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.

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/ m^2), 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 [redacted] GLP). The study to assess bendamustine on hERG channel current was conducted by [redacted] (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 see 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 thoracocentesis

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 thoracocentesis 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 x 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 x 10^9/L), grade 2 blood lactate dehydrogenase increased (LDH: 1054 µ/L), and grade 3 hyperbilirubinemia (bilirubin: 87.1 µmol/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;

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.