

Clinical Review
 Qin Ryan, MD, PhD for efficacy review
 Virginia Kwitkowski, MS, RN, CRNP for safety review
 NDA 22249
 Treanda (bendamustine)

consists of individual reports, a report of a 398 patient postmarketing study, and an Overall Safety Update Report (SUR). According to Astellas, approximately — patients were exposed to bendamustine during this time period. Reliance on postmarketing reports for estimation of adverse reaction incidence and severity is limited due to the passive nature of the collection of spontaneous reports, the voluntary nature of reporting, the insufficient detail contained in these reports, and difficulty calculating event rates due to the relatively unknown safety population denominator.

Demographics

The demographics presented below in Table 7-6 are from the major study used for the safety analysis (02CLLIII). All patients had histologically-confirmed chronic B-cell lymphocytic leukemia and symptomatic Binet stage B or Binet stage C disease. Patients were predominantly men (62% vs. 38%), with an average age of 63.3 years, exactly half were less than 65 years of age versus ≥65 years of age. In study 02CCLLIII, patients in each treatment group were well-matched for age, gender, race, and body height. The data in Table 7-6 below were confirmed using the raw datasets provided by the Applicant in the application.

Table 7-6 Demographic Information (Treated Analysis Set; Applicant Table)

Demographic information Variable/Statistic	Bendamustine (N=153)	Chlorambucil (N=148)	Total (N=301)
Age, (years)			
Mean	63.0	63.6	63.3
SD	7.68	8.62	8.15
Median	63.0	66.0	64.0
Min. max	45.0, 77.0	38.0, 78.0	38.0, 78.0
Age group			
<65 years	82 (54)	69 (47)	151 (50)
≥65 years	71 (46)	79 (53)	150 (50)
Sex, n (%)			
Men	97 (63)	90 (61)	187 (62)
Women	56 (37)	58 (39)	114 (38)
Race, n (%)			
White	153 (100)	147 (-99)	300 (-99)
Other ^a	0	1 (<1)	1 (<1)
Weight (kg)			
n	152	145	297
Mean	78.2	74.0	76.1
SD	15.06	13.26	14.35
Median	77.4	72.0	75.0
Min. max	50.0, 133.0	48.8, 118.0	48.8, 133.0
Height (cm)			
n	153	145	298
Mean	169.0	168.4	168.7
SD	8.60	9.04	8.80
Median	170.0	168.0	169.0
Min. max	147.0, 190.0	149.0, 189.0	147.0, 190.0

SOURCE: Summary 15.3.1, Listing 4.
^a Race for patient 10516 in the chlorambucil treatment group was not specified.
 Min=minimum; max=maximum; SD=standard deviation.

Data in above table was confirmed by review of raw and derived datasets and CRFs.

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Reviewer Comments: The bendamustine and chlorambucil treatment groups appear to be well-balanced for demographic criteria that could potentially impact the safety analysis for bendamustine. Age, gender, and weight did not significantly vary between groups. An insufficient number of non-caucasian patients were enrolled to address potential impacts upon race.

The demographics of this study population may not mirror those of the potential population who will be treated with bendamustine after its marketing approval in that Treanda may be reserved for previously treated patients. The proposed dose and schedule in this application is supported by the dose and schedule studied in trial 02CLLIII. The study design allowed continued treatment until intolerable toxicity, progression of disease, or investigator decision. The median number of cycles received in both groups was six. The typical experience with purine analogs to treat CLL is also with six courses.

7.2.2 Explorations for Dose Response

The Applicant did not perform a study comparing different doses of bendamustine. Therefore, and exploration for dose response could not be performed. Overall, the application submitted does contain adequate numbers of patients in the proposed population of CLL, at the proposed dose (100 mg/m²), and schedule. Additionally, the patients in both treatment groups appear to have been exposed to similar doses and exposures of the respective agents.

7.2.3 Special Animal and/or In Vitro Testing

Reprotoxicity

Development and reproductive toxicology studies were performed in mice and rats. These studies were non-GLP and are considered to be supportive, although reproductive toxicity is expected for any alkylating agent. Other nonclinical toxicology studies conducted with bendamustine were local tolerance studies in rabbits (GLP) and immunotoxicity studies in mice and human peripheral blood lymphocytes (non-GLP).

QT Prolongation

Safety pharmacology studies conducted with bendamustine included in vitro evaluations of action potential duration using Beagle dog Purkinje fibers, an in vitro assessment of hERG channel current, and an assessment of renal function in the Sprague-Dawley rat. The study to evaluate the effects of bendamustine on the action potential duration in dog Purkinje fibers and the study to assess potential effects on renal function in rats were conducted by _____ (GLP). The study to assess bendamustine on hERG channel current was conducted by _____ (GLP).

According to the Applicant:

Bendamustine had no effect in vitro on dog Purkinje fiber action potential parameters, including amplitude, resting potential, maximal

rate of depolarization, and action potential duration under both normal (60 ppm) and slow (20 ppm) stimulation rates over a concentration range of 1.5 to 7.5 µg/mL. In an in vitro study to evaluate the potential effects of bendamustine on hERG channel current, a concentration of 2 µg/mL had no effect on hERG channel current, while concentration of 20 µg/mL and 200 µM had a dose-dependent inhibition of hERG channel current ranging from 20% to 65%, respectively. Based upon the results of these in vitro cardiovascular safety pharmacology studies, bendamustine demonstrated a low arrhythmogenic risk at concentrations that are equivalent to, or slightly greater than those being observed in patients.

Reviewer Comments: The non-clinical testing of bendamustine appears adequate to explore potential adverse reactions. The reader is referred to the PharmTox review for further details of the non-clinical testing for bendamustine.

7.2.4 Routine Clinical Testing

Reviewer Comment: The clinical evaluations of trial participants were adequate to assess expected and unexpected adverse reactions in the CLL population.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to Section 4.4 (Clinical Pharmacology). In vitro data suggest that plasma protein binding was approximately 95%, with albumin being the main binding protein at therapeutic plasma concentrations. In vitro data suggest that bendamustine is not likely to displace or be displaced by other highly protein-bound drugs.

Bendamustine is primarily metabolized by hydrolysis to the relatively inactive metabolites, monohydroxy bendamustine (HP1) and dihydroxy bendamustine (HP2). The active metabolites of bendamustine (-hydroxybendamustine [M3] and N-des-methylbendamustine [M4]) are formed primarily via cytochrome (CYP) P450 system CYP1A2. However, both metabolites are present in low concentrations relative to the parent. In vitro data suggest that P-glycoprotein, BCRP, and/or other efflux transporters may have a role in bendamustine transport. Based on in vitro data, bendamustine is not likely to inhibit human CYP isoenzymes 1A2, 2C9/10, 2D6, 2E1, or 3A4/5. In addition, in vitro data indicate that bendamustine is not likely to induce substrates of CYP enzymes.

There was no formal clinical pharmacology study conducted to specifically evaluate the effects of race, sex, or age on the pharmacokinetics of bendamustine. A cross-study comparison of the bendamustine exposures from study SDX-105-03 (7 Caucasians, 1 Other) and study 2006001 (6 Japanese subjects) indicate that exposures in Japanese patients were slightly higher (20%) than those seen in the Caucasian subjects. However, because of the limited number of patients, no conclusions can be drawn. More data are required to make definitive recommendations.

7.2.6 Evaluation for Potential Adverse Reactions for Similar Drugs in Drug Class

Class effects typically seen with alkylating agents include nausea, vomiting, and myelosuppression. These effects were properly evaluated in study 02CLLIII and were some of the most commonly seen toxicities.

Reviewer Comments: The Applicant's efforts to detect class-specific adverse reactions were adequate for the indication sought. Pre-clinical testing indicated that bendamustine will not likely lead to QT prolongation. The sponsor has not conducted adequate clinical analyses to assess this potential in humans per ICH guidelines. This evaluation should be requested as a post-marketing commitment.

7.3.1 Deaths

Thirty-four deaths occurred during the conduct of study 02CLLIII. An equal number (17) of deaths occurred in each treatment group. Seventy-one percent of deaths in both groups occurred more than 100 days after the last study drug dose. The most common attribution for death was progression of disease (41% of patients in each group). Four patients died during the treatment phase of the study or within 30 days of the last study drug dose, one patient in the bendamustine group (patient 10303) and three patients in the chlorambucil group (patients 10114, 10902, and 20902). The Applicant provided the reported cause of death for these four patients. A review of the death narratives and eCRFs was undertaken to evaluate the attributions of these deaths. A description of the information reviewed about each event are provided below.

Deaths Within 30 days of Last Study Drug Treatment

The section below provides the verbatim patient narratives for deaths provided by the Applicant.

Bendamustine Group

Patient 10303: Patient was a 69-year-old, white man with symptomatic Binet stage B, chronic lymphocytic leukemia. Significant medical history included chronic obstructive pulmonary disease (COPD) and pleural effusion, which was reported as grade 3 at baseline. On Cycle 1, Day 1, the patient experienced an adverse event of grade 1 pleural effusion and a thoracentesis

procedure was performed the same day. On day 15, the pleural effusion was reported as a serious adverse event of grade 3 severity. In addition, on day 15, he experienced non-serious adverse reactions of grade 3 respiratory failure, dyspnea, and hypoxia, and results of an electrocardiogram noted a grade 2 supraventricular arrhythmia. The pleural effusion, respiratory failure, dyspnea, and hypoxia all required hospitalization, and the patient was treated with corticosteroids for systemic use and oxygen. On day 18, cefipime was added to the patient's treatment regimen and all of the events continued. Subsequently, on day 19, the pleural effusion, respiratory failure, dyspnea, and hypoxia all increased in severity to grade 4, and a second thoracentesis was performed. On day 20 (19 days after last dose of study drug), the patient died due to pleural effusion, respiratory failure, dyspnea, and hypoxia as a consequence of underlying COPD. All of the events reported for this patient were considered unrelated to study drug treatment by the investigator.

Adverse Reaction(s) Leading to Death: Pleural effusion, respiratory failure, dyspnea, hypoxia

Chlorambucil Group

Patient 10114: Patient was a 47-year-old, white woman with symptomatic Binet stage C, chronic lymphocytic leukemia. On Cycle 1, Day 22, the patient had an adverse reaction of grade 2 neutropenia (absolute neutrophil count [ANC]: $1.485 \times 10^9/L$), which was considered possibly related to study drug treatment by the investigator and continued. On day 27, she experienced grade 3 cough and grade 4 pyrexia (reported as non-serious adverse reactions) and was diagnosed with a serious adverse reaction of grade 4 bacterial pneumonia the same day. In addition, on day 27, the patient also experienced a non-serious adverse reaction of grade 3 rash. The patient was hospitalized due to the bacterial pneumonia, cough, pyrexia, and rash, and she was treated with ceftriaxone sodium, amikacin sulfate, ciprofloxacin, human albumin, digoxin, oxygen, and meropenem for the bacterial pneumonia. On day 29 (14 days after last dose of study drug), the patient died due to massive bacterial pneumonia, as a result of treatment for chronic lymphocytic leukemia. The bacterial pneumonia and rash were considered possibly related to study drug treatment by the investigator and the cough and pyrexia were considered unrelated to study drug treatment.

Adverse Reaction(s) Leading to Death: Neutropenia, pneumonia bacterial, cough, pyrexia, rash

Patient 10902: Patient was a 67-year-old, white woman with asymptomatic Binet stage B, chronic lymphocytic leukemia. Significant medical history included heart failure and right plural effusion. On day 76, she experienced a serious adverse reaction of grade 1 hemorrhage, which resulted in hospitalization; also on day 76, she had non-serious adverse reactions of grade 4 thrombocytopenia (platelets: $90 \times 10^9/L$), grade 2 blood lactate dehydrogenase increased (LDH: $1054 \mu/L$), and grade 3 hyperbilirubinemia (bilirubin: $87.1 \mu\text{mol/L}$). The patient was treated with hydrocortisone and methylprednisolone for the thrombocytopenia, and received platelets. The hemorrhage was considered possibly related; the thrombocytopenia was considered unrelated; and the elevated LDH and hyperbilirubinemia were considered unlikely related to study drug treatment by the investigator. On day 81, the severity of the hemorrhage increased to grade 3;

and the severity of the elevated LDH decreased to grade 1; the severity of the hyperbilirubinemia decreased to grade 2; and the thrombocytopenia was ongoing. That same day (day 81), the patient also had a grade 2 adverse reaction of anemia, which was ongoing and considered unrelated to study drug treatment by the investigator. On day 84, the severity of the hemorrhage increased to grade 4, and the patient subsequently died on day 88 (17 days after last dose of study drug) due to the hemorrhage. The grade 4 hemorrhage was considered possibly related to study drug treatment by the investigator.

Adverse Reaction(s) Leading to Death: Hemorrhage

Patient 20902: Patient was a 63-year-old, white man with asymptomatic Binet stage C, chronic lymphocytic leukemia. Significant medical history included diabetes mellitus, myocardial ischemia, pneumonitis related to tumor infiltration, and heart failure. Prior to the study and concomitantly, the patient took allopurinol for prevention of hyperuricemia, furosemide and metildigoxin for heart failure, and isosorbide dinitrate for chronic cardiac ischemia. On day 29, the patient had nonserious adverse reactions of grade 3 anemia (hemoglobin: 77 g/L) and grade 2 respiratory tract infection. The patient received red blood cells for the anemia, and midecamycin, ciprofloxacin, and ambroxol hydrochloride for the respiratory tract infection. On day 35, the patient experienced the serious adverse reaction of grade 3 cardiac failure, which resulted in hospitalization and for which the patient continued concomitant treatment with furosemide and metildigoxin. In addition, on day 35, the patient experienced the non-serious adverse reaction of grade 3 dyspnea, for which he was treated with concentrated oxygen and methylprednisolone. The respiratory tract infection was noted as having resolved on day 36 and the anemia, dyspnea, and cardiac failure continued until the patient's death on day 37 (8 days after last dose of study drug), which was due to all 4 of these events. With the exception of respiratory tract infection, which was considered unlikely related to study drug treatment by the investigator, all of these events were considered unrelated to study drug treatment.

Adverse Reaction(s) Leading to Death: Anemia, respiratory tract infection, dyspnea, cardiac failure

Neither narratives nor case report forms were provided for patients who died more than 30 days after study drug treatment. Therefore, the data on attribution of death could not be confirmed. In the bendamustine group, 2 (possibly 3) patients died from cardiac causes (10401, 20204, and 23601). None of these three patients had any baseline medical conditions recorded in the medical history datasets that might increase the risk of such events. However, the concomitant medication datasets contained some medications used that could potentially be related to a history of cardiac disease. Patient 10401 was receiving amiodarone at baseline for a history of supraventricular arrhythmia. Patient 20204 was taking nifedipine for arterial hypertension at baseline and while on study. Patient 23601 was not recorded as taking any baseline medications that could be linked to cardiac death. The attribution cannot be clearly made to bendamustine because the patients were at increased risk of such events due to age (6th decade of life) and the lack of a close temporal relationship between bendamustine and the fatal event.

Three patients (10102, 11001, & 20701) died of cerebrovascular events which are also increased in this age group. None of these three patients had any baseline medical conditions recorded that might increase the risk of such events. However, patient 11001 was recorded as taking nifedipine for arterial hypertension before the study began. Neither patient 10102 or 20701 were recorded as having used any medication at baseline that would indicate and increased risk of cerebrovascular events. The lack of temporal relationship to the study drug and the event makes an attribution to bendamustine less likely.

Reviewer Summary of Fatal Events Within 30 Days of Treatment:

Three patients died within 30 days of study drug in the chlorambucil treatment group as compared to 1 in the bendamustine group. The only patient in the bendamustine treatment group to die within 30 days of treatment appeared to die from a baseline (non-cancer) medical condition. The narrative indicates that the patient was medically decompensating secondary to his baseline grade 3 pleural effusions on the first day of treatment. It is probable that this patient should have been excluded from trial eligibility due to an unstable medical condition. This death is not likely to be related to bendamustine therapy.

7.3.2 Nonfatal Serious Adverse Reactions

Severe (Grade 3-4) Adverse Reactions

Eighty-eight (58%) patients in the bendamustine treatment group and 44 (31%) patients in the chlorambucil treatment group reported at least one grade 3 or 4 adverse reaction. Both grade 3 and 4 adverse reactions occurred more frequently in the bendamustine treatment group than in the chlorambucil treatment group. Grade 3 events were reported in 33% of the bendamustine patients as compared to 22% in the chlorambucil patients. Grade 4 events were reported in 25% of patients in the bendamustine group as compared to 8% of patients in the chlorambucil group. The most common severe adverse reactions in the bendamustine treatment group by System Organ Class in the bendamustine treatment group were blood and lymphatic system disorders (41%), infections and infestations (7%), general disorders and administrative site conditions (5%), and vascular disorders (5%).

Grade 3/4 hematologic adverse reactions with a frequency greater than 10% in the bendamustine treatment group were neutropenia (24%), leukopenia (15%), and thrombocytopenia (13%). Grade 3/4 non-hematologic adverse reactions were reported by 52 (34%) patients in the bendamustine treatment group and 25 (17%) patients in the chlorambucil treatment group. Grade 3/4 non-hematologic adverse reactions with a frequency greater than 1% in the bendamustine treatment group were pyrexia (4%), pneumonia (3%), rash (3%), hypertension (3%), hypertensive crisis (2%), hyperuricemia (2%), and infection (2%). Five patients (3%) in the bendamustine treatment group experienced febrile neutropenia compared with none in the chlorambucil group. Neutropenic infection occurred in 10 bendamustine patients compared with 1 in the chlorambucil group. There were 2 events of grade 3 sepsis, both in patients in the bendamustine treatment group. Both patients recovered. Grade 3/4 hematologic adverse reactions

with a frequency greater than 5% in the chlorambucil treatment group were neutropenia (9%) and thrombocytopenia (8%) (Table 7-7).

Table 7-7 Grade 3 and 4 Adverse Reactions Occurring in Either Treatment Group by System Organ Class, Preferred Term, and Severity (Treated Analysis Set; Applicant Table)

System organ class Preferred term	Number (%) of patients*					
	Bendamustine (N=153)			Chlorambucil (N=143)		
	Grade			Grade		
	3	4	3 or 4	3	4	3 or 4
Total number of patients with at least 1 adverse event	50 (33)	38 (25)	88 (58)	32 (22)	12 (8)	44 (31)
Total number of patients with at least 1 nonhematologic adverse event	40 (26)	12 (8)	52 (34)	20 (14)	5 (3)	25 (17)
Blood and lymphatic system disorders	36 (24)	27 (18)	63 (41)	17 (12)	9 (6)	26 (18)
Neutropenia	16 (10)	20 (13)	36 (24)	5 (3)	8 (6)	13 (9)
Leukopenia	20 (13)	3 (2)	23 (15)	2 (1)	0	2 (1)
Thrombocytopenia	16 (10)	4 (3)	20 (13)	10 (7)	1 (<1)	11 (8)
Lymphopenia	10 (7)	0	10 (7)	0	0	0
Anemia	3 (2)	1 (<1)	4 (3)	0	0	0
Febrile neutropenia	1 (<1)	0	1 (<1)	0	0	0
Hemolysis	1 (<1)	0	1 (<1)	0	0	0
Granulocytopenia	0	0	0	2 (1)	0	2 (1)
Hemolytic anemia	0	0	0	1 (<1)	0	1 (<1)
Cardiac disorders	2 (1)	1 (<1)	3 (2)	3 (2)	0	3 (2)
Arrhythmia supraventricular	1 (<1)	0	1 (<1)	0	0	0
Cardiovascular disorder	1 (<1)	0	1 (<1)	0	0	0
Myocardial infarction	0	1 (<1)	1 (<1)	0	0	0
Cardiac failure	0	0	0	1 (<1)	0	1 (<1)
Extrasystoles	0	0	0	1 (<1)	0	1 (<1)
Ventricular extrasystoles	0	0	0	1 (<1)	0	1 (<1)
Ear and labyrinth disorders	1 (<1)	0	1 (<1)	0	0	0
Vertigo	1 (<1)	0	1 (<1)	0	0	0
Eye disorders	1 (<1)	0	1 (<1)	0	0	0
Retinal detachment	1 (<1)	0	1 (<1)	0	0	0
Gastrointestinal disorders	4 (3)	0	4 (3)	3 (2)	0	3 (2)
Diarrhea	2 (1)	0	2 (1)	0	0	0
Nausea	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Vomiting	1 (<1)	0	1 (<1)	0	0	0
Abdominal pain	0	0	0	1 (<1)	0	1 (<1)
Palatal disorder	0	0	0	1 (<1)	0	1 (<1)
General disorders and administration site conditions	7 (5)	0	7 (5)	2 (1)	1 (<1)	3 (2)
Pyrexia	6 (4)	0	6 (4)	1 (<1)	1 (<1)	2 (1)
Fatigue	2 (1)	0	2 (1)	0	0	0
General physical health deterioration	0	0	0	1 (<1)	0	1 (<1)
Hepatobiliary disorders	2 (1)	0	2 (1)	2 (1)	0	2 (1)
Cholestasis	1 (<1)	0	1 (<1)	0	0	0
Hepatotoxicity	1 (<1)	0	1 (<1)	0	0	0
Jaundice	1 (<1)	0	1 (<1)	0	0	0
Hyperbilirubinemia	0	0	0	2 (1)	0	2 (1)

Abbreviations and footnotes are provided on the last page of this table.

(continued)

Data in above table was confirmed by review of raw and derived datasets and CRFs.
 Table continues on next page.

Continuation of Table 7.7

System organ class Preferred term	Number (%) of patients ^a					
	Bendamustine (N=153)			Chlorambucil (N=143)		
	Grade			Grade		
	3	4	3 or 4	3	4	3 or 4
Immune system disorders	2 (1)	0	2 (1)	0	0	0
Hypersensitivity	2 (1)	0	2 (1)	0	0	0
Infections and infestations	10 (7)	0	10 (7)	4 (3)	1 (<1)	5 (3)
Pneumonia	4 (3)	0	4 (3)	0	0	0
Infection	3 (2)	0	3 (2)	1 (<1)	0	1 (<1)
Pseudomonal sepsis	1 (<1)	0	1 (<1)	0	0	0
Sepsis	1 (<1)	0	1 (<1)	0	0	0
Tracheobronchitis	1 (<1)	0	1 (<1)	0	0	0
Upper respiratory tract infection	1 (<1)	0	1 (<1)	0	0	0
Viral infection	1 (<1)	0	1 (<1)	0	0	0
Hepatitis B	0	0	0	1 (<1)	0	1 (<1)
Herpes zoster	0	0	0	1 (<1)	0	1 (<1)
Pneumonia bacterial	0	0	0	0	1 (<1)	1 (<1)
Respiratory tract infection	0	0	0	1 (<1)	0	1 (<1)
Investigations	4 (3)	2 (1)	6 (4)	4 (3)	2 (1)	6 (4)
Blood lactate dehydrogenase increased	2 (1)	0	2 (1)	0	0	0
Blood alkaline phosphatase increased	1 (<1)	0	1 (<1)	0	0	0
Blood bilirubin increased	1 (<1)	0	1 (<1)	0	0	0
Blood creatinine increased	0	1 (<1)	1 (<1)	0	0	0
Blood uric acid increased	0	1 (<1)	1 (<1)	0	0	0
Gamma-glutamyl transferase increased	1 (<1)	0	1 (<1)	2 (1)	0	2 (1)
Hemoglobin decreased	1 (<1)	0	1 (<1)	0	1 (<1)	1 (<1)
Alanine aminotransferase increased	0	0	0	1 (<1)	0	1 (<1)
Aspartate aminotransferase increased	0	0	0	1 (<1)	0	1 (<1)
Platelet count decreased	0	0	0	0	1 (<1)	1 (<1)
Weight increased	0	0	0	1 (<1)	0	1 (<1)
Metabolism and nutrition disorders	3 (2)	3 (2)	6 (4)	2 (1)	0	2 (1)
Hyperuricemia	0	3 (2)	3 (2)	0	0	0
Dehydration	1 (<1)	0	1 (<1)	0	0	0
Hyperglycemia	1 (<1)	0	1 (<1)	0	0	0
Hyperkalemia	0	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)
Hypokalemia	1 (<1)	0	1 (<1)	0	0	0
Anorexia	0	0	0	1 (<1)	0	1 (<1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (1)	1 (<1)	3 (2)	0	0	0
Tumor lysis syndrome	1 (<1)	1 (<1)	2 (1)	0	0	0
Bronchial carcinoma	1 (<1)	0	1 (<1)	0	0	0
Nervous system disorders	1 (<1)	0	1 (<1)	2 (1)	0	2 (1)
Paraplegia	1 (<1)	0	1 (<1)	0	0	0
Facial palsy	0	0	0	1 (<1)	0	1 (<1)
Neuralgia	0	0	0	1 (<1)	0	1 (<1)

Abbreviations and footnotes are provided on the last page of this table.

(continued)

Data in above table was confirmed by review of raw and derived datasets and CRFs.
 Table continues on next page.

Continuation of Table 7.7

System organ class Preferred term	Number (%) of patients ^a					
	Bendamustine (N=153)			Chlorambucil (N=143)		
	Grade			Grade		
	3	4	3 or 4	3	4	3 or 4
Renal and urinary disorders	2 (1)	1 (<1)	3 (2)	0	0	0
Renal impairment	1 (<1)	1 (<1)	2 (1)	0	0	0
Pollakiuria	1 (<1)	0	1 (<1)	0	0	0
Renal failure acute	1 (<1)	0	1 (<1)	0	0	0
Reproductive system and breast disorders	1 (<1)	0	1 (<1)	0	0	0
Epididymitis	1 (<1)	0	1 (<1)	0	0	0
Respiratory, thoracic and mediastinal disorders	2 (1)	2 (1)	4 (3)	4 (3)	1 (<1)	5 (3)
Cough	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Dyspnea	0	1 (<1)	1 (<1)	2 (1)	0	2 (1)
Hypoxia	0	1 (<1)	1 (<1)	0	0	0
Lung infiltration	1 (<1)	0	1 (<1)	0	0	0
Pleural effusion	0	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)
Pulmonary embolism	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Respiratory failure	0	1 (<1)	1 (<1)	0	0	0
Skin and subcutaneous tissue disorders	7 (5)	0	7 (5)	4 (3)	0	4 (3)
Rash	4 (3)	0	4 (3)	3 (2)	0	3 (2)
Rash generalized	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Skin burning sensation	1 (<1)	0	1 (<1)	0	0	0
Urticaria	1 (<1)	0	1 (<1)	0	0	0
Vascular disorders	5 (3)	3 (2)	8 (5)	3 (2)	1 (<1)	4 (3)
Hypertension	4 (3)	0	4 (3)	2 (1)	0	2 (1)
Hypertensive crisis	1 (<1)	2 (1)	3 (2)	0	0	0
Circulatory collapse	0	1 (<1)	1 (<1)	0	0	0
Arterial occlusive disease	0	0	0	1 (<1)	0	1 (<1)
Hemorrhage	0	0	0	0	1 (<1)	1 (<1)

SOURCE: Summary 15.30, Summary 15.25, and Listing 20.

^a If a patient reported an adverse event more than once, the greatest severity is presented for that adverse event.

NOTE: Patients are counted only once in each preferred term category and only once in each system organ class category, at the greatest severity for each.

Data in above table was confirmed by review of raw and derived datasets and CRFs.

Serious Adverse Events

Fifty-two serious adverse events (SAEs); were reported by 43 patients during the study; including those that led to death. Among these, 27 (18%) patients receiving bendamustine reported 32 SAEs and 16 (11%) patients receiving chlorambucil reported 20 SAEs.

The most common SAE was infection with 7 (5%) patients treated with bendamustine and 6 (4%) patients treated with chlorambucil reporting this SAE. SAEs occurring in ≥2 patients in the bendamustine group were pneumonia (3 patients), hypersensitivity (3 patients), anemia (2

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patients), tumor lysis syndrome (2 patients), and vomiting (2 patients). The SAE occurring in 2 or more patients receiving chlorambucil was herpes zoster (2 patients). All other SAEs in each group were reported in only one patient each. One patient in the chlorambucil group reported two occasions of hypersensitivity (Table 7-8).

Table 7-8 Serious Adverse Reactions Occurring in Either Treatment Group by System Organ Class and Preferred Term (Treated Analysis Set; Applicant Table)

System organ class Preferred term	Bendamustine (N=153)		Chlorambucil (N=143)	
	Number (%) of patients ^a	Number of events	Number (%) of patients ^a	Number of events
Patients reporting at least 1 serious adverse event	27 (18)	32	16 (11)	20
Blood and lymphatic system disorders	4 (3)	5	1 (<1)	1
Anemia	2 (1)	2	0	0
Anemia hemolytic autoimmune	1 (<1)	1	0	0
Hemolysis	1 (<1)	1	0	0
Pancytopenia	1 (<1)	1	0	0
Hemolytic anemia	0	0	1 (<1)	1
Cardiac disorders	1 (<1)	1	1 (<1)	1
Myocardial infarction	1 (<1)	1	0	0
Cardiac failure	0	0	1 (<1)	1
Eye disorders	1 (<1)	1	0	0
Retinal detachment	1 (<1)	1	0	0
Gastrointestinal disorders	2 (1)	2	1 (<1)	1
Vomiting	2 (1)	2	0	0
Abdominal pain	0	0	1 (<1)	1
General disorders and administration site conditions	2 (1)	2	1 (<1)	1
General physical health deterioration	1 (<1)	1	0	0
Pyrexia	1 (<1)	1	1 (<1)	1
Hepatobiliary disorders	1 (<1)	1	0	0
Gallbladder pain	1 (<1)	1	0	0
Immune system disorders	3 (2)	4	1 (<1)	2
Hypersensitivity	3 (2)	4	1 (<1)	2
Infections and infestations	7 (5)	7	6 (4)	6
Pneumonia	3 (2)	3	0	0
Herpes zoster	1 (<1)	1	2 (1)	2
Infection	1 (<1)	1	0	0
Respiratory tract infection	1 (<1)	1	0	0
Sepsis	1 (<1)	1	0	0
Hepatitis B	0	0	1 (<1)	1
Meningitis	0	0	1 (<1)	1
Pneumonia bacterial	0	0	1 (<1)	1
Upper respiratory tract infection	0	0	1 (<1)	1
Injury, poisoning and procedural complications	0	0	1 (<1)	1
Head injury	0	0	1 (<1)	1
Metabolism and nutrition disorders	1 (<1)	1	0	0
Dehydration	1 (<1)	1	0	0
Musculoskeletal and connective tissue disorders	1 (<1)	1	0	0
Sacral pain	1 (<1)	1	0	0

Abbreviations and footnotes are provided on the last page of this table.

(continued)

Data in above table was confirmed by review of raw and derived datasets and CRFs.

Continuation of Table 7.8

System organ class Preferred term	Bendamustine (N=153)		Chlorambucil (N=143)	
	Number (%) of patients ^a	Number of events	Number (%) of patients ^a	Number of events
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (1)	2	0	0
Tumor lysis syndrome	2 (1)	2	0	0
Nervous system disorders	1 (<1)	1	1 (<1)	1
Paraplegia	1 (<1)	1	0	0
Neuralgia	0	0	1 (<1)	1
Reproductive system and breast disorders	1 (<1)	1	0	0
Epididymitis	1 (<1)	1	0	0
Respiratory, thoracic and mediastinal disorders	2 (1)	2	3 (2)	3
Lung infiltration	1 (<1)	1	0	0
Pleural effusion	1 (<1)	1	0	0
Epistaxis	0	0	1 (<1)	1
Laryngeal edema	0	0	1 (<1)	1
Pulmonary embolism	0	0	1 (<1)	1
Skin and subcutaneous tissue disorders	1 (<1)	1	0	0
Urticaria	1 (<1)	1	0	0
Vascular disorders	0	0	3 (2)	3
Arterial occlusive disease	0	0	1 (<1)	1
Hemorrhage	0	0	1 (<1)	1
Phlebitis	0	0	1 (<1)	1

SOURCE: Summary 15.28, Ad Hoc Summary 11, Listing 21.

^a Patients may have reported more than 1 adverse event.

Data in above table was confirmed by review of raw and derived datasets and CRFs.

Reviewer Comments: The bendamustine group experienced more serious and severe (grade 3 & 4) adverse events than the chlorambucil group. The serious and severe (grade 3 & 4) adverse reactions seen with bendamustine are not unusual for a cytotoxic agent in this patient population. The reactions seen can typically be managed by an oncologist. Serious adverse reactions are not as clinically useful as severe (grade 3 and 4) adverse reactions because SAEs include hospitalizations. Some countries admit patients for reasons that would not result in a U.S. admission; partly due to the variations in health care systems.

7.3.3 Dropouts and/or Discontinuations

Adverse reactions were the most frequent cause of study withdrawal. Twenty-two patients were withdrawn from the study because of adverse reactions; 17 (11%) patients who received bendamustine and 5 (3%) patients who received chlorambucil. The most frequent adverse

reactions causing withdrawal were hypersensitivity (occurring in 3 bendamustine patients and 1 chlorambucil patient) and pyrexia (occurring in 2 bendamustine patients and 1 chlorambucil patient). The other adverse reactions leading to withdrawal that occurred in more than 1 patient were neutropenia (1 bendamustine and 1 chlorambucil patient) and rash (2 bendamustine patients). All other adverse reactions causing withdrawal occurred in 1 patient each (Table 7-9).

Table 7-9 Adverse Reactions Leading to Withdrawal From Study Drug Treatment By Treatment Group (Applicant Table)

System organ class Preferred term	Number (%) of patients*	
	Bendamustine (N=153)	Chlorambucil (N=143)
Total number of patients with at least 1 adverse event leading to withdrawal	17 (11)	5 (3)
Blood and lymphatic system disorders	3 (2)	1 (<1)
Anemia hemolytic autoimmune	1 (<1)	0
Leukopenia	1 (<1)	0
Neutropenia	1 (<1)	1 (<1)
Thrombocytopenia	1 (<1)	0
Cardiac disorders	1 (<1)	0
Arrhythmia supraventricular	1 (<1)	0
General disorders and administration site conditions	2 (1)	1 (<1)
Pyrexia	2 (1)	1 (<1)
Hepatobiliary disorders	1 (<1)	0
Hepatotoxicity	1 (<1)	0
Immune system disorders	3 (2)	1 (<1)
Hypersensitivity	2 (1)	1 (<1)
Drug hypersensitivity	1 (<1)	0
Infections and infestations	3 (2)	2 (1)
Pneumonia	1 (<1)	0
Sepsis	1 (<1)	0
Viral infection	1 (<1)	0
Hepatitis b	0	1 (<1)
Herpes zoster	0	1 (<1)
Nervous system disorders	1 (<1)	0
Paraplegia	1 (<1)	0
Skin and subcutaneous tissue disorders	6 (4)	1 (<1)
Rash	2 (1)	0
Dermatitis allergic	1 (<1)	0
Erythema	1 (<1)	0
Rash generalized	1 (<1)	0
Urticaria	1 (<1)	0
Skin reaction	0	1 (<1)
Vascular disorders	0	1 (<1)
Phlebitis	0	1 (<1)

Best Possible Copy

Data in above table was confirmed by review of raw and derived datasets and CRFs.

Reviewer Comments: The bendamustine group experienced more patient withdrawals due to adverse reactions than the chlorambucil group. Overall, the percentage of patients that withdrew was small and not likely to be significant.

7.3.4 Significant Adverse Events

- **Myelosuppression:** Neutropenia, leukopenia, thrombocytopenia, and anemia occurred frequently with bendamustine. These events were captured via complete blood counts with differential. These adverse reactions may lead to serious and life-threatening infections and hemorrhage in this population which already has an increased risk of

infection from the disease CLL. Infections were captured by notations of increased temperature, symptoms of localized infection, radiological studies, and microbiological laboratory test results. Five patients (3%) in the bendamustine treatment group experienced febrile neutropenia compared with none in the chlorambucil group. Neutropenic infection occurred in 10 bendamustine patients compared with one in the chlorambucil group. The details of infections were captured on a specialized eCRF. It is recommended that the absolute neutrophil count recover to $1 \times 10^9/L$ and platelet count to $75 \times 10^9/L$ prior to the initiation of the next cycle of therapy.

Red blood cell transfusions were administered to 20% of patients in the bendamustine group compared with 6% of patients in the chlorambucil group. Platelet transfusions were received by only one patient per group (<1%). Patients in the bendamustine treatment group received hematologic support (blood products or growth factors) in 10% of treatment cycles. The use of granulocyte growth factors for the prevention of chemotherapy-induced neutropenia may be used, which may reduce the risk of infection. The reader is referred to section 7.4.2 for further discussion of laboratory abnormalities seen in study 02CLLIII.

- **Infections:** Infections, typically related to myelosuppression, including pneumonia and sepsis, have been reported in patients in bendamustine clinical studies and in postmarketing reports. In rare cases, infection has been associated with hospitalization, septic shock, and death. Patients with neutropenia and/or lymphopenia following treatment with bendamustine are more susceptible to infections. Patients with myelosuppression following bendamustine treatment should be advised to contact a physician if they have symptoms or signs of infection, including fever or respiratory symptoms. The use of granulocyte growth factors for the prevention of chemotherapy-induced neutropenia may be used, which may reduce the risk of infection.
- **Tumor Lysis Syndrome:** Two cases of grade 3 or 4 tumor lysis syndrome were reported in the study, both in the group treated with bendamustine. The events were both associated with complete resolution of nodal masses. The onset tends to be within 48 hours of the first dose of bendamustine and, without intervention, may lead to acute renal failure and death. Both events resolved on study without sequelae. One of the events was associated with grade 4 hyperuricemia and grade 3 renal impairment. There were 2 additional reports of grade 4 hyperuricemia in the bendamustine treatment group. No deaths occurred secondary to tumor lysis syndrome during the study. Tumor lysis syndrome was detected by laboratory analysis of serum uric acid, phosphorus, potassium, calcium, creatinine, and BUN. The reader is referred to section 7.4.2 for further discussion of laboratory abnormalities seen in study 02CLLIII.
- **Hypersensitivity Reactions:** Reactions suggestive of infusion reactions to bendamustine have occurred commonly in clinical studies. Symptoms are generally mild and include fever, chills, pruritis, and rash. Hypersensitivity reactions were more common in the second and subsequent cycles of therapy. There were two grade 3 events of

hypersensitivity in the bendamustine group. These events are typically considered anaphylactoid. No grade 4 (anaphylactic) events were reported in either treatment group. When evaluating events that occurred within 24 hours of study drug administration, the preferred term “hypersensitivity” was assigned to five events (all grades) in four patients treated with bendamustine. Two events were grade 2 hypersensitivity reactions and one event each were grade 1 allergic reaction, grade 3 suspected allergy, and grade 1 allergy. Hypersensitivity reactions were the most frequent cause for withdrawal from the study (3 due to hypersensitivity and 6 due to rash). Most of the hypersensitivity reactions appeared to be dermatologic in nature. The lower grade (1 & 2) reactions were improved with the use of systemic antihistamines and both topical and systemic corticosteroids. No patients with grade 3 allergic or hypersensitivity reaction were rechallenged with bendamustine. The onset typically occurred after 25 days of exposure and the duration of the rash was occasionally weeks long. The hypersensitivity reactions were detected by patient complaints of itching or rash or by physical examination. Most patients with significant rash discontinued therapy. No deaths resulted from hypersensitivity reactions to bendamustine.

- **Hypertension:** The bendamustine treatment group patients reported more hypertensive events (hypertension and hypertensive crisis) than did the chlorambucil patients. Worsening of baseline hypertension was reported in 3% of patients in the bendamustine treatment group compared with 1% in the chlorambucil treatment group. Hypertensive crisis was reported in 2% of the bendamustine treatment group compared with no reports in the chlorambucil treatment group. Five events in three patients on the bendamustine group of hypertensive crisis were reported. All three patients had a baseline diagnosis of hypertension, were managed by additional antihypertensive medications, and none were hospitalized due to the event. From the vital signs data, the highest blood pressures associated with the events in the 3 patients were 180/120, 170/100, and 194/110 mm Hg.
- **Other Cardiac Events:** Cardiac-related events were reported by 6 (4%) patients in the bendamustine treatment group and 4 (3%) patients in the chlorambucil treatment group. There were 3 severe (grade 3 or 4) events reported in each treatment group. In the bendamustine treatment group, the cardiovascular disorders were considered by the investigator to be possibly and probably related to study drug and the supraventricular arrhythmia was considered definitely related and led to withdrawal of the patient from the study. In the chlorambucil treatment group, the ventricular extrasystoles were considered possibly related to study drug and contributed to the death of the patient. All other cardiac disorders were considered unlikely related, not related, or had a missing relationship to study drug treatment.

Cardiac events also occurred in other bendamustine studies; both single agent and combination therapy studies. In study SDX105-03 SAEs of congestive heart failure (CHF) and myocardial infarction (MI) were seen at doses of 120mg/m² Days 1 & 2 every 21 days. In study 20BEN03, with doses ranging from 120-180 mg/ m² Days 1&2 every

21 days, non-dose limiting toxicities of sinus tachycardia, PSVT, AV block, PAC, LVH, and PVCs were reported. In study 98B02W atrial flutter was a dose-limiting toxicity at 60 mg/m². In study 98B02 AV block was a dose-limiting toxicity at 160 mg/ m² on Days 1 & 8 every 28 days. In study 20BEND1, dose-limiting toxicities at 280 mg/ m² every 21 days were frequently cardiac events (QT prolongation, ischemia, T-wave changes) and 77% had new ECG findings with no dose relationship noted.

- **Secondary Malignancies:** One patient in the bendamustine treatment group was diagnosed with bronchial carcinoma approximately 1 year after stopping treatment with study drug. Bronchial carcinomas have been reported as a secondary malignancy after prior chemotherapy or radiation therapy. No patients in the chlorambucil group were reported to experience a new malignancy after study enrollment. Secondary malignancies (and Myelodysplastic Syndrome) were also seen in three NHL studies SDX105-01, SDX105-03, and 93BOP01.

Reviewer Comment: Non-clinical studies described dose-related cardiac toxicity in animals. The clinical dose-escalation studies demonstrated dose-related cardiac toxicities. Though the overall incidence of cardiac toxicity in the bendamustine arm was low (and similar to the chlorambucil arm); bendamustine may have cardiac toxicities, particularly at higher doses than those utilized in the pivotal trials for CLL and NHL. The large variety of cardiac events reported in these smaller studies make it difficult to provide firm attribution to bendamustine. Prescribers should be cautioned to closely monitor patients receiving bendamustine for cardiac events. ECG monitoring in this study was not adequate to evaluate the potential for QT prolongation because ECGs were only obtained at baseline and end of study; and interval measurements were not obtained.

Pertinent Negative Findings:

There were no cases of cardiac failure, impaired hearing, hypothyroidism, abdominal discomfort/distension, stomatitis, disorientation, or insomnia in the bendamustine treatment group.

7.3.5 Submission Specific Primary Safety Concerns

See section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common Adverse Reactions

At least one adverse reaction was reported by 89% of the bendamustine patients compared with 79% of the chlorambucil patients. Adverse reactions that were considered by the investigator to be treatment-related (or were missing attribution information) were reported in 127 (83%) patients in the bendamustine treatment group and 95 (66%) patients in the chlorambucil treatment group.

In study 02CLLIII the most common hematologic adverse reaction (any grade) on the bendamustine group that occurred with a frequency greater than 15% were: neutropenia (28%), thrombocytopenia (23%), anemia (19%), and leukopenia (18%). The most common non-hematologic adverse reaction (any grade) on the bendamustine group that occurred with a frequency greater than 15% were pyrexia (24%), nausea (20%), and vomiting (16%). These events were also reported in earlier single-group studies of bendamustine. All of these common adverse reactions were more frequently reported in the bendamustine group than in the chlorambucil group. Administration related adverse reactions such as chills, pyrexia, rash, and urticaria were more common with intravenous administration of bendamustine than with oral chlorambucil. The reader is referred to Table 7-10 below for a direct comparison of adverse reactions between treatment groups.

Due to data collection issues discovered at Sites 01 and 02 during Sponsor site visits, the adverse reactions were also reported in a format that excluded these sites. In this analysis, the incidence of adverse reactions increased in both groups (from 89% to 94% for bendamustine and from 79% to 81% for chlorambucil. No significant differences were found in the incidence of patients with individual adverse reaction. Table 7-11 below contains a summary of adverse reactions in more than 5% of patients excluding sites 01 & 02.

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Table 7-10 Adverse Reactions Occurring in at Least 5% of Patients in Either Treatment Group by System Organs Class and Preferred Term (ITT; Applicant Table)

System organ class Preferred term	Number (%) of patients ^a	
	Bendamustine (N=153)	Chlorambucil (N=143)
Total number of patients with at least 1 adverse event	136 (89)	113 (79)
Blood and lymphatic system disorders		
Neutropenia	43 (28)	20 (14)
Thrombocytopenia	35 (23)	28 (20)
Anemia	29 (19)	16 (11)
Leukopenia	28 (18)	4 (3)
Lymphopenia	10 (7)	0
Gastrointestinal disorders		
Nausea	31 (20)	21 (15)
Vomiting	24 (16)	9 (6)
Diarrhea	14 (9)	5 (3)
General disorders and administration site conditions		
Pyrexia	36 (24)	8 (6)
Fatigue	14 (9)	8 (6)
Asthenia	13 (8)	6 (4)
Chills	9 (6)	1 (<1)
Immune system disorders		
Hypersensitivity	7 (5)	3 (2)
Infections and infestations		
Nasopharyngitis	10 (7)	12 (8)
Infection	9 (6)	1 (<1)
Herpes simplex	5 (3)	7 (5)
Investigations		
Weight decreased	11 (7)	5 (3)
Metabolism and nutrition disorders		
Hyperuricemia	11 (7)	2 (1)
Respiratory, thoracic and mediastinal disorders		
Cough	6 (4)	7 (5)
Skin and subcutaneous tissue disorders		
Rash	12 (8)	7 (5)
Pruritus	8 (5)	2 (1)

SOURCE: Summary 15.24, Listing 20, Listing 24.

^a Patients may have reported more than 1 adverse event.

NOTE: Patients are counted only once in each preferred term category and only once in each system organ class category.

Data in above table was confirmed by review of raw and derived datasets and CRFs.

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Table 7-11 Adverse Reactions Occurring in at Least 5% of Patients in Either Treatment Group by System Organs Class and Preferred Term (Excluding Centers 1 & 2)

System organ class Preferred term	Number (%) of patients ^a	
	Bendamustine (N=126)	Chlorambucil (N=116)
Total number of patients with at least 1 adverse event	119 (94)	94 (81)
Blood and lymphatic system disorders		
Neutropenia	36 (29)	15 (13)
Thrombocytopenia	29 (23)	18 (16)
Anemia	24 (19)	14 (12)
Leukopenia	20 (16)	3 (3)
Lymphopenia	9 (7)	0
Gastrointestinal disorders		
Nausea	30 (24)	19 (16)
Vomiting	23 (18)	8 (7)
Diarrhea	14 (11)	5 (4)
General disorders and administration site conditions		
Pyrexia	35 (28)	6 (5)
Fatigue	14 (11)	8 (7)
Asthenia	13 (10)	6 (5)
Chills	9 (7)	1 (<1)
Immune system disorders		
Hypersensitivity	7 (6)	3 (3)
Infections and infestations		
Nasopharyngitis	10 (8)	12 (10)
Infection	9 (7)	1 (<1)
Herpes simplex	5 (4)	7 (6)
Investigations		
Weight decreased	8 (6)	4 (3)
Metabolism and nutrition disorders		
Hyperuricemia	8 (6)	1 (<1)
Anorexia	6 (5)	2 (2)
Nervous system disorders		
Dizziness	4 (3)	6 (5)
Respiratory, thoracic and mediastinal disorders		
Cough	6 (5)	6 (5)
Skin and subcutaneous tissue disorders		
Rash	10 (8)	4 (3)
Pruritus	8 (6)	2 (2)
Urticaria	6 (5)	2 (2)

SOURCE: Ad Hoc Summary 18, Listing 20, Listing 24.

^a Patients may have reported more than 1 adverse event.

NOTE: Patients are counted only once in each preferred term category and only once in each system organ

Data in above table was confirmed by review of raw and derived datasets and CRFs.

Less Common Adverse Reactions

Adverse reactions with a 5% or higher incidence were reported in Section 7.4.1. Less common adverse reactions in a patient population this small are not likely to reach clinical or statistical significance.

Table 7-12 below summarizes the major safety events in study 02CLLIII.

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Table 7-12 Overview of Adverse Reactions in the Safety Population of Study 02CLLIII

Category	Number (%) of patients	
	Bendamustine (N=153)	Chlorambucil (N=143)
Any adverse event	136 (89)	113 (79)
Severe adverse events (grade 3 or grade 4)	88 (58)	44 (31)
Severe nonhematologic adverse events (grade 3 or 4)	52 (34)	25 (17)
Treatment-related adverse events	127 (83)	95 (66)
Deaths	17 (11)	17 (12)
Serious adverse events	27 (18)	16 (11)
Withdrawals due to adverse events	17 (11)	5 (3)

Data in above table was confirmed by review of raw and derived datasets and CRFs.

7.4.2 Laboratory Findings

Overview of laboratory testing in the development program

Adequate laboratory testing was performed in the development program to identify both expected and unexpected laboratory adverse reaction. Study 02CLLIII collected laboratory results on the following schedule from participating patients in both the bendamustine and chlorambucil treatment groups:

Baseline testing:

- Hematology
- Chemistry
- Urinalysis
- Coomb's test
- Serum immunoglobulin assay

Testing after each cycle:

- Hematology
- Chemistry
- Urinalysis

Weekly (and more frequently as clinically indicated):

- Hemoglobin
- WBC and differential
- Creatinine
- LDH
- AST
- ALT
- Bilirubin

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- Uric acid

End of Cycle 6:

- Hematocrit
- **Coomb's test**
- Serum immunoglobulin assay

End of Treatment:

- Hematology
- Chemistry
- Urinalysis
- Serum immunoglobulin assay

Selection of studies and analyses for drug-control comparisons of laboratory values

The study design of 02CLLIII provides an adequate drug-control comparison of laboratory values because the population was treatment-naïve (and less likely to enter the study with baseline chemistry laboratory abnormalities) and bendamustine was compared to chlorambucil in a randomized fashion. The analysis of laboratory studies was conducted using data from 02CLLIII.

Standard analyses and explorations of laboratory data

Chemistry Laboratory Values

The most common chemistry laboratory abnormalities were glucose, AST, ALT, total bilirubin, and creatinine. The majority of these abnormalities were of grade 1 or 2 severity. The overall frequencies of chemistry laboratory abnormalities were relatively similar between the bendamustine and chlorambucil treatment groups.

Few patients in the bendamustine or chlorambucil treatment groups had grade 3 or 4 serum chemistry laboratory test results reported (see Table 7-13 below).

Glucose

The most common glucose laboratory abnormality was hyperglycemia. Most of these events were grade 1, with slightly more in the bendamustine group. Grade 2 hyperglycemia was equal between groups (10%). The rare grade 3 hyperglycemias were equal between treatment groups (2%).

AST

Patients in the bendamustine group had more reported elevations of AST (40% vs. 36%). The majority of the events were grade one. There were no grade 4 elevations of AST in either group.

ALT

Patients in the bendamustine group had more reported elevations of ALT (36% vs. 31%). Most were of grade 1 severity and no grade 4 instances were reported for either group.

Bilirubin

Patients in the bendamustine group had more hyperbilirubinemia than those in the chlorambucil group (34% vs. 30%). Most of these increases were grade 1 for both treatment groups. Bendamustine had less grade 1 elevations, more grade 2 elevations, less grade 3 elevations, and more grade 4 (one versus zero) than chlorambucil.

Creatinine

Increased serum creatinine was more frequent in the bendamustine group in all grades of the toxicity. Thirty-one percent of patients in the bendamustine group experienced any grade increased creatinine compared with 24% in the chlorambucil group. Two percent of patients in the bendamustine group experienced grade 3 or 4 increased creatinine compared to none in the chlorambucil group. This could be partially explained by the difference in the incidence of tumor lysis syndrome between the groups (more common in bendamustine). The reader is referred to Table 7-13 below for further details about chemistry laboratory studies in 02CLLIII.

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Table 7-13 Worst CTC Grades for Serum Chemistry Laboratory Tests Results Overall by Treatment Group (Treated Analysis Set; Applicant Table)

Serum chemistry variable	Treatment group	Number (%) of patients				
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 1-4
Potassium (mmol/L) low values	Bendamustine (N=149)	3 (2)	0	2 (1)	1 (<1)	6 (4)
	Chlorambucil (N=140)	1 (<1)	0	0	0	1 (<1)
Potassium (mmol/L) high values	Bendamustine (N=149)	9 (6)	7 (5)	2 (1)	4 (3)	22 (15)
	Chlorambucil (N=140)	5 (4)	7 (5)	5 (4)	2 (1)	19 (14)
Glucose (mmol/L) low values	Bendamustine (N=149)	4 (3)	1 (<1)	1 (<1)	0	6 (4)
	Chlorambucil (N=140)	4 (3)	2 (1)	0	0	6 (4)
Glucose (mmol/L) high values	Bendamustine (N=149)	59 (40)	15 (10)	3 (2)	0	77 (52)
	Chlorambucil (N=140)	44 (31)	14 (10)	3 (2)	0	61 (44)
Creatinine (µmol/L)	Bendamustine (N=149)	39 (26)	4 (3)	1 (<1)	2 (1)	46 (31)
	Chlorambucil (N=140)	29 (21)	4 (3)	0	0	33 (24)
Albumin (g/L)	Bendamustine (N=149)	21 (14)	2 (1)	0	0	23 (15)
	Chlorambucil (N=140)	6 (4)	2 (1)	0	0	8 (6)
SGOT (AST) (U/L)	Bendamustine (N=149)	53 (36)	5 (3)	2 (1)	0	60 (40)
	Chlorambucil (N=140)	42 (30)	6 (4)	2 (1)	0	50 (36)
SGPT (ALT) (U/L)	Bendamustine (N=149)	43 (29)	6 (4)	4 (3)	0	53 (36)
	Chlorambucil (N=140)	36 (26)	4 (3)	4 (3)	0	44 (31)
Alk phos (U/L)	Bendamustine (N=149)	26 (17)	1 (<1)	1 (<1)	0	28 (19)
	Chlorambucil (N=140)	26 (19)	2 (1)	0	0	28 (20)
Total bilirubin (µmol/L)	Bendamustine (N=149)	29 (19)	17 (11)	3 (2)	1 (<1)	50 (34)
	Chlorambucil (N=140)	30 (21)	7 (5)	5 (4)	0	42 (30)

SOURCE: Summary 15.39.1, Summary 15.39.2.1, Summary 15.39.2.2, Summary 15.39.2.3, Summary 15.39.2.4, Listing 29.1.

CTC=common toxicity criteria; alk phos=alkaline phosphatase; ALT (SGPT)=alanine aminotransferase; AST=aspartate aminotransferase; SGOT=serum glutamate-oxaloacetate transaminase; SGPT=serum glutamate-pyruvate transaminase.

NOTE: Overall is the worst postbaseline CTC grade value for each patient and laboratory test across all cycles.

Data in above table was confirmed by review of raw and derived datasets and CRFs.

Hematology Laboratory Values

Hematologic laboratory data were graded according to the NCI CTC criteria version 2.0. Hemoglobin, platelets, and neutrophils were also graded according to criteria proposed by Cheson et al (1996); however, all summary tables report CTC grades. Hemoglobin, platelets, and neutrophils were also graded according to criteria proposed by Cheson et al (1996); however, all summary tables report CTC grades. Measurements were weekly; scheduled days were 7, 14, 21, and 28 days with slotted intervals.

Absolute Lymphocyte Count

Bendamustine treatment resulted in a more profound reduction in absolute lymphocyte count with 47% of patients having grade 3 or 4 lymphopenia compared to only 4% of patients in the chlorambucil treatment group. The marked reduction in absolute lymphocyte count in the bendamustine treatment group is evident even by week 1 of the first cycle. This laboratory parameter includes both normal lymphocytes and CLL cells, and the higher incidence of grade 3 or 4 toxicity in the bendamustine treatment group is consistent with the mode of action of bendamustine in this population of patients.

Neutropenia

Bendamustine treatment resulted in twice as many instances of grade 3 or 4 neutropenia which was recorded in 43% of patients in the bendamustine treatment group and 21% of patients in the chlorambucil treatment group. Ten percent of patients in cycle 1 experienced a neutrophil nadir of <500/mm³ (grade 4 neutropenia). This incidence decreased as successive cycles were administered. When the mean and median absolute neutrophil counts are plotted by cycle it is apparent that the decline in neutrophil levels occurred more rapidly with bendamustine than chlorambucil with marked decreases over the first and second cycles. Eight percent of patients in the bendamustine treatment group received granulocyte growth factor support compared to none in the chlorambucil group. The trends indicate that the use of these factors lessened as cycles of treatment advanced.

Anemia

Bendamustine treatment resulted in more instances of grade 3 or 4 anemia (13% of patients compared with 9% of patients in the chlorambucil treatment group). An equal number (1%) of patients in each group received red blood cell growth factors (Table 7-15). The trends indicate that the use of growth factors lessened as cycles of treatment advanced. Twenty percent of the patients in the bendamustine group received red blood cell transfusions compared with 6% in the chlorambucil group (Table 7-16). The use of blood products decreased with increasing numbers of treatment cycles. A review of hemoglobin change trends in the patients who experienced objective responses indicate that this improvement in anemia was most likely due to disease response. Patients with complete responses (CRs) had more improvement in hemoglobin than those with partial responses (PRs).

Thrombocytopenia

The incidence of grade 3 or 4 thrombocytopenia was similar between the treatment groups; i.e., 11% and 10% of patients for the bendamustine and chlorambucil treatment groups, respectively. Mean and median platelet values were lower for chlorambucil-treated patients than bendamustine-treated patients for cycles 2 through 6.

The incidence of grade 3 or 4 anemia, thrombocytopenia, and neutropenia decreased with increasing number of treatment cycles, while the incidence of grade 3 or 4 lymphopenia in the bendamustine treatment group increased with the number of treatment cycles. Platelet transfusions occurred in equal numbers across the treatment groups (<1%).

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The reader is referred to Table 7-14 below for further details about hematology laboratory studies in 02CLLIII.

Table 7-14 Worst CTC Grades 3 & 4 Hematology Laboratory Tests Results by Treatment Group (Treated Analysis Set)

Table 2-- Incidence of Hematology Laboratory Abnormalities in Patients Who Received Bendamustine or Chlorambucil in the Randomized CLL Clinical Trial				
Laboratory Abnormality	Bendamustine n=150		Chlorambucil n=141	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Hemoglobin Decreased	134 (89)	20 (13)	115 (82)	12 (9)
Platelets Decreased	116 (77)	16 (11)	110 (78)	14 (10)
Leukocytes Decreased	92 (61)	42 (28)	26 (18)	4 (3)
Lymphocytes Decreased	102 (68)	70 (47)	27 (19)	6 (4)
Neutrophils Decreased	113 (75)	65 (43)	86 (61)	30 (21)

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Table 7-15 Growth Factors by Cycle and Treatment Group (Treated Analysis Set; Applicant Table)

Cycle Growth factor	Number (%) of patients	
	Bendamustine (N=153)	Chlorambucil (N=143)
Patients treated with at least 1 growth factor	14 (9)	2 (1)
Overall, n	153	143
Granulocyte growth factors	13 (8)	0
Red blood cells growth factors	2 (1)	2 (1)
Cycle 1, n	153	143
Granulocyte growth factors	8 (5)	0
Red blood cells growth factors	2 (1)	0
Cycle 2, n	142	133
Granulocyte growth factors	7 (5)	0
Red blood cells growth factors	2 (1)	1 (<1)
Cycle 3, n	125	120
Granulocyte growth factors	5 (4)	0
Red blood cells growth factors	1 (<1)	0
Cycle 4, n	114	98
Granulocyte growth factors	3 (3)	0
Red blood cells growth factors	1 (<1)	1 (1)
Cycle 5, n	106	88
Granulocyte growth factors	4 (4)	0
Red blood cells growth factors	0	0
Cycle 6, n	92	80
Granulocyte growth factors	3 (3)	0
Red blood cells growth factors	0	0

SOURCE: Summary 15.53.2, Listing 42.

NOTE: A growth factor may be counted in multiple cycles. The denominator for the percentages is the number of patients treated in each cycle or overall.

Data in above table was confirmed by review of raw and derived datasets and CRFs.

Table 7-16 Blood Products by Cycle (Treated Analysis Set; Applicant Table)

Cycle Blood product	Number (%) of patients	
	Bendamustine (N=153)	Chlorambucil (N=143)
Patients treated with at least 1 blood product	30 (20)	8 (6)
Overall, n	153	143
Red blood cells ^a	30 (20)	8 (6)
Platelets, human blood	1 (<1)	1 (<1)
Cycle 1, n	153	143
Red blood cells ^{a,b}	20 (13)	3 (2)
Platelets, human blood	1 (<1)	0
Cycle 2, n	142	133
Red blood cells ^a	12 (8)	6 (5)
Platelets, human blood	0	0
Cycle 3, n	125	120
Red blood cells, concentrated	8 (6)	3 (3)
Platelets, human blood	0	1 (<1)
Cycle 4, n	114	98
Red blood cells, concentrated	1 (<1)	0
Platelets, human blood	0	0
Cycle 5, n	106	88
Red blood cells, concentrated	1 (<1)	0
Platelets, human blood	0	0
Cycle 6, n	92	80
Red blood cells, concentrated	0	0
Platelets, human blood	0	0

SOURCE: Summary 15.53.1, Listing 42.

^a Red blood cells include concentrated red blood cells.

^b Patient 12603 received a blood transfusion for anemia (Listing 39) which was classified as "blood and related products" (Listing 42). This product has been grouped with red blood cells.

NOTE: A blood product factor may be counted in multiple cycles. The denominator for the percentages is the number of patients treated in each cycle or overall.

Data in above table was confirmed by review of raw and derived datasets and CRFs.

Analyses focused on measures of central tendency

Chemistry Values

Best Possible Copy

There were no trends in serum chemistry values over cycles for the bendamustine or chlorambucil treatment groups, with the exception of uric acid and alkaline phosphatase, which are not clinically significant in this population.

Hematology Values

Mean and median nadir values of neutrophils, leukocytes, and lymphocytes were lower for bendamustine-treated patients than for chlorambucil-treated patients, whereas mean and median nadirs for platelets were lower for chlorambucil-treated than for bendamustine-treated patients (Table 7-17). The neutrophil nadir values decreased with successive treatment cycles more rapidly with bendamustine treatment than with chlorambucil treatment, and this is consistent with the greater frequency of dose delay and granulocyte colony stimulating factor usage in the earlier bendamustine treatment cycles. The greatest difference between treatment groups was the marked reduction in lymphocyte counts in the bendamustine treatment group relative to the chlorambucil treatment group.

Reviewer Comments: Myelosuppression was more significant in the group treated with bendamustine. Accordingly, blood product transfusions and growth factor support were more common in the bendamustine treatment group.

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Table 7-17 Hematologic Nadir Values by Treatment Group (Treated Analysis Set; Applicant Table)

Hematologic parameter Cycle	Mean nadir value		Median nadir value		Mean time to nadir (days)	
	BEN (N=153)	CLB (N=143)	BEN (N=153)	CLB (N=143)	BEN (N=153)	CLB (N=143)
Hemoglobin, g/L						
Cycle 1	109.6	116.8	114.7	120.0	17.4	19.3
Cycle 2	112.4	115.8	114.7	117.6	16.5	15.8
Cycle 3	118.0	118.4	120.0	120.0	16.8	16.7
Cycle 4	122.5	121.5	125.0	123.0	16.9	16.9
Cycle 5	122.9	124.7	124.1	126.0	19.2	16.7
Cycle 6	124.6	125.4	126.5	127.5	17.6	16.6
Platelets, x10⁹/L						
Cycle 1	121.3	135.6	116.0	127.0	19.9	19.4
Cycle 2	143.3	124.5	139.5	117.0	18.5	16.9
Cycle 3	150.3	123.5	142.0	119.5	22.0	17.2
Cycle 4	152.3	129.3	143.5	122.5	20.8	17.4
Cycle 5	152.1	126.7	141.5	123.0	21.8	17.7
Cycle 6	160.3	132.1	151.5	124.0	18.5	17.5
Leukocytes, x10⁹/L						
Cycle 1	14.4	38.5	5.3	27.9	20.4	24.8
Cycle 2	11.0	25.6	4.2	11.9	17.3	21.8
Cycle 3	6.2	22.9	4.2	9.3	18.2	20.4
Cycle 4	5.7	17.1	3.9	6.9	17.4	19.3
Cycle 5	4.7	12.6	3.8	6.7	17.3	18.0
Cycle 6	4.9	11.7	4.1	6.4	16.5	18.2
Lymphocytes, x10⁹/L						
Cycle 1	10.1	31.6	1.9	20.8	22.7	24.4
Cycle 2	6.4	19.6	1.1	8.3	18.7	21.9
Cycle 3	2.9	18.2	0.8	5.7	15.7	21.3
Cycle 4	2.5	13.1	0.8	4.1	16.8	20.8
Cycle 5	1.5	8.6	0.7	3.3	15.6	19.9
Cycle 6	1.4	8.1	0.7	2.8	14.7	19.8
Neutrophils, x10⁹/L						
Cycle 1	2.3	3.5	1.9	2.8	18.9	20.5
Cycle 2	2.2	2.9	1.9	2.6	18.9	18.9
Cycle 3	2.3	2.8	2.0	2.5	19.4	18.7
Cycle 4	2.2	2.8	2.1	2.5	19.1	17.5
Cycle 5	2.4	2.6	2.5	2.4	19.6	18.8
Cycle 6	2.5	2.7	2.4	2.5	17.9	18.7

SOURCE: Summary 15.43, Summary 15.44, Listing 30.1 and Listing 30.2.

BEN=bendamustine; CLB=chlorambucil.

NOTE: For each patient and each laboratory test, the nadir for a particular cycle is defined as the minimum value occurring after the start of the first dose for the cycle and prior to the start of the first dose for the subsequent cycle.

Data in above table was confirmed by review of raw and derived datasets and CRFs.

Hematologic Nadirs With Bendamustine

Mean hemoglobin nadir values rose with each successive cycle of therapy with bendamustine. The mean nadir values rose from 109.6 g/L in cycle 1 to 124.6 g/L in cycle 6. A similar trend in median hemoglobin nadir was observed from 114.7 g/L in cycle 1 to 126.5 g/L in cycle 2. The mean time to hemoglobin nadir ranged from 15.8 days in cycle 2 to 19.3 days in cycle 1.

Mean platelet nadir values rose with each successive cycle of therapy with bendamustine. The mean nadir values rose from 121.3 x10⁹/L in cycle 1 to 160.3 x10⁹/L in cycle 6. A similar trend

in the median platelet nadir values was observed from $116 \times 10^9/L$ in cycle 1 to $151.5 \times 10^9/L$ in cycle 6. The mean time to platelet nadir ranged from 18.5 days in cycles 2 and 6 to 21.8 days in cycle 5.

Mean leukocyte nadir values declined with each successive cycle of therapy with bendamustine. The mean nadir values fell from $14.4 \times 10^9/L$ in cycle 1 to $4.9 \times 10^9/L$ in cycle 6. A similar trend in the median leukocyte nadir values was observed from $5.3 \times 10^9/L$ in cycle 1 to $4.1 \times 10^9/L$ in cycle 6. The mean time to leukocyte nadir declined over time from 20.4 days in cycle 1 to 16.5 days in cycle 6.

Mean lymphocyte nadir values dramatically declined with each successive cycle of therapy with bendamustine. The mean nadir values fell from $10.1 \times 10^9/L$ in cycle 1 to $1.4 \times 10^9/L$ in cycle 6. A downward trend in the median lymphocyte nadir values was observed from $1.9 \times 10^9/L$ in cycle 1 to $0.7 \times 10^9/L$ in cycle 6. The mean time to lymphocyte nadir declined over time from 22.7 days in cycle 1 to 14.7 days in cycle 6.

Mean neutrophil nadir values were relatively stable with each successive cycle of therapy with bendamustine. The mean nadir values ranged from $2.2 \times 10^9/L$ in cycle 2 to $2.5 \times 10^9/L$ in cycle 6. A slight upward trend in the median neutrophil nadir values was observed from $1.9 \times 10^9/L$ in cycle 1 to $2.4 \times 10^9/L$ in cycle 6. The mean time to neutrophil nadir was relatively stable over time from 18.9 days in cycle 1 to 17.9 days in cycle 6 (Table 7-17).

Reviewer Comment: The accuracy of the nadir assessments may be limited by the frequency of laboratory sampling in this study (weekly for most hematologic values). Based on the mean time to nadir in patients in the randomized study, the hematologic nadirs should be expected in the third week of therapy and may require dose delays if recovery to the recommended values have not occurred by day 28.

Immunoglobulin Values

There were increases in mean concentrations in immunoglobulin A, G, and M in the bendamustine treatment group and slight decreases in concentrations in all 3 immunoglobulin subtypes in the chlorambucil treatment group (Table 7-18). This is a measure of mature lymphocyte function.

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Table 7-18 Actual Values and Changes From Baseline to Endpoint for Patients with Both a Baseline and Endpoint Immunoglobulin Value by Treatment Group (Treated Analysis Set; Applicant Table)

Immunoglobulin class	Statistic	Bendamustine (N=153)			Chlorambucil (N=143)		
		Baseline	Endpoint	Change	Baseline	Endpoint	Change
Immunoglobulin A (g/L)	n	58	58	58	58	58	58
	Mean	1.0	1.3	0.2	1.7	1.5	-0.1
	SD	0.72	0.92	0.77	1.08	0.84	0.66
	Median	0.8	1.1	0.2	1.3	1.4	-0.1
	Min. max	0.2, 2.8	0.1, 4.5	-1.9, 2.2	0.3, 4.1	0.2, 3.8	-2.0, 1.2
Immunoglobulin G (g/L)	n	60	60	60	58	58	58
	Mean	8.7	10.6	1.9	10.3	10.3	-0.0
	SD	4.34	7.40	6.30	5.69	5.63	4.81
	Median	7.8	8.2	0.7	9.3	9.1	-0.0
	Min. max	2.2, 24.4	2.8, 37.5	-6.2, 32.4	2.7, 35.5	0.3, 35.3	-10.6, 26.7
Immunoglobulin M (g/L)	n	59	59	59	58	58	58
	Mean	0.6	0.9	0.3	1.8	0.8	-1.0
	SD	0.51	1.29	1.23	7.28	0.65	7.19
	Median	0.4	0.7	0.0	0.6	0.6	0.0
	Min. max	0.0, 2.6	0.1, 8.4	-1.0, 8.0	0.0, 56.0	0.0, 3.0	-54.7, 1.7

SOURCE: Ad Hoc Summary 15, Listing 32
 SD=standard deviation; min=minimum; max=maximum.

Analyses focused on outliers or shifts from normal to abnormal

Shifts in serum chemistry values by grade at baseline compared with worst post-baseline value grade were summarized within each cycle, at endpoint, and overall. There were very few shifts to grade 3 or grade 4 values; most shifts occurred from grade 0 at baseline to grade 1 at endpoint. Most patients with shifts to grade 4 chemistry values experienced changes in serum potassium; one in the bendamustine group with hypokalemia (none in chlorambucil), four with hyperkalemia (two in chlorambucil). Hyperkalemia can occur as a result of tumor lysis syndrome. One patient in the bendamustine group experienced grade 4 hyperbilirubinemia compared to none in the chlorambucil group (Table 7-19).

Table 7-19 Patients with Grade 4 Serum Chemistry Values (Treated Analysis Set; Applicant Table)

Patient number	Parameter, unit	Baseline value, grade	Grade 4 value	Day of grade 4 value ^a	Subsequent grade 0 or lowest grade value	Day of grade 0 or lowest grade value ^a
Bendamustine						
14201	Potassium, mmol/L	4.06, 0	2.17	28	3.8, 0	36
23601	Potassium, mmol/L	4.6, 0	8.8	8	4.2, 0	29
15402	Potassium, mmol/L	6.35, 3	7.29	30	5.52, 0	57
22003	Potassium, mmol/L	4.56, 0	7.26	57	4.1, 0	85
15103	Potassium, mmol/L	Not done ^b	8.77	142	5.55, 2	175
10410	Creatinine, µmol/L	100, 1	751	13	91, 0	35
22005	Creatinine, µmol/L	121, 1	800	21	130, 1	57
14106	Bilirubin, µmol/L	17.6, 0	212.0	18 ^c	16.7, 0	98
Chlorambucil						
13202	Potassium, mmol/L	Not done	7.3 ^d	28	4.16, 0	86
15101	Potassium, mmol/L	4.41, 0	7.67	170	7.67, 4	170

SOURCE: Listing 29.1.

^a Relative to day 1 of study drug administration.

^b First on-study value was 4.59, grade 0, on day 29.

^c From day 18 through day 45, patient had values of grade 3 or 4.

^d First on-study value.

Data in above table was confirmed by review of raw and derived datasets and CRFs.

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Marked outliers and dropouts for laboratory abnormalities

There were 10 patients with grade 4 serum chemistry laboratory values, 8 patients in the bendamustine treatment group and 2 patients in the chlorambucil treatment group. Two patients (patient 10410 and patient 23601) in the bendamustine treatment group had adverse reactions reported in association with their grade 4 chemistry laboratory values. Patient 10410 had adverse reactions of grade 4 elevated creatinine on day 13 that decreased in severity to grade 2 on day 20 and grade 1 on day 27. These events were reported as being related to tumor lysis syndrome; they resolved and were considered definitely related to treatment with study drug. This patient also had grade 3 SGOT (141 μ /L on day 18) and SGPT values (range: 171 to 236 u/L, days 18 through 37) (Table 7-19).

Additional analyses and explorations

None.

Special assessments

None.

Reviewer Comments: In study 02CLLIII, most laboratory abnormalities were hematologic. The clinically significant chemistry abnormalities that were observed were likely to be related to tumor lysis syndrome. The laboratory abnormalities that were observed were consistent with those observed with other alkylating agents.

7.4.3 Vital Signs

Vital signs (pulse, systolic and diastolic blood pressure, and temperature) were monitored at baseline, at the end of each cycle, and at each follow-up visit until progression of disease.

Temperature

The analysis of body temperature changes by using the vital signs dataset indicated that the mean and median change in body temperature for patients on the bendamustine group was 0.22 and 0.2 degrees C respectively, compared to the mean and median change on the chlorambucil group at 0.21 and 0.2 degrees C. This analysis is not informative for the true assessment of change on body temperature, because the recorded values are probably limited to those present at the time of clinic visits, and did not capture the fevers that were reported by 24% of patients in the bendamustine treatment group.

A more illustrative assessment for temperature change is from the adverse reaction reporting which demonstrated a 24% incidence of pyrexia in the bendamustine group as compared with 6% of patients in the chlorambucil group. The fevers experienced by these patients were clinically significant because of the chills that were experienced by 6 percent of the bendamustine patients as compared to <1% of the chlorambucil patients.

Pulse

The analysis of pulse changes by using the vital signs dataset indicated that the mean and median pulse change in the bendamustine group was 5.7 and 4.5 BPM respectively compared with the mean and median for the chlorambucil group at 5.7 and 6 BPM respectively. This analysis indicates that more pulse elevations occurred in the chlorambucil group, but the clinical significance of these changes is unknown. A pulse change in these ranges is typically not clinically significant. The assessment of clinically significant pulse changes is better performed with adverse event reporting of tachycardias and arrhythmias.

Blood Pressure

The analysis of blood pressure changes by using the vital signs dataset indicated that the mean and median sitting systolic blood pressure changed by 9.3 and 10 mmHg respectively in the bendamustine group. This is compared to a mean and median sitting systolic blood pressure that changed by 3.8 and 5 mmHg respectively in the chlorambucil group. The analysis of blood pressure changes by using the vital signs dataset indicated that the mean and median sitting diastolic blood pressure changed by 6.4 and 5 mmHg respectively in the bendamustine group. This is compared to a mean and median sitting diastolic blood pressure that changed by 4.8 and 5 mmHg respectively in the chlorambucil group. This assessment demonstrates a trend of rising blood pressures in the bendamustine group as compared with chlorambucil. This trend is mirrored by the increased incidence of the adverse reaction of hypertension and hypertensive crisis in the bendamustine treatment group. In the bendamustine treatment group, worsening of baseline hypertension was reported in 3% of patients compared with 1% in the chlorambucil treatment group. Hypertensive crisis was reported in 2% of patients in the bendamustine treatment group, compared with none in the chlorambucil treatment group.

Body Weight

Body weight was measured at baseline, at the end of each cycle, and at each follow-up visit until progression of disease. Similar numbers of patients between groups experienced weight gain during the study. Twelve percent of bendamustine patients, compared with 11% in the chlorambucil, experienced some grade of weight gain. There was only one patient (in the chlorambucil group) who experienced a grade 3 weight gain and there were no grade 4 weight gains reported. The mean and median weight change in the bendamustine group was 2.3kg and 1.3 kg compared with 1.5 kg and 1 kg for chlorambucil.

Weight loss seems to have been a more common problem for study participants with 18 % of bendamustine patients compared with 13% of chlorambucil patients experiencing this event. All events were of grades 1-2, none more severe.

Reviewer Comments: Bendamustine does not appear to cause marked changes in weight or pulse. Bendamustine does appear to induce hypertension and fever. Hypertensive crisis was reported in only the bendamustine treatment group. Worsening of baseline hypertension was reported more frequently in the bendamustine treatment group than in the chlorambucil treatment group. Patients receiving bendamustine should have assessment of blood pressure at baseline and during therapy.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed at baseline and at cycle 6 or at the end of treatment. Data were not collected on ECG interval lengths. Any assessment of ECG data in this study is limited by the significant amount of missing data. Thirty-eight percent of patients in the bendamustine treatment group were missing post-baseline ECGs compared with 43% of chlorambucil patients. The ECGs were recorded as being in one of three categories: normal, abnormal, or missing. Less than 1% of each group went from having a “normal” ECG to having an “abnormal” ECG at the post-baseline reading.

The Applicant reports two patients with clinically significant ECG findings during the study.

- Patient 22005 had baseline left heart failure, hypertension, and tachyarrhythmia and a baseline abnormal ECG (at Day -5). The ECG remained abnormal and consistent with left heart failure. This patient had no cardiac adverse reactions reported and received bendamustine.
- Patient 17003 had a normal baseline ECG (day -25) but an abnormal ECG on day 169 (after receiving bendamustine). The ECG was interpreted as ventricular bigeminy. The patient did experience cardiac adverse reactions; grade 2 extrasystoles on day 91 and grade 3 extrasystoles on day 121. These episodes did not resolve.

Reviewer Comments: This study was not adequately designed to detect clinically significant changes in ECG because of the low frequency of assessment and lack of interval measurements. In addition, there was a high percentage of missing post-baseline ECG assessments which limits the usefulness of this data in an already limited population. Of the abnormal ECGs that were found, equality was in place between treatment arms.

7.4.5 Special Safety Studies

None.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse reactions was not evaluated because study 02CLLIII was implemented with a fixed dose per metered square.

7.5.2 Time Dependency for Adverse Events

Hypersensitivity reactions typically occurred after 25 days of exposure (2nd and subsequent cycles).

Tumor Lysis Syndrome typically occurred during the first cycle of treatment with bendamustine.

The incidence of severe anemia, thrombocytopenia, and neutropenia occurred more frequently in the first two cycles and decreased over time and subsequent treatment cycles of bendamustine. These decreases over time can be possibly explained by the efficacy of the study drugs and disease response leading to improved hematopoietic function. The incidence of severe lymphopenia increased over time and subsequent treatment cycles of bendamustine. This increase can be directly related to the effect of the study drugs on normal and abnormal lymphocytes and response of disease.

7.5.3 Drug-Demographic Interactions

Study 02CLLIII did not enroll an adequate variety of patients of race to provide an assessment of a particular demographic group that may be at increased risk of adverse reactions of a particular type. No significant differences were observed in the frequency of adverse reactions within a specific gender or age group.

7.5.4 Drug-Disease Interactions

All patients enrolled in study 02CLLIII were diagnosed with CLL so no differences in safety variables can be assessed for different diagnoses. The concomitant diseases were assessed for variations in the incidence of adverse reactions. Patients who were hypertensive at baseline were more likely to experience hypertensive crisis while on study than those who were not hypertensive at baseline. No other significant findings were identified that would indicate an increased risk associated with the use of bendamustine in a given concomitant disease.

7.5.5 Drug-Drug Interactions

Ciprofloxacin was taken by 27 patients in the study. These patients had a higher incidence of myelosuppression which may not be clinically significant because patients with severe neutropenia and fever are often administered ciprofloxacin as an oral outpatient regimen for febrile neutropenia. Additionally, ciprofloxacin is utilized for many infections, which bendamustine frequently causes. It is doubtful that this correlation actually represents a true drug-drug interaction.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

One case of bronchial carcinoma was noted in follow-up for study 02CLLIII, approximately one year after the last dose of bendamustine. Earlier single agent and combination therapy studies with bendamustine have reported other secondary malignancies and Myelodysplastic Syndrome.

7.6.2 Human Reproduction and Pregnancy Data

The Applicant states that no experience with bendamustine use during pregnancy is available. Non-clinical data demonstrated significant malformations of soft tissues and skeleton in mice who were given bendamustine at doses of 210 mg/ m² during organogenesis. Bendamustine is very likely to cause fetal harm if given to pregnant women.

7.6.3 Pediatrics and Effect on Growth

The safety of bendamustine in children has not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Doses as high as 280 mg/m² have been administered in the bendamustine clinical program. This dose level resulted in significant cardiac toxicity so the dose below it was determined to be the Maximum Tolerated Dose. No systematic studies to investigate withdrawal or rebound phenomena have been undertaken. Given the nature of malignant disease, the toxicities associated with this agent, and the intravenous route of administration, it is unlikely that bendamustine will be abused.

7.7 Additional Submissions

The 4 month safety update was received on 01/18/08. The data cutoff date for this submission for study 02CLLIII was 05/31/07. In summary, the toxicity profile remained unchanged from that reported in the NDA. Overall, the adverse event profile for bendamustine differed from that for chlorambucil in two important respects, increased nausea and vomiting and an increased incidence of administration-associated events such as rash, urticaria, pyrexia, and chills. Consistent with its potent cytotoxic action, bendamustine was also more myelosuppressive than chlorambucil. The more common dose delays seen in the bendamustine treatment group and modest increases in the incidence of infection and fever were an expected consequence of the higher degree of myelosuppression.

No new deaths were reported within 30 days of last treatment and similar numbers of new deaths beyond 30 days were reported between groups (25 in the bendamustine group; 30 in the chlorambucil group).

There were 3 new reports of malignancies in patients treated with bendamustine; grade 1 adverse event of inguinal cutaneous infiltration (preferred term: metastases to the skin), lung neoplasm and benign adenoma (right side parapharyngeal). There was 1 report of a malignancy in the chlorambucil treatment group; 1 patient had a cause of death of "CA Auriculi" which has not yet been successfully translated. The information on the lung neoplasm, benign adenoma, and CA Auriculi was received after the submission of the NDA.

There were no new trends in worse grades overall in serum chemistry for either group.

8 Postmarketing Experience

Bendamustine is a new molecular entity in the United States. No U.S. postmarketing information is available. European postmarketing data has been provided by the Applicant.

The following are the most commonly reported adverse reactions from postmarketing sources: hypersensitivity (16 patients), leukopenia (8), pyrexia (7), pneumonia (6), thrombocytopenia (5), and dysgeusia (5). There have been 13 postmarketing spontaneous reports associated with death;

the main causes of death were disease progression (7 patients), infections/immune suppression (3), other, pulmonary embolism, pulmonary fibrosis, and hepatocellular damage (1 each).

Review of the postmarketing reports revealed the following medical events of special interest: acute renal failure, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, cardiac failure, cardiogenic shock, depressed level of consciousness, hypersensitivity, pulmonary embolism, pulmonary fibrosis, and tumor lysis syndrome.

The safety information available in the literature is very similar to that seen in clinical studies and postmarketing reports. The most frequently reported adverse reactions include hematologic toxicities (i.e., reported as myelosuppression, myelotoxicity, neutropenia, anemia, thrombocytopenia, and other terms) and gastrointestinal toxicities including nausea, vomiting, dry mouth, stomatitis, and diarrhea. A number of terms consistent with skin reactions (i.e., skin effect, skin reaction, and allergic skin reaction) have also been reported. As seen in safety data from other sources, infections including sepsis and pneumonias (including *Pneumocystis Carinii* pneumonia) have been reported in patients who have received treatment with bendamustine. As reported in clinical studies, a number of cardiac events have been observed in patients treated with bendamustine; however, there is no consistent pattern that would associate the use of this drug to a specific cardiac event.

Given the long history of pre- and postmarketing development of bendamustine in Germany, study reports for investigator-sponsored studies and studies sponsored by other companies in Europe that have been reported in medical literature may not be available to Cephalon.

Overall, review of the literature confirms the safety profile of bendamustine reported elsewhere and there are no newly observed or previously unreported toxicities associated with treatment with bendamustine.

Reviewer Comments: The non-US postmarketing data provided by the Applicant does not provide new safety concerns that would affect the regulatory decision to approve bendamustine for CLL.

9 Appendices

9.1 Literature Review/References

Bendamustine was first registered in the former German Democratic Republic in 1971 and became available for marketing in the unified Germany in 1992. Bendamustine was subject to the German re-registration procedure which was successfully completed July 21, 2005. A marketing authorization according to the current legislation was granted for NHL and MM.

Chronic lymphocytic leukemia (B-CLL) is a blood and bone marrow disease with a usually slow progression. For a long time alkylating agents such as chlorambucil have been the treatments of choice for CLL. The complete response rates were in the range of 5% only and therefore a number of other agents were investigated with the objective to improve response rates, time to progression and finally survival of patients. Fludarabine showed higher response rates, longer duration of remission and longer progression-free survival in chemotherapy naive CLL patients treated with fludarabine compared to chlorambucil, but overall survival was not increased.

Bendamustine was studied as single-agent in several small phase II clinical trials in B-CLL patients and CR rates similar to or even higher than those resulting from standard therapy with chlorambucil were achieved. In those studies, bendamustine has been used in patients with advanced relapsed or refractory CLL with and without prior fludarabine exposure.

In vitro evaluations with CLL cells taken from treated and untreated patients showed that the apoptotic signals induced by bendamustine is comparable to that of fludarabine and the combination of both agents led to a high synergistic effect in inducing apoptosis. While the results with bendamustine for the treatment of CLL were promising, response rates and data on progression-free survival from a comparative study in first line treatment with bendamustine versus standard agents (fludarabine, rituximab, cyclophosphamide, etc.) other than chlorambucil are not available.

Scientific Protocol Review Board Meeting; February 15, 2002, Munich, Germany.
Bergmann MA, Goebeler ME, Herold M, Emmerich B, Wilhelm M, Ruelfs C, et al.
Efficacy of bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase I/II study of the German CLL Study Group. *Haematologica*. 2005 Oct;90(10):1357-64.

Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, Rai RK. National Cancer Institute-sponsored working group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. *Blood* 1996;87:4990-97.

CLL Trialists' Collaborative Group. chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized Trials. *J Natl Cancer Inst* 1999;19(10):861-868.

Eichhorst BF, Busch R, Hopfinger G, Pasold R, Hensel M, Steinbrecher C, et al; German CLL Study Group. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood*. 2006;107(3):885-91.

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Clinical Review
Qin Ryan, MD, PhD for efficacy review
Virginia Kwikowski, MS, RN, CRNP for safety review
NDA 22249
Treanda (bendamustine)

Oncol. 2007 Mar 1;25(7):793-8. Epub 2007 Feb 5.

Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. The World Health Organization classification of neoplasms of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting—Airlie House, Virginia, November, 1997. *Hematol. J.* 2000;1(1):53-66.

Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting—Airlie House, Virginia, November 1997. *J. Clin. Oncol.* 1999 Dec;17(12):3835-49.

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Kath R, Blumenstengel K, Fricke HJ, Höffken K. Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia. *J Cancer Res Clin Oncol* 2001; 127: 48-54

Lissitchkov T, Arnaudov G, Peytchev D, Merkle Kh. Phase-I/II study to evaluate dose limiting toxicity, maximum tolerated dose, and tolerability of bendamustine HCl in pre-treated patients with B-chronic lymphocytic leukaemia (Binet stages B and C) requiring therapy. *J Cancer Res Clin Oncol.* 2006 Feb;132(2):99-104.

Strumberg D, Harstrick A, Doll K, Hoffmann B, Seeber S. Bendamustine hydrochloride activity against doxorubicin-resistant human breast carcinoma cell lines. *Anticancer Drugs.* 1996 Jun;7(4):415-21.

Travis LB, Curtis RE, Hankey BF, Fraumeni JF. Second cancers in patients with chronic lymphocytic leukemia. *J. Natl. Cancer Inst.* 1992 Sep 16;84(18):1422-7.

Wendtner CM, Schmitt B, Wilhelm M, Dreger P, Montserrat E, Emmerich B, Hallek M. Redefining the therapeutic goals in chronic lymphocytic leukemia: Towards an evidence-based, risk adapted therapy. *Ann Oncol* 1999;10:505-9.

9.2 Labeling Recommendation

See final label.

9.3 Advisory Committee Meeting

None.

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

/s/

Qin Ryan
3/5/2008 01:22:19 PM
MEDICAL OFFICER
The new version

Virginia Kwitkowski
3/5/2008 03:02:54 PM
MEDICAL OFFICER

Amna Ibrahim
3/5/2008 04:46:42 PM
MEDICAL OFFICER

CLINICAL FILING CHECKLIST

NDA Number: 22-249

Applicant: Cephalon

Stamp Date:

Drug Name:

NDA Type: Original NDA

Bendamustine/Treanda

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			Hybrid format
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English, or are English translations provided when necessary?	x			All sections but not all 20,000 pages were checked
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56 ¹ and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	x			The lines have not been numbered.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			Section not labeled ISS (is labeled Summary of Clinical Safety), but appears to integrate all studies.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			Section not labeled ISE (is labeled Summary of Clinical Efficacy), but appears to integrate all studies.
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?		x		
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product	x			Can not be determined before a detailed

¹ http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

	Content Parameter	Yes	No	NA	Comment
	short course), have the requisite number of patients been exposed as requested by the Division?				
23.	Has the sponsor submitted the coding dictionary ³ used for mapping investigator verbatim terms to preferred terms?			x	Information has been provided in the data set.
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	Need detailed review
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?			x	No additional study requested by the clinical team.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Waiver was included in NDA submission
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			Page 14, 2.5 Clinical Overview
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
34.	Are all datasets to support the critical safety analyses available and complete?		x		Need all 5 MedDRA hierarchical terms. Info coming 10/24/07.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse	x			

³ The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	drop-outs) as previously requested by the Division?				
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	x			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

 Reviewing Medical Officer

 Date

 Clinical Team Leader

 Date

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

/s/

Amna Ibrahim
10/31/2007 11:47:51 AM