteristics for the safety database are summarized below according to type of study (activity/efficacy vs. expanded access) for the 620 patients for whom safety data were provided. All studies enrolled patients with a diagnosis of follicular and/or low-grade non-Hodgkin's lymphoma, with or without transformation to a higher grade histology, which had recurred after at least one prior cytotoxic chemotherapy regimen. The baseline entry characteristics of the two groups are generally similar, although those enrolled in the efficacy/activity studies were more heavily pretreated and had a higher proportion of intermediate grade histology and tumors with histologic transformation.

Baseline Entry Characteristics of ISS database according to type of Study		
	ISS-audited studies (n=271)	ISS-expanded access (n=393)
Age (years)		
Median(range)	55 (23-82)	58 (29-88)
Q1; Q3	46; 64	50; 67
Gender		
Males (%)	60%	53%
Race		
Caucasian (%)	92%	93%
Histologic diagnosis at entry		
W/o transformation	199 (73%)	313 (80%)
Low grade	178 (66%)	313 (80%)
Intermediate grade	19 (7%)	0
High grade	2 (<1%)	0
With transformation	72 (27%%)	80 (20%)
Low grade	10 (4%)	3 (1%)
Intermediate grade	59 (22%)	74 (19%)
High grade	3 (1%)	3 (1%)
Stage of disease		
I	4 (1%)	9 (2%)
II	24 (9%)	33 (8%)
III	58 (21%)	100 (25%)
IV	185 (68%)	250 (64%)
Missing	0	1
IPI category		
0	7 (3%)	10 (3%)
1	48 (18%)	27 (7%)
2	103 (38%)	114 (29%)
3	76 (28%)	157 (40%)
4	24 (9%)	50 (13%)
5	2 (1%)	1 (0.3%)
Missing	11 (4%)	34 (9%)
Max. tumor diam		
< 5 cm	153 (56%)	393 (100%)
≥ 5, ≤10 cm	95 (35%)	0
> 10 cm	23 (9%)	0
# Prior chemo regimens		
Median (range)	3 (1-13)	2 (1-10)
25 th , 75 th quartiles	2, 4	1, 3
# Prior RT regimens		
Median (range)	0 (0-7)	0 (0-1)
25 th , 75 th quartiles	0, 1	0, 0
Prior BMT	15 (6%)	2 (<1%)
Yrs from diagnosis to entry		
Median (range)	3.7 (0.5-27.8)	3.9 (0.2- 22.9)
25 th , 75 th quartiles	2.2, 6.8	2.1, 6.7

In the analysis of this application, it became apparent that there were significant amounts of missing study, in part due to a high rate of withdrawal from study, but also due to failure to collect data for patients who remained alive for analysis of survival. In an attempt to identify a subset of subjects with complete information for hematologic toxicity, the dose-limiting toxicity associated with Iodine I 131 tositumomab, FDA initially requested that the sponsor attempt to collect all possible information through a review of the primary medical records and to collect additional safety data from ongoing studies. In response, the sponsor submitted a safety database containing additional data from studies RIT-II-002, CP97-012, and CP98-020.

In review of this dataset, FDA determined that there were even greater amounts of missing information particularly for the patients who were enrolled in the expanded access protocol (CP 98-020). The proportion of patients in the expanded access experience with missing data for hematologic toxicity through the period at risk (weeks 5-9) and for documentation of recovery from hematologic toxicity (week 13) was higher than in the other studies. In addition, there were insufficient numbers of patients followed beyond 4 months post-treatment to permit accurate assessments of prolonged and persistent hematologic toxicity. There was also evidence of lack of reporting of non-hematologic adverse events. Specifically, the proportion of patients in whom any adverse events was reported in the aggregate, the proportion of patients with adverse events within organ system (e.g., GI, respiratory), and the number of adverse events per patient was lower in the expanded access dataset as compared to the efficacy/activity studies. Of note, the sponsor has not audited any of the study sites participating in the expanded access study or in sponsor-investigator studies/single patient INDs. Because of the concerns with regard to under-reporting of the adverse events, the data from CP 98-020 has not been included in the ISS with the following exceptions: Serious adverse events are included in the ISS and analysis presented as time to event data (development of HAMA seropositivity, development of hypothyroidism, development of myelodysplasia and/or secondary leukemia) include data from CP98-020.

Adverse Events- Overall

Ninety-five percent of the patients enrolled in the efficacy activity studies experienced one or more adverse events. The most common toxicities of any severity as well as the most common severe (NCI grade 3-4) toxicities were neutropenia, thrombocytopenia, and anemia. The hematologic toxicity will be presented as a separate section. The most common non-hematologic adverse events were asthenia, fever and chills, gastrointestinal toxicities (nausea, vomiting, anorexia, and diarrhea), musculoskeletal (myalgias, arthralgias), pain (unspecified and abdominal pain), headache, and rash. The most common serious adverse events were infections and second malignancies. Separate discussion will be provided for the following categories of adverse events: hematologic, infection, hemorrhagic events, infusion-related, gastrointestinal, hypersensitivity, thyroid, immune responses (HAMA), MDS and second malignancies.

**Per-Patient Incidence of Adverse Events
Occurring in $\geq 5\%$ of Subjects**

Preferred Term	Cumulative (n=229)	
	Any Grade	Grades 3-4
Body as a Whole		
Fever	37%	2%
Infection	20%	<1%
Pain	16%	3%
Headache	16%	0
Chills	15%	1%
Asthenia	14%	2%
Back pain	8%	<1%
Chest pain	6%	0
Cardiovascular		
Hypotension	7%	<1%
Gastrointestinal		
Nausea	30%	3%
Vomiting	15%	1%
Abdom. pain	15%	3%
Anorexia	14%	0
Diarrhea	12%	0
Dyspepsia	6%	<1%
Metabolic		
Peripheral edema	9%	0
Musculoskel		
Myalgia	13%	<1%
Arthralgia	10%	0
Nervous syst		
Dizziness	5%	0
Respiratory		
Cough increased	20%	<1%
Pharyngitis	12%	0
Dyspnea	11%	3%
Rhinitis	10%	0
Skin		
Rash	17%	0
Pruritus	10%	0
Sweating	8%	0

Hematologic Adverse Events and Toxicity

The acute, dose-limiting toxicity of Iodine I 131 tositumomab therapy is severe neutropenia and/or thrombocytopenia with a median time from initiation of treatment (dosimetric dose) to nadir of 6 weeks (neutropenia) and 4.2 weeks (thrombocytopenia) and median duration of grade 3-4 toxicity of approximately 4 weeks. In order to achieve an accurate assessment of the depth

and duration of the nadir and to confirm recovery from toxicity, FDA determined that subjects would need to be assessed at least weekly during 4 of the 5 weeks when the onset of the nadir was noted (weeks 5-9) and once at the recovery period (week 13). FDA reviewed the data from 620 patients, including 271 from studies RIT-II-000, 001, 002, 004 and CP 97-012 and 393 patients enrolled in the expanded access experience (6 patients in single patient INDs and 387 in the expanded access study CP98-020).

Patients Excluded from Hematology Safety Analyses:

Patients were excluded from all analyses of hematologic toxicity, including sensitivity analyses, if they had no laboratory data following study entry. There are nine patients in this category are summarized below. Of the 620 patients, 8 had no post-treatment platelet counts, 7 had no post-treatment hemoglobin values, and 9 had no post-treatment ANC values.

Patient ID	MISSING FOLLOW-UP DATA			Reason for Missing Data
	Platelet	Hemoglobin	ANC	
004-018-001	X	X	X	Patient died on study day 14
020-013-467	X		X	Patient died on study day 10
020-028-126			X	ANC (differentials) not done in follow-up
020-039-016	X	X	X	Patient withdrew; did not receive therapeutic dose; no follow-up lab
020-042-138	X	X	X	Patient withdrew; did not receive therapeutic dose; no follow-up lab
020-047-365	X	X	X	Patient died on study day 39
020-052-159	X	X	X	Patient died on study day 57
020-053-326	X	X	X	Patient lost to follow-up-Had ANC missing at the baseline
020-061-179	X	X	X	Patient died on study day 41
Total w/ Missing Data	8	7	9	
Patients included in Analyses	612	613	611	

Among the remaining patients in the ISS database, 47 patients enrolled in RIT-II-000 who received a therapeutic dose below the MTD (which was based on hematologic toxicity) were excluded from analyses the analyses below. The remaining 229 subjects constitute the most complete dataset for assessment of efficacy

Missing Data

Based on the pattern of toxicity observed in individual patients and in a scatterplot of the study population, FDA considered that only those patients with a sufficient data obtained during the predicted likely period of hematologic toxicity could be adequately assessed. FDA defined sufficient data to assess for hematologic toxicity as having complete blood counts obtained in at least 4 of the 5 weeks (weeks 5-9) when the nadir might occur and at the time of the predicted recovery, which coincided with the end of the treatment period (week 13). Approximately 10% of the 229 patients enrolled in the activity/efficacy studies did not have CBC data during ≥ 2 of the 5 weeks of expected toxicity (weeks 5-9) or a recovery time point (week 13). Approximately 15%

of the 393 patients in the expanded access studies did not have CBC data during ≥ 2 of the 5 weeks of expected toxicity.

The reasons provided for lack of hematology data, in descending order of frequency, were: missing, died, withdrew from study, not required by protocol, received alternate therapy, shifted outside window. Subjects who withdrew from study or died should not be censored in the analysis of safety, as it is likely that such patients experienced toxicity more often than those who remained on study. In order to adjust for the large amount of missing data and to determine the possible extent of the risk of severe hematologic toxicity, FDA conducted sensitivity analyses for the incidence and duration of severe hematologic toxicity. In the worst-case sensitivity analyses below, all subjects with missing data were assumed to have NCI CTC grade 3 or 4 neutropenia, thrombocytopenia, or anemia, respectively. The number of subjects in the analyses for whom an adverse event was documented and those for whom it was imputed are also provided. The data are provided only for those patients enrolled in the efficacy/activity studies (n=229) since there is a lower proportion of patients with missing data in this subset. The incidence and duration of severe hematologic toxicity was slightly lower in the expanded access subset than observed in the patients in the more controlled studies.

**Per-Patient Incidence of
Grade 3-4 Hematologic Toxicity**

Hematologic Toxicity	Efficacy studies n=229
Neutropenia % Documented Grade 3-4 toxicity % Grade 3/4 toxicity (worst case scenario) Median days to nadir Median duration of documented Grade 3-4 toxicity 75 th percentile -duration of documented Gr 3-4 90 th percentile -duration of documented Gr 3-4 Maximum observed % documented Grade 4 % Grade 4 (worst case scenario)	51% 64% 43 days 29 days 43 days 62 days 383+ days 21% 25%
Thrombocytopenia % Documented Grade 3-4 toxicity % Grade 3-4 toxicity (worst case scenario) Median days to nadir Median duration of documented Grade 3-4 toxicity 75 th percentile duration of documented Gr ¾ 90 th percentile -duration of documented Gr 3-4 Maximum duration observed % documented Grade 4 % Grade 4 (worst case scenario)	42% 54% 34 days 30 days 36 days 102 days 211 days 18% 2%
Anemia % Documented Grade 3-4 toxicity % Grade 3-4 toxicity (worst case scenario) Median days to nadir Median duration of documented Grade 3-4 toxicity 75 th percentile duration of documented Gr ¾ 90 th percentile -duration of documented Gr 3-4 Maximum duration observed % documented Grade 4 % Grade 4 (worst case scenario)	15% 29% 47 days 19 days 34 days 40 days 78 days 4% 4%

Per-Patient Incidence of Grade 3-4 Hematologic Toxicity

Hematologic Toxicity	Efficacy studies n=229
Neutropenia and/or thrombocytopenia	
% Documented Grade 3-4 toxicity	59%
% Grade 3-4 toxicity (worst case scenario)	70%
% Documented Grade 4	26%
% Grade 4 (worst case scenario)	30%
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Neutropenia, anemia, and/or thrombocytopenia	
% Documented Grade 3-4 toxicity	60%
% Grade 3-4 toxicity (worst case scenario)	71%
% Documented Grade 4 toxicity	26%
% Grade 4 toxicity (worst case scenario)	30%

Both infections and hemorrhagic events may occur as a complication of treatment induced cytopenias. The following analyses pooled preferred terms that may relate to either infection or to hemorrhagic events to obtain a clearer picture of the overall risks.

Infections

- fever reported in 84 patients (31%)
- infections (type not specified) reported in 47 patients (20%)
- pharyngitis reported in 27 patients (12%)
- pneumonia reported in 12 patients
- bronchitis reported in 9 patients
- Herpes zoster reported in 8 patients
- urinary tract infections reported in 7 patients
- sepsis reported in 7 patients
- sinusitis reported in 6 patients
- Herpes simplex reported in 4 patients
- cellulitis reported in 4 patients
- fungal dermatitis reported in 2 patients
- periodontal abscess reported in 1 patient
-

Hemorrhagic events

- epistaxis reported in 10 patients
- ecchymosis reported in 9 patients
- melena reported in 3 patients
- GI hemorrhage reported in 2 patients
- hemorrhage (not specified) reported in 2 patients
- hemoptysis reported in 2 patients
- gum hemorrhage reported in 2 patients
- lung hemorrhage reported in 1 patient

Analyses were conducted to assess the per-patient incidence of infections and of hemorrhagic events, which pooled the terms listed in the table below to avoid “double-counting” multiple infections in the same patient. The analysis of infectious events does not include fever as a term nor does it include febrile neutropenia. In FDA’s review, the incidence of febrile neutropenia has been under-reported in the database and the figures are not reliable. FDA will conduct an analysis of fevers occurring during a period of documented neutropenia in order to derive a more appropriate figure. An updated analysis will be available at the time of the Dec. 17, 2002, ODAC meeting.

The per-patient incidence of infection in the efficacy/activity studies was 48% (98/229) with 149 events reported in these 98 patients. The incidence in the expanded access (17%) is substantially lower and deemed unreliable by FDA. The per-patient incidence of hemorrhagic events is 12% (28/229) with 31 events reported among 28 patients enrolled in the efficacy/activity studies. The 5% incidence reported in the expanded access population is deemed unreliable.

AE Preferred Name	All Number of Patients with AE All n=620	All Number of AEs in All n=620	ISS-A Number of Patients with AE Efficacy n=229	ISS-A Number of AEs in Efficacy n=229	ISS-B Number of Patients with AE Other n=391	ISS-B Number of AEs in Other n=391
Infection (type not specified), Pharyngitis, Pneumonia, Bronchitis, Herpes zoster, Urinary tract infection, Sepsis, Sinusitis, Herpes simplex, Cellulitis, Fungal dermatitis, Periodontal abscess	163	223	98	149	65	74
Hemorrhagic events (epistaxis, ecchymosis, Melena, Gastrointestinal hemorrhage, hemoptysis, Gum hemorrhage, Lung hemorrhage	46	52	28	31	18	21

B-cell lymphopenia.

The impact of Iodine I 131 tositumomab therapy on the number of circulating lymphocytes was assessed in patients enrolled in two studies: RIT-1-000, the Phase 1 study conducted previously treated subjects) and RIT-1-003, a single arm Phase 2 study conducted in patients with low grade NHL who had received no prior chemotherapy. As can be observed, there is considerable drop-off in the number of patients followed over time. The comparisons of time points is likely to be biased by selective retention of patients who are responding. Therefore, FDA will attempt to conduct analyses within patients over time in addition to the pooled analyses at various time points displayed below. Of note, the majority of the samples was obtained in a patient population (chemotherapy naïve) which differs from the population for which 131-Iodine tositumomab would be indicated. While the data may be qualitatively representative of the effects on CD20+ cells, the quantitative results would likely differ, as chemotherapy naïve patients would be expected to have higher pretreatment counts.

CD20+ cells in the Peripheral blood Samples obtained
in Selected Patients with Sampling in RIT-I-000 & RIT-II-003

PERIPHERAL CD20+ CELLS COUNTS PRE-TREATMENT AND POST-TREATMENT					
Time point (number of samples)	Baseline (n=125)	7 wks (n=111)	13 wks (n=74)	6 mos (n=57)	12 mos (n=14)
Mean (cells/ μ l)	197	15	35	75	168
25 TH Quartile (cells/ μ l)	63	0	0	19	42
Median (cells/ μ l)	118	2	13	49	101
75 TH Quartile (cells/ μ l)	196	14	38	100	177

The sponsor cites a normal range for peripheral CD20+ cells as 14-246 cells/ μ l

Infusional Toxicity

A constellation of symptoms, including fever, rigors or chills, hypotension, dyspnea, bronchospasm, and nausea, have been reported in the peri-infusional period. This constellation of adverse events is commonly observed with infusions of large proteins in doses of tens to hundreds of milligrams. All patients in the clinical studies received pretreatment with acetaminophen and an antihistamine. The value of premedication in preventing infusion-related toxicity was not evaluated in any of the clinical studies. Infusional toxicities were managed by slowing and/or temporarily interrupting the infusion. Symptomatic management was required in more severe cases.

The following table provides a listing of adverse events that occurred within 2 days of the dosimetric infusion.

Per-patient incidence of Infusion-related (Study days 0-2) Adverse Events

Costart Preferred Term	All Grades N=229
Fever	17%
Pruritus	7%
Nausea	7%
Chills	7%
Rash	6%
Asthenia	6%
Pain	5%
Headache	5%
Pharyngitis	5%
Rhinitis	4%
Hypotension	3%
Vomiting	3%
Vasodilatation	3%
Cough Increased	3%
Chest pain	3%
Urticaria	2%
Arthralgia	2%
Diarrhea	2%
Back pain	2%
Anaphylactoid reaction	<1%

Toxicities related to the antibody itself rather than the radioisotope were observed within 28 of days of the dosimetric infusion (21-14 days of the therapeutic infusion). These toxicities are attributed to infusion of a large protein load and to direct antibody binding. In assessing case reports, infusion-related toxicities included fever, chills, sweating, rigors, hypotension, and nausea. The table below provides the per-patient incidence for some of the commonly observed infusion-related toxicities. Analysis including a more comprehensive listing of the symptoms in this symptom complex that are temporally related to the dosimetric or therapeutic infusion, will be conducted. Based upon the list of preferred terms cited in the table below, and unrestricted by study day, the per-patient incidence of 40% for a pooled analysis of the preferred terms for fever, sweating, chills & fever and 23% for chills, sweating, and chills and fever. The latter grouping is probably more representative of the infusion-related events since fever is also a component on infectious events.

AE Preferred Name	All Number of Patients with AE All n=620	All Number of AEs in All n=620	ISS-A Number of Patients with AE Efficacy n=229	ISS-A Number of AEs in Efficacy n=229	ISS-B Number of Patients with AE Other n=391	ISS-B Number of AEs in Other n=391
Fever, sweating, chills & fever	153	234	91	151	62	83
Chills, sweating, chills & fever	100	152	53	80	47	72

Hypersensitivity reactions

Tositumomab is a murine (mouse) antibody; administration of murine proteins to humans can result in the development of a serologic immune response commonly referred to as HAMA (human anti-murine antibody) response. Prior to the 2001 amendment for long-term follow-up, the clinical studies assessed patients for HAMA for a relatively limited period following treatment. Unfortunately, unlike antibodies directed against other targets, tositumomab therapy directly causes a reduction in the number of circulating CD20+ (B) lymphocytes, may transiently mask any immune response that may occur. This phenomenon has been observed with other CD20+-directed antibodies as well. In these circumstances, evidence of an immune response may not be detectable until the CD20+ cell population returns to pretreatment levels

A pooled analysis utilizing was conducted using only those preferred terms that may denote a severe hypersensitivity reaction. Specifically, the preferred terms were allergic reaction, face edema, injection site hypersensitivity, anaphylactoid reaction, laryngismus & serum sickness.

There were 14 patients in the efficacy/activity studies identified with one or more of these terms for a per-patient incidence of 6%. In the expanded access experience there were 10 events reported among 9 of the 391 patients for a per-patient incidence of 2%.

In review of the narrative summaries of the serious adverse events, there is one additional significant allergic reaction that was reported as hypotension in a single patient. The narrative summaries and CRFs are being re-assessed to identify any additional subjects with allergic reactions coded under other terms to further refine the estimated incidence.

Gastrointestinal Toxicity

Images obtained following the dosimetric dose have demonstrated localization of the radioisotope in the gastrointestinal tract. This localization is felt to be direct binding of tositumomab to CD20+ cells in the gastrointestinal mucosa (e.g, Peyer's patches). The clinical

studies have demonstrated a range of gastrointestinal toxicities, which are temporally related to the infusion of the antibody. These toxicities are increased higher in patients who receive 131-iodine tositumomab as compared to those who receive only the unlabeled tositumomab antibody. For example, in study RIT-II-002, the incidence of nausea (48% vs. 17 %) and abdominal pain (17 vs. 8%) were higher in Arm A (receiving 131-iodine tositumomab) than in Arm B (unlabeled tositumomab). Infusion-related gastrointestinal toxicities appear to be related to upper GI symptoms, however lower GI symptoms are also frequent but generally occur more distant from infusion. As such, the lower GI events may reflect not only antibody binding but localized irradiation. FDA conducted a pooled analysis of the following gastrointestinal adverse events to identify the per-patient incidence of upper GI and lower GI toxicity.

AE Preferred Name	All Number of Patients with AE All n=620	All Number of AEs in All n=620	ISS-A Number of Patients with AE Efficacy n=229	ISS-A Number of AEs in Efficacy n=229	ISS-B Number of Patients with AE Other n=391	ISS-B Number of AEs in Other n=391
UGI (Nausea, Vomiting, Nausea & Vomiting, Gastrointestinal disorder)	166	251	86	136	80	115
UGI (Nausea, Vomiting, Nausea & Vomiting, Intestinal obstruction)	166	251	86	135	80	116
LGI (Diarrhea, Abdominal pain, Abnormal stools, Gastroenteritis, Intestinal Perforation, Ulcerative colitis, Colitis)	103	136	55	78	48	58

The per-patient incidence of UGI adverse events is 38% (86/229) with 136 events observed among 86 patients. The per-patient incidence in the expanded access study is 20% (80/391). FDA believes that this figure is falsely low and is likely due to under-reporting of non-serious events. The per-patient incidence of LGI adverse events is 24% (55/229) with 78 events observed among 55 patients. The per-patient incidence in the expanded access study is 12% (48/391).

EXPANDED ACCESS EXPERIENCE

The expanded access experience includes serious adverse events reported among 387 subjects enrolled across 60 sites under Protocol CP 98-020 and 6 patients enrolled under single patient studies in investigator-sponsored INDs. The sponsor-investigator experience includes three patients treated at the University of Michigan Medical Center (Protocols -----), two patients treated at Memorial Sloan-Kettering Cancer center (Protocols -----), and one patient treated at Stanford University Medical Center (Protocol-----). None of these studies were audited by the sponsor. The protocol specified requirements for adverse event monitoring and reporting of adverse events were different from those in the activity and efficacy studies conducted by the sponsor, with the exception of the requirement for reporting of serious adverse events. Data from these studies are less reliable but can be included in limited safety assessments, specifically, reports of serious adverse events and time-to-event analyses (e.g., for HAMA, hypothyroidism).

Hypothyroidism

Hypothyroidism can be reliably achieved through the delivery of radioactive iodine. All protocol required that patients be “blocked” with Lugol’s solution, SSKI or potassium perchlorate tablets administered from 24 hours prior to the first dosimetric infusion until 14 days after infusion of the dosimetric dose or therapeutic dose (whichever is the last infusion). The investigators have documented that patient compliance was a problem and this is confirmed by visual evidence of thyroid uptake on gamma camera images obtained for calculating the therapeutic dose.

Thyroid (TSH) Evaluation

The protocol-specified laboratory TSH schedule was Baseline, Month 6 and every 3 months up to year 2 (one year for RIT-II-001) for all the studies and additional week 7 and week 13 for the study RIT-I-000 and week 13 for the study RIT-II-002.

There were 598 patients (out of 620 patients in the Safety database) who had TSH measured at baseline. Forty-eight of 598 (8%) patients had an elevated TSH prior to the therapeutic dose, and an additional 22 patients had a history of thyroid medication. Thus 70 of 620 (11%) patients had a history of hypothyroidism prior to receiving their therapeutic dose. These patients were excluded from analyses of post-iodine I 131 tositumomab hypothyroidism. There were 528 patients who had normal TSH values at the baseline and did not have Thyroid medication prior to Iodine I 131 tositumomab treatment. The data are summarized below:

Elevated TSH Values at Baseline prior to therapeutic dose					
Any Thyroid Medication Pre-Iodine I 131 tositumomab		No (0)	Yes (1)	Missing	Total
	No (0)	528	41	21	590
	Yes (1)	22	7	1	30
	Total	550	48	22	620

There were 362 patients (out of 620 patients in the Safety database) who had a TSH value after treatment. There were 34 patients who had an elevated TSH (event) during the course of follow-up. For these 34 patients, the median time to TSH elevation 10.9 months (95% CI on median 6.0 to 13.6 months; range: 1.8 months to 76.3 months, IQ range 5.7 to 18.6 months).

Algorithm:

Once patients become hypothyroid, they continue to be hypothyroid. Therefore, the event was assumed to have occurred the first time a patient had elevated TSH for these 34 patients. The remaining 328 patients are assumed to have non-elevated TSH at their last day of TSH evaluation during the TSH follow-up, and are censored at individual patient’s last evaluation day of TSH measurements.

Laboratory TSH Followup: Integrated Safety Population (N=620)

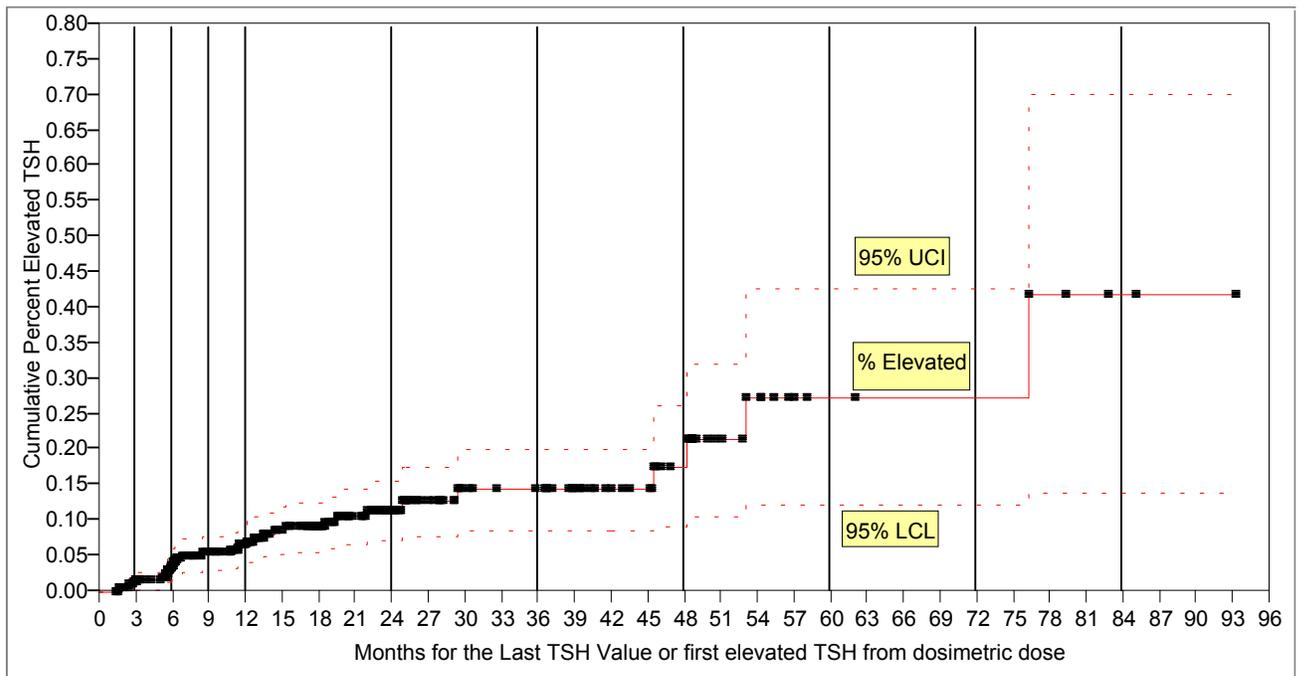
Time Interval	Number of Patients with a TSH Value within or after Interval ^a	Number Initially Elevated ^b in Time Interval	Number of Patients with a TSH Value or Thyroid Medication Assessment within or after Interval ^a	Number Initially Elevated or Initiating Thyroid Medication ^b in Time Interval
>0 – 3 months	362	4	516	3
>3 – 6 months	346	7	469	10
>6 – 12 months	298	9	421	10
>12 – 24 months	226	8	347	10
>24 months	90	6	170	9
Overall	362	34	507	42

^a Excludes patients with elevated baseline TSH or prior history of thyroid medication. There were 533 patients who did not have elevated TSH at the baseline or Pre-Iodine I 131 tositumomab treatment. Out of 533 patients, 170 patients had missing TSH after treatment and 362 patients had a TSH value after treatment (34 elevated and 328 not elevated).

^b Patients with an elevated TSH in time interval, no elevated TSH in previous intervals, and a low/normal TSH at baseline. Thus 34 of 362 (9%) TSH evaluable (i.e., patients with low/normal baseline TSH level, no history of prior thyroid medication, and with follow-up TSH data) patients developed an elevated TSH following therapy and 42 patients (8%) with low/normal baseline TSH level became hypothyroid (i.e., developed an elevated TSH or initiated thyroid medication).

Analyses were conducted assessing the time to hypothyroidism based on elevated TSH value alone and based on elevated TSH value and/or initiation of thyroid supplementation. The latter analysis provided a lower cumulative incidence. This appeared to be due to that fact that when a patient did not have TSH assessment, the patient was censored in the former analysis but would not be censored in the latter analysis if he/she indicated that he was not taking thyroid supplementation. FDA was concerned that the latter assay may have been falsely reassuring by use of data from patients who were not appropriately followed for this adverse event. Therefore, FDA has chosen only to provide the analysis based on TSH testing (shown below).

Percent Elevated TSH by Months Censored at the Last available TSH Value (Cumulative)



Time to event: Months Last TSH or first elevated; Censored by: Censor Day at Last TSH value

Months	0	3	6	12	24	36	48	60	72	84	96
Elevated	0	4	11	20	28	30	31	33	33	34	34
#Censored	0	14	60	128	252	288	309	323	324	326	328
# at Risk	362	344	291	214	82	44	22	6	5	2	0

#s are cumulative

HAMA

HAMA Values (Site or Central Evaluation)

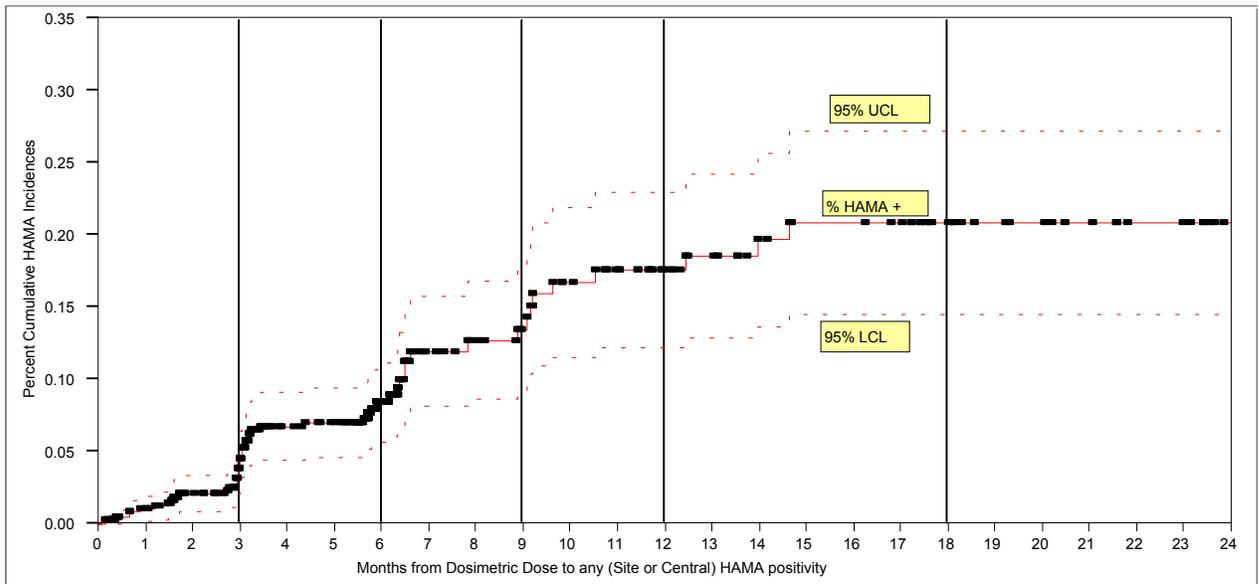
For the **site or central assay**, the data were pooled and patients were classified as HAMA positive if they were positive either the site or central assay. There were 604 patients (out of 620 patients in the Safety database) who had a negative baseline HAMA, 10 had a positive baseline HAMA and 6 had missing value. Out of 604 with negative baseline HAMA, 515 patients had had at least one follow-up assessment. A total of 51 of the 515 patients (10%) with a negative baseline HAMA and follow-up HAMA converted to HAMA positivity. For these 51 patients, the median time to HAMA positivity converting to HAMA positivity was 96 days (range: 5–446 days, IQ range 90 to 198 days). Forty-one of 51 (80%) patients converting to HAMA positivity on or prior to their Month 6 scheduled evaluation (228 days), and 10 of the 51 (20%) converted to HAMA positivity after the Month 6 evaluation. Only three of the 84 (4%) patients who were HAMA negative prior to 12 months and were later assayed became HAMA positive. No patient converted to HAMA positivity after 15 months.

The event (HAMA positive) was assumed to have occurred the first time a patient was HAMA positive for these 51 patients. The remaining 464 patients are assumed to be HAMA negative at their last day of HAMA evaluation during the HAMA follow-up, and are censored at individual patient's last available day of HAMA measurements.

Ref: Safety update (BLA Submission 125011.-----, -----, clinstat\liss\liss.pdf, page 63- the protocol specified Laboratory HAMA schedules were baseline, week 7 (except CP-98-020 study), week 13, month 6 and semi-annual for two years following the dosimetric dose.

The cumulative incidence for conversion to HAMA positivity is presented in the figure below.

Any HAMA positive (Site or Central) by Months Censored at the Last available HAMA Value (Cumulative)



Time to event:: APOSMON, Censored by : APOSDAYC

Months	0	3	6	9	12	18	24
# HAMA+	0	18	35	43	48	51	51
# Censored	0	84	273	364	383	406	427
# at Risk	515	413	207	108	84	58	88
#s are cumulative							

The concordance between the site central HAMA assays was 96% with 417 of 436 blood samples assayed by both the site and central HAMA assays in agreement. For site or central HAMA assay, almost all evaluable patients had at least one HAMA assessment at Week 7, Week 13, and/or Month 6. This is the time interval of the greatest incidence of conversion to HAMA positivity.

Source: HAMAOUT data - The variable APOSDAY when AEVAL=1 (baseline) and APOSDAYC=0 (censor) and APOSDAY identify the times for any HAMA central or site patients, for central assay use the variable CPOSDAY when CEVAL=1 and CPOSDAYC=0. Ref: Safety update (BLA Submission 125011.-----, clinstat\iss\iss.pdf, page 63- protocol specified Laboratory HAMA schedules were baseline, week 7 (except ----- study), week 13, month 6 and semi-annual for two years following the dosimetric dose.

HAMA incidence in a chemotherapy-naïve population

The rates of HAMA were higher in RIT-II-003, “Phase II Trial of Iodine I 131 tositumomab for Previously Untreated, Advanced-Stage, Low-Grade Non-Hodgkin’s Lymphoma”. This single arm, single center (University of Michigan Medical Center) study was intended to assess the activity (response rates, complete response rates, response duration) and safety of Iodine I 131 tositumomab in patients who had received no prior therapy for treatment of lymphoma. The dose and schedule of Iodine I 131 tositumomab was the same as for that described in RIT-II-004. There were 77 subjects who received at least one dose (dosimetric dose) of tositumomab. In this study, the estimated cumulative incidence of HAMA following treatment is 56% at one year and 63% at two years following treatment. These findings would suggest that use of Iodine I 131 tositumomab in less heavily pretreated patients who are more immunocompetent will

Serious Adverse Events

FDA’s review of the serious adverse events is ongoing. The data provided below are based upon the sponsor’s preferred terms for reported events. In the majority of cases, FDA agrees with the sponsor’s assessment of the event and categorization by preferred term. However, in review of the narrative summaries of these events, FDA would categorize certain events differently. Discussions of specific cases will be conducted with the sponsor to discuss FDA’s concerns and arrive at an acceptable categorization of disputed terms. Examples of such cases are patients with febrile neutropenia coded as “fever” or as “neutropenia” and patients with apparent hypersensitivity reactions recorded as “hypotension”. Any changes in the incidence of serious adverse events will be provided as an update at the Dec. 17, 2002, ODAC meeting.

The listing of serious adverse events, in descending order according to number of events observed in the efficacy/activity trials, are presented in the following table. This is not a per-patient incidence of events.

PREFERRED TERM	N Patient s All n=620	N Events All n=620	N Patient s ISE n=229	N Events ISE n=229
MYELOPROLIFERATIVE DISORDER	18	18	17	17
FEVER	19	21	9	9
SEPSIS	15	16	7	8
PNEUMONIA	12	12	6	6
DYSPNEA	11	13	5	7
THROMBOCYTOPENIA	10	11	5	5
PLEURAL EFFUSION	8	8	5	5
ANEMIA	9	9	4	4
HYPERCALCEMIA	6	6	4	4
HYPOTENSION	6	6	4	4
ACUTE MYELOBLASTIC LEUKEMIA	4	4	4	4
NEUTROPENIA	9	9	3	3

ABDOMINAL PAIN	7	7	3	3
DEEP THROMBOPHLEBITIS	3	3	3	3
GASTROINTESTINAL CARCINOMA	3	3	3	3
LEUKOPENIA	5	5	3	3
PAIN	9	11	2	3
ARTHRALGIA	3	3	2	2
ASTHENIA	8	10	2	2
KIDNEY FAILURE	6	6	2	2
PANCYTOPENIA	3	3	2	2
BLADDER CARCINOMA	2	2	2	2
BRONCHITIS	2	2	2	2
VOMITING	8	8	2	2
ABDOMEN ENLARGED	2	2	2	2
LYMPHOMA LIKE REACTION	2	2	2	2
POSTURAL HYPOTENSION	2	2	2	2
CONSTIPATION	2	2	2	2
DEHYDRATION	7	7	1	1
GASTROINTESTINAL HEMORRHAGE	3	5	1	1
NAUSEA	5	5	1	1
BACK PAIN	4	4	1	1
CHILLS	3	4	1	1
CONFUSION	4	4	1	1
HYPOCHROMIC ANEMIA	2	4	1	3
BONE DISORDER	3	3	1	1
CELLULITIS	3	3	1	1
INTESTINAL OBSTRUCTION	3	3	1	1
PATHOLOGICAL FRACTURE	2	3	1	1
ARRHYTHMIA	2	2	1	1
COUGH INCREASED	2	2	1	1
DYSPHAGIA	2	2	1	1
HEMORRHAGE	2	2	1	1
HYPERURICEMIA	2	2	1	1
HYPOXIA	2	2	1	1
LUNG DISORDER	2	2	1	1
PERIPHERAL EDEMA	2	2	1	1
SYNCOPE	2	2	1	1
ARTHRITIS	1	1	1	1
ASPIRATION PNEUMONIA	1	1	1	1
ATAXIA	1	1	1	1
ATRIAL FLUTTER	1	1	1	1
CARCINOMA	1	1	1	1
CARDIOMEGALY	1	1	1	1
CHOLECYSTITIS	1	1	1	1
CHRONIC LEUKEMIA	1	1	1	1
EDEMA	1	1	1	1
ENCEPHALOPATHY	1	1	1	1
ERYTHEMA NODOSUM	1	1	1	1
FLATULENCE	1	1	1	1

INJECTION SITE REACTION	1	1	1	1
MELENA	1	1	1	1
OLIGURIA	1	1	1	1
PULMONARY EMBOLUS	1	1	1	1
RECTAL DISORDER	1	1	1	1
SERUM SICKNESS	1	1	1	1
SHOCK	1	1	1	1
SKIN CARCINOMA	1	1	1	1
SKIN ULCER	1	1	1	1
SUBDURAL HEMATOMA	1	1	1	1
THROMBOSIS	1	1	1	1
ULCERATIVE COLITIS	1	1	1	1
URINARY TRACT DISORDER	1	1	1	1
URINARY TRACT INFECTION	1	1	1	1
APNEA	4	4		
CHEST PAIN	2	2		
INFECTION	2	2		
ABSCCESS	2	2		
ACIDOSIS	1	1		
ANOREXIA	1	1		
AV BLOCK COMPLETE	1	1		
CACHEXIA	1	1		
COLITIS	1	1		
CONVULSION	1	1		
DEATH	1	1		
DIARRHEA	1	1		
ESOPHAGITIS	1	1		
FACIAL PARALYSIS	1	1		
GASTROINTESTINAL DISORDER	1	1		
HEART ARREST	1	1		
HYDRONEPHROSIS	1	1		
HYPERKALEMIA	1	1		
HYPERTHYROIDISM	1	1		
HYPOGLYCEMIA	1	1		
INTESTINAL PERFORATION	1	1		
KETOSIS	1	1		
PARESTHESIA	1	1		
PELVIC PAIN	1	1		
PERICARDIAL EFFUSION	1	1		
PHARYNGITIS	1	1		
PNEUMOTHORAX	1	1		
SOMNOLENCE	1	1		
THINKING ABNORMAL	1	1		
VENTRICULAR TACHYCARDIA	1	1		

Myelodysplasia (MDS)

There were a total of 19 reported cases of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML); 18 cases in the 271 patients enrolled in the 5 efficacy/activity studies and one case in the expanded access experience (CP98-020).

A masked, independent review was performed by an expert hemato-morphologist, Dr. John Bennett of the University of Rochester. Based on Dr. Bennett's masked review, 5 patients (1 in the EAP and 4 in the other studies) had preexisting MDS by morphological and clinical criteria before administration of iodine I 131 tositumomab therapy and 1 patient was found to have a morphologically normal marrow and peripheral blood. Given the limited duration of follow-up in the expanded access experience, data are only summarized for the other studies. Thus, based on the masked independent review, 11 of the 229 (4.8%, 95% CI: 2.4%–8.4%) patients were diagnosed with MDS/AML following iodine I 131 tositumomab therapy for an annualized incidence of 2.2%/year (95% CI: 1.2%/year–3.9%/year).

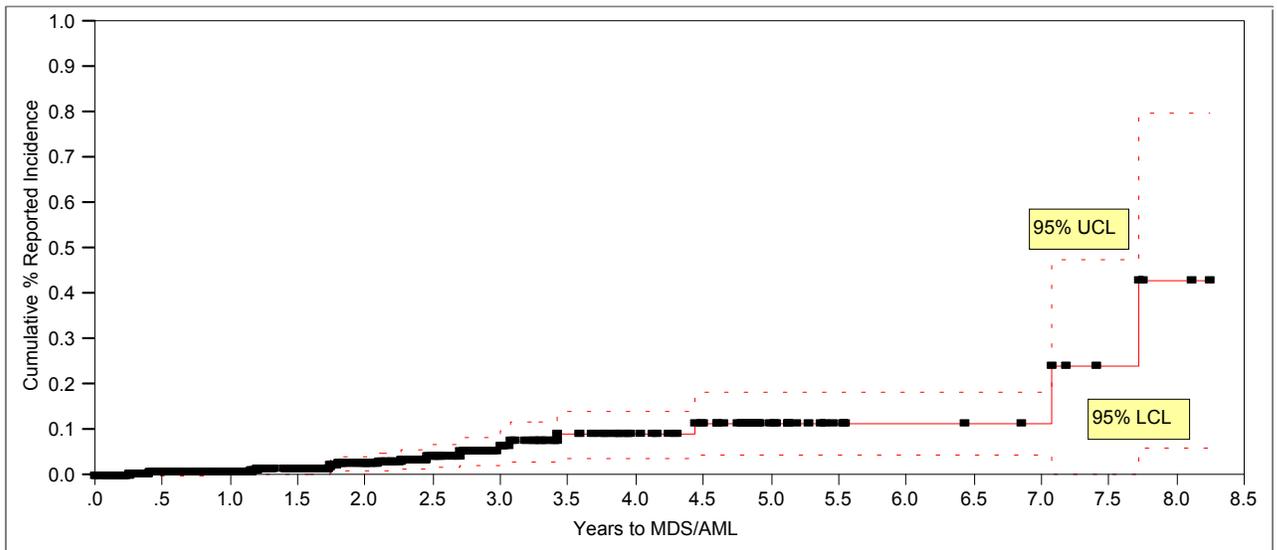
INCIDENCE RATE OF MYELODYSPLASIA/ACUTE LEUKEMIA (MDS or AML)

Study	N	# Incidence	Crude Rate Percent	Median Time to MDS/AML (Years)	IQ Range (Years)	Mean (Years)	95% CI on Mean
RIT-I-000	22	5	18.2%	3.9	1.5 to 7.4	4.2	0.3 to 8.1
RIT-II-001	47	5	8.5%	1.8	1.3 to 3.4	2.2	0.6 to 3.9
RIT-II-002	61	3	4.9%	1.2	0.9 to 1.2	1.2	0.0 to 2.1
RIT-II-004	59	4	6.8%	2.7	1.9 to 3.3	2.7	1.5 to 3.8
CP-97-012	40	1	2.5%				
CP-98-020	387	1	0.3%				
Overall	620	19	3.1%	2.1	1.2 to 3.1	2.5	1.5 to 3.5

Over all: N = 19 with 1 AML and 18 MDS. The crude incidence of MDS/AML is 3.1% (95% CI: 1.9%–4.7%) and the annualized incidence is 1.7%/year (95% CI: 1.1%/yr–2.7%/yr).

There is no apparent marked increase in MDS/AML during the first 18 months post treatment with iodine I 131 tositumomab. Only one patient in the expanded access experience (n= 387) was diagnosed with MDS/AML, which would be expected given the shorter duration of follow-up in the expanded access experience (median follow-up 1.5 years vs. 2.4 years in the efficacy/activity studies). Among the 233 patients enrolled in the efficacy/activity other studies, eighteen patients developed MDS and/or acute leukemia with a crude incidence of MDS/AML of 7.7% (95% CI: 4.6%–11.9%) and an annualized incidence of 3.0%/year (95% CI: 1.9%/yr–4.8%/yr).

Cumulative Incidence of MDS/AML in patients treated with Iodine I 131 tositumomab by Year



Years	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5
# MDS/																		
AML	0	3	4	6	9	12	13	16	16	17	17	17	17	17	17	18	19	19
Censored	0	97	177	283	388	469	524	543	559	567	583	592	594	595	596	598	599	601
# at Risk	620	520	439	337	223	139	83	61	45	36	20	11	9	8	7	4	2	0

#s are cumulative; Time to event: :MDSYr; Censored by : MDSYrC

Second malignancies

There were 5 secondary hematologic malignancies reported. These included 4 patients who developed AML and one patient who developed CML. Non-hematologic secondary neoplasms were also reported. The most common included non-melanomatous skin cancers, colon cancer,

superficial bladder cancer and breast cancer. Some of these events included recurrence of an earlier diagnosis of cancer. The excretion of the radioisotope is through the gastrointestinal tract rather than the genitourinary system. Therefore, surveillance for gastrointestinal malignancies as a delayed toxicity should be conducted.