Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Bendamustine hydrochloride

Proprietary Product Name: Ribomustin

Sponsor: Janssen-Cilag Pty Ltd

First round evaluation: 7 November 2013
Second round evaluation: 24 March 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of commonly used abbreviations

Abbreviation	Meaning
ABC	Advanced Breast Cancer
ADR	Adverse Drug Reactions
AE	Adverse Events
AL	Acute Leukaemia
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
ASCO	American Society of Clinical Oncology
ASCT	Autologous Stem Cell Transplant
ASH	American Society of Hematology
AUC	Area Under the Curve
B	Bendamustine
B-CLL	B-cell chronic lymphocytic leukaemia
BEN	Bendamustine
BLEO	Bleomycin
BMF	Bendamustine, Methotrexate, 5-Fluorouracil
BOP	Bendamustine, Vincristine, Prednisone
BP	Bendamustine, Prednisolone
BR	Bendamustine, Rituximab
BSA	Body surface area
C	Chlorambucil
CER	Clinical evaluation report
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone

Abbreviation	Meaning
CI	Confidence Interval
CLB	Chlorambucil
CLL	Chronic Lymphocytic Leukaemia
Cmax	Peak Concentration
CMF	Cyclophosphamide, Methotrexate, 5-Fluorouracil
COP or CVP	Cyclophosphamide, Vincristine, Prednisone
CR	Complete Response, Complete Remission
Creat	Creatinine
CRF	Case report form
CRP	C-reactive Protein
CRO	Clinical Research Organization
CRu	Complete Response Unconfirmed
CSR	Clinical study report
CT	Computed tomography
CTC	Common Toxicity Criteria
CTD	Common Technical Document
CTX	Cyclophosphamide
CYP	Cytochrome P450
d	Day
DEX	Dexamethasone
DNA	Deoxyribonucleic Acid
DNR	Daunorubicin
DOXO	Doxorubicin
DTIC	Dacarbacin
eCRF	Electronic case report form
EFS	Event Free Survival

Abbreviation	Meaning
EU	European Union
FDA	Food and Drug Administration
FAMP	Fludarabine
GCLLSG	German Chronic Lymphocytic Leukaemia Study Group
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GLSG	German Low Grade Lymphoma Study Group
HD	Hodgkin's Disease
HIV	Human Immunodeficiency Virus
HP1	Monohydroxy-bendamustine
HP2	Dihydroxy-bendamustine
Hyper-CVAD	Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone
ICH	International Conference on Harmonisation
ICRA	Independent Committee for Response Assessment
IDA	Idarubicin
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Independent review board
ITP	Immune Thrombocytopenia
ITT	Intention to treat
iv	Intravenous
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
LP	Lymphoplasmocytoid

Abbreviation	Meaning
lp-ic	Lymphoplasmacytoid Immunocytoma
M3	Bendamustine oxidised metabolite
M4	N-desmethyl-bendamustine
MCL	Mantle Cell Lymphoma
MM	Multiple Myeloma
MTD	Maximum Tolerated Dose
MTX	Methotrexate
NA	Not applicable
NC	No change
NCI	National Cancer Institute
NCI-WG	National Cancer Institute Working Group
NHL	Non-Hodgkin's Lymphomas
NDA	New Drug Application
nPR	Nodular Partial Remission
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
po	Per Os; by mouth
PR	Partial Response, Partial Remission
PP	Per-protocol
PR	Partial response
PT	Preferred term
QoL	Quality of life
R	Rituximab
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine,

Abbreviation	Meaning
	Prednisolone
R-FCM	Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone
SAE	Serious Adverse Event
SD	Stable Disease
SLL	Small Lymphocytic Leukaemia
SmPC	Summary of Product Characteristics
StiL	Study Group Indolent Lymphoma
SUSAR	Suspected Unexpected Serious Adverse Reactions
tmax	Time of Maximal Plasma Concentration
TTNT	Time to Next Treatment
TTF	Time to Treatment Failure
UK	United Kingdom
VACy	Vincristine, Doxorubicin, Bendamustine
VAD	Vincristine, Doxorubicin, Dexamethasone
VBL	Vinblastine
VCR	Vincristine
VP-16	Etoposide
W, w	Week
WBC	White Blood Cell Count
WHO	World Health Organization

1. Clinical rationale

The sponsor's application letter states that bendamustine was first synthesized in the former German Democratic Republic (GDR) in the early 1960s. It goes on to state that "in vitro studies have demonstrated that bendamustine's anti-tumour activity and mode of action is different to other structurally related compounds, which may contribute to the distinct profile observed in the clinical studies described in [the submitted] dossier". The application letter included an attachment from an Australian haematologist supporting the use of bendamustine in combination with rituximab for the treatment of previously untreated indolent NHL and MCL in CD20 positive patients, and as monotherapy for the treatment of relapsed/refractory NHL.

Comment: The clinical rationale for the submission is acceptable.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission was a hybrid containing both literature-based and conventional study reports. The study was provided in Common Technical Document (CTD) format. The submitted data package was large and included clinical pharmacology studies and reports, clinical efficacy and safety studies supporting the three proposed indications, post-marketing data reports, and a number of written summaries of the data. The clinical evaluation of the submission is based on the electronic data (CD) provided by the sponsor. The CD was well structured and easy to navigate.

The relevant clinical data provided in the submission are summarized below:

- Module 5
  - 13 clinical PK reports (located in M5.3.3.2 and M5.3.3.3).
  - 5 reports (located in M5.3.5.1) relating to 1 controlled clinical study pertinent to the CLL indication including initial study report, 1 follow-up study report with Appendix 14 (listing of tables), Appendix 14 (actual tables) and Appendix 16.1.9 (Biometric report).
  - 2 uncontrolled clinical study reports (located in M5.3.5.2) pertinent to the CLL indication.
  - 2 other clinical study reports (located in M5.3.5.4) pertinent to the CLL indication.
  - 18 reports (located in M5.3.5.1) relating to 1 controlled clinical study pertinent to the indication for first-line treatment of NHL and MCL with bendamustine in combination with rituximab.
  - 7 uncontrolled study report (located in M5.3.5.2) pertinent to the indication for relapsed/refractory NHL in patients refractory to rituximab.
  - 1 controlled clinical study report (located in M5.3.5.1) pertinent to the treatment of MM.
  - 5 reports (located in M5.3.6) relating to post-marketing experience.
  - Literature references (located in M5.4).
  - 6 *in vitro* method validation reports (located in M5.3.1.4) relating to bioanalytical and analytical methods for human studies.
  - 1 *in vitro* report (located in M5.3.2.2) relating to *in vitro* production of metabolites M3 and M4.

2.2. Paediatric data

The sponsor submitted a statement relating to the paediatric development program (located in M1.12). This statement indicated that no paediatric data supporting the use of bendamustine in a paediatric population has been submitted to the TGA. However, paediatric data in children aged 2 to 11 years have been submitted to the EU, while paediatric data in children from the age of 28 days up to adolescents aged 17 years have been submitted to the FDA (USA).

Comment: It is unclear from the submitted document which indications being sought in Australia are being sought in the EU and/or the USA for a paediatric population. No reasons were provided in the document for not submitting paediatric data to the TGA. This will be followed-up in a first-round question to the sponsor.

2.3. Good clinical practice

All pivotal and supportive clinical efficacy and safety studies have been under in accordance with the principles of good clinical practice (GCP). All studies undertaken by the sponsor or sponsors of bendamustine have been undertaken in accordance with GCP.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

3.1.1. Phase I studies (M5.3.3.2 and M5.3.3.3)

The submission included 12 clinical study reports identified as "Patient PK and Initial Tolerability Study Reports" (Module 5, section 5.3.3.2), and 1 clinical study report listed under "Intrinsic Factor PK Study Reports (Module 5, section 5.3.3.3). In addition, the submission included 1 *in vitro* report listed under "Reports of Hepatic Metabolism and Drug Interaction Studies" (Module 5, Section 5.3.2.2) and 6 *in vitro* method validation reports listed under "Reports of Bioanalytical and Analytical Methods for Human Studies" (Module 5, Section 5.3.1.4). The 13 clinical PK reports from M5.3.3.2 (12 reports) and M5.3.3.3 (1 report) are summarized below in Table 1.

Table 1: Clinical PK reports (M5.3.3.2 and M5.3.3.3)

Study ID	Subject Matter
BioProof R1-01-02	Detection of bendamustine and related compounds in human plasma using HPLC/FL.
BioProof R1-01-02 Addendum 1	Detection of bendamustine and related compounds in human plasma using HPLC/FL.
BioProof R1-02-Juni-2002	PKs of bendamustine and related compounds in patients of Phase I study 20BEND 1.
Humb-Uni-Berlin 1987	Expert report on studies on kinetics of bendamustine.
Klinge 6000683-01	Analytics of bendamustine in 3 selected patients from Phase I studies.
Klinge 6000683-02	PKs of bendamustine in 3 selected patients of Phase 1 study 98B02.
riboseph 20BEND 1	CSR bendamustine days 1 and 2 every 3 weeks, open-label, non-randomized, Phase 1 study.
riboseph 20BEN03	CSR bendamustine days 1 and 2 every 3 weeks, open-label, non-randomized, Phase 1 study.
riboseph 98B02	MTD, DLT, PK, safety and tolerability after repeated iv bendamustine administration.
riboseph 98B02W	MTD, DLT, PK, safety and tolerability after weekly iv bendamustine administration.

Study ID	Subject Matter
Uni Leipz 2002	Determination of bendamustine and related compounds in human urine using HPLC/FL.
Uni Leipz 2004	Biliary elimination, efficacy and toxicity of bendamustine and metabolites, cholangiocarcinoma
riboseph 98B03	Phase 1 study, PK, clearance, toxicity of bendamustine, hepatic and renal impairment.

Note: MTD = maximum tolerated dose; DLT = dose limiting toxicity; HPLC/FL = high performance liquid chromatography / fluorescent detection.

The evaluation of pharmacokinetics in this CER focuses on the PK data from the clinical study reports listed in Module 5, sections 5.3.3.2 and 5.3.3.3 in patients with cancer. The PK data were based on a number of relatively small Phase I studies undertaken between about 1985 and 2005. There were no clinical PK studies in healthy volunteers, which is not unexpected for a cytotoxic drug.

3.1.2. Phase III studies

In addition to the Phase 1 PK studies provided in M5.3.3.2 and M5.3.3.3, the Phase III efficacy and safety study (SDX-105-03) provided in M5.3.5.2 included PK data on 12 patients with indolent NHL who are refractory to rituximab. This Phase III study is considered to be the pivotal efficacy and safety study supporting bendamustine for the treatment of "relapsed/refractory indolent NHL". The PK data for study SDX-105-03 was provided as a separate report identified as Report Number DP-2007-043 in Appendix 16.1.3 to SDX-105-03, and these data have been evaluated. The SDX-105-03 study report also stated that a population PK analysis (CP-07-002) and a pharmacokinetic /pharmacodynamic analysis (CP-07-003) had been undertaken and were to be reported separately. However, these two analyses could not be identified in the submitted data. There were no PK data for bendamustine from the pivotal Phase III studies supporting the indications for "first-line treatment of CLL" or for "first-line treatment of NHL and MCL".

3.2. Summary of pharmacokinetics

3.2.1. Review of clinical Phase I studies from M5.3.3.2 and M5.3.3.3 with PK data

3.2.1.1. Overview

The submission included five (5) studies in 54 cancer patients providing PK data on bendamustine and metabolites (HP1, HP2, M3 and M4) in plasma, urine, and/or bile (Preiss/Humb-Uni-Berlin 1987; 98B02; 98B03; 20BEN D1; BE04). All 5 studies were provided in M5.3.3.2 or M5.3.3.3 as conventional study reports. The PK data in patients with cancer were based on single dose administration, which was the first day of treatment for those studies that were aimed primarily at establishing maximum tolerated dose (MTD) and dose limiting toxicity (DLT).

In the initial PK studies with bendamustine (e.g., Preiss 1990/Humb-Uni-Berlin 1987), the drug was administered as a bolus iv injection over 3 minutes. However, early clinical experience showed that bolus iv injection of bendamustine was associated with an increased incidence of injection site disorders such as thrombophlebitis. Consequently, in clinical studies starting after 1990 bendamustine was administered as an iv infusion over at least 30 minutes.

The proposed dose of bendamustine as monotherapy for first-line treatment for patients with CLL is 100 mg/m^2 on days 1 and 2, every 4 weeks for at least 6 cycles, and the proposed dose for

monotherapy for patients with indolent NHL refractory to rituximab is 120 mg/m² on days 1 and 2, every 3 weeks for at least 6 cycles for patients. The proposed dose of bendamustine for first-line combination therapy with rituximab for the treatment of patients with NHL and MCL is 90 mg/m² on days 1 and 2, every 4 weeks for up to 6 cycles, with rituximab being administered on day 1 of each cycle. Bendamustine doses used in the clinical PK studies submitted for evaluation in M5.3.3.2 and M5.3.3.3 are summarized below in Table 2, as are the main PK parameters from these studies. The sponsor's Clinical Overview (Module 2.5) identifies studies 20BEND1, 20BEN03 and 98B03 as the most important PK studies.

Table 2: Brief outline of studies with PK data (mean±SD) in patients with cancer in M5.3.3.2 and M5.3.3.3.

ID	Dose	n	Cmax µg/mL	AUC *µg•hr/mL	$t_{1/2}$ **min	CL	V_{dss}	Vz L
Hum-U 1987	0.8-4.8 mg/kg iv 3 minutes	20	-	-	28.3	615.3 mL/min	15.8 L	10.4
98B02	100 mg/m² ivi 30 minutes	3	10.8± 8.7	10.4± 9.2	37.8± 7.6	304.2±283.5 mL/min/m²	-	-
20BEN D1	160-280 mg/m² ivi 30 minutes	13	17.1± 9.1	16.6± 13.3	30.5± 9.3	304.5±170.9 mL/min/m²		12.0 L/m²
98B03 [1]	120 mg/m² ivi 30 minutes	12	10.8± 7/0	11.7± 10.6	28.2± 15.9	639.4±601.6 mL/min		19.4
98B03 [2]	120 mg/m² ivi 30 minutes	12	9.9±3. 3	8.9±4. 3	29.6± 7.6	471.9±244.4 mL/min		16.6
98B03 [3]	120 mg/m² ivi 30 minutes	12	9.7±2. 5	8.0±3. 4	26.4± 6.4	485.0±239.9 mL/min		17.0
BE04	100 mg/m² ivi 30 minutes	6	15.5± 7.8	11.6± 2.9	47.0± 20.9	384.4±186.3 mL/min		26.7

Notes: * AUC refers to AUCall or AUCinf; ** Elimination half-life (t1/2); [1] 98B03 patients with normal renal/hepatic function; [2] 98B03 patients with hepatic impairment; [3] 98B03 patients with renal impairment. Vz = volume of distribution based on the terminal phase.

Studies 20BEND1, 20BEN03, and 9803 used the same validated high performance liquid chromatography/fluorescence detection (HPLC/FC) method for the determination of bendamustine and the metabolites mono-hydroxy-bendamustine (HP1), di-hydroxy-bendamustine (HP2), gamma-hydroxy-bendamustine (M3) and N-desmethyl-bendamustine (M4) in plasma allowing good comparability of the results. The lower limit of quantification (LLOQ) of HP2 in plasma of 500 ng/mL was not sufficient to investigate the PKs of this metabolite in detail. Urine and dialysate samples from studies 20BEND1, 20BEN03 and 98B03 were analyzed at one single centre using validated HPLC/FC methods. Quantitative determination of M3 and M4 was based on the standard curve of bendamustine. The sponsor stated that the results obtained for M3 and M4 are to be regarded as a semi-quantitative estimation.

3.2.1.2. Preiss (Humboldt University Berlin 1987)

PK data on 20 patients with cancer and normal hepatic function were presented by Preiss in a conventional PK report (Humboldt University 1987), and in a published abstract (Preiss 1990). Bendamustine demonstrated linear PKs over the dose range 0.8 to 4.8 mg/kg administered as iv bolus doses over 3 minutes. The drug was rapidly eliminated from plasma according to a two-compartment model. The bendamustine plasma PK parameters were: $t_{1/2\alpha}$ = 6.0 minutes; $t_{1/2\beta}$ = 28.3 minutes; Vc = 10.35 L; Vdss = 15.81 L; and CLtotal = 36.92 L/h. The drug was highly protein bound (95%), and protein binding was independent of concentration. The main plasma binding protein was identified as albumin.

The study identified the following tentative metabolites of bendamustine (B): a beta-hydroxy derivative of the butanic acid side chain of bendamustine defined as beta-hydroxy-bendamustine according to the HPLC analytical method used in this study (β-OH-B); N-desmethyl-B bendamustine; monohydroxy-bendamustine (HP1); and dihydroxy-bendamustine (HP2). The main metabolite identified in plasma was β-OH-B, and this product accounted for about 25% of the parent compound following iv administration. The elimination half-life of β-OH-B was 26.7 minutes, which was similar to the parent compound.

Evaluation of the amount of the administered drug excreted in the urine after iv bolus injection of 125 mg or 150 mg was investigated in 8 patients. Urine was sampled up to 3 hours post-dose by bladder catheter. The fraction of the dose eliminated in urine as bendamustine and metabolites within 3 hours was 19.5%, principally as bendamustine, HP1 and HP2. Bendamustine accounted for 42.6%, HP1 for 21.4% and HP2 for 11.3% of the excreted amount. Excretion into the bile was investigated in 3 patients. In bile, bendamustine and its hydrolysis products were eliminated in insignificant amounts, and other polar metabolites predominated.

> Comment: The metabolite identified as β-OH-B (according to the HPLC analytical method used in this study) and accounting for about 25% of the parent compound in plasma does not appear to have been identified in the subsequent PK studies identified in the clinical overview as being the main PK studies (i.e., 20BEND1, 20BEN03, and 9803). Presumably it was an artefact of the analytical method used in this study. However, the sponsor should clarify the status of β-OH-B, and a first-round question has been raised.

3.2.1.3. Study 98B02 (ribosepharm GmbH, Germany)

The primary objective of this Phase I study was to define the MTD and DLT of bendamustine in patients with refractory solid tumours. Other objectives included the determination of "some" basic PK data for bendamustine and its "main metabolite" (β-OH-B). The study was carried out in one centre in Germany between June 1998 and April 1999 in 19 Caucasian patients with advanced progressive tumours (PK data available for 3 patients only). Bendamustine was administered at a dose of 100 mg/m^2 ivi over 30 minutes on days 1 and 8 of a 4 week cycle for at least 2 cycles, and increments of 20 mg/m^2 were allowed to a maximum dose of 180 mg/m^2.

The PK results for 98B02 for the 3 patients with relevant data were summarized in the Klinge Pharma Report (6000683-02). The PKs of bendamustine were assessed on day 1 of treatment following a dose of 100 mg/m^2 administered by iv infusion over 30 minutes. Blood samples for PK analysis were taken pre-dose (0) and following initiation of the infusion at 10, 20, 30, 35, 45, 50, 55, 60, 75, 90, 105, 120, 240 and 360 minutes. An additional trough sample was collected on day 8 of the first cycle before the next dose was administered. The plasma samples were assayed using a validated HPLC/FL method with a limit of quantification (LOQ) of 2.06 ng/mL. PK calculations were performed using the WinNonlin Pro 3.0 software package, and PK parameters were determined by both non-compartmental and compartmental model analysis.

Based on non-compartmental analysis, the mean±SD C_{max} was 10.8±7 µg/mL (range: 3.2, 20.3) with a CV of 80.8%, the mean±SD $AUC_{0\text{-}inf}$ was 10.4±9.2 µg•hr/mL (range: 2.7, 20.6) with a CV of 88.5%, the mean± $t_{1/2}$ was 37.8±7.6 minutes (range: 30.0, 45.3) with a CV of 20.2%, and the mean±SD CL was 304.2±283.5 mL/min/m^2 (range: 80.7, 623.1), with a CV of 93.2%. The trough concentrations on day 8 in all samples were below the LOQ, which is not unexpected given the short half-life of the drug.

> Comment: The PK data in this study were based on information from only 3 patients. The C_{max}, AUC_{inf} and CL showed high inter-subject variability with the CV being more than 80% for each of these parameters. Consequently, the summary statistics for the study are of limited value. The sponsor speculates that the high inter-subject variability in the parameters might be due to inadequate handling of the samples. The stability of bendamustine in "biological matrices" is low, and the sponsor states that immediate cooling of the samples (even during separation of the plasma) needs to be ensured. It is also noted that the study refers to β-OH-B as the main metabolite of bendamustine.

3.2.1.4. Study 20BEND1 (ribosepharm GmbH, Germany)

The primary objective of this Phase I study was to define the MTD and DLT of bendamustine in patients with advanced malignant disease. Other objectives included the evaluation of "key kinetic variables" (a secondary objective). The study was carried out in one centre in Belgium between August 2000 and November 2002 in 26 Caucasian patients with histologically confirmed, advanced malignant disease. The starting dose of bendamustine was 160 mg/m^2 administered iv over 30 minutes on day 1 every 3 weeks, with dose escalations planned in steps of 20 mg/m^2. Each patient was expected to complete at least two treatment cycles.

The PK results for 20BEND1 were summarized in the BioProof Report (RI-01-02). The PK subset included 14 of the first 22 patients enrolled in 20 BEND1 (10 males, 4 females). Only clinically stable patients were chosen for inclusion in the PK analysis. Bendamustine was administered at doses ranging from 160 mg/m^2 to 280 mg/m^2: 3 patient at 160 mg/m^2; 1 patient at 180 mg/m^2; 2 patients at 200 mg/m^2; 2 patients at 220 mg/m^2; 2 patients at 240 mg/m^2; 2 patients at 260 mg/m^2; and 1 patient at 280 mg/m^2. Blood samples for PK analysis were taken on the first day of treatment pre-dose (0) and following initiation of the infusion at 10, 20, 30, 35, 40, 45, 50, 60, 75, 90, 105, 120, 180, 280, 360 and 480 minutes. Trough samples were drawn immediately before the infusions on the first days of the subsequent cycles. Urine samples were collected before the first dose, and following the first micturition (complete sample) following the first and second infusions.

Plasma and urine samples were analyzed using validated HPLC/FL methods for bendamustine, hydrolysis product 1 (HP1), hydrolysis product 2 (HP2), M3 (unknown metabolite), and M4 (N-desmethyl-bendamustine [tentative metabolite]). LLQs in plasma for bendamustine, HP1, HP2, M3, and M4 were 2, 100, 500, 2 and 2 ng/mL, respectively. LOQs in urine samples for bendamustine, HP1, HP2, M3, and M4 were 7, 68, 160, 7 and 7 ng/mL, respectively. Due to interfering matrix peaks the concentrations of HP1/HP2 in some urine samples were not quantifiable. Furthermore, due to very low concentrations of HP1 no complete PK evaluation for this product was possible.

PK calculations were performed using WinNonlin Pro 3.0 and 3.3 software packages, and PK parameters were determined by non-compartmental analysis (NCA). For the total population with PK data (n=13), the mean±SD $t_{1/2}$ was 30.5±9.3 minutes, the mean±SD t_{max} was 32.3±2.6 minutes, the mean±SD C_{max} was 17.1±9.1 µg/mL, the mean±SD AUC_{all} was 16.6±13.4 µg•hr/mL, the mean CL was 304.5±170.9 mL/min/m^2, and the mean±SD V_c was 12.1±4.9 L/m^2. The trough concentrations of all analytes were at or below the LOQ. The PK parameters for each dose level are summarized below in Table 3.

Table 3: PK parameter by administered dose (mg/m^2).

	160 n=3	180 n=1	200 n=2	220 n=2	240 n=2	260 n=2	280 n=1
t1/2 minutes	29.6	24.1	25.3	28.8	42.5	36.9	16.5
tmax minutes	33.3	30.0	35.0	30.0	32.5	30.0	35.0
Cmax ng/mL	10,734	20,779	15,818	10,858	21,016	30,873	12,545
AUCall ng•min/mL	497,344	1,149,348	885,155	507,776	1,412,117	2,143,295	417,271
CL mL/min/m^2	331.8	156.6	253.3	465.0	180.1	172.3	665.0
Vc mL/m^2	13,808	5,450	9,187	19,020	10,406	8,394	15,824

Comment: No conclusions can be drawn from this study concerning the PKs of bendamustine metabolites due to the poor and contradictory results for these analytes.

3.2.1.5. Study 98B03 (ribosepharm GmbH)

This Phase 1, open-label, three-arm, parallel group, PK study in patients with cancer (n=37) was undertaken in one centre in Germany from August 1998 to March 2003. The study compared the PKs of bendamustine and metabolites (HP1, HP2, M3 and M4) in patients with cancer and normal renal and hepatic function, liver impairment or renal impairment. The study also examined the 4-week toxicity profile of the drug (determined in the first treatment cycle) in these patient groups.

In patients with normal renal and hepatic function (n=12), no or < 10% liver tumour/metastatic involvement was required on ultrasound and/or CT, in addition to normal liver function tests and normal serum creatinine. In patients with hepatic impairment (n=12), 30-70% liver tumour/metastatic involvement was required on ultrasound and/or CT, and serum bilirubin was < 1.2 mg/dL in 10 patients and was between 1.2 and 2.0 mg/dL in 2 patients. In patients with renal impairment (n=12), no or < 10% liver tumour/metastatic involvement was required on ultrasound and/or CT, creatine clearance was in the range 9.1 to 35.7 mL/min and 5 patients were dialysis dependent.

Plasma and urine samples were analyzed using validated HPLC/FL methods for bendamustine, HP1, HP2, M3 and M4. LLOQ in plasma for bendamustine, HP1, HP2, M3, and M4 were 2, 100, 500, 2 and 2 ng/mL, respectively. LLOQs in urine samples for bendamustine, HP1, HP2, M3, and M4 were 7, 17, 161, 7 and 7 ng/mL, respectively. LLOQs in dialysate for bendamustine, HP1, HP2, M3, and M4 were 0.5, 1.1, 10.7, 0.5 and 0.5 ng/mL, respectively.

Bendamustine 120 mg/m^2 was administered as an iv infusion over 30 minutes on days 1 and 2 (anuric patients received only 120 mg/m^2 on day 1), in 4 week intervals for 4 cycles. The PKs of bendamustine and metabolites in plasma and urine were determined on day 1 of treatment following the first infusion. Blood samples for plasma PK analysis were taken before the start of the infusion and after the start of the infusion at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 90,

110, 140, 180, 240, 360 and 480 minutes. Urine for PK analysis was sampled in all patients with renal impairment and in the control group. Urine sampling intervals were 0 to 1.5 h, 1.5 to 3 h, 3 to 6 h, 6 to 10 h, 10 to 14 h and 14 to 24 h. In haemodialysis dependent patients, bendamustine hydrochloride and metabolites were investigated in the dialysate.

PK calculations were performed using WinNonlin Pro 3.3 software package, and PK parameters were determined by non-compartmental analysis (NCA). The PK parameters for the three study groups are summarized below in Table 4.

Table 4: PK parameters (mean±SD) for patients with cancer and normal renal/hepatic function, hepatic impairment, or renal impairment.

	n	t_{max} min	C_{max} ug/mL	$t_{1/2}$ min	AUC_{all} µg•hr/mL	Vz L	CL mL/min
Normal	12	29.6 ±7.2	10.8±7.0	28.2 ± 15.9	11.7 ± 10.6	19.3 ± 14,6	639.4 ± 601.6
Liver impaired	12	29.6 ± 4.0	9.9 ± 3.3	26.9 ± 7.6	8.9 ± 4.3	16.6±5.9	471.9 ± 244.4
Renal impaired	12	31.3 ± 10.0	9.7 ± 2.5	26.4 ± 6.4	8.0 ± 3.4	17.0 ± 6.1	485.0 ± 239.9

The bioequivalence of the C_{max} and AUC_{all} of bendamustine and metabolites in cancer patients with normal renal/hepatic function, hepatic impairment and renal impairment were tested using an ANOVA procedure following ln-transformation of the data and calculation of the 90% confidence intervals (CIs).

For the comparison between cancer patients with liver impairment (Group 2) and normal renal/hepatic function (Group 1), the point estimates (90% CI) for Group 2 vs Group 1 were 104.1% (64.8, 167.2) for AUC_{all} and 105.5% (76.3, 145.9) for C_{max}.

For the comparison between cancer patients with renal impairment (Group 3) and normal renal/hepatic function (Group 1), the point estimates (90% CI) for Group 3 vs Group 1 were 95.8% (59.6, 153.9) for AUC_{all} and 106.5% (77.0, 147.3) for C_{max}.

Similar bioequivalence analyses were undertaken for HP1, M3 and M4.

In cancer patients with normal renal/hepatic function, approximately 20% of the administered dose of bendamustine was recovered in the urine as unchanged bendamustine (10.6 mg) plus metabolites (16.8 mg HP1, 8.1 mg HP2, 1.2 mg M4, and 0.4 mg M4). In patients with renal impairment, approximately 5% of the administered dose of bendamustine was recovered in the urine and in the dialysate as unchanged bendamustine plus metabolites. Recovery of bendamustine (B), HP1, M3 and M4 in the dialysate of patients with renal impairment undergoing haemodialysis compared with the urine of patients with normal renal function was 5.99 vs 10.65 mg for B, 1.27 vs 16.78 mg for HP1, 0.51 vs 1.23 mg for M3, and 0.04 vs 0.24 mg for M4.

> Comment: This was a good quality PK study. However, cancer patients with hepatic impairment were not categorized using common methods for PK studies such as Child-Pugh scores. Based on AUC_{all} and C_{max} values, bendamustine was not bioequivalent in patients with normal hepatic function and impaired hepatic function, or in patients with normal renal function and impaired renal function. The standard bioequivalence limits of 80% to 125% were not enclosed within the 90% CIs for the point estimates of the AUC and C_{max} ratios for the relevant comparisons.

No toxic effects on bendamustine on renal or hepatic function were found. The toxicity of bendamustine was generally similar in the three treatment groups. However, there was a higher incidence of leucopenia and thrombocytopenia in patients with hepatic impairment compared with patients with renal impairment or normal renal/hepatic function. All patients with hepatic impairment had plasmacytoma, and the study authors comment that this condition might have contributed to the higher incidence of haematological toxicity in this patient group. The study authors conclude that, based on the results of this study, both patients with moderate to severe (30% to 70%) tumour/metastatic involvement and moderate abnormalities of liver function tests and patients with end-stage renal disease (including dialysis dependent patients) do not require dose reduction. However, in patients with both severe hepatic and renal impairment, the authors recommend a 50% reduction in bendamustine dose.

3.2.1.6. Study BE04/University of Leipzig 2004

The objectives of this Phase I, non-randomized, open-label, PK and safety study included the determination of the biliary elimination kinetics and the plasma and renal elimination kinetics of bendamustine and metabolites HP1, HP2, M3 and M4 in 6 patients with malignant disease after a single-dose of bendamustine 140 mg/m^2 administered by iv infusion over 30 minutes. The study was undertaken in a single-centre in Germany from July 2002 to May 2003.

The study included 6 patients (3 males, 3 females) aged between 61 and 74 years of age with cholangiocarcinoma. In addition to the PK objectives, the study also aimed to evaluate the efficacy and toxicity profile of bendamustine administered at a single-dose of 140 mg/m2 on day 1 (cycle 1), and after 100 mg/m^2 on each of days 1 and 2 for a further 3 cycles.

The PK calculations were performed using the WinNonlin Pro 4.0 software package, and the PK parameters were determined by non-compartmental analysis. Measurement of plasma, urine and bile concentrations of bendamustine and metabolites was undertaken using validated HPLC/FL methods. The LLOQ was for plasma concentrations were 2 ng/mL for bendamustine, M3 and M4, and 100 ng/mL for HP1 and 500 ng/mL for HP2. The LLOQ for urinary concentrations were 7 ng/mL for bendamustine and M3, 11 ng/mL for M4, 17 ng/mL for HP1, and 161 ng/mL for HP2. The LLOQ for biliary concentrations were 5 ng/mL for bendamustine M3, and M4, and 100 ng/mL for HP1 and HP2. Blood samples were taken before the start of the infusion and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 90, 110, 140, 180, 240, 360 and 480 minutes after the start of the infusion.

The plasma PKs (mean±SD) of bendamustine (n=6) were: elimination half-life = 47.0±20.9 min; t_{max} = 31.7±8.8; C_{max} = 15.5±7.8 µg/mL; AUC_{inf} = 11.6±2.9 ng•hr/mL; Vz of 26.7±20.5 L; and CL of 384.4±186.3 mL/min. One (1) of the 6 patients, in contrast to the other 5 patients, had a high bilirubin plasma concentration (3 mg/dL) due to severe impairment of liver function. The terminal half-life of bendamustine was longer in this patient than in the 5 other patients. The plasma PKs (mean±SD) for the 5 patients in the study, excluding the patient with hepatic impairment were: elimination half-life = 38.8±7.4 min; t_{max} 33.0±9.1 min; C_{max} = 16.8±7.9 µg/mL; AUC_{inf} = 12.5 ±4.8 µg•hr/mL; Vz = 18.7±7.0 L; and CL = 356.0±193.2 mL/min.

The metabolites of bendamustine were identified as HP1, HP2, M3 and M4, but detection of HP2 was limited. Based on C_{max} and AUC values, and in accordance with the results from study 98B03, the following quantitative order was found: HP2>HP1; and M3>M4. The C_{max} and AUC values for M3 in the patient with liver impairment amounted to only 20% of the values in the other 5 patients, indicating that conversion from bendamustine to M3 is reduced in patients with liver impairment.

Urine was sampled for up to 24 hours following administration of bendamustine. The mean amount of bendamustine, HP1, HP2, M3 and M4 recovered was 10.95 mg (5% of dose), 6.92 mg (3%), 3.65 mg (2%), 0.61 mg (0.3%) and 0.25 mg (0.1%), respectively. The renal elimination of bendamustine and metabolites was completed after 6-10 hours.

Bile was collected pre-dose and during 16 collection intervals for up to 24-hours post application. Only minor amounts of bendamustine, HP1, HP2, M3 and M4 were detected in bile. Ten (10) additional mainly polar metabolites were identified in the bile. It was calculated that about 9% (n=5) of the administered bendamustine dose was excreted into the bile as bendamustine and its metabolites. More than 80% of biliary bendamustine equivalents are accounted for by HP1, HP2, M3 and M4. During further analysis of samples of this study, phase II metabolites have been identified following conjugation with glutathione (Teichert 2005). The percentage of administered dose recovered in the urine as cysteine-S-conjugates ranged from 0.9 to 4.1%.

3.2.2. Review of PK data from Phase III study SDX-105-103

Study SDX-105-103 is considered to the pivotal Phase III study supporting the proposed indication for bendamustine as monotherapy for the treatment of patients with indolent NHL who are refractory to rituximab. This study included a non-compartmental analysis (NCA) of the plasma PKs of bendamustine and its two active circulating metabolites (gamma-hydroxy-bendamustine [M3] and N-desmethyl-bendamustine [M4]) in 12 patients with indolent NHL refractory to rituximab (Report DP-2007-043).

In this study, patients were treated with bendamustine 120 mg/m^2 by iv infusion over 60 minutes on days 1 and 2 of each 21-day treatment cycle, for up to 6 cycles. For the purpose of PK evaluation, 36 patients were assigned to 1 of 5 Groups (A-E). The 22 patients assigned to Groups A-D were sampled according to a "sparse sampling schedule", and the 12 patients assigned to Group E (the General Clinical Research Center [GCRC] Group) were sampled more extensively. The plasma concentration results derived from these 36 patients formed the core dataset to be used for the development of a population PK model and for subsequent population PK/PD modelling. The reports from these two analyses were not provided in the submission.

For the GCRC group, blood samples were collected on day 1 of cycle 1 pre-dose (before the start of the infusion), at the mid-point of the infusion, at the end of the infusion, and at 15, 30, 45 minutes, and 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours post-infusion. In addition, 3 more samples were collected on day 1 of cycle 2 prior to dosing (pre-dose) and at 0.25 to <0.50 hours and 1 to <3 hours after the start of the infusion.

PK parameters for bendamustine, M3 and M4 were estimated in individual patients by NCA methods using WinNonlin® software. Plasma concentration of bendamustine, M3 and M4 were analyzed during June 2006 through March 2007 using a validated high-performance liquid chromatography method with tandem mass spectrometric detection (LC-MS/MS). The quantifiable range of the assay was from 0.10 to 100.00 ng/mL for bendamustine, 0.11 to 106.00 ng/mL for M3 and 0.10 to 95.00 ng/mL for M4.

The demographics of the 11 patients (5 males, 6 females) in the GCRC group for whom PK parameters could be estimated for bendamustine and at least one of M3 or M4 were: mean age 63 years (range: 44, 82 years); mean weight 75.8 kg (range: 55.8, 109.5 kg); mean height 169.3 cm (range: 154.5, 190.5 cm); and mean body surface area 1.89 m^2 (range: 1.54, 2.41 m^2).

PK parameters were estimated in 11 of the 12 patients enrolled in the GCRC group for both bendamustine and M4, and in 1 of 12 patients for M3. No parameters could be estimated for bendamustine or M4 for 1 of the 12 enrolled patients. Additionally, no parameters could be estimated for the M3 metabolite for 11 of the 12 enrolled patients since the majority of the plasma samples from these patients were stored beyond the period of demonstrated frozen stability for M3. In addition, the infusion time for 1 patient was 120 minutes rather than 60 minutes. While PK parameters were calculated for this patient, the concentration data and certain of the PK parameters (i.e., C_{max} and t_{max}) were not averaged with those obtained after the 60 minute infusions.

The key plasma PK results for bendamustine, M3, and M4 are summarized below in Table 5.

Table 5: Report DP-2007-043 - All PK values are mean ± SD unless otherwise stated.

	n	t_{max} [a] hour	C_{max} µg/mL	AUC_{inf} µg•hr/mL	$t_{1/2}$ hour	CL mL/min	Vss, L
Bendam-ustine	11	0.99 (0.58, 1.08) [b]	[b]	7.2 ± 3.8 [c]	4.9 ± 4.5 [c]	716.6 ± 682.8 [c]	25.3 ± 28.6 [c]
M3	1	1.00	0.6	0.8	2.9	NA	NA
M4	11	1.01 (0.97, 1.28) [b]	0.06 ± 0.02 [b]	0.08 ± 0.04	0.48 ± 0.08	NA	NA

a = median (range). b = 10 patients, 1 patient excluded due to infusion be given over approximately 2 hours. c = 9 patients, the terminal elimination rate could not be calculated for 1 patient

Comment: The sponsor comments that the results of the analysis suggest that bendamustine is a "low-clearance" drug in the patients studied as the mean CL was much less than the estimated hepatic flow rate of 1450 mL/min. In addition, the sponsor commented that the drug does not readily distribute beyond the extracellular space as the mean V_{dss} was similar to the estimated volume of extracellular fluid of 18.2 L. The median t_{max} for bendamustine (0.99 hours) occurred at the first sampling point after the infusion. In this study, the clearance of bendamustine from plasma was basically tri-phasic with the majority of the drug (>90%) being removed during the initial 2 disposition phases. The plasma concentration of the M4 metabolite was approximately 1% of the parent compound based on the AUC_{inf} values, and in the one patient with M3 metabolite data the concentration was approximately 10% of the parent compound based on AUC_{inf} values.

3.3. Summary of PKs

3.3.1. Absorption

Following single-dose bendamustine, peak plasma concentrations occurred typically just after completion of the 30 or 60 minute infusions, after which the drug was rapidly cleared from the plasma. The PK data from study SDX-105-103 showed that, following bendamustine 120 mg/m^2 infused over 60 minutes, the mean ± SD C_{max} was 5.6 ± 2.4 µg/mL and the mean± SD AUC_{inf} was 7.2 ± 3.8 µg•hr/mL. The data from this study showed that bendamustine was eliminated from the plasma in a generally tri-phasic manner characterized by an initial rapid distribution phase, a slower secondary phase, and a longer terminal phase. However, for some patient profiles, only the first 2 disposition phases were evident due to the drug concentrations falling below the limit of quantitation of the assay (i.e., <0.10 ng/mL) prior to reaching the terminal phase. The basic PK parameters from the Phase I studies following bendamustine infused over 30 minutes to patients with cancer with normal renal/hepatic function are summarized below in Table 6.

Table 6: Brief outline of studies with PK data (mean±SD) in patients with cancer in M5.3.3.2 and M5.3.3.3.

ID	Dose iv infusion 30 minutes	n	C_{max} µg/mL	AUC * g•hr/mL	$t_{1/2}$ ** min	CL (total)	Vz
98B02	100 mg/m^2	3	10.8 ± 8.7	10.4 ± 9.2	37.8 ± 7.6	304.2 ± 283.5 mL/min/m^2	-

ID	Dose iv infusion 30 minutes	n	C_{max} µg/mL	AUC * g•hr/mL	$t_{1/2}$ ** min	CL (total)	Vz
20BEN D1	160-280 mg/m²	13	17.1 ± 9.1	16.6 ± 13.3	30.5 ± 9.3	304.5 ± 170.9 mL/min/m²	
98B03	120 mg/m²	12	10.8 ± 7.0	11.7 ± 10.6	28.2 ± 15.9	639.4 ± 601.6 mL/min	19.4 L
BE04	100 mg/m²	6	15.5 ± 7.8	11.6 ± 2.9	47.0 ± 20.9	384.4 ± 186.3 mL/min	26.7 L

Notes: * AUC refers to AUCall or AUCinf; ** Elimination half life (t1/2);

There were no formal dose proportionality studies following administration of bendamustine iv in humans. However, bendamustine plasma PK parameters appeared to be dose-independent and non-capacity limited over the dose range 100 to 260 mg/m² when the results from 4 studies were compared (see Table 7, below).

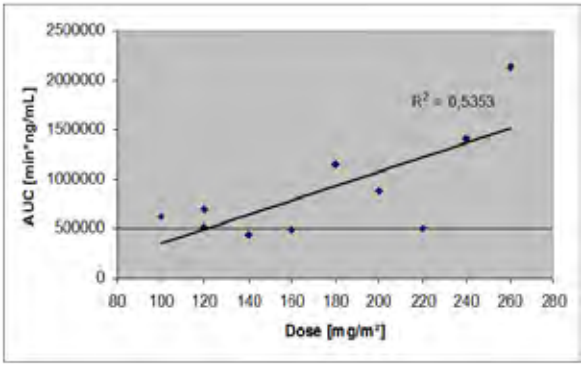
Table 7: Mean plasma bendamustine PK parameters following iv infusion over 30 minutes over the dose range 100 to 280 mg/m²

Dose [mg/m²]	100	120		140	160	180	200	220	240	260	280
Study	98B02	98B03	20BEN03	20BEN03	20BEND1	20BEN D1	20BEND1	20BEND1	20BEN D1	20BEN D1	20BEND1
pts	3	12*	2	1	3	1	2	2	2	2	1
$t_{½}$ [min]	37.8	28.2	24.7	16.5	29.6	24.1	25.3	28.8	42.5	36.9	16.5
t_{max} [min]	-	29.6	35.0	30.0	33.3	30.0	35.0	30.0	32.5	30.0	35.0
C_{max} [ng/mL]	10,766	10,780	8,959	9,978	10734	20779	15818	10858	21016	30873	12545
AUC_{all} [min*ng/mL]	626,053	699,471	515,866	437,717	497,344	1 149,348	885,155	507,776	1 412,117	2 143,295	417,271
CL [mL/min*m²]	304.2	355.2	233.1	319.7	331.8	156.6	253.3	465.0	180.1	172.3	665.0
Vc [mL/m²]	-	10,706	8,181	7,589	13,808	5,450	9,187	19,020	10,406	8,394	15,824

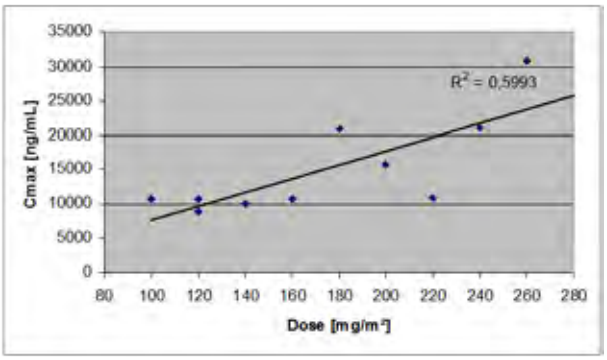
The correlation factors for bendamustine dose and AUC or C_{max} in the dosage range 100 to 260 mg/m² were R^2= 0.5353 and R^2= 0.5993, respectively (see Figure 1, below).

Figure 1: Correlation between dose and AUC (panel a) and dose and Cmax (panel b), over the dose range 100 to 260 mg/m²

(a) Dose (100-260 mg/m2) vs AUC.



(b) Dose (100-260 mg/m2) vs Cmax.



3.3.2. Distribution

The mean±SD steady state volume of distribution observed in study SDX-105-03 was 25.3 ± 28.6 L. This value is consistent with the mean steady state volume of distribution of 15.8 L following bendamustine (0.8 to 4.8 mg/kg) bolus iv injection over 3 minutes (Preiss/Humboldt University Berlin 1987). The steady state volume of distribution data suggest that bendamustine does not readily distribute beyond the extracellular space, as the observed value were similar to the estimated volume of extracellular fluid.

In vitro plasma protein binding of bendamustine has been investigated in study BioD-KLG-06. ^{14}C-bendamustine (radioactive purity 98.9%) was incubated with human plasma, human serum albumin and α-1-acid glycoprotein, and after centrifugation the radioactive concentration of the ultrafiltrate was determined by scintillation counting. ^{14}C-bendamustine was 94% to 96% bound to plasma protein, and protein binding was independent of concentration across a 50 fold concentration range. Binding of ^{14}C-bendamustine (0.1 to 100 µg/mL) to human serum albumin ranged from 80% (at the highest concentration) to 92% (at the lowest concentration), and binding to α-1-acid glycoprotein ranged from 2% (at the highest concentration) to 6% (at the lowest concentration). Following incubation with ^{14}C-bendamustine (nominal concentrations 10, 50, 100 µg/mL) in human blood, radioactivity was evenly distributed between plasma and red blood cell and this was consistent across the concentration range.

When ^{14}C-bendamustin (10 and 50 µg/mL) and ^{14}C-warfarin (4 and 10 µg/mL) were co-incubated in human serum albumin, bendamustine did not displace protein bound warfarin. The drugs prednisone (0.1 and 5 µg/mL), doxorubicin (1 and 10 µg/mL), vincristine (0.1 and 1 ng/mL) and mitoxantrone (0.1 and 1 ng/mL) when co-incubated individually with ^{14}C-bendamustine HCl (10 and 50 µg/mL) had no effect on the proportion of protein bound radioactivity observed when ^{14}C-bendamustine was incubated alone. Following a 6 hour incubation of ^{14}C-bendamustine at concentrations of 10 and 50 µg/mL with human serum albumin, approximately 14% and 26% of the initial radioactivity, respectively, was apparently "covalently" bound to human serum albumin.

3.3.3. Metabolism

In vitro metabolism of ^{3}H-bendamustine (radioactive purity > 97%) was investigated by incubating the drug with microsomes and S9 fractions from human liver for up to 50 minutes (BioD-99-37-KLG-01). Two (2) components (M3, M4) were identified following incubation of bendamustine (20, 200 µM) with liver microsomes. M3 is an oxidation product of bendamustine identified as gamma-hydroxy-bendamustine, and M4 is the N-desmethyl metabolite of bendamustine.

In vitro incubation with human liver microsomes from 14 individual donors indicated that the production of M3 and M4 was highly correlated with CYP 1A2 activity. The microsomes had been previously characterized for CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5 and 4A9/11 enzyme activity. Incubation with selective inhibitors showed that the CYP 1A2 inhibitor furafylline was the only P450 inhibitor to notably reduce M3 and M4 production at the lowest concentration of 0.1 µM. The inhibitors 4-methylpyrazole (CYP2E1), quinidine (CYP2D6) and sulfaphenazole (CYP2C9/10) had no notable effect on M3 and M4 production. Ketoconazole (CYP3A4 inhibitor) and tranylcypromine (CYP2C19 inhibitor) inhibited M3 and M4 production only at the highest concentrations (50 µM). Bendamustine hydrochloride (20, 200 µM) did not inhibit CYP 1A2, 2C9/10, 2D6, 2E1 and 3A4. The major hydrolysis products of bendamustine were not identified in this study (i.e., HP1 and HP2). Bendamustine undergoes rapid chemical hydrolysis in an aqueous environment which is unaffected by enzymatic processes.

In vitro, bendamustine (1, 10, 100 µM) incubated in human hepatocytes for 3 consecutive days did not cause consistent or concentration-dependent increases or decreases in any of the tested CYP activities (XenoTech DM-2005-004; experimental completion date 2006). Under conditions where prototypical inducers caused anticipated increases in CYP activity, treatment of cultured human hepatocytes with up to 100 µM of bendamustine had no effect on CYP1A2, CYP2A6,

CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 activity. Therefore, at the concentrations tested, bendamustine is not an inducer or repressor of these human liver microsomal enzymes.

In vivo plasma concentration data showed that the concentrations of the M3 and M4 metabolites of bendamustine were notably lower than the parent compound. In *study 98B03*, M3 accounted for about 3% and M4 for about 0.6% of the AUC_{all} of bendamustine in patients (n=12) with cancer and normal renal and hepatic function. In *study SDX-105-03*, M4 accounted for approximately 1% of the parent compound based on AUC_{inf} values and M3 (one patient only) accounted for approximately 10% of the parent compound. These results suggest that the cytotoxic activity of bendamustine is derived primarily from the parent compound.

In *study 98B03*, HP1 accounted for about 1.6% of the AUC_{all} of bendamustine in patients (n=12) with cancer and normal renal and hepatic function, while HP2 concentrations could not be determined. Information provided in Module 2.5 indicates that the anti-tumour activity of HP1 and HP2 is more than 10 times lower than the activity of bendamustine. Consequently, HP1 and HP2 account for a clinically insignificant proportion of the anti-tumour activity of bendamustine.

Phase II metabolites have been identified following conjugation with glutathione, and the percentage of administered bendamustine dose recovered in the urine as cysteine-S-conjugates ranges from 0.9 to 4.1% (Teichert 2005).

3.3.4. Excretion

No mass-balance study of bendamustine has been undertaken in humans. In cancer patients with normal renal and hepatic function, mean total CL following bendamustine 100 mg/m^2 iv was 304 mL/min/m^2 in 3 patients (study 98B02) and 384 mL/min in 6 patients (study BE04), and mean total CL following bendamustine 120 mg/m^2 iv was 639 mL/min in 12 patients (study 98B03). Overall, the terminal elimination half-life of bendamustine ranges from about 28 minutes to 47 minutes following bendamustine 100-120 mg/m^2 in 21 cancer patients with normal renal and hepatic function (Studies 98B02, 98B03, and BE04). The terminal half life of bendamustine suggests that the drug will be completely cleared from the plasma in less than 6 hours. Consequently, accumulation of the drug is unlikely for treatment regimens involving therapy on days 1 and 2 of 3 or 4 week cycles.

In *study 98B03*, in cancer patients with normal renal/hepatic function, approximately 20% of the administered dose of bendamustine was recovered in the urine (unchanged bendamustine plus metabolites HP1, HP2, M3 and M4). The amounts of parent and metabolites excreted via the urine were HP1 > bendamustine > HP2 > M3 > M4. In *study 98B03*, the percentage of the administered dose eliminated in the urine as unchanged bendamustine in cancer patients with normal renal and hepatic function was 5.5%. Therefore, based on the total clearance of 639.4 mL/min in these patients it can be estimated that renal clearance is about 35 mL/min.

In *study SDX-105-03*, mean±SD total clearance was 716.2±682.8 mL/min (CLnormalized 365.4±306.1 mL/min/m^2) and the mean±SD elimination half-life was 4.9±4.5 hours. The mean half live was notably longer following 120 mg/m^2 infused over 60 minutes (SDX-105-03) than 100 mg/m^2 infused over 30 minutes (98B03) (i.e., 4.9 hours vs 28.2 minutes).

Biliary excretion of bendamustine and its metabolites account for about 9% of the administered dose of the drug. Only small amounts of bendamustine, HP1, HP2, M3 and M4 were detected in bile, and an additional 10 mainly polar metabolites were identified. More than 80% of biliary bendamustine equivalents are accounted for by HP1, HP2, M3 and M4.

3.3.5. Special populations

3.3.5.1. Hepatic impairment

There was one PK study in 12 patients with cancer and hepatic impairment (study 98B03). In this study, hepatic impairment was characterized by 30% to 70% liver tumour/metastatic

involvement, serum bilirubin < 1.2 mg/dL in 10 patients and between 1.2 and 2.0 mg/dL in 2 patients, and mean GGT level 2.8-fold above the normal limit. Bendamustine 120 mg/m² iv over 30 minutes was administered to patients with hepatic impairment (n=12) and patients with hepatic function (n=12), and the PK results are summarized below in Table 8.

Table 8: Study 98B03 - PK data (mean ± SD) in patients with cancer with normal hepatic function (HF) and impaired hepatic function (HF) following bendamustine 120 mg/m² ivi over 30 minutes

Patients	n	T_{max} min	C_{max} µg/mL	AUC_{all} µg•hr/mL	$t_{1/2}$ min	CL mL/min	Vz L
Normal HF	12	29.6 ± 7.2	10.8 ± 7.0	11.7 ± 10.6	28.2 ± 15.9	639.4 ± 601.6	19.3 ± 14.6
Impaired HF	12	29.6 ± 4.0	9.9 ± 3.3	8.9 ± 4.3	26.9 ± 7.6	471.9 ± 244.4	16.6 ± 5.9

In a bioequivalence comparison based on ln-transformed data (impaired HF vs normal HF), the point estimates (90% CI) were 104.1% (90% CI: 64.8, 167.2) for AUC_{all} and 105.5% (90% CI: 76.3, 145.9) for C_{max}. The 90% CIs were not in the accepted bioequivalence range (i.e., 80% to 125%), but based on the limited safety data in this study there was no clinically significant difference in bendamustine toxicity between cancer patients with normal and impaired hepatic function.

> Comments: While the study suggests that dose modifications are not required for cancer patients with impaired hepatic function, the study appears to have included only a small number of patients with moderate or severe hepatic impairment based on serum bilirubin levels (i.e., only 2 patients with levels > 1.2 to 2 mg/dL). Consequently, in the absence of adequate data in patients with moderate or severe hepatic impairment it is recommended that bendamustine be avoided in these patient groups.

3.3.5.2. Renal impairment

There was one PK study in cancer patients with renal impairment (study 98B03). In this study, 12 patients had renal impairment characterized by creatinine clearance values in the range 9.1 to 35.7 mL/min. Bendamustine 120 mg/m² iv over 30 minutes was administered to patients with impaired renal function (n=12) and patients with normal renal function (n=12), and the PK results are summarized below in Table 9.

Table 9: Study 98B03 - PK data (mean ± SD) in patients with cancer with normal renal function (RF) and impaired renal function (RF) following bendamustine 120 mg/m² ivi over 30 minutes

Patients	n	T_{max} min	C_{max} ug/mL	AUC_{all} µg•hr/mL	$t_{1/2}$ min	CL mL/min	Vz L
Normal RF	12	29.6 ± 7.2	10.8 ± 7.0	11.7 ± 10.6	28.2 ± 15.9	639.4 ± 601.6	19.3 ± 14.6
Impaired RF	12	31.3 ± 10.0	9.7 ± 2.5	8.0 ± 3.4	26.4 ± 6.4	485.0 ± 239.9	17.0 ± 6.1

In a bioequivalence comparison based on ln-transformed data (impaired RF vs normal RF), the point estimates (90% CI) were 95.8% (90% CI: 59.6, 153.9) for AUC_{all} and 106.5% (90% CI: 77.0, 147.3) for C_{max}. The 90% CIs were not in the accepted bioequivalence range (i.e., 80% to 125%), but based on the limited safety data in this study there was no clinically significant difference in bendamustine toxicity between cancer patients with normal and impaired renal

function. With respect to HP1, M3 and M4 the ratio (impaired RF vs normal RF) for AUC ranged from 88.6% to 163.9%, for C_{max} from 78.9% to 132.7% and for t_{max} from 86.1% to 114.0%.

> Comment: This was a reasonable PK study in patients with moderate to severe renal impairment. In 3 of the 5 dialysis dependent patients, the dialysate was quantitatively collected and bendamustine and its metabolites measured. In the dialysate, bendamustine and metabolites HP1, M3 and M4 were detectable, but at levels notably lower than in patients with normal renal function (i.3., 5.99 vs 10.65 mg for bendamustine; 1.27 vs 16.78 for HP1; 0.51 vs 1.23 for M3; and 0.04 vs 0.24 for M4).

3.3.5.3. Elderly population

There were no PK studies specifically in an elderly population, nor in children or adolescents. The PKs of bendamustine have been studied in cancer patients ranging from 31 years to 84 years.

3.3.5.4. Sex

There no studies comparing the PKs of bendamustine in males and females.

3.3.5.5. Race

The PKs of bendamustine in different racial groups. The PK studies appear to have been undertaken primarily in Caucasian cancer patients.

3.3.6. Pharmacokinetic interactions

There were no *in vivo* PK drug-drug interaction studies involving bendamustine. The *in vitro* data showed that the formation of the active metabolites of bendamustine, gamma-hydroxy bendamustine (M3) and N-desmethyl bendamustine (M4), is mediated through CYP 1A2. Consequently, inhibitors of CYP 1A2 (e.g., fluvoxamine, ciprofloxacin) have the potential to increase plasma bendamustine concentration, while inducers of CYP 1A2 (e.g., omeprazole, smoking) have the potential to decrease plasma bendamustine concentration. The absence of *in vivo* drug-drug interaction studies involving bendamustine and CYP 1A2 inhibitors and inducers is a notable deficiency in the PK data. *In vitro* data showed that bendamustine does not inhibit CYP 1A2, 2C9/10, 2D6, 2E1 or 3A4, and is not an inducer or inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, or CYP3A4/5. *In vitro* data showed that bendamustine did not displace protein-bound warfarin when co-incubated with human serum albumin, and prednisone, doxorubicin, vincristine, or mitoxantrone had no effect on the proportion of protein-bound radioactivity observed when ^{14}C bendamustine was incubated alone. There were no PK studies assessing the role of active transporters in bendamustine distribution.

3.4. Evaluators overall conclusions on pharmacokinetics

The submitted PK data included information on 78 patients with cancer of various types from five Phase I studies, and 11 patients with indolent NHL refractory to rituximab from the pivotal Phase III efficacy and safety study (SDX-1050-03). The Clinical Overview (M2.5) identifies the most important PK studies as 20BEND1 (n=13), 98B03 (n=36), and BE04 (n=6). However, the Clinical Overview (M2.5) did not discuss the PK results from the Phase III study SDX-1050-03, and the PK report from this study was not identified or cross-referenced in the relevant PK Table of Contents (TOC) section of the submission (i.e., M5.3.3). Nevertheless, the PK data from study SDX-105-03 are considered to be clinically relevant and have been reviewed in this CER. There were no PK data from the pivotal Phase III studies in patients with CLL or in patients with previously untreated indolent NHL and MCL. There were some deficiencies in the submitted PK data, but in view of the extensive clinical efficacy and safety data submitted by sponsor it is considered that these deficiencies should not preclude approval of bendamustine.

In *study 98B03*, bendamustine 120 mg/m^2 administered iv over 30 minutes to 12 cancer patients with normal renal and hepatic function resulted in a mean±SD C_{max} of 10.8±7.0 µg/mL

and a mean±SD AUC_{all} of 11.7±10.6 µg•hr/mL. The intersubject variability in the C_{max} and AUC_{all} values was high with the coefficients of variation (CVs) being 65% and 91%, respectively. In this study, bendamustine peak plasma concentration was achieved at the end of the 30 minute infusion and the drug was rapidly cleared from the plasma with mean±SD elimination half-life of 28.2±15.9 minutes and mean±SD total plasma clearance of 639.4±601.6 mL/min.

In *study SDX-105-03*, bendamustine 120 mg/m^2 administered iv over 60 minutes to patients with indolent NHL refractory to rituximab resulted in a mean±SD C_{max} of 5.6±2.4 µg/mL (n=10) and a mean±SD AUC_{inf} of 7.2±3.8 µg•hr/mL (n=9). The intersubject variability in the C_{max} and AUC_{inf} values was moderate with the coefficients of variation (CVs) being 43% and 53%, respectively. In this study, median bendamustine peak plasma concentration was achieved at the end of the 60 minute infusion and the drug was relatively rapidly cleared from the plasma with mean±SD elimination half-life of 4.9±4.5 hours and mean±SD total plasma clearance of 716.6±682.8 mL/min.

The mean half-life in *study SDX-105-3* following a 60 minute infusion of 120 mg/m^2 of 4.9 hours was notably longer than the mean half-life in *study 98B03* of 28.2 minutes following a 30 minute infusion of 120 mg/m^2. Nevertheless, the mean half-life data from both studies suggests that there will be no significant accumulation of bendamustine on day 2 of the proposed regimens or across cycles (i.e., bendamustine administered on days 1 and 2, every 21 or 28 days for at least 6 cycles).

There were no formal dose proportionality studies. However, cross-study comparative data showed that the plasma PK parameters for bendamustine appeared to be dose-independent and non-capacity limited over the dose range 100 to 260 mg/m^2 following iv infusion over 30 minutes (98B02, 98B03, 20BEN03, 20BEND1).

The mean ± SD steady state volume of distribution in study SDX-105-03 was 25.3 ± 28.6 L. The result indicates that inter-subject variability in this parameter is very high (i.e., CV > 100%). Bendamustine was highly protein bound (94% to 96%), and binding was independent of concentration over the range 1 to 50 µg/mL. Binding of bendamustine was predominantly to serum albumin (80% to 92%), and with minor binding to α-1-acid glycoprotein (2% to 6%). The drug was evenly distributed between plasma and red blood cells, and distribution was concentration independent.

In vitro data indicate that bendamustine is metabolized via CYP 1A2 to gamma-hydroxy-bendamustine (M3) and desmethyl-bendamustine (M4) (BioD-99-37-KLG-01). *In vivo* data indicate that the concentrations of the M3 and M4 metabolites were notably lower than the parent compound. In *study 98B03*, M3 and M4 accounted for about 3% and 0.6%, respectively, of the AUC_{all} of bendamustine in patients (n=12) with cancer and normal renal and hepatic function. In *study SDX-105-03,* based on AUC_{inf} values, M4 accounted for about 1% of the parent compound in 11 patients and M3 accounted for about 10% of the parent compound in 1 patient. These results suggest that the cytotoxic activity of bendamustine is derived primarily from the parent compound rather than its M3 and M4 metabolites. In addition to Phase I metabolites formed from CYP 1A2 activity, Phase II metabolites have been identified following conjugation with glutathione (Teichert 2005).

In addition to Phase I and II metabolism, bendamustine also undergoes chemical hydrolysis to monohydroxy-bendamustine (HP1) and dihydroxy-bendamustine (HP2). In *study 98B03*, plasma HP1 concentration was about 1.6% of the parent compound and HP2 was undetectable. The anti-tumour activity of HP1 and HP2 is more than 10 times lower than the anti-tumour activity of bendamustine. Consequently, it can be estimated HP1 and HP2 account for a clinically insignificant amount of anti-tumour activity.

In *study 98B03*, in 12 cancer patients with normal renal and hepatic function the total plasma clearance of bendamustine was 639.4±601.6 mL/min, and about 20% of the administered dose of the drug was excreted in the urine as bendamustine and metabolites (HP1 > bendamustine > HP2 > M3 > M4). Approximately 5.5% of the dose was eliminated in the urine as unchanged

bendamustine. The results suggest that bendamustine is primarily cleared from the plasma by non-renal mechanisms, and that the renal clearance is approximately 35 mL/min. As the renal clearance of bendamustine is less than the fraction of the drug unbound x glomerular filtration rate (GFR), bendamustine must be reabsorbed from the renal tubules and may or may not be secreted.

Biliary excretion of bendamustine and its metabolites account for about 9% of the administered dose of the drug. Only small amounts of bendamustine, HP1, HP2, M3 and M4 were detected in bile, and an additional 10 mainly polar metabolites were identified. More than 80% of the metabolites appearing in the bile were accounted for by HP1, HP2, M3 and M4.

The effects on hepatic and renal impairment on the PKs of bendamustine were investigated in *study 98B03*. There was no data on patients severe hepatic impairment and limited data on patients with moderate hepatic impairment. The PK results suggest that no dosage adjustment is required in patients with mild hepatic impairment, but administration of bendamustine to patients with moderate or severe hepatic impairment should be avoided due to the absence of adequate data in these patient groups. The PK data on patients with severe renal impairment are limited, but suggest that while no dosage adjustments are required caution is required when the drug is used in this patient population. The total renal elimination of bendamustine and metabolites HP1, HP2, M3 and M4 was reduced by 75% (vs normal renal function) in patients (n=12) with end-stage renal disease (ESRD), and by 80% (vs normal renal function) in patients (n=3) with dialysis-dependent ESRD.

There are no *in vivo* drug-drug PK interactions studies. The *in vitro* data suggest that CYP 1A2 inhibitors have the potential to increase the plasma bendamustine concentration, while CYP 1A2 inducers have the potential to decrease the plasma bendamustine concentration. *In vitro* data showed that bendamustine does not inhibit CYP 1A2, 2C9/10, 2D6, 2E1 or 3A4 (BioD-99-37-KLG-01), and is not an inducer or inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, or CYP3A4/5 (XenoTech DM-2005-004). *In vitro* data showed that bendamustine did not displace protein-bound warfarin when co-incubated with human serum albumin, while co-incubation of bendamustine with prednisone, doxorubicin, vincristine, or mitoxantrone individually suggests that these drugs do not displace protein-bound bendamustine. There were no PK studies assessing the role of active transporters in bendamustine distribution.

The main deficiencies in the submitted PK data (human) are listed below:

- No *in vivo* drug-drug PK studies were submitted assessing the potential interaction between bendamustine and drugs which inhibit or induce CYP 1A2. The *in vitro* data indicate that bendamustine is metabolized via CYP 1A2 to the active metabolites gamma-hydroxy-bendamustine (M3) and N-desmethyl-bendamustine (M4). Consequently, CYP 1A2 inhibitor and inducers have the potential to increase or decrease plasma bendamustine concentration, respectively, when administered concomitantly.
- No *in vitro* studies with active transporters.
- No mass-balance studies in humans.
- No PK studies in patients with severe hepatic impairment and limited data on patients with moderate hepatic impairment. The provided study is considered not to reflect current best practice for PK studies in patients with renal or hepatic impairment.
- No PK studies in special groups including only elderly patients, only males or females, and different racial groups.

4. Pharmacodynamics

The clinical pharmacodynamic studies related primarily to the determination of MTD and DLT in Phase I studies in patients with specific cancers. These studies were aimed at defining the

most appropriate bendamustine dosage regimens for assessment in subsequent Phase III studies. In this CER, the Phase I studies supporting the proposed dose regimens for the proposed indications have been reviewed in under Dosage Selection for the pivotal study. No PK/PD data relating specifically to efficacy or safety outcomes could be identified in the submission. However, a PK/PD study based on data from study SDX-105-03 (report CP-07-003) appears to have been undertaken. The pharmacodynamics of the drug appears to have been extensively investigated in the nonclinical studies.

5. Dosage selection for the pivotal studies

5.1. Chronic lymphocytic leukaemia

The sponsor's proposed regimen for bendamustine for the treatment of CLL is 100 mg/m^2 administered by iv infusion over 30 to 60 minutes on days 1 and 2, every 4 weeks for up to 6 cycles. This is the dose that was used in the pivotal study submitted in support of the proposed CLL indication (02CLIII). The sponsor states that two dose finding studies were carried out with bendamustine (Lissitchkov et al., 2005/ Ribosepharm GmbH 99CLL2E (BG); Bergmann et al., 2005 / Ribosepharm GmbH 99CLL2E [DR]). There were no formal dose ranging studies.

Ribosepharm GmbH 99CLL2E (BG), was a Phase I/II open-label study sponsored by Astellas Pharma GmbH, Germany, and was conducted in one centre in Bulgaria from March 2001 to September 2002. The primary objectives of the study were to determine the DLT and MTD of second-line bendamustine monotherapy in patients with symptomatic B-cell CLL (Binet stage B or C) requiring therapy after failure of prior chemotherapy, and at least one treatment had to be chlorambucil (with or without prednisone). A total of 15 fludarabine-naive patients were treated with bendamustine at a starting dose of 100 mg/m^2 on days 1 and 2 every 3 weeks. The MTD was defined as the dose at which ≤ 1 patient experienced DLT after the first course of a dose level (maximum 6 patients). DLT was considered to be any CTC grade 3/4 non-haematological toxicity, or CTC grade 4 haematological toxicity. In this study, the MTD was 110 mg/m^2 (1/6 patients with a DLT), and the bendamustine dose recommended for further study in patients with previously untreated CLL was 100 mg/m^2 on days 1 and 2 every 4 weeks.

Ribosepharm GmbH 99CLL2E [DR] was sponsored by Astellas Pharma GmbH, Germany, and reported the findings of a Phase I/II, open-label study of the German CLL study group. The study was conducted in multiple centres in Germany from October 200 to March 2002. The primary objectives of the study were the same as those for *Ribosepharm GmbH 99CLL2E (BG),* except that patients were required to have received at least one prior therapy that included chlorambucil or fludarabine. A total of 16 patients (median age 67 years) with relapsed or refractory CLL were enrolled. All patients had been pre-treated with a median of three different regimens. Bendamustine was given at a starting dose of 100 mg/m^2 on days 1 and 2 every 3-4 weeks. If no DLT occurred in the first 3 patients after the first treatment course, a dose escalation of 10 mg/m^2/day was planned for the next dose cohort. In this study, the MTD was 70 mg/m^2. Six (6) patients had DLT resulting in three dose de-escalation steps from 100 mg/m^2 to 70 mg/m^2. In this study, the recommended dose in refractory CLL was 70 mg/m^2 on days 1 and 2 every 4 weeks.

Scientific Protocol Review Board experts for study 02CLLIII considered the data from the two dose finding studies and recommended bendamustine 100 mg/m^2 on days 1 and 2 every 4 weeks for first-line chemotherapy of CLL. The dose of chlorambucil selected for the control arm of study 02CLLIII was 0.8 mg/kg (Broca's weight) on days 1 and 15 every 4 weeks, which followed the German CLL Study Group's (GCLLSG) recommendation for adequate chlorambucil dosing.

5.2. Relapsed/refractory indolent NHL (refractory to rituximab)

The sponsor's proposed regimen for the treatment of relapsed/refractory indolent NHL (refractory to rituximab) is 120 mg/m^2 administered iv over 30 to 60 minutes on days 1 and 2, every 3-weeks for at least 6 cycles. The sponsor identified two published studies supporting the dosage used in the pivotal study (Heider and Niederle, 2001; Weidmann et al., 2002). There were no formal dose ranging studies.

In *Heider and Niederle (2001)*, the efficacy and toxicity of bendamustine 120 mg/m^2 administered iv over 60 minutes on two consecutive days repeated every 3 weeks was assessed in a single-centre (Germany), single-arm, open-label study in 52 evaluable patients with histologically confirmed low grade NHL who had progressed or relapsed after at least one cytostatic pretreatment. Complete remission (CR) was induced in 11% of patients, partial remission (PR) in 62%, and stable disease (SD) in 10%. The median duration of remission was 16 months and the median survival time was 36 months. The most commonly reported toxicities (WHO grades) were: nausea/vomiting (37% [grade 1]; 19% [grade 2]); leukopenia (56% [grade 2], 23% [grade 3], 6% [grade 3]); RBC decreased (63% [grade 1], 17% [grade 2]); and thrombocytopenia (33% [grade 1], 10% [grade 2]). Allergies were reported in 8% of patients (2% grade 1 and 6% grade 2). There were no reports of cardiotoxicity, neurotoxicity, or alopecia. The authors of this study concluded that "bendamustine proved to be very effective and was well tolerated in pretreated patients with relapsed or primary resistant low-grade NHL".

In *Weidmann et al (2002),* the efficacy and toxicity of bendamustine 120 mg/m^2 administered iv over 30 minutes on days 1 and 2, every 3 weeks for up to 6 cycles was assessed in a two-centre (Germany), single-arm, open-label study in 18 evaluable patients with relapsed or refractory high grade NHL. Response was evaluated after 2, 4 and 6 cycles and every 3 months after completion of treatment. Complete response (CR) was induced in 17% of patients and partial response (PR) in 28% of patients, resulting in a total response rate of 38% (8/18). In 10 (56%) patients, treatment progressed during treatment. In 60 evaluable treatment cycles, WHO grade 3 or 4 events were reported in 8% to 13% of cycles (anaemia in 8%, thrombocytopenia in 13%, leukopenia in 12%, granulocytopenia 10%). In 2 patients, bendamustine had to be stopped because of prolonged grade 4 thrombocytopenia and leukopenia. Overall, haematological toxicities resulted in dose delays or dose reduction in 22% of the scheduled treatment cycles. None of the patients received myeloid growth factors. In 60 evaluable treatment cycles, non-haematological WHO grade 3 or 4 events of nausea/vomiting occurred in 2% of cycles, fever in 2% of cycles, infections in 3% of cycles, alopecia in 7% of cycles, and diarrhea in 0% of cycles. No treatment related deaths occurred. The authors of this study concluded that "bendamustine is effective in aggressive lymphoma and can be recommended for [palliative treatment]".

5.3. First-line treatment of NHL and MCL

The sponsor's proposed combination regimen for the first-line treatment of NHL and MCL is bendamustine 90 mg/m^2 administered over 30 to 60 minutes on days 1 and 2, every 4 weeks for up to 6 cycles, with rituximab being administered on the first day or each cycle. There were no formal dose ranging studies with the proposed combination therapy.

6. Clinical efficacy

6.1. First line treatment of chronic lymphocytic leukaemia (Binet stage B or C)

6.1.1. Clinical studies providing efficacy data

The sponsor's covering letter identifies one pivotal Phase III study (02CLLIII) supporting the submission to register bendamustine for the first line treatment of CLL (Binet stage B of C). No

other studies were identified in the covering letter as being pivotal or supportive for the registration of bendamustine for this indication. Examination of the Module 5 data (Section 5.3.5, Reports of Efficacy and Safety Studies - Indication CLL) identifies one study in Section 5.3.1 (study 02CLLLIII), two studies in Section 5.3.2 (riboseph 99CLL.2E-BG; riboseph 99CLL.2E-DE), and two studies in Section 5.3.3 (Friedr-Schiller-Uni-Jena; riboseph 96BMF02-01). In addition to the five studies included in Section 5.3.5, Section 5.4 (Literature references) included a number of studies providing background information on bendamustine for the treatment of CLL.

None of the four additional studies submitted in Module 5, Sections 5.3.2 and 5.3.3, are considered to provide pivotal or supportive data for the proposed indication. Two studies (*riboseph 99CLL.2E-BG* and *riboseph 99CLL.2E-DE*) were Phase I/II, open-label, dose-finding studies designed to determine MTD and DLT of bendamustine in second-line treatment of patients with relapsed or refractory CLL. These two studies have been described above in this CER. Two studies (*Friedr-Schiller-Uni-Jena; riboseph 96BMF02-01*) were Phase III, open-label studies comparing bendamustine in combination with methotrexate and 5-fluorouracil with a combination of cyclophosphamide, methotrexate, and 5-fluorouracil for the treatment of metastatic breast cancer.

6.2. CLL - pivotal efficacy study 02CLLII

6.2.1. Study design, objectives, locations and dates

6.2.1.1. Overview

Study 02CLLII was a Phase III, open-label, randomized, multicentre, efficacy and safety study of bendamustine versus chlorambucil in treatment-naive patients with B-cell chronic lymphocytic leukaemia (Binet Stage B or C) requiring therapy. Binet stage B includes patients with ≥ 3 lymph node regions, haemoglobin ≥ 10 g/dL, and platelets ≥ $100x10^9$/L, and Binet stage C included patients with haemoglobin < 10 g/dL and platelets < 100x109/L, regardless of the number of lymph node regions involved.

The first patient was recruited on 5 February 2002 and the last patient completed the study on 13 June 2008 (i.e., last follow-up visit). The submission included two Clinical Study Reports (CSRs): the first (CSR1) was dated 23 August 2007 and reported the results of the third interim (final confirmatory) analysis on 305 patients with a cut-off date of 18 May 2006; and the second (CSR2) was dated 25 November 2009 and reported the follow-up analysis on 319 patients (i.e., 14 more than in final confirmatory analysis).

The study was multinational (8 European countries) and multicentre (45 centres). The number of centres in each country were: 22 centres in Germany, 8 centres in Bulgaria, 5 centres in Italy, 3 centres in Spain, 2 centres in France, 2 centres in Sweden, 2 centres in Austria and 1 centre in the UK. The co-ordinating investigator was located in Germany. The clinical trial was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guideline (ICH-GCP), the Declaration of Helsinki, the German Medicinal Products Act (AMG), and applicable local laws. The study was approved by local independent ethics committees (IECs) and/or institutional review boards (IRBS). All patients provided written informed consent. The study was sponsored by Mundipharma Research Ltd, England.

The **objective** of this study was to demonstrate superior efficacy of bendamustine compared with chlorambucil in the initial treatment of patients with CLL (stage Binet B or C) requiring treatment.

The study has been the subject of a number of publications including, Knauf et al., 2003 (abstract); Knauf et al., 2004 (abstract); Knauf et al., 2007 (abstract); Knauf et al., 2008 (abstract); Knauf et al., 2008 (peer reviewed paper); Knauf et al., 2012 (peer reviewed paper).

Comment: In CSR2, the sponsor states that "based on the results from the planned third interim analysis the [Independent Data Monitoring Committee] recommended to close the study and to perform the final confirmative analysis". The sponsor also stated that any "additional analyses performed after this final confirmative analysis, including [the additional follow-up analysis reported in CSR2], may support the study results but have no effect on the study outcome". However, in this CER the emphasis will be on the results of the follow-up analysis reported in CSR2 as it is considered that this analysis includes more mature data.

6.2.1.2. Description of overall study plan

Following baseline assessment (day -14 through day -1), patients were randomized (1:1) to open-label with either bendamustine or chlorambucil. The dosage regimen for bendamustine was 100 mg/m^2/day (30 minute iv infusion) on days 1 and 2 every 4 weeks. The dosage regimen for chlorambucil was 0.8 mg/kg oral (po) on days 1 and 15 (or, if necessary, given as divided doses on d1/2 and d15/16) every 4 weeks.

Recruitment was planned to extend over 2 years, but due to sluggish recruitment the time frame was extended for at least a further year. The follow-up period was 1 year from the time the last patient completed treatment. The duration of treatment depended on the response. After completing 3 treatment cycles an interim tumour assessment was performed. Patients with partial remission (PR) or complete remission (CR) continued therapy with 2 consolidating cycles for up to a maximum of 6 cycles. Patients with no change (NC) received at least another 3 cycles of therapy. Patients experiencing progressive disease (PD) discontinued the study. At the end of the treatment phase another tumour assessment was performed. Patients with CR or PR were followed-up at 3 month intervals until progression, and then at 3 month intervals for survival. Patients with NC (stable disease [SD]) or PD were followed-up only for survival at 3 month intervals. The study followed a five stage adaptive design allowing for four interim analyses and one final analysis.

There have been 7 amendments to the original study protocol. In general the amendments were administrative or clarified the clinical aspects of the study and are considered to have no significant effects on the objectives of the study.

6.2.1.3. Inclusion and exclusion criteria

Patients with B-CLL requiring therapy who met all inclusion and exclusion criteria were eligible for participation in the study. Patients with small cell lymphocytic leukaemia (SLL) were also eligible as this disease is classified as CLL according to the WHO classification scheme.

General inclusion criteria were: treatment-naive, legally competent adult patients < 75 years of age capable of following study instructions; written informed consent had been given; WHO Performance Status (PS) 0-2 (i.e., fully active to ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours); life expectancy > 3 months; and contraception for at least 6 months after therapy.

Study and indication specific criteria were: confirmed B-cell CLL (co-expression of CD5, CD23 and either CD19 or CD20 or both); and symptomatic Binet stage B or C disease. In addition, all patients had to meet the need-to-treat criteria (Cheson et al., 1988) for B-CLL (see below in Section 6.1.2.3).

The study also included comprehensive criteria for removal of patients from therapy or assessment. These criteria have been examined and are considered to be appropriate.

Comment: In general, the inclusion and exclusion are considered to be satisfactory. However, the study only included patients younger than 75 years. In Australian clinical practice, depending on the characteristics of the disease, it is likely that patients 75 years and older would be offered treatment for CLL.

6.2.1.4. Need to treat criteria

All patients were required to meet the need-to-treat criteria according to *Cheson et al (1988)*. The need-to-treat criteria are summarized below:

- Haematopoetic insufficiency with non-hemolysis-induced Hb < 10 g/dL;

and/or

- Thrombocytopenia < $100x10^9$/L (equivalent to Binet stage C);

and/or

- B symptoms defined as:
  - Unexplained > 20% weight loss in the last 6 months;
  - Persistent or recurrent fever of unknown origin (FUO) > 38°C;
  - Night sweats;

and/or

- Rapidly progressive disease (such as rapid lymphoma growth, rapid increase in lymphocyte count, rapid fall in Hb or platelet count not due to autoimmune phenomena);

and/or

- Risk of organ complications from bulky lymphomas (e.g. vascular compression).

6.2.1.5. Study treatments

- **Bendamustine:** 100 mg/m^2/day administered by iv infusion over 30 minutes on days 1 and 2 every 4 weeks. The next cycle was to start on day 29.
- **Chlorambucil:** 0.8 mg/kg (Broca's normal weight in kg [i.e., height in cm minus 100]) administered orally (po) on days 1 and 15 or, if necessary given as divided doses on days 1/2 and days 15/16, every 4 weeks. The next cycle was to start on day 29. The drug was to be taken fasting if at all possible.

No dose increases or individual dose adjustments were planned for this study.

All patients who received study drug started at least 1 cycle and received up to 6 cycles. The proportion of patients in the safety population receiving treatment for 6 cycles was 64.0% (104/161) in the bendamustine arm and 62.9% (95/151) in the chlorambucil arm. The mean (SD) number of cycles was 4.9 (1.7) for both treatment arms (safety population).

6.2.1.5.1. Dose adjustment - non-disease related haematological toxicity:

Dose adjustments were allowed in case of non-disease related haematological toxicity. All treatment-induced transfusions (platelets, red blood cells) were to be avoided if at all possible. Therapy was to be suspended if:

- platelets fell to less than $20x10^9$/L;
- haemoglobin fell to less than 7.0 g/dL; or
- the absolute neutrophil count fell to less than $0.5x10^9$/L.

In addition, dose modifications according to *Cheson et al (1996)* were applied in cases where the haematological values were outside the normal range (see Table 10, below). For toxicity assessments, the value observed at start of the next cycle was the basis for dose reduction. The final decision concerning the dose reduction was at the discretion of the treating investigator.

Table 10: Study 02CLLLIII - Dose modification guidelines according to haematological toxicities according to Cheson et al (1996)

Percent fall in Hb or platelets versus baseline

In case of therapy-induced myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils were to be monitored at least weekly, and treatment was not to be resumed until:

- the white cell count had returned to > $2.5x10^9$/L or baseline;
- the neutrophil count had returned to > $1.5x10^9$/L or baseline;
- haemoglobin had returned to > 10.0 g/dL or baseline;
- the platelet count had returned to > $100x10^9$/L or baseline.

6.2.1.5.2. Dose adjustments - non-haematological toxicity

Dose reduction was based on the worst CTC grades in the preceding cycle as follows:

- No dose reduction for CTC grade 0-2 (and grade 3 nausea and/vomiting and alopecia);
- 50% dose reduction for CTC grade 3 (except nausea/vomiting and alopecia);
- Off study for CTC grade 4

Investigators were urged to suspend chlorambucil if a patient showed signs or symptoms of pulmonary toxicity or developed severe skin reactions.

In cases where patients experienced therapy induced > CTC grade 2 non-haematologic toxicities (except nausea/vomiting and alopecia), they were to be monitored at least weekly, and treatment was not to be resumed until symptoms had returned (decreased) to baseline intensity or were < CTC grade 2.

6.2.1.5.3. Reintroduction of original dose

Patients experiencing haematological and/or non-haematological toxicities could subsequently have their dose increased to the original level, if the reduced dose had been tolerated. If therapy was delayed by more than 4 weeks, the patient had to go off study.

6.2.1.5.4. Duration of treatment with the study drugs

The patient recruitment period was expected to last approximately three years. Individual duration of treatment depended on response with the goal to achieve a CR or at least PR. The follow-up period was one year from when the last patient completed study treatment. Patients with PR or CR were to receive two consolidation cycles and a maximum of 6 cycles. Patients with NC were to receive at least 3 cycles. Patients with PD were to go off study.

6.2.1.5.5. Concomitant therapy

Concomitant treatments were to be kept to a minimum during the trial, but were permissible, if deemed necessary by the investigator for the patient's well-being and did not compromise the assessment of the study results. For prevention of uric acid induced nephropathy, prophylactic anti-hyperuricaemic treatment (e.g., allopurinol) during the first three cycles was recommended, and treatment beyond this time was at the discretion of the investigator. Treatment with antineoplastic drugs was not permitted. If at all possible, treatment during the study with immunoglobulins, prednisone, or G-CSFs was to be avoided.

Comment: The choice of chlorambucil as an active control is considered to be appropriate. However, a combination fludarabine regimen might have been a preferable active control in the patient population included in the study. The sponsor states that the study was planned and designed towards the end of 2001 and the only approved first-line treatment for CLL at that time was chlorambucil. The sponsor states that "even today" chlorambucil is one of the main therapeutic options for the first-line treatment of CLL for most patients older than 65 years. It is noted that in the EU, bendamustine is approved for the first-line treatment of CLL (Binet stage B or C) in patients for whom combination fludarabine combination chemotherapy is not appropriate. The ESMO Clinical Practice Guidelines for CLL recommend combination fludarabine, cyclophosphamide and rituximab (FCR) as first-line therapy for physically active patients with low co-morbidity burden and Binet stage C disease or symptomatic disease (any stage) (Eichhorst et al., 2011). In patients with relevant co-morbidity, the ESMO guidelines states that chlorambucil "seems to be standard therapy" for patients with Binet B/Rai II disease, and lists bendamustine as an alternative therapy for these patients.

Chlorambucil is approved in Australia for first-line therapy of CLL at a recommended dose of 0.15 mg/kg/day until the total leucocytes count has fallen to $10x10^3/\mu L$, with treatment being resumed 4 weeks after the end of the first course and continued at a dosage of 0.1 mg/kg/day. The Clinical Overview (Module 2.5) provided the results of an analysis using IMS data on the use of chlorambucil or fludarabine for first line treatment of CLL in Europe. The data showed that, in the 5 countries studied, chlorambucil was used in 44% of patients (n=21,174) and fludarabine in 56% of patients (n=26,652). In the UK, the figures were 69% for chlorambucil and 31% for fludarabine.

6.2.1.6. Efficacy variables and outcomes

6.2.1.6.1. Primary efficacy endpoint

The two primary efficacy endpoints in this study were the overall response rate (ORR) and progression-free survival (PFS), assessed in the intent-to-treat (ITT) population and based on adjudicated responses and dates of progression determined by an Independent Committee for Response Assessment (ICRA).

- **ORR** was defined as the proportion of patients in each treatment arm with a best response of complete response (CR) or partial response (PR) or nodular partial remission (nPR)**.** The best response was required to be met for at least 8 weeks.
- **PFS** was defined as the time from randomization to first PD or relapse after inter-current remission or death for any cause.

6.2.1.6.2. Secondary efficacy endpoints

- Time to progression.
- Duration of remission/response.
- Overall survival
- Quality of life, as assessed by QLQ-30 and CLL Specific Questionnaire (EORTC)

6.2.1.6.3. Assessment of the efficacy endpoints

The response assessment was based on the criteria defined by the NCI-Sponsored Working group (NCI-WG) on CLL (Cheson et al., 1988, 1996). The methods used for evaluation of tumour response to chemotherapy were to be clearly defined and documented prior to patient enrolment, and the same methods were to be used for evaluation at baseline and all repeat determinations (e.g., CT, X-ray, ultrasound, palpation).

Response was assessed by three different methods:

- The electronic CRF (eCRF) calculated the overall response according to a programmed algorithm based on the NCI-WG Criteria for response assessment (Cheson, 1996).
- The investigator assessed the overall response at his/her discretion. If the outcome was different from the overall response calculated by the algorithm, the investigator was allowed to change the overall response calculated by the eCRF.
- The ICRA was provided with line listings and assessed the response on a per-patient basis in a blinded manner. The ICRA was established prior to the third interim analysis and consisted of three independent experts. It was established in order to allow similar response evaluations for all patients, as it had become evident from the first two interim analyses that investigator assessments were inconsistent. The ICRA was the decisive assessment.

The sponsor stated that the NCI-WG Criteria provide "a general guideline for the response assessment in CLL but [do] not [reflect the progress of] individual [patients]". Therefore, the ICRA "agreed on a complementary approach to the response assessment" to ensure standardized procedures. Each tumour evaluation supplied by the sponsor to the ICRA consisted of bone marrow data, size of measurable disease (lymph nodes), size of spleen and liver, information containing B-symptoms, and haematology results. In the follow-up analysis provided in CSR2, all patients assessed in the three interim analyses and the follow-up analysis were evaluated (or re-evaluated) using the ICRA's final agreement to the response assessment made at its meeting on 23 October 2008.

One of the major issues discussed by the ICRA related to the assessment of patients with CR, PR, or SD who progressed prior to response confirmation after 8 weeks, or at first follow-up for SD patients. First it was agreed that such patients were to evaluated as having PD, independent of the fact of the short remission time reached. Starting with the meeting on 4 February 2008, such a patient was evaluated with SD at study termination and with PD at the first follow-up visit, and finally at the meeting of 23 October 2008 it was agreed that such patients were to be assessed with PD if the duration from the date of best response to PD was less than 2 months. All other agreements remained unchanged over all three ICRA meetings and are summarized below:

- Following the WHO classification patients with small cell leukaemia SLL were eligible for thestudy.
- Disease progression was met if at least 1 parameter worsened by 50% compared with the best response during the study.
- Patients with stable disease may present a minor response to study treatment for one or more parameters. The worsening of one parameter by 50% or more relative to the best value reached during the study was to be defined as PD.
- Evaluation of spleen and liver size could be done by palpation, imaging (CT or ultrasound) or both. Evaluation by palpation was to be decisive for the ICRA response assessment. If no palpation was done, the ICRA response assessment was carried out based on the imaging.
- The sum of all measurable lymph nodes (target lesions) was decisive for the assessment of the overall response. To reach PD, a lymph node needed to increase by at least 50% relative to the best response reached during the study. New lymph nodes that were not found at baseline resulted in PD assessment.
- CR was reached when the patient showed CR for all parameters according to the NCI-WG-Criteria. A bone marrow biopsy should be performed within 2 months after clinical and laboratory results demonstrate that all CR requirements have been reached. The date of best response was defined as the date of first observation of CR provided that the response was confirmed by bone marrow biopsy at the end of treatment or 8 to 12 weeks later. The marrow sample must present less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent.

6.2.1.7. Randomization and blinding methods

Each participating patient was randomized to either chlorambucil or bendamustine in a ratio of 1:1, stratified by centre and Binet stage (Binet B or Binet C). All patients were randomized consecutively in the order of notification by the study entry by IOMEDICO, GmbH, Germany. The study was open-label.

6.2.1.8. Analysis populations

The intention-to-treat (ITT) population included all patients randomized regardless of whether a patient received study drug.

The per-protocol (PP) population included all patients with no violations of the inclusion and exclusion criteria or protocol deviations that might interfere with outcome evaluation. Patients were excluded from the PP population for the following reasons: WHO PS > 2; no confirmed B-cell CLL; no symptomatic Binet stage B or C disease; previous treatment with other cytotoxic drugs; history of a second malignancy (except cured basal cell carcinoma or cured cervical cancer); Richter's syndrome or transformation to PLL at baseline; major surgery within 30 days before the start of the trial; hypersensitivity to any of the study drugs; and/or failed to fulfil the "need to treat criteria" according to the NCI-Working Group Criteria (Cheson, 1996).

The safety population included all patients who received at least one application of study medications.

6.2.1.9. Sample size

The sample size calculations were based on an anticipated ORR of approximately 60% in the bendamustine arm compared with 30% in the chlorambucil arm, and a median PFS of approximately 20 months compared with 14 months, respectively,

The sample size required for an ORR at an α of 5% and a power of 1–β of 80% was approximately 2 x 42. The sample size required for PFS hazard ratio 1.429 was 326, based on a 24 month recruitment period, follow-up of 12 months, and PFS of 20 months in the bendamustine arm and 14 months in the chlorambucil arm.

Based on the outcome assumptions, 326 evaluable patients would have been required for a study with one endpoint and no interim analysis. As it could not be estimated whether these assumptions would hold for this study, a five-stage adaptive group sequential procedure was planned. The first interim analysis was performed after 40 patients in each group were followed up for at least 5 months (corresponding to 5 cycles). The sample size of the next sequence was recalculated after the interim analysis. The final number of recruited patients could not be calculated *a priori*, but it was assumed to be approximately 350 patients.

> Comment: The outcome assumptions used to calculate the sample size were based on the study by *Rai et al (2000)*. In this study, previously untreated patients with CLL were assigned to treatment with fludarabine, chlorambucil, or combined fludarabine plus chlorambucil. The rates of complete + partial remission were 63% (107/170) in the fludarabine arm and 37% (67/181) in the chlorambucil arm. The median PFS was 20 months in the fludarabine arm and 14 months in the chlorambucil arm. Based on the results from *Rai et al (2000)* for the comparison between fludarabine and chlorambucil, the outcome assumption used to calculate the sample size for study 02CLLIII are considered to be satisfactory.

6.2.1.10. Statistical methods

6.2.1.10.1. Primary efficacy analyses

The ORR (first primary efficacy endpoint) was analysed by a Cochran-Mantel-Haenszel (CMH) test, and PFS (second primary efficacy endpoint) was analysed by a log-rank test. Both analyses were performed stratified according to Binet stage (B or C). The analyses were performed using the correct Binet stage, as stratification errors had occurred during randomization resulting in

28 patients being incorrectly classified. The primary analysis of both endpoints was in the ITT analysis set using ICRA assessments.

In order to adjust for multiple significance testing, statistical analysis of the two primary efficacy endpoints was performed by a priori-sequenced hypothesis testing. The following null hypotheses were tested:

- H_{01} Pr (BEN) = Pr (CLB), where Pr is the overall remission rate for the two treatment arms;
- H_{02} $h_{BEN}(t) = h_{CLB}(t)$, where h is the is the hazard rate at point t for the two treatment arms

ORR was tested first, and PFS was tested at the level α_1=0.016 only if the ORR was significant at α_1, thus controlling for the multiple significance level (Lehmacher, Kieser & Hothorn, 2000).

6.2.1.10.2. Secondary efficacy analyses

The secondary efficacy endpoints of time to progression, duration of response and overall survival were analyzed using the log-rank test controlling for Binet stage. Quality of life, as assessed by QLQ-C30 was evaluated as recommended in the EORTC QLQC30 Scoring Manual. The primary endpoint of the quality of life analysis was the QLQ-C30. As two different versions of the not yet validated CLL module were applied, only specific items concerning side effects and symptoms of CLL were descriptively analysed. Time to disease progression and duration of response were assessed in the ITT analysis set using ICRA assessments, and overall survival was based on calculated assessment in the ITT population.

6.2.1.10.3. Interim analyses

A five-stage adaptive group sequential procedure was planned, using Pocock cut-offs of α =0.016, with a maximum of four interim analyses and one final analysis. In each interim analysis, the first primary endpoint (ORR) was tested first, and the second primary endpoint (PFS) was tested only if the first endpoint was significant, thus controlling for the multiple testing of the significance level (Lehmacher, Kieser & Hothorn, 2000).

The five-step group sequential procedure was performed adaptively, with the sample size of the next sequence being recalculated after each interim analysis. The *P* values of the individual sequences were combined using the inverse-phi method (Lehmacher & Wassmer, 1999). As the *P* values obtained at the times of the interim analyses were not definitive because the patients were still under observation, these values were only used to determine whether to stop the study or continue the study using the new sample size. Final inferential analysis of the study data used the *P* values obtained with the data available from the third interim analysis. After each interim analysis an Independent Data Monitoring Committee (IDMC) reviewed the safety and efficacy data and made a recommendation to the sponsor regarding continuation of the study.

Three of the four pre-planned interim analyses were performed:

1. The first interim analysis was conducted after 86 patients were available for the safety analysis and 85 for the efficacy analysis (ORR and PFS).
2. The second interim analysis was conducted after an additional 76 and 73 patients were evaluable for safety and efficacy, respectively.
3. The third interim analysis was conducted after a total of 298 patients were available for the safety analysis and 264 for the efficacy analysis (139 bendamustine; 125 chlorambucil). Patients available for efficacy analysis at the time of the third interim analysis were summarized.

At the third interim analysis (primary efficacy endpoints and safety assessment) the IDMC recommended to close recruitment and to perform the final analysis (all primary and secondary efficacy endpoints and safety) with the data available. Therefore the third interim analysis and

the final confirmatory analysis are identical, with the exception that in the final confirmatory analysis all secondary endpoints were also assessed.

6.2.1.10.4. Follow-up analysis

The follow-up analysis included patients who were not included in the final analysis because they did not meet the cut-off criterion for that analysis (completed Day 1 Cycle 6 on 27 February 2006).

6.2.1.11. Participant flow

In the follow-up analysis described in CSR2, the ITT population included 319 patients (162 in the bendamustine [BEN] arm and 157 in the chlorambucil [CLB] arm). Patient disposition for the follow-up analysis is summarized below in Table 11.

Table 11: Study 02CLLIII - Patient disposition; ITT analysis set

	BEN (N = 162)	CLB (N = 157)	Total (N = 319)
Number of patients randomised	162 (100.0%)	157 (100.0%)	319 (100.0%)
Number of patients in the Intention-to-treat analysis set	162 (100.0%)	157 (100.0%)	319 (100.0%)
Number of patients randomised but not treated	1 (0.6%)	6 (3.8%)	7 (2.2%)
Number of patients treated (safety population)	161 (99.4%)	151 (96.2%)	312 (97.8%)
Number of patients in the Per-protocol analysis set	108 (66.7%)	121 (77.1%)	229 (71.8%)
Number of patients completed study	122 (75.3%)	127 (80.9%)	249 (78.1%)
Reason for ending treatment:			
Unacceptable toxicity	15 (9.3%)	5 (3.2%)	20 (6.3%)
Subject refusal	9 (5.6%)	6 (3.8%)	15 (4.7%)
Investigator's decision	2 (1.2%)	6 (3.8%)	8 (2.5%)
Death	1 (0.6%)	3 (1.9%)	4 (1.3%)
Protocol violation	1 (0.6%)	2 (1.3%)	3 (0.9%)
Risk/ benefit assessment no longer acceptable	3 (1.9%)	0 (0.0%)	3 (0.9%)
Lack of compliance	1 (0.6%)	1 (0.6%)	2 (0.6%)
Final examination not done	1 (0.6%)	0 (0.0%)	1 (0.3%)
Lost to follow up	0 (0.0%)	1 (0.6%)	1 (0.3%)
Other	7 (4.3%)	6 (3.8%)	13 (4.1%)

Comment: The completion rate was greater in the chlorambucil arm than the bendamustine arm (80.9% vs 75.3%, respectively). Unacceptable toxicity resulting in treatment discontinuation occurred notably more frequently in the bendamustine arm than in the chlorambucil arm (9.3% vs 3.2%), which appears to be the main reason accounting for a lower completion rate in the bendamustine arm compared with the chlorambucil arm.

6.2.1.12. Major protocol violations/deviations

Of the 319 randomized patients, at least one protocol violation or protocol deviation was reported in 123 (38.6%) patients: 68 (42.0%) bendamustine; 55 (35.0%) chlorambucil. There were 31 patients with "no symptomatic Binet stage B or stage disease" (19, 11.7%, bendamustine; 12, 7.6%, chlorambucil), and 1 (0.6%) patient in the chlorambucil arm with "no need to treat criteria". There were 45 randomized patients with an exclusion criteria (19, 11.7%, bendamustine; 15, 16.6%, chlorambucil).

Comment: It is considered that the protocol violations/deviations in this study are unlikely to have invalidated the efficacy or safety analyses.

6.2.1.13. Baseline data

6.2.1.13.1. (1) Demographics

In the pivotal ITT population (n=319), the mean (SD) age of the patients in the bendamustine arm was 63.0 (7.5) years, ranging from 47 to 77 years, and the mean age of the patients in the chlorambucil arm was 63.6 (8.8) years, ranging from 35 to 78 years. The majority of patients in total ITT population were male (male 197, 61.8% vs female 122, 38.2%). Nearly all patients in the study were Caucasian, with only 2 (1.3%) patients in the chlorambucil arm being identified as "other ethnic group". The WHO PS was 0 for the majority of patients in both treatment arms (113, 69.8%, bendamustine; 102, 65.0% chlorambucil), with most of the remaining patients being classified as PS 1 (43, 26.5%, bendamustine; 45, 28.7%, chlorambucil). In the total ITT population, 45 patients had an abnormal ECG at baseline (21, 13.0%. bendamustine; 24, 15.3%, chlorambucil). The mean height of the two treatment arms was similar, but the mean weight in the bendamustine arm was greater than in the chlorambucil arm (78.6 vs 73.9 kg, respectively), as was the mean BSA (1.9 vs 1.8 m^2, respectively).

Comment: Overall, the baseline demographic factors were comparable between the two treatment arms, and the observed differences are unlikely to be clinically significant. The median age of the population at first-diagnosis was 63 years in the bendamustine arm and 66 years in the chlorambucil arm, which is younger than expected in a Caucasian population with CLL. In the SEER cancer statistics data from the USA, the median age at diagnosis of CLL in a "white" population was 72 years for data collected from 2006 to 2010 (Howlader et al., 2012). The majority of patients in the study were fully active (based on a WHO PS estimate of 0) with the remainder being active and able to carry out non strenuous activities (based on a WHO PS estimate of 1).

6.2.1.13.2. (2) Medical history

In the ITT population (n=319), 132 patients had previous disease (70, 43.2%, bendamustine; 62, 39.5%, chlorambucil). The most commonly reported previous disorders (SOC) in patients in the ITT population (bendamustine vs chlorambucil) were "surgical and medical procedures" (25, 14.1% vs 20, 12.7%) followed by "infections and infestations" (17, 10.5%, vs 15, 9.6%), "gastrointestinal" (8, 4.9% vs 8, 5.1%), "neoplasms, benign, malignant and unspecified" (10, 6.2% vs 5, 3.2%), "nervous system" (4, 2.5% vs 7, 4.5%), "cardiac" (6, 3.7% vs 3, 1.9%), "respiratory, thoracic, and mediastinal" (5, 3.1% vs 4, 2.5%), "injury, poisoning and procedural complications" (5, 3.1% vs 2, 1.3%), and "renal" (4, 2.5% vs 3, 1.9%). All other disorders (SOC) occurred in < 2% of patients in the combined treatment arms. Overall, there were no marked differences in previous medical conditions between the two treatment arms, and observed differences are unlikely to be clinically significant.

6.2.1.13.3. (3) Physical examination

In the ITT population (n=319), physical examination at baseline showed pathological findings in 265 patients (135, 83%, bendamustine; 127, 80.9%, chlorambucil). Not unexpectedly, the majority of patients in both treatment arms (bendamustine vs chlorambucil) had pathological disorders (SOC) in the "blood and lymphatic system" (132, 81.5% vs 127, 80.9%), consisting primarily of lymphadenopathy (128, 79.0% vs 126, 80.3%), spleen disorder (33, 20.4% vs 32, 20.4%), and splenomegaly (28, 17.3% vs 29, 18.5%). "Hepatobiliary disorders" were reported in 38 (23.5%) patients in the bendamustine arm and 36 (22.9%) patients in the chlorambucil arm, and hepatomegaly was reported in 38 (23.5%) and 36 (22.9%) patients in the treatment arms, respectively. Overall, there were no marked differences in physical examination at baseline between the two treatment arms, and observed differences are unlikely to be clinically significant.

6.2.1.13.4. (4) Concomitant disease

In the ITT population (n=319), concomitant diseases present prior to the start of study medication were reported in 236 patients (121, 74.6% bendamustine; 112, 73.5%

chlorambucil). Concomitant diseases (preferred term) occurring in ≥ 2% of patients (bendamustine vs chlorambucil) in the total ITT population were hypertension 39.8% (69, 42.6% vs 58, 36.9%), diabetes mellitus 9.7% (16, 9.9% vs 15, 9.6%), hypothyroidism 4.7% (10, 6.2% vs 5, 3.2%), cholelithiasis 3.8% (3, 1.9% vs 9, 5.7%), hypercholesterolaemia 3.8% (5, 3.1% vs 7, 4.5%), hyperglycaemia 3.4% (4, 2.5% vs 7, 4.5%), obesity 3.4% (6, 3.7% vs 5, 3.2%), hyperuricaemia 3.1% (9, 5.6% vs 1, 0,6%), chronic pyelonephritis 2.8% (7, 4.3% vs 2, 1.3%), coronary artery disease 2.8% (3, 1.9% v 6, 3.8%), osteoarthritis 2.5% (7, 4.3% vs 1, 0.6%), weight decreased 2.5% (5, 3.1% vs 3, 1.9%), hepatic steatosis 2.5% (4, 2.5% vs 4, 2.5%), anaemia 2.2% (6, 3.7% vs 1, 0.6%), depression 2.2% (2, 1.2% vs 5, 3.2%), benign prostatic hyperplasia 2.2% (5, 3.1% vs 2, 1.3%), and emphysema 2.2% (3, 1.9% vs 4, 2.5%). Overall, there were no marked differences in concomitant diseases present prior to the start of study medication between the two treatment arms, and observed differences are unlikely to be clinically significant.

6.2.1.13.5. (5) Concomitant medications

Patients in the two treatment arms taking previous and/or concomitant medication are summarized below in Table 12. The list of reported previous and concomitant medications in the ITT population was extensive and demonstrated a wide variety of products.

Table 12: Study 02CLLIII - Patients with previous and/or concomitant medication; ITT population

Patients (same patient could be in more than one class)	BEN (n=162)	CLB (n=157)	Total (n=319)
All patients with medication	150 (92.6%)	139 (88.5%)	289 (90.6%)
Patients with previous medication	14 (8.6%)	9 (5.7%)	23 (7.2%)
Patients with concomitant medication	147 (90.7%)	135 (86.0%)	282 (88.4%)
Patients with medication started after last study medication	52 (32.1%)	27 (17.2%)	79 (24.8%)

In the ITT population, the concomitant use of antibiotics was significantly higher in patients in the bendamustine arm than in the chlorambucil arm (60, 37.0% vs 28, 17. 8%; p=0.0002, Fisher's exact test). The most commonly reported therapeutic use for antibiotics in the bendamustine arm was for pyrexia (18, 11.1%, bendamustine vs 1, 0.6%, chlorambucil), followed by infection (5, 3.1%, bendamustine vs 1, 0.6%, chlorambucil).

In the ITT population, antineoplastic therapy starting after the last study medication was reported in 79 (48.8%) patients in the bendamustine arm and 99 (63.1%) patients in the chlorambucil arm.

The study protocol stated that the use of growth stimulation factors (GSFs) should be avoided if at all possible. However, use of GSFs varied in the participating countries according to local practice. In the ITT population, the use of GSFs were reported in notably more commonly in patients in the bendamustine arm compared with the chlorambucil arm (19, 11.7% vs 3, 1.9%, respectively).

6.2.1.13.6. (6) CLL characteristics

· Binet stage B or C classification

Stratification errors relating to the Binet stage occurred in 28 patients. In the corrected data for the ITT population (n=319), 227 (71.2%) patients were classified as Binet stage B (116, 71.6%,

bendamustine; 111, 70.1%, chlorambucil) and 92 (28.8%) patients were classified as Binet stage C (46, 28.4%, bendamustine; 46, 29.3%, chlorambucil).

· Immuno-phenotype

Chronic B-cell lymphocytic leukaemia was required to be confirmed by co-expression of CD5, CD23 and at least one of CD19 or CD20. In both treatment groups, 90% of patients in the ITT population had immuno-phenotypic confirmation of CLL. In total, the immuno-phenotype for 31 patients was not fulfilled or unknown. These patients were excluded from the per-protocol population. The immuno- phenotype for the ITT population was summarized.

· Time between tumour diagnosis and registration in ITT population

The mean (SD) time from the first tumour diagnosis to "registration" in the ITT population was shorter in the bendamustine arm compared with the chlorambucil arm: 18.8 (32.3) months in 162 patients vs 24.6 (33.9) months in 154 patients, respectively. The median time in the bendamustine arm was 7.75 months (range: 0.3, 193.5. months) compared with 8.24 months (range: 0.03, 148.7 months) in the chlorambucil arm.

· Bone marrow evaluation

The evaluation of the bone marrow (cellularity, lymphocytes fraction of nucleated cells, lymphoid nodules) in the ITT population is summarized below in Table 13. There was no marked difference between the two treatment arms in bone marrow characteristics.

Table 13: Study 02CLLIII - Bone marrow characteristics at baseline; ITT population

	BEN (N = 162)	CLB (N = 157)	Total (N = 319)
	N (%)	N (%)	N (%)
Cellularity			
Not done	7 (4.3%)	5 (3.2%)	12 (3.8%)
normal	16 (9.9%)	27 (17.2%)	43 (13.5%)
hyper cellular	129 (79.6%)	115 (73.2%)	244 (76.5%)
hypo cellular	8 (4.9%)	9 (5.7%)	17 (5.3%)
not evaluable (NE)	2 (1.2%)	1 (0.6%)	3 (0.9%)
Lymphocytes [%]			
n	144	138	282
Mean (SD)	72.9 (21.1)	74.7 (20.9)	73.8 (21.0)
95% CL	[69.4; 76.4]	[71.2; 78.2]	[71.3; 76.2]
Min-Max	5.0 - 100.0	10.0 - 100.0	5.0 - 100.0
Median	80.0	80.0	80.0
Q1-Q3	60.0 - 90.0	62.0 - 90.0	60.0 - 90.0
Lymphoid nodules			
absent	81 (50.0%)	92 (58.6%)	173 (54.2%)
bone marrow not done	7 (4.3%)	5 (3.2%)	12 (3.8%)
lymphoid nodules not judgeable	0 (0.0%)	1 (0.6%)	1 (0.3%)
lymphoid nodules: about there is no information in the report	1 (0.6%)	0 (0.0%)	1 (0.3%)
Present	73 (45.1%)	59 (37.6%)	132 (41.4%)

· Spleen and liver enlargement

Evaluation of the spleen and liver was performed by palpation and/or by imaging (ultrasound and/or CT). Palpation was the preferred method and the size below costal margin was recorded in the eCRF. In cases where the spleen/liver size was measured by imaging the maximum diameter was to be entered into the eCRF. The liver and spleen sizes were not documented for all patients.

In the ITT population (n=319), ***the spleen*** (bendamustine vs chlorambucil) was enlarged in 246 (77.1%) patients (124, 76.5% vs 122, 77.7%), not enlarged by in 68 (21.3%) patients (37, 22.8% vs 31, 19.7%), and examination not done in 5 (1.6%) patients (1, 0.6% vs 4, 2.5%). The mean±SD (range) maximum size of the spleen below the costal margin (bendamustine vs

chlorambucil) by palpation was 2.7±3.4 cm (0, 17) vs 3.0±3.5 cm (0, 16) in 146 and 137 patients, respectively, and by imaging was 7.9±6.9 cm (0, 22) vs 8.5±6.4 cm (0, 21) in 82 and 81 patients, respectively.

In the ITT population (n=319), ***the liver*** (bendamustine vs chlorambucil) was enlarged in 151 (47.3%) patients (80, 49.4% vs 71, 45.2%), not enlarged in 163 patients (82, 50.6% vs 81, 51.6%), and examination not done in 5 (1.6%) patients (0, 0% vs 5, 3.2%). The mean±SD (range) maximum size of the liver below the costal margin (bendamustine vs chlorambucil) by palpation was 1.4±2.7 cm (0, 16) vs 1.2±1.7 (0, 8) cm in 148 and 134 patients, respectively, and by imaging was 3.5±5.6 cm (0, 24) vs 2.6±4.7 cm (0, 18) in 69 and 63 patients, respectively.

· Indicator lesions

In the ITT population (n=319), documented indicator lesions (bendamustine [n=162] vs chlorambucil [n=157]) occurred most commonly in the axilla (117, 72.2% vs 116, 73.9%), followed by cervical (103, 63.6% vs 103, 65.6%), inguinal (73, 45.1% vs 73, 46.5%), supraclavicular (18, 11.1% vs 23, 14.6%), para-aortal/peri-aortal (21, 13.0% vs 17, 10.8%), and mandibular/sub-mandibular (20, 12.3% vs 14, 8.9%). All other indicator lesion sites involved ≤ 10% of patients in the total ITT population.

· Constitutional symptoms

In the ITT population (n=319), the following constitutional features (bendamustine [n=162] vs chlorambucil [n=157]) were reported: fever > 38°C for > 2 weeks without evidence of infection (15, 9.3% vs 27, 17.2%); night sweats without evidence of infection (74, 45.7% vs 75, 47.8%); weight loss > 10% within the previous 6 months (37, 26.6% vs 34, 27.2%); any fever, night sweats or weight loss (80, 49.4% vs 79, 50.3%). Transformation to Richter's Syndrome, PLL, or other high grade lymphoma was reported in no patients in the bendamustine arm, and no patients in chlorambucil arm, but assessment appears not to have been undertaken in the chlorambucil arm in 4 patients.

· Immunological parameters

In the ITT population (bendamustine vs chlorambucil), pathological IgA values were reported in 60 (37.0%) patients and 58 (36.9%) patients, pathological IgG values were reported in 64 (39.5%) patients and 70 (44.6%) patients, and pathological IgM values were reported in 84 (51.9%) patients and 79 (50.3%) patients, respectively. Clinically relevant abnormalities were reported for 1 patient only.

· Haematological parameters

There were no significant differences between the two treatment arms in baseline haematological parameters. The baseline haematological parameters (mean, SD) for the ITT population (bendamustine [n=162] vs chlorambucil [n=157]) were: haemoglobin g/dL - 12.3 (2.2) vs 12.3 (2.0); lymphocytes G/L - 68.9 (75.0) vs 62.4 (53.0); platelets G/L - 166.4 (77.9) vs 163.2 (73.8); and neutrophil count G/L - 8.1 (19.6) vs 7.1 (8.6). In the ITT population, blood transfusion at baseline was performed in 7 (4.3%) patients in the bendamustine arm and 5 (3.2%) patients in the chlorambucil arm.

6.2.2. Results for the primary efficacy outcomes

6.2.2.1. Overall remission/response rate

The ORR based on ICRA assessment in the ITT population was statistically significantly higher in the bendamustine arm compared with the chlorambucil arm (67.9%, 110/162 vs 30.6%, 48/157, respectively; p<0.0001). The overall response includes patients with a best response of complete response (CR) plus partial response (PR) plus nodular partial response (nPR). The results are summarized below in Table 14. The results for the overall response rate in the PP population were 77.8% (84/108) in the bendamustine arm and 33.1% (40/121) in the chlorambucil arm, and these results were consistent with those in the ITT population. The

overall response rate, for response assessed by the ICRA in the ITT population, was also statistically significantly greater in the bendamustine arm compared with the chlorambucil arm in part 1 (first interim analysis), part II (second interim analysis) and part III (third interim analysis/confirmatory analysis) of the study.

Table 14: Overall response rate based on ICRA; ITT analysis for the follow-up data 31 May 2008 includes combined data from parts I, II, and III

ICRA	BEN (n=162)	CLB (n=157)	p-value [1]	Total (n=319)
Overall response rate	110 (67.9%)	48 (30.6%)	p < 0.0001	158 (49.5%)
Complete response	50 (30.9%)	3 (1.9%)		53 (16.6%)
Nodular partial response	17 (10.5%)	4 (2.5%)		21 (6.6%)
Partial response	43 (26.5%)	41 (26.1%)		84 (26.3%)
Unconfirmed response	4 (2.5%)	5 (3.2%)		9 (2.8%)
Stable disease	19 (11.7%)	32 (20.4%)		51 (16.0%)
Progressive disease	15 (9.3%)	53 (33.8%)		68 (21.3%)
Not examined	14 (8.6%)	19 (12.1%)		33 (10.3%)

1 = The p-value for study parts I-III were calculated using the CMH tests stratified for Binet stage. The p-value for all study parts combined (I+II+III) was calculated using the inverse phi method (Lehmacher and Wassmer, 1999).

Overall response according to ICRA by Binet stage: The ORR (ICRA assessment) by Binet stage (B or C) compared between groups, and the difference in proportion between groups adjusted for Binet stage are summarized below in Table 15. The treatment effect (difference in proportions) between the two treatment arms after adjusting for Binet stage was 37.3% (95% CI: 21.7%, 47.4%), in favour of bendamustine (p<0.001).

Table 15: Study 02CLLIII - Overall response rate (ICRA assessment) - fixed effects analysis of difference in the response probability - stratified according to Binet stage (B or C); ITT population

	Bendamustine		Chlorambucil			
Binet stage	n	Response	n	Response	Difference in proportions [1]	p
Binet B	116	82 (70.7%)	111	38 (34.2%)	36.5%	
Binet C	46	28 (60.9%)	46	10 (21.7%)	39.1%	
Overall	162	110 (67.9%)	157	48 (30.6%)	37.3% (95% CI: 27.1%, 47.4%)	p<0.001

1 = Difference in proportion and 95% CI of overall response is adjusted for Binet stage.

Investigator assessment (sensitivity analysis): In the ITT population (investigator assessment), the overall response rate was 74.7% (121/162) in the bendamustine arm and 39.5% (62/147) in the chlorambucil arm; p<0.0001. The treatment effect (difference in proportions) after adjusting for Binet stage was 35.2% (95% CI: 25.2%, 45.3%), in favour of bendamustine (p<0.001). The CR in the bendamustine arm was notably greater than in the chlorambucil arm (29.6%, 48/162 vs 3.8%, 6/157; respectively).

Comparison between ICRA and investigators for response assessment: The results for the investigator and ICRA were consistent. Assessment between ICRA and investigator was concordant for 85% (137/162) of patients in the bendamustine arm and for 82% (129/157) of patients in the chlorambucil group. For 7 patients in each arm (4%, bendamustine; 5% chlorambucil) ICRA assessed the patient as responder but not the investigator. Eighteen (18) patients (11%) in bendamustine arm and 21 patients (13%) in the chlorambucil arm were assessed as non-responders according to ICRA but as responders according to the investigator.

Subgroup analyses (overall response rate by treatment group and Binet stage): In the ITT population, patients with Binet B had a higher response rate than patients with Binet C in both the bendamustine and chlorambucil treatment arms. In patients with Binet B, the overall response rate was 70.8% (82/116) in the bendamustine arm and 34.2% (38/111) in the chlorambucil arm. In patients with Binet C, the overall response rate was 60.9% (28/46) in the bendamustine arm and 21.7% (10/46) in the chlorambucil arm.

Subgroup analyses (overall response rate by treatment group and gender): In the ITT population, overall response rates were similar for females and males. In female patients, the overall response rates were 68.3% (41/60) in the bendamustine arm and 32.3% (20/62) in the chlorambucil arm. In male patients, the overall response rates were 67.6% (69/102) in the bendamustine arm and 29.5% (28/95) in the chlorambucil arm.

Subgroup analyses (overall response rate by treatment group and age): In the ITT population, the overall response rate in the bendamustine arm was greater in patients aged < 65 years compared with patients aged ≥ 65 years (71.6%, 63/88 vs 63.5%, 21/74, respectively), and the overall response rate in the chlorambucil arm was greater in patients aged ≥ 65 years compared with patients aged < 65 years (32.5%, 27/83 vs 28.4%, 21/74). In both age groups, the overall response rate was notably greater in the bendamustine arm compared with the chlorambucil arm.

Subgroup analyses (overall response rate by treatment group and country): In the ITT population, the overall response rate was notably greater for patients in the bendamustine arm

compared with the chlorambucil arm for Bulgaria, Germany, and other countries combined (Austria, France, Spain, Sweden, UK).

6.2.2.2. Progression free survival

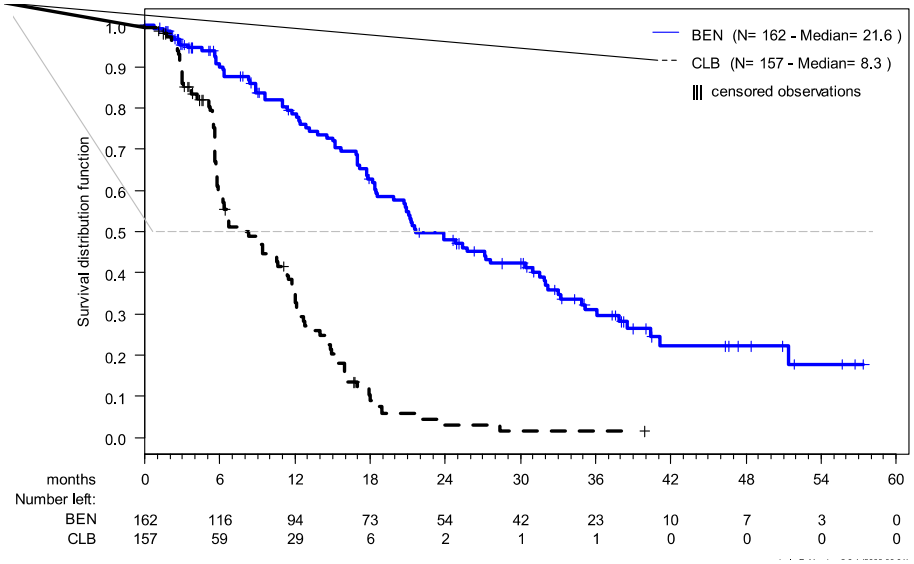
PFS was defined as the time in months from the date of randomization to the date of first PD or relapse after intercurrent remission or to the date of death for any cause. The primary evaluation of PFS was based on the ICRA assessment, and an additional analysis of PFS was based on investigator assessment. Median PFS based on ICRA assessment was 21.6 months in the bendamustine arm and 8.3 months in the chlorambucil arm, p< 0.0001 (see Table 16, and Figure 2, below). According to Kaplan-Meier estimates of onset of events, 78.6% of patients in the bendamustine arm and 34.9% of patients in the chlorambucil arm were free of progression 12 months after randomization. Analyses based on the three study parts also showed longer PFS in the bendamustine arm compared with the chlorambucil arm (p < 0.0001).

Table 16: Study 02CLIII - PFS based on ICRA - KM estimates; ITT population

Statistic	Bendamustine (n=162)	Chlorambucil (n=157)	CLB/BEN HR [95%CI] 1	p-value 2
Patients with events	86 (53.1%)	101 (64.3%)	4.37 [3.14; 6.07]	<0.0001
Censored patients	76 (46.9%)	56 (35.7%)		
25th percentile (95%CI)	13.1 (9.6; 17.0) months	5.6 (4.2; 5.6) months		
50th percentile (95%CI)	21.6 (18.6; 31.0) months	8.3 (5.9; 11.3) months		
75th percentile (95% CI)	40.4 (33.2; NA) months	14.0 (12.0; 15.9) months		

1 = Hazard ratios and 95% CIs are adjusted for Binet stage and based on the Cox regression proportional hazard model. 2 = The p-value is from a stratified log-rank test adjusted for Binet stage.

Figure 2: Study 02CLLIII - PFS based on ICRA - KM estimates; ITT population.



Investigator assessment (sensitivity analysis): In the ITT population, investigator assessment of PFS was consistent with the ICRA assessment. The median PFS based on investigator assessment was 21.2 months (95% CI: 17.7, 27.1) in the bendamustine arm and 8.9 months (95% CI: 8.4, 10.0) in the chlorambucil arm; p<0.0001. According to KM estimates of onset of events, 71.2% (99 patients) of patients in the bendamustine arm were free of progression at 12 months after randomization compared with 32.2% (35 patients) in the chlorambucil arm.

Influence of Binet stage: In the ITT population, Binet stage did not influence PFS with median duration in Binet B patients (n=227) being 14.5 months (95% CI: 12.0, 16.2 months) and 17.0 months (95% CI: 11.5, 21.3 months) in Binet C patients (n=92). In the Binet B group, 60.8% (138/238) of patients had events compared with 53.3% (49/92) of patients in the Binet C group: HR (95% CI) Binet B/Binet C = 0.94 (0.68, 1.31); p=0.7187.

Subgroup analysis (PFS by gender, females): The median PFS (ITT population) for females was 18.4 months (95%CI: 8.9, 15.7 months) in the bendamustine arm and 9.4 months (95%CI: 5.8, 12.8 months) in the chlorambucil group; p<0.0001. The HR (95% CI) CLB/BEN was 2.82 (1.69, 4.701).

Subgroup analysis (PFS by gender, males): The median PFS (ITT population) for males was 25.7 months (95% CI: 21.1, 34.9 months) in the bendamustine arm and 6.7 months (95%CI: 5.8, 11.4 months) in the chlorambucil arm; p<0.0001. The HR (95%CI) CLB/BEN was 5.89 (3.78, 9.171).

Subgroup analysis (PFS by age group, < 65 years): The median PFS (ITT population) patients < 65 years of age was 23.9 months (95% CI: 11.4, 18.2 months) in the bendamustine arm and 6.7 months (95%CI: 5.8, 10.3 months) in the chlorambucil arm; p<0.0001. The HR (95%CI) CLB/BEN was 5.32 (3.38, 8.37), and p<0.0001.

Subgroup analysis (PFS by age group, ≥ 65 years): The median PFS (ITT population) patients ≥ 65 years of age was 21.6 months (95% CI: 15.0, 34.9 months) in the bendamustine arm and 11.7 months (95%CI: 5.8, 12.5 months) in the chlorambucil arm; p<0.0001. The HR (95%CI) CLB/BEN was 3.52 (2.17, 5.70).

Subgroup analysis (PFS by Binet stage, Binet B). The median PFS (ITT population) in Binet B patients was 21.4 months (95% CI: 18.2, 16.9 months) in the bendamustine arm and 9.0 months (95%CI: 6.2, 11.6 months) in the chlorambucil arm; p<0.0001. The HR (95%CI) CLB/BEN was 4.13 (2.81, 6.06).

Subgroup analysis (PFS by Binet stage, Binet C). The median PFS (ITT population) in Binet C patients was 25.4 months (95% CI: 17.7, 34.9 months) in the bendamustine arm and 6.3 months (95%CI: 4.2, 11.9 months) in the chlorambucil arm; p<0.0001). The HR (95%CI) CLB/BEN was 5.18 (2.66, 10.07).

Subgroup analysis (PFS by country): In the ITT population, the median PFS for patients treated with bendamustine in Bulgaria was lower (17.7 months) compared with patients in Germany (32.2 months) and in other countries combined (27.1 months). For patients treated with chlorambucil the median PFS for patients in Bulgaria was 6.7 months, for patients in Germany 11.9 months and for patients in the other countries 8.3 months. Superiority of bendamustine compared with chlorambucil was shown to be independent of country (p=0.0001 for Germany, for Bulgaria and for other countries, KM estimates, ITT population).

Comment: The break-down of PFS into its component parts could not be identified for any of the analyses (i.e., no patient numbers for progression, relapse or death contributing to the total number of events). The sponsor will be requested to provide this data for the round two clinical evaluation.

6.2.3. Results for the secondary efficacy outcomes

1. Time to progression:

Time to progression (TTP) was the time from the start of therapy to PD or relapse after intercurrent remission or CLL related death. In the ITT population, the median TTP based on the ICRA was similar to the median PFS. The median TTP was 23.9 months (95% CI: 20.7, 31.5 months) in the bendamustine arm and 8.3 months (95% CI: 6.0, 11.4 months) in the chlorambucil arm; p<0.0001.

2. Duration of response:

The duration of response was the time from maximum therapeutic response (CR, nPR, PR) to PD or death. In the ITT population, the median duration of response was 21.8 months (95% CI: 17.4, 27.0 months) in the bendamustine arm and 8.0 months (95% CI: 6.3, 9.3 months) in the chlorambucil arm; p<0.0001. The median duration of response for patients with CR, nPD, and PR in the ITT population was longer for each outcome in the bendamustine arm compared with the chlorambucil arm.

3. Overall survival (OS):

Overall survival was the time interval from randomization to death for any cause. A total of 72 patients died during the observational period, 31 (19.3%) patients in the bendamustine arm and 41 (26.1%) patients in the chlorambucil arm. The KM estimate of median duration of survival was available only for patients in the chlorambucil arm (65.4 months [95%: 55.1, NA months]). No statistically significant difference in OS between the two treatment arms was seen (p=0.1623, log-rank test stratified according to Binet stage). The HR CLB/BEN was 1.45 (95% CI: 0.91, 2.31), suggesting a small non-statistically significant survival benefit for patients in the bendamustine compared with patients in the chlorambucil.

4. Quality of life:

There were no new quality of life data in the follow-up analysis. Therefore, the quality of life results are summarized for the final analysis. In the final analysis, quality of life was assessed at start of therapy and at the beginning of all subsequent treatment cycles. At each cycle patients completed two questionnaires, the general cancer questionnaire EORTC QLQ C-30 and a CLL-specific version, CLL-25 that was still under development (all countries, except Italy). A total of 260 (98.5%) patients in the ITT population completed and returned at least one QoL questionnaire (97.1%, 135/139, bendamustine; 100%, 125/125, chlorambucil).

The results for the EORTC QLQ C-30 questionnaire at completion/end of treatment showed a statistically significant improvement in favour of chlorambucil compared with placebo for "Physical Functioning" (questions 1-5), and a statistically significant improvement in favour of bendamustine compared with chlorambucil for "Cognitive Functioning" (questions 20, 25). No significant difference between the two treatment arms was evident for “Role functioning” (questions 6-7), “Emotional functioning” (questions 21-24), “Social functioning” (questions 26, 27), or "Global Health Status" (questions 29, 30).

For the symptom scales of the EORTC QLQ C-30, no differences between the two treatment arms were seen for fatigue (questions 10, 12, 18), pain (questions 9, 19), insomnia (question 11), constipation (question 16), and financial difficulties (question 28). However, patients in the bendamustine arm experienced more nausea and vomiting than patients in the chlorambucil arm, particularly after cycles 4 and 5. In addition, patients in the bendamustine arm experienced more frequent dyspnoea, diarrhoea, and loss of appetite than patients in the chlorambucil arm, with the highest difference being after completion of cycle 4.

Single items for CLL specific questions from EORTC Questionnaire QLQ-CLL25 were descriptively analyzed and showed night sweats were reduced more by treatment with bendamustine, while not surprisingly bendamustine resulted in more problems associated with repeated injections or infusions.

6.3. Relapsed/refractory indolent Non-Hodgkin's Lymphoma (NHL)

6.3.1. Clinical studies providing efficacy data

The sponsor is seeking approval of bendamustine for the treatment of relapsed/refractory indolent NHL with monotherapy 120 mg/m^2 on days 1 and 2, every 3 weeks for at least 6 cycles. The sponsor has nominated 4 studies that it considers to be pivotal for the proposed indication (see Table 17 below). However, of the 4 studies nominated by the sponsor, only 2 are considered to be directly relevant to the proposed bendamustine monotherapy dosing regimen (SDX-105-03; SDX-105-01). Furthermore, the sponsor's proposed indication relating to relapsed/refractory indolent NHL does not specify that patients should be refractory to rituximab. However, the only dosage regimen being proposed by the sponsor for treatment of relapsed/refractory indolent NHL is bendamustine as monotherapy for patients who are refractory to rituximab.

The pivotal study is considered to be SDX-105-03 (Phase III) and the supportive study is considered to be SDX-105-01 (Phase II). In both of studies, the monotherapy bendamustine treatment regimen was that proposed for by the sponsor for approval. Both the pivotal study (SDX-105-03) and the supportive study (SDX-105-01) have been evaluated (see below in Sections 6.3.2 and 6.3.3, respectively). Studies SDX-105-02 and 93BOP01 are considered not to be directly relevant to the proposed indication. Both studies used bendamustine in combination regimens not being proposed for approval, and both studies included patients who were not refractory to rituximab. However, both of these studies have been reviewed and the results summarized below in Section 6.4.4.

Table 17: Studies nominated by the sponsor to be pivotal for relapsed/refractory indolent NHL

ID	Design	Efficacy endpoints	n	Treatment
SDX-105-03 Cephalon	Phase III, mc (USA, Canada), open-label, single-arm BEN monotherapy, in patients with indolent NHL refractory to rituximab.	Prim: ORR & DR. Sec: PFS & DR.	100	BEN: 120 mg/m^2 on days 1 and 2, repeated every 21 days for a minimum of 6 cycles.
SDX-105-01 Cephalon	Phase II, mc (USA, Canada), open-label, single-arm BEN monotherapy, in patients with indolent NHL refractory to rituximab.	Prim: ORR. Sec: DR & PFS	76	BEN: 120 mg/m^2 on days 1 and 2, repeated every 3 weeks, for a minimum of 6 cycles depending on response. If patients still receiving benefit after 12 cycles then consideration given to continuing treatment for 1 year.

ID	Design	Efficacy endpoints	n	Treatment
SDX-105-02 Cephalon	Phase II, mc (USA, Canada, Australia), open-label, single-arm BEN in combination with RIT in patients with relapsed indolent or mantle cell NHL	Prim: ORR. Sec: DR & PFS.	66	RIT 375 mg/m^2 7 days before the first 28 days cycle of BEN + RIT. RIT 375 mg/m^2 single-dose on day 1 followed by BEN 90 mg/m2 on days 2 and 3; 4 x 28 day cycles planned + 2 more cycles if disease regression occurred, 6th cycle followed by single-agent RIT 28 days later.
93BOP01 ribosepharm	Phase II, mc (Germany), open-label, randomized, parallel-group, first-line combination regiments of BOP vs COP in advanced low-grade NHL.	Prim: CR. Sec: PR, DR, QoL	162	BOP = BEN 60 mg/m^2 iv on days 1-5 + VIN 2 mg iv on day 1 + PRED 100 mg/m^2 iv on days 1-5. COP = CYC 400 mg/m^2 iv on days 1-5 + VIN 2 mg iv on day 1 + PRED 100 mg/m^2 on days 1-5.

Note: NHL = non-Hodgkin's lymphoma; mc = multicentre; BEN = bendamustine; RIT = rituximab; VIN = vincristine; PRED = prednisone; BOP = bendamustine + vincristine + prednisone; COP = cyclophosphamide + vincristine + prednisone.

6.3.2. Pivotal study SDX-105-03 (Phase III)

6.3.2.1. Design, objective, location, and dates

6.3.2.1.1. (a) Design, location and dates

Study SDX-105-03 was a Phase III, multicentre, open-label, single-arm, clinical trial designed to investigate the safety and efficacy of bendamustine in patients with indolent NHL refractory to rituximab. The study was conducted from 11 October 2005 (first patient enrolled) to 16 July 2007 (data cut-off date), and the approval date for the CSR was 6 December 2007. The study was undertaken at 24 study centres in the USA and 4 centres in Canada. The principal investigator was located at the University of Wisconsin-Madison (USA). The study was sponsored by Cephalon (USA). The sponsor states that the study was conducted in compliance with Good Clinical Practice, according to the ICH Harmonised Tripartite Guideline, and applicable national and local laws and regulations. The protocol and amendments were submitted for approval to the relevant Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). All patients provided written informed consent.

The protocol for this study was developed in accordance with feedback from the US Food and Drug Administration (FDA) under the Special Protocol Assessment (SPA) process. There were a total of 4 amendments to the protocol, and the first 3 amendments or revisions were finalized before patients entered the study. The FDA agreed to the revised protocol on 2 February 2006

and amendment 4 (version 5) was issued on 17 February 2006 to reflect this agreement. The protocol amendments have been examined and raise no concerns about the conduct of the study.

6.3.2.1.2. (b) Objectives

The **primary objective** was to describe the overall response rate (ORR) and duration of response (DR) to a regimen of bendamustine in patients with rituximab-refractory indolent NHL.

The **secondary objectives** were: to assess the safety profile of bendamustine in this patient population; to assess the duration of progression-free survival (PFS); to estimate the basic PK parameters and between-subject variability of bendamustine and its 2 active metabolites (gamma-hydroxy-bendamustine [M3] and N-desmethyl-bendamustine [M4]); to assess the effects of clinical and demographic covariates on the PKs of bendamustine and its active metabolites; and to assess the effects of plasma concentrations of bendamustine and its active metabolites on the efficacy and safety of bendamustine.

6.3.2.1.3. (c) Overall study design and plan

The study consisted of 3 periods: pretreatment (screening); treatment; and follow-up. Baseline procedures and assessments were performed no more than 28 days before the administration of the first dose of study drug. During the treatment period, all patients received bendamustine administered by iv infusion at a dose of 120 mg/m^2 on days 1 and 2 every 21 days, for a minimum of 6 cycles. Assessment of disease response was performed at week 6 (day 42), week 12 (day 84), and then every 12 weeks (± 3 days) until the patient completed treatment.

Assessment was performed by clinical and radiologic (CT scans) evaluation of lymph nodes and other organs with disease involvement, and by biochemical evaluation (lactate dehydrogenase [LDH] levels). Blood samples for LDH levels were collected at the beginning of each cycle and within a week of disease assessments. Bone marrow biopsy was performed to confirm complete response (CR), if the bone marrow was involved before study drug treatment. The biopsy was repeated at the first CR only. An Independent Review Committee (IRC) assessed response on the basis of radiographic and selected clinical information received from the study centres.

All patients had an end-of-treatment evaluation including an end-of-treatment scan within 28 days of the last dose of study drug. Follow-up data were collected at least every 12 weeks (±1 week) after the end-of-study evaluation until resolution of study drug-related adverse events or until adverse events were deemed to be chronic. Patients who did not exhibit disease progression at the end-of-study evaluation were monitored for a minimum of 12 weeks (±1 week), for up to 2 years until disease progression, initiation of another treatment for the disease, or death occurred.

Patients could be withdrawn from the study at any time for one or more of the following reasons: consent withdrawn; progressive disease; unacceptable toxicity; failure to meet inclusion and/or exclusion criteria, but sponsor could grant waiver; noncompliance with study requirements; administrative decision by investigator or sponsor; and death.

6.3.2.2. Inclusion and exclusion criteria

The study population included patients aged 18 years or more (WHO PS 0 to 2) with rituximab-refractory B-cell NHL. Patients were considered to be refractory to rituximab if the disease had progressed during treatment (i.e., no response) or within 6 months of treatment (i.e., time to progression < 6 months) with rituximab or a rituximab containing regimen. In addition, patients were required to have received treatment with at least 1 previous chemotherapy regimen with a maximum of 3 previous chemotherapy regimens, and rituximab alone was not considered to be 1 of the 3 prior chemotherapy regimens.

Diagnosis of NHL was documented using the Revised European American Lymphoma (REAL) subcategories of NHL developed by the International Lymphoma Study Group (Harris et al.,

1994). Patients with the following subtypes of indolent NHL were eligible for inclusion in the study:

- small lymphocytic lymphoma (absolute lymphocyte count [ALC] <5000 cells/mm^3);
- lymphoplasmacytic lymphoma;
- splenic marginal zone B-cell lymphoma (±villous lymphocytes);
- extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type;
- nodal marginal zone lymphoma (±monocytoid B-cells);
- follicle centre lymphoma;
- and follicular (grades 1-3) lymphoma.

Patients were enrolled in the study only if all inclusion criteria were met, and none of the exclusion criteria were present.

6.3.2.3. Study treatments

Bendamustine 120 mg/m^2 administered by iv infusion over 60 minutes on days 1 and 2, repeated every 21 days for a minimum of 6 cycles. If patients were still receiving clinical benefit after 6 cycles, treatment could continue for a further 2 cycles to a maximum of 8 cycles. This was a single-arm study and all patients were assigned to receive the same treatment.

Dose reduction was permitted if the patient experienced toxicities at the initial or subsequent doses. Patients who experienced grade 3 or 4 non-haematologic or grade 4 haematologic toxicity (Common Terminology Criteria for Adverse Events [CTCAE], version 3.0) at a starting dose of 120 mg/m^2 had their dose decreased to 90 mg/m^2 for the next cycle, provided recovery criteria were met. Patients who experienced CTCAE grade 3 or 4 non-haematologic or grade 4 haematologic toxicity at the reduced dose of 90 mg/m^2 had their dose further decreased to 60 mg/m^2 for the next cycle, provided recovery criteria were met. Patients who continued to experience toxicity at the 60 mg/m^2 dose were withdrawn from the study.

6.3.2.3.1. Prior and concomitant studies

Any previous therapy or medication received within 28 days of cycle 1, day 1, and the first day of study drug administration was recorded in the CRF. Investigators were permitted to prescribe supportive treatment for patients with AEs, including anti-emetic, anti-diarrheal, anti-pyretic, anti-allergic, anti-hypertensive, analgesic, and antibiotic medications, and other therapies, such as blood products. Chronic erythropoietin therapy was permitted.

The prophylactic use of cytokines to stimulate white blood cells (WBC), such as granulocyte-colony stimulating factor (G-CSF), was discouraged during the first cycle. However, cytokines were allowed in conjunction with the study drug in patients who demonstrated the need for cytokine support as a result of prolonged neutropenia (grade 4 leukopenia lasting at least 1 week, failure of WBC count to recover to at least grade 1 toxicity by the next scheduled dose, or febrile neutropenia in a prior cycle of treatment). Study personnel were advised to follow the American Society of Clinical Oncology (ASCO) guidelines when these products were administered.

Treatment with low doses of chronic steroids (up to 10 mg/day of prednisone or equivalent) was permitted for non-neoplastic disorders. However, other on-study treatment with corticosteroids was not allowed, with the exception of single doses of steroids used as anti-emetics (2 doses per cycle). Treatment with radiation was not allowed on study, and patients requiring palliative radiation were removed from the study for disease progression. No other anti-tumour treatment was permitted during the course of the study.

6.3.2.4. Efficacy variables and outcomes

6.3.2.4.1. Primary efficacy measures and variables

The primary efficacy variables were:

- **ORR (overall response rate)**: Defined as the proportion of patients who achieved a best response of complete response (CR), unconfirmed complete response rate (CRu), or partial response (PR) during the study, according to the International Workshop Response Criteria for NHL modified for this study; and
- **DR (duration of response)**: DR was determined for patients with a response of CR, CRu, or PR and was defined as the time interval from the date of first documentation of the response to the first documentation of disease progression, death (regardless of cause), or change of therapy due to disease progression, whichever occurred first.

The disease status was defined for each patient at each assessment as one of the following: complete response (CR); complete response/unconfirmed (CRu); partial response (PR); or stable disease (SD). The response criteria are summarized below in Table 18. The modifications made to the International Working Group Response Criteria for Lymphoma for this study were summarized.

Table 18: Study SDx-105-03 - Response criteria for NHL

Response category	Physical examination	Lymph nodes	Lymph node masses	Bone marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	>75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Relapse/progression	Enlarging liver/spleen, new sites	New or increased	New or increased	Reappearance

CR=complete response; CRu=complete response unconfirmed; PR=partial response.

Target lesions were measured at the study centre and the measurements recorded in the CRF. Non-target lesions were measured at the study centre when being used to determine CR or PD. Each non-target lesion was assigned 1 of the following codes: resolved (lymph nodes returned to normal size); too small to measure; stable (decreased or increased but not meeting criteria for progressive disease); increased, meeting criteria for progressive disease (50% or more increase from nadir in the greatest transverse diameter [GTD] for this lesion, and GTD ≥ 2 cm); or new disease (nodal disease was 2 cm or more).

The definition for measurable disease or new disease was ≥ 1 cm for lymph nodes, or ≥ 1 cm non-lymph node disease. Lesions that were deemed too small to measure were assigned a measurement of 0.5 cm x 0.5 cm. New lymph nodes that were ≥ 2 cm or more in one diameter were considered new disease indicating progressive disease. Any new non-nodal lesion indicated progressive disease.

6.3.2.4.2. Secondary efficacy measures and variables

The secondary efficacy variable was PFS. It was defined as the time interval from the date of the first bendamustine dose to the first documentation of disease progression, death (regardless of cause), or change of therapy due to disease progression, whichever occurred first. There were also a number of planned exploratory efficacy criteria that will not be considered for the purposes of this evaluation.

6.3.2.5. Randomization and blinding methods

This study was open-label. All patients were assigned to the same dose of bendamustine.

6.3.2.6. Analysis populations

- The **enrolled patients set** included all patients who complied with all entry criteria. Patients who did not comply with all entry criteria but had protocol exceptions granted and were treated with study drug were also included.
- The **primary analysis set** included all enrolled patients who were treated with study drug.
- The **evaluable set** included all patients who met the following criteria:
  - treated with study drug**;**
  - had none of the following major eligibility violations: missing CT scans at baseline; missing bone marrow biopsy at baseline; baseline CT scans deemed to be inadequate as determined by a third-party radiology review Image Quality Assessment (IQA) process; disease that did not meet criteria to be an indolent lymphoma; disease was not refractory to rituximab (patients who were enrolled via protocol exception before amendment 4 were considered evaluable if they passed the amended criteria); no history of chemotherapy or more than 3 previous unique courses; no measurable disease lesion (≥ 2 cm); use of systemic steroids within 14 days of study treatment, other than low doses of chronic steroids; history of transformed disease; history of CNS or leptomeningeal lymphoma;
  - had a baseline ALC less than $5x10^9$/L; and
  - had at least 1 post-baseline response assessment, or withdrew before having a post-baseline response assessment due to rapid disease progression or death.

All evaluability criteria were determined by automatic, programmed algorithms, except for determination as to whether the patient had disease refractory to rituximab treatment. An internal meeting with the statistician and medical monitor was held before locking the database with the purpose of determining the refractoriness status for each patient, based on listings of prior drug treatment.

6.3.2.7. Sample size

The null hypothesis was an ORR of 40% or less to bendamustine treatment. Assuming patients treated with the study drug had an ORR of at least 60%, the planned sample size of 100 patients gave more than 90% power at a 1-sided alpha of 0.025 or less.

For the duration of response, the null hypothesis was a median of 4 months (17 weeks) or less. The alternative hypothesis was a median duration of response of 6 months (26 weeks). Simulations had shown that the power to reject the null hypothesis was at least 90% for the primary analysis at a data cut-off point of 6 months (26 weeks) after the enrollment of the last patient. These assumptions were based on 1000 simulated clinical studies.

6.3.2.8. Statistical methods

6.3.2.8.1. (a) Overview

The data cut-off date for the CSR report was 16 July 2007. This cut-off date was approximately 6 months after the last patient was enrolled, and is the time point prespecified in the statistical analysis plan for the purpose of statistical inference. All patients had completed treatment, but 3 patients had not completed their end-of-treatment evaluation. Available AE data with a start date before the cut-off date, but a stop date after the cut-off date were also included. Minor amendments to the original Statistical Analysis Plan were made and submitted to the US FDA in response to the SPA, and the amended and final statistical analysis plan was issued on 22 August 2007 (i.e., before database lock).

An Independent Review Committee (IRC) (RadPharm in Princeton, New Jersey, USA) assessed responses on the basis of radiographic and selected clinical information received from the study centres. Two radiologists independently assessed each time point response (TPR) and certain

key variables, including best response and date of disease progression. If the assessments of the two radiologists differed in any of these key variables, a third radiologist adjudicated the assessment. An oncologist from RadPharm considered the assessments of the arbitrating radiologist together with selected clinical data, to determine the key variables for each patient. The analysis of efficacy was based primarily on the assessment of the IRC oncologist's TPR; oncologic tumour response ratings, which included a response category of CR, CRu, PR, SD, PD, or "unevaluable" (UE) at each assessment; response assessment date; best response during the study; response onset date; and disease progression date. Information regarding undocumented disease progression, change of therapy, and death were incorporated to modify disease progression date according to the rules specified for the sensitivity analyses.

The progression date was the date of the first observation indicating progression, or otherwise, the last date of assessment. Adequate tumour assessments comprised scans of abdomen, chest, neck, and pelvis. Target lesions that were too small to be measured after baseline were assigned a value of 25 mm^2. Target lesions that could not be measured for other reasons were assigned a rating of UE. Tumor assessments that comprised only part of these data, but were sufficient to diagnose PD were also considered adequate. Otherwise, the assessment was labeled as UE. Data from scans not occurring on the same date were combined for analysis. If a target lesion was classified as UE, the response for that time point was also UE unless disease progression could be documented on the basis of other criteria (e.g., new lesions). There was no imputation of missing values except for partial dates, which were estimated using specified criteria if determination of the date was necessary in order to calculate response criteria.

The statistical analysis plan prospectively identified the following covariates as being likely to have an effect on the efficacy outcomes of ORR, DR, and PFS: number of previous chemotherapy courses; previous exposure to alkylators; response to last chemotherapy regimen, alkylator regimen, or radio-immunotherapy; follicular lymphoma prognostic index (FLIPI); and bulky disease at baseline. The effects of these covariates on efficacy were investigated by a number of subgroup analyses. ORR was modelled using logistic regression, and DR and PFS were modelled using proportional hazard regression. However, the calculated p-values were descriptive only, as no adjustment was made for multiplicity of testing. Furthermore, the planned exploratory analyses were not specified in the protocol, but were described in the statistical analysis plan.

No interim analyses were conducted. The data cut-off date for this report was prospectively defined in the statistical analysis plan as the decisive inferential analysis time point. A final analysis will be conducted when all long-term follow-up data are accrued.

6.3.2.8.2. (b) Planned methods of analysis.

The ORR included patients with a best response of CR, CRu, or PR. Patients who did not have at least 1 post-baseline response assessment were treated as not having a response. The test of the null hypothesis was a response rate less than or equal to 40% versus the alternative hypothesis of a response rate more than 40% at a 1-sided alpha of 0.025 in the primary analysis set. The exact p-value to test against the null hypothesis of ORR less than or equal to 40% and a 2-sided 95% exact CI for the ORR was calculated on the basis of binomial distributions. Response success was the rejection of the null hypothesis.

DR was based on a confidence interval (CI). The median DR was not to be significantly less than 6 months (26 weeks) and the lower bound of the 95% CI was to be greater than 4 months (17 weeks). The median DR was assessed using the Kaplan-Meier method.

The median PFS and its 2-sided 95% CI were assessed based on a nonparametric method. Kaplan-Meier estimates of DR and PFS were graphed.

Both primary and sensitivity analyses were performed for the DR and the PFS.

Comment: No statistical adjustment for multiplicity was made for the testing of the two primary efficacy endpoints (ORR and DR). However, the CSR comments that "on the basis of written agreements with the FDA it is clear that both endpoints were to be statistically

significant in order to claim success. Since this is a more stringent requirement than meeting only 1 endpoint the overall type 1 error is less than 5%".

6.3.2.8.3. (c) IRC and investigator assessments

The primary analysis set and the evaluable set using both IRC and investigators' response assessments were used for the primary efficacy analyses. The analyses of response assessments by IRC were considered primary and were used to draw conclusions regarding efficacy for this study. IRC and investigators' assessments were cross-tabulated in order to assess consistency of these assessments.

6.3.2.9. Participant flow

In this study, 102 patients with relapsed, refractory indolent NHL were enrolled, and 100 (98%) patients received at least 1 dose of study drug and were evaluable for efficacy and safety. Two (2) enrolled patients did not receive any treatment because they were subsequently considered ineligible for the study. Overall, of the 100 patients who received at least 1 dose of the study drug, 40 received treatment for < 6 cycles and 60 received treatment for ≥ 6 cycles. The disposition of the patients at the end of study drug treatment is summarized below in Table 19.

Table 19: SDX-105-03 - Disposition of patients (end of drug treatment); all patients

Patient disposition	Number (%) of patients[a]
Enrolled	102[b]
Enrolled not treated	2
Primary analysis set	100 (100)
Treated and not completed end-of-treatment evaluation (ongoing extended treatment)	3 (3)
Treated and completed end-of-treatment evaluation[b]	97 (97)
Reason for discontinuation of study drug treatment[c]	
Received maximum benefit of therapy (investigator assessment)[d]	52 (52)
Adverse event	28 (28)
Disease progression	11 (11)
Patient refused further treatment (for reason other than AE)	2 (2)
Other[e]	4 (4)

a. Percentages are based on the number of patients treated (N=100). b. Includes patients who received treatment for less than 6 cycles (n=40), or 6 or more cycles (n=60). c. Includes reasons for discontinuation of study drug treatment for patients who received treatment for less than 6 cycles (n=40), 6 cycles (n=39), or more than 6 cycles (n=21). d. Includes patients who received treatment for 6 cycles or less, or more than 6 cycles, who did not discontinue due to any other reason. e. Other reasons included delay in therapy for more than 4 weeks, referral for bone marrow transplant or the patient had 8 treatment cycles, the maximum as allowed by the protocol.

Of the 100 patients who were treated with bendamustine, 79 (79%) continued into the long-term follow-up period, 18 (18%) did not continue long-term follow-up, and 3 (3%) are receiving ongoing extended treatment. The reasons for patients not continuing into the long-term follow-up period were disease progression (10 patients), death (6 patients), or new anti-cancer treatment (2 patients). Of the 79 patients who entered the long-term follow-up period, 57 (57%) withdrew from further participation in the study. The reasons that patients withdrew from the long-term follow-up period were disease progression (41 patients), death (9 patients), new anti-cancer treatment (6 patients), or other reasons (1 patient; large B-cell lymphoma and was referred for radiation and BMT). Of the patients who entered the long-term follow-up, 22 (22%) remain in the follow-up period.

6.3.2.10. Major protocol violations/deviations

Of the 100 patients who received treatment with bendamustine, 83 had at least 1 protocol deviation. The protocol deviations were: 28 patients had disease assessment outside of the protocol window; 22 patients did not satisfy eligibility criteria; 13 patients missed disease assessment; 7 patients received wrong treatment or incorrect dose; 1 patient received an excluded concomitant treatment; and 67 patients had other deviations. Of the 102 patients enrolled, 15 were not included in the evaluable data set due to significant protocol violations.

6.3.2.11. Baseline data

6.3.2.11.1. Demographics

The median age of the patients (n=100) treated with bendamustine was 60 years (mean 59.3 [SD=10.6]), ranging from 31 to 84 years. The majority of patients were white (88%). Sixty-five (65%) patients were men and 35 (35%) were women. The mean weight and body surface area of the patients were 86.7 kg (SD=21.3) and 2.0 m^2 (SD=0.29), respectively.

6.3.2.11.2. Characteristics of lymphoma

The mean age at onset of disease was 54.7 years (SD=10.6). The mean time since the original primary diagnosis was 56.9 months (SD=40.8), ranging from 4 to 185 months. The most recent biopsy was obtained, on average, 27.2 months before enrollment into the study, ranging from 0 to 184 months.

Of the 100 treated patients, 62 (62%) had follicle centre lymphoma, 21 (21%) had B-cell chronic lymphocytic leukaemia /small lymphocytic lymphoma, 9 (9%) had extra-nodal marginal zone B-cell lymphoma, 7 (7%) had nodal marginal zone lymphoma, and 1 (1%) had lymphoplasmacytic lymphoma. Most patients with follicle centre lymphoma had either grade 1 (33 patients) or grade 2 (16 patients) disease at diagnosis, with grade 3 being reported in 8 patients and grade unknown in 8 patients.

The Ann Arbor lymphoma staging system was used to categorize the 100 patients with bendamustine. This resulted in 8 patients with stage 1, 16 patients with stage II, 33 patients with stage III, and 43 with stage IV. In addition, 84 patients were asymptomatic (A symptoms) and 16 patients had B symptoms (fever > 38°C, drenching night sweats or weight loss > 10% of body weight).

Patients with follicular lymphoma (n=62) were categorized according to the FLIPI score into the following 3 risk groups: low risk, FLIPI score 0-1 (18 patients, 29%); intermediate risk, FLIPI score of 2 (26 patients, 42%), and high risk, FLIPI score ≥ 2 (18 patients, 29%).

Of the 100 patients treated with bendamustine, 52 patients had 4 or fewer lymph node areas involved and 48 had more than 4 lymph node areas involved. As assessed by the IRC, 8 patients had bulky disease (lymph node size of ≥ 10 cm) at the time of entry into the study, 89 patients did not have bulky disease, and data were missing for 3 patients.

6.3.2.11.3. Previous treatments for lymphoma

Previous treatments for lymphoma included cancer surgery, radiotherapy, radioimmunotherapy, chemotherapy with or without rituximab treatment, single-agent rituximab treatment, and single-agent chemotherapy. All patients (n=100) had received previous treatment with rituximab and/or chemotherapy, 25 had received previous radio-immunotherapy, 20 had received previous radiation therapy, and 8 had undergone cancer surgery. The mean number of previous treatments for lymphoma was 3.6 (median 3, range 1-10).

In the 100 bendamustine treated patients who had received previous rituximab treatment, the median number of previous rituximab containing courses was 2, ranging from 1 to 6 courses. The mean total dose of rituximab was 4701 mg/m^2 (median 3750 mg/m^2), and the cumulative dose ranged from 1500 to 20075 mg/m^2. Fifty-eight (58%) patients had disease refractory to

rituximab monotherapy/ maintenance treatment, 26 (26%) had disease refractory to therapy with rituximab combination chemotherapy, and 13 (13%) had disease refractory to therapy with both rituximab monotherapy and combination chemotherapy. These numbers include patients who had relapsed within 6 months of rituximab therapy. Three patients (3%) had lymphomas that were not refractory to rituximab treatment. The mean time between the last rituximab containing treatment and the first dose of study drug was 10 months (median 6 months, range 0.9 to 48.5 months). The mean time from progression after any therapy and the first dose of the study drug was 3.2 months (median 2.1 months, range 0 to 30.5 months).

Of the 100 bendamustine treated patients, 99 had received previous chemotherapy (91 previous alkylator based treatment, 44 previous purine-analog based treatment), and 1 had not received previous chemotherapy but had received rituximab monotherapy. The most common treatment regimen was R-CHOP (37 patients) followed by CVP (19 patients) and R-CVP (19 patients). Two (2) patients had more than 3 previous chemotherapy regimens. The mean number of previous chemotherapy courses was 1.9 (median 2, range 0 to 6). Thirty-six (36) patients had disease refractory to their most recent chemotherapy and 30 patients had disease refractory to their most recent alkylator-containing regimen.

6.3.2.11.4. Medical history

At baseline, all 100 patients had 1 or more medical history abnormalities or ongoing abnormalities. The most frequently reported medical history abnormalities and ongoing abnormalities were those related to the gastrointestinal/digestive system (80% and 71%, respectively). Abnormal physical examination findings were reported in 62 (62%) patients at the time of study entry, and the most frequently reported abnormal physical examination findings were abdominal/gastrointestinal (19, 19%, patients). Among the 97 patients who had ECGs at baseline, 42 had normal findings and 55 had abnormal findings (not clinically significant).

6.3.2.11.5. Prior and concomitant therapy

Prior medications had been taken within 28 days of the first dose of bendamustine by 93% of treated patients (n=100), and prior medications taken by ≥ 20% of patients were analgesics (39%), psycholeptics (37%), drugs for acid-related disorders (32%), anti-thrombotic agents (29%), agents acting on the renin-angiotensin system (28, 28%), anti-inflammatory/anti-rheumatic products (24%), serum lipid-reducing agents (25%) psychoanaleptics (24%), mineral supplements (23%), and antibacterials for systemic use (20%).

Medications taken concomitantly with bendamustine during the study were taken by all patients (100, 100%), and concomitant medications taken by ≥ 20% of patients were anti-emetics and anti-nauseants (96%), corticosteroids for systemic use (70%), analgesics (67%), antibacterials for systemic use (65%), psycholeptics (64%), drugs for acid-related disorders (58%), vitamins (48%) anti-anaemic preparations (41%), immuno-stimulants (38%), anti-histamines for systemic use (37%), anti-thrombotic agents (37%), mineral supplements (36%), blood substitutes and perfusion solutions (32%), anti-gout preparations (29%), laxatives (29%), psychoanaleptics (29%), diuretics (24%), agents acting on the renin-angiotensin system (28%), anti-inflammatory/anti-rheumatic products (28%), serum lipid-reducing agents (28%), anti-virals for systemic use (24%), beta-blocking agents (21%), and drugs for obstructive airways disease (20%).

6.3.3. Efficacy variables - results

6.3.3.1. Primary efficacy variable - overall response rate (ORR)

The ORR for patients in the primary analysis set (n=100) is summarized below in Table 20. The lower 95% CIs of the point estimates for the overall response rates (IRC assessment) were > 40% for the majority of pre-defined subgroup analyses based on baseline disease characteristics. The ORR for 87 patients in the evaluable set was 76% ([95% CI: 66%, 84%], p<0.0001), based on adjudicated IRC assessment, with 14 (16%) patients having CR, 3 (3%)

patients having CRu, and 49 (56%) patients having PR. The ORR was 81% ([95% CI: 71%, 88%], p<0.0001), based on investigator assessment, with 19 (22%) patients having CR, 4 (5%) patients having CRu, and 47 (54%) patients having PR. ORRs ≥ 40% were observed for all pre-defined subgroups in the primary analysis set.

Table 20: Study SDX-105-03 - Overall response rate (IRC assessment); primary analysis set

	Number (%) of patients (95% confidence interval)	
	Bendamustine (N=100)	
Response	**By IRC**	**By investigator**
Overall response (CR+CRu+PR)	75 (75) (65.34, 83.12)	80 (80) (70.82, 87.33)
Complete response (CR)	14 (14)	22 (22)
Complete unconfirmed response (CRu)	3 (3)	5 (5)
Partial response (PR)	58 (58)	53 (53)
Stable disease (SD)	16 (16)	13 (13)
Progressive disease (PD)	7 (7)	5 (5)
Clinical disease progression	0	1 (1)
Unknown	2 (2)	1 (1)
p-value[a]	<0.0001	<0.0001

a. The p-value is calculated against the null hypothesis of a response rate of ≤ 40%. Note: The most positive response for each patients during the study was counted. The 95% CI was calculated using exact method based on binomial distribution.

Most (n=91) patients had received previous alkylator therapy. The ORR was 74% (95% CI: 63%, 82%) for these patients. The ORR was 86% (95% CI: 74%, 94%) for the 51 patients sensitive to the last alkylator therapy, and 60% (95% CI: 41%, 77%) for the 30 patients with disease refractory to the last alkylator therapy.

The ORR was 88% (95% CI: 76%, 96%) for the 51 patients sensitive to the last chemotherapy regimen, and 64% (95% CI: 46%, 79%) for the 36 patients with disease refractory to the last chemotherapy regimen.

The ORR was 75% (95% CI: 65%, 83%) for the 92 patients who had received 3 or less previous chemotherapy courses, and 75% (95% CI: 35%, 97%) for the few patients (n=8) who had received more than 3 previous chemotherapy courses.

The ORR was 63% (95% CI: 41%, 81%) for 24 patients with previous radio-immunotherapy, and 79% (95% CI: 68%, 87%) for the 76 patients without previous radio-immunotherapy.

For the 62 patients with follicular lymphoma, in patients in the low, intermediate, and high risk FLIPI categories, the ORRs were 72%, 77%, and 72% respectively. The ORR was 81% (95%: CI 67%, 91%) in the 48 patients with more than 4 involved lymph nodes, and 69% (95% CI: 55%, 81%) in the 52 patients with 4 or less involved lymph nodes.

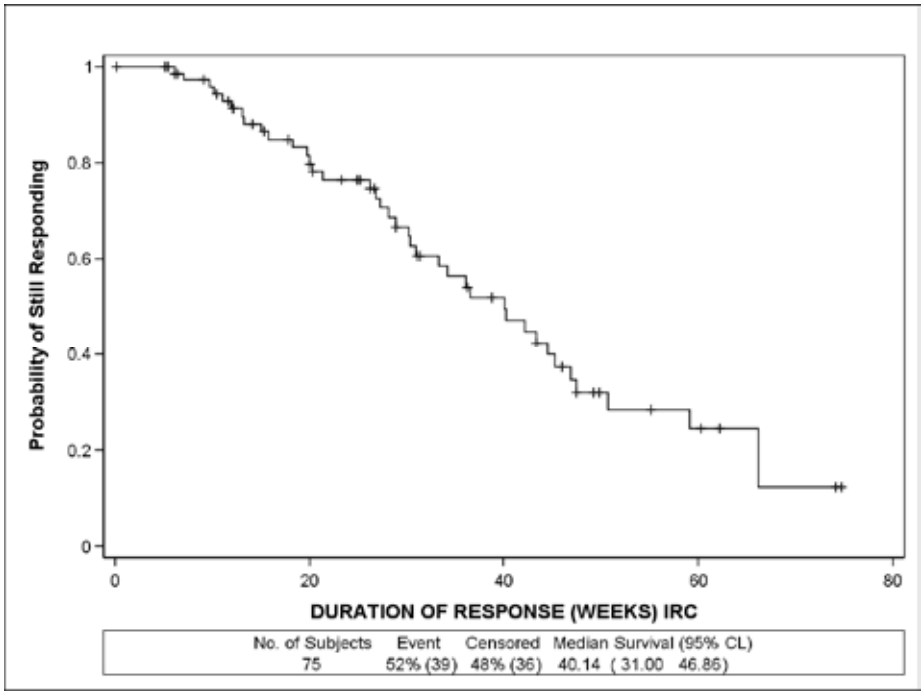
> Comment: The ORR in the primary analysis (IRC assessment) was 75% (95% CI: 65%, 83%). This was statistically significant as the ORR was ≥ 40% (p<0.0001), and the pre-specified null hypothesis was rejected. The ORR results are primarily driven by patients with a partial response. The point estimates of the ORR were ≥ 40% for each of the subgroup analyses based on baseline disease characteristic specified in the statistical analysis plan.

6.3.3.2. Primary efficacy variable - duration of response (DR)

The median DR (based on IRC assessment) for patients in the primary analysis set with CR, CRu, or PR was 40.1 weeks (95% CI: 31.0, 46.9 weeks), and the median DR (based on investigator assessment) was 39.4 weeks (95% CI: 33.7, 60.1 weeks). The KM plot for the primary analysis based on the IRC assessment is provided below in Figure 3. The median DR based on both

analyses was significantly longer than 6 months (26 weeks) and the lower boundary of the 95% CI was greater than 4 months (17 weeks). The results for the median DR and 95% CI based on ICRA were identical to the corresponding results for the primary analysis when the stringent rules of the sensitivity analysis were applied. The sensitivity analysis did not use data from last assessment dates that were performed more than 1.5 times the protocol-planned time after the second to last assessments.

Figure 3: Study SDX-105-03 - DR (IRC assessment); patients in the primary analysis set with CR, CRu, or PR.



The lower bound 95% CIs of the point estimates for the median DR (IRC assessment) were ≥ 4 months (17 weeks) for all subgroup analyses based on baseline disease characteristics, apart for the small number of patients (n=6) with > 3 prior chemotherapies.

> Comment: The median DR (IRC assessment) was 40 weeks (95% CI: 31, 47 weeks), based on 39 (52%) patients with PD/death/change of therapy and 36 (48%) censored patients out of the 75 patients included in the analysis. The results were significant as the median DR was > 6 months (26 weeks) and the lower bound of the 95% CI was > 4 months (17 weeks).

6.3.3.3. Secondary efficacy variable - progression free survival

For patients in the primary analysis set (n=100), the median PFS (based on IRC assessment) was 40.3 weeks (95% CI: 35.0, 51.9), and the median PFS (based on investigator assessment) was 42.4 weeks (95% CI: 35.0. 51.9). The results for the median PFS and 95% CI based on ICRA were identical to the corresponding results for the primary analysis when the stringent rules of the sensitivity analysis were applied.

Median PFS by best response (ICRA) was 51.1 weeks (95% CI: 46.3, 64.9) for patients with CR (n=14), 64.9 weeks (95% CI: 35.0, NA weeks) for patients with CRu (n=3), 42.3 weeks (95% CI: 35.9, 53.3 weeks) for patients with PR (n=58), 32.4 weeks (95% CI: 18.1, NA weeks) for patients with SD (n=16), and 2.9 weeks (95% CI: 1.6, 5.7 weeks) for patients with PD (n=7).

The median PFS (IRC assessment) ranged from 30.1 to 71.6 months for the subgroup analyses based on baseline disease characteristics.

Comment: The PFS (IRC assessment) was 40.3 weeks (95% CI: 35.0, 41.9 weeks), based on 57 (57%) patients with PD/death/change of therapy and 43 (43%) censored patients out of the 100 patients in the analysis. The analysis was primarily driven by disease progression (47 patients) followed by death (5 patients) and change of therapy (5 patients).

6.3.4. Supportive study - SDX-105-01 (Phase II)

6.3.4.1. (a) Design

Study SDX-105-01 is considered to be a supportive study for the proposed indication. Study SDX-105-01 was a Phase II, multicentre, single-arm, open-label clinical trial designed to investigate bendamustine monotherapy for the treatment of indolent NHL refractory to rituximab. It was undertaken in 12 centres in the USA and 2 centres in Canada between 29 September 2003 and 15 August 2006. The CSR approval date was 5 April 2007, and the study was sponsored by Cephalon (USA). The sponsor states that the study was conducted in compliance with GCP, according to the ICH guideline. After consultation with the FDA, the pivotal study SDX-105-03 was subsequently undertaken to further evaluate the efficacy and safety of bendamustine monotherapy for the treatment of patients with indolent NHL refractory to rituximab.

6.3.4.2. (b) Objectives

The primary objective of study SDX-105-01 was to determine the overall response rate (ORR) in patients with indolent NHL who were refractory to rituximab.

6.3.4.3. (c) Inclusion and exclusion criteria

The main inclusion criteria were patients at least 18 years old at the screening visit with documented indolent or transformed B-cell NHL and an estimated life expectancy of at least 3 months. In order to be included in the study, patients were required to have been treated with no more than 3 prior chemotherapy regimens. A regimen was defined as a new combination or agent, and pre-treatment with the identical regimen or agent did not count as a new regimen. However, change from cyclophosphamide, vincristine, and prednisolone (CVP) to cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) was counted as a new regimen. In addition, patients were also required to have been treated with rituximab, and further rituximab treatment was considered to be inappropriate due to the disease being refractory to rituximab or due to an untoward reaction to prior rituximab treatment. Rituximab treatment alone was not considered to be 1 of the 3 allowed prior chemotherapy regimens. Patients were also required to have a WHO PS of 0 to 2, an absolute neutrophil count of ≥ 1,000 cells/mm^3, a platelet count of ≥ 100,000 cells/m^3, a creatinine clearance of > 30 mL/min, and adequate hepatic function.

6.3.4.4. (d) Bendamustine treatmen

Treatment consisted of bendamustine 120 mg/m^2 administered as an iv infusion over 30-60 minutes on days 1 and 2 of a 3-week cycle. Pre-specified dose reductions were allowed for patients who experienced grade 3 or 4 non-haematological toxicity or grade 4 haematological toxicity. Patients who achieved CR, CRu, PR, or SD were treated for a minimum of 6 cycles of therapy. If patients were still receiving clinical benefit after 12 cycles of therapy, consideration was given to continuing therapy for up to 1 year. Follow-up data from patients who did not show disease progression at the end-of-study evaluation were collected every 3 months, for up to 2 years, until the occurrence of disease progression, initiation of another treatment for the disease, or death.

6.3.4.5. (e) Analysis sets

The primary analysis set (n=76) included all enrolled patients who were treated with at least 1 dose of bendamustine. The evaluable set (n=64) included all patients who were treated with at least 1 dose of bendamustine, met inclusion criteria 1, 2, 3, 4 and did not violate exclusion criteria 1, 2, 5, 7, and 8 as described in protocol amendment 3, had a baseline absolute

lymphocyte count less than $5x10^9$/L, and had at least 1 post-baseline response assessment or had withdrawn before having a post-baseline response assessment due to rapid disease progression or death.

6.3.4.6. (f) Efficacy variables

The primary efficacy variable was ORR defined as proportion of patients who achieved a best response of CR, CRu, or PR during the study according to the International Workshop Response Criteria for NHL.

The secondary efficacy variables included duration of response (DR) and progression-free survival (PFS). There were a number of planned exploratory efficacy analysis that are not considered to be relevant to this clinical evaluation report.

6.3.4.7. (f) Sample size

Determination of sample size was based on the two-stage design for phase II clinical trials described by *Simon (1989)*. First stage accrual and response criteria were to be met before initiation of the second stage of accrual. Efficacy in this study was to be measured by the ORR (CR + CRu + PR). Bendamustine was to be considered promising if the true ORR was 35% or higher, and was to be considered unworthy of further investigation if the true ORR was less than 20%. This design effectively discriminated between true response rates of 20% and 35%. It yielded an 0.80 probability of a positive result if the true ORR was 35% or higher and an 0.05 probability of a positive result if the true ORR was 20% or lower.

6.3.4.8. (g) Statistical methods

All data that were available at the study centres as of 15 August 2006 were included in the CSR. Included in that database are data for all patient visits from the treatment period of the study. In addition, all post-treatment follow up data that occurred on or before 15 August 2006 were included with the exception of 1 visit each for 3 patients that could not be retrieved for the database lock. The data from later follow-up visits for 12 patients who were continuing in the study were not included. The results from this data cut-off are considered primary and the efficacy conclusions are based on these results. Additional analyses are to be performed when all patients have finished 2 years of follow-up or have died, had disease progression, or had change of therapy.

For the primary efficacy analysis, ORR was the number of patients with a best response of CR, CRu or PR. Patients who did not have at least 1 response assessment were treated as not having a response. A 95% exact CI for the ORR was calculated on the basis of a binomial distribution.

The median duration of response (DR) was assessed using Kaplan-Meier method. The 2-sided 95% CI was assessed based on nonparametric method by Brookmeyer and Crowley The median PFS with 2-sided 95% CI were assessed based on nonparametric method by Brookmeyer and Crowley. Kaplan-Meier estimates of duration of response and PFS were graphed.

The primary analysis set and the evaluable set were used for the primary efficacy analysis. The SAP stated that the primary analysis set was to be used to draw conclusions about the efficacy of the study drug, and the results from the evaluable set were to be used as supportive evidence. The secondary efficacy endpoints were duration of response (DR) and progression free survival (PFS).

6.3.4.9. (h) Study population

The study was designed as a 2-stage procedure with an initial enrollment target of 22 patients. The response data on 9 of the first 14 enrolled patients showed that 6 of these 9 patients had a documented objective response. Therefore, an additional 50 patients were enrolled for a planned total of 72 patients. The study enrolled 77 patients, and 76 (99%) received at least 1 dose of study drug and 34 (44%) received at least 6 cycles of treatment. The median age of the

patients was 63 years (range 38 to 84 years). The majority of patients were white (89%). The proportion of men and women enrolled were 54% and 46% women, respectively.

6.3.4.10. (i) Primary efficacy end-point results - overall response rate (ORR)

In the primary analysis set (n=76), the ORR (CR+CRu+PR) was 76.3% (95% CI: 65.2%, 85.3%). Of the 76 patients in the primary analysis set, 58 (76%) achieved a response (11, 14%, CR; 14, 18%, CRu; 33, 43%, PR), while SD was reported in 3 (4%) and PD in 13 (17%) with missing/unknown results for 2 (3%). The results in the evaluable set were consistent with those in the primary analysis set.

The results for selected subgroups (primary analysis set) are summarized below.

- In patients with transformed disease at baseline (n=15) the ORR was 67% (95% CI: 38%, 88%), and in patients without transformed disease at baseline (n=61) the ORR was 79% (95% CI: 66%, 88%).
- In patients with ≤ 1 previous chemotherapy regimens (n=36) the ORR was 78% (95% CI: 61%, 90%), and in patients with ≥ 2 previously chemotherapy regimens (n=40) the ORR was 75% (95% CI: 59%, 87%).
- In patients who were sensitive to their last prior chemotherapy regimen (n=39) the ORR was 92% (95% CI: 79%, 98%), and in patients who were refractory to their last prior chemotherapy regimen (n=24) the ORR was 54% (95% CI: 33%, 74%).
- In patients with previous alkylator therapy (n=64) the ORR was 77% (95% CI: 64%, 86%), and in patients without previous alkylator therapy (n=12) the ORR was 75% (95% CI: 43%, 95%).
- In patients who were sensitive to their last prior alkylator therapy (n=34) the ORR was 91% (95% CI: 76%, 98%), and in patients who were refractory to their last prior alkylator therapy (n=23) the ORR was 61% (95% CI: 39%, 80%).

6.3.4.11. (j) Secondary efficacy endpoint results

Duration of Response (DR): DR was determined for patients with a response of CR, CRu or PR and was defined as the time interval from the date of first documentation of the response for a patient to the first documentation of disease progression, death (regardless of cause), or change of therapy due to disease progression, whichever occurred first. The median DR in the primary analysis set (n=58) was 29.0 weeks (95% CI: 22.1, 43.1 weeks), based on 38 patients with progressive disease/death/change of therapy and 20 censored patients.

Progression-Free Survival (PFS): PFS was determined for all patients and was defined as the time interval from the date of the first bendamustine dose to the first documentation of disease progression, death (regardless of cause), or change of therapy due to disease progression, whichever occurred first. For the patients in the primary analysis set (n=76), the median PFS was 31.0 weeks (95% CI: 26.1, 38.7 weeks), based on 55 patients with progressive disease/death and 21 censored patients. The KM estimate of the proportion of patients in the primary analysis set remaining progression-free after 48 weeks was 21%.

Comment: In this study, it was specified that bendamustine was to be considered promising if the true ORR was 35% or higher, and was to be considered unworthy of further investigation if the true ORR was less than 20%. Based on the ORR results for patients in the primary analysis set bendamustine can be considered to be promising as the lower bound of the 95% CI for the point estimate was > 35%. The results of this study should be considered to be exploratory rather than confirmatory.

6.4. Other studies

6.4.1. Study SDX-105-02

Study SDX-105-02 was nominated by the sponsor as a "pivotal study" supporting approval of bendamustine for the treatment of relapsed/refractory indolent NHL (application letter). However, this Phase II study, multicentre, open-label, single-arm is considered neither pivotal nor supportive for the proposed indication as bendamustine was used in combination with rituximab rather than as monotherapy.

The study was conducted at 13 centres in the USA, 5 centres in Canada, and 4 centres in Australia from 13 April 2004 to 13 December 2005. The patients were at least 18 years old with documented relapsed/indolent CD 20-positive B-cell NHL or mantle cell lymphoma (MCL). In order to be included in the study, patients were required to have been treated with a maximum of three previous chemotherapy regimens (defined as a new combination or agent). Previous treatment with rituximab was allowed provided the disease was not refractory to this agent. Patients were excluded if their disease was refractory to rituximab, defined as progression of disease while being treated with rituximab or progression within 6 months of the last dose of rituximab.

The primary efficacy variable was the overall response rate (ORR), defined as best response of CR, CRu or PR during the study. Assessment of response was done by investigators after the second cycle of therapy (approximately day 50) and again at the end of treatment (within 8 weeks of the last dose of rituximab). Responses and progressive disease were evaluated using the International Workshop Response Criteria for NHL. The secondary efficacy variables were the duration of response (DR) and progression-free survival (PFS). The analysis of the primary efficacy endpoint was undertaken using the primary analysis set (i.e., all enrolled patients who were treated with bendamustine), and the analyses of the secondary efficacy endpoints were undertaken using the primary analysis set and the evaluable set.

Each patient in this single-arm study received an initial dose of rituximab 375 mg/m^2 administered 7 days before the first 28-day cycle of combination treatment with bendamustine and rituximab. Patients then received rituximab on the first day of a cycle at a single dose of 375 mg/m^2, followed on the second and third days of a cycle by bendamustine at a dose of 90 mg/m^2 per day administered by iv infusion over 30-60 minutes. Patients were treated for a minimum of 4 cycles. If there was documented disease regression between cycle 2 and cycle 4 assessments, patients could receive 2 more cycles of combination therapy at 28-day intervals. The sixth cycle was then followed by single-agent rituximab 375 mg/m^2 28 days later. Patients who experienced grade 3 or 4 non-haematologic or grade 4 hematologic toxicity (according to the CTCAE, version 3.0) during or after a cycle of combination treatment with rituximab and bendamustine at 90 mg/m2 had their dose of bendamustine decreased to 60 mg/m^2 for the next cycle. Patients who continued to experience grade 3 or 4 non-haematologic or grade 4 haematologic toxicity at this reduced dose were withdrawn from the study.

In this study, 67 patients with relapsed indolent NHL or MCL were enrolled; 66 (99%) patients received at least 1 dose of bendamustine and rituximab and were evaluable for safety, and 61 (91%) patients received at least 4 cycles of treatment with bendamustine and rituximab. The median age of the patients was 60 years (range: 40-84 years). The majority of patients were white (83%). Thirty-nine (59%) men and 27 (41%) women were treated.

The ORR (primary efficacy variable) was 92.4% (95% CI: 83.2%, 97.5%) in 66 patients in the primary analysis set, consisting of CR in 27 (41%) patients, CRu in 9 (14%) patients and PR in 25 patients (38%). In the primary analysis set, 5 (8%) were categorized as having SD while no patients had PD.

The ORR in patients with indolent NHL (n=54) was 92.6% (95% CI: 82.1%, 97.9%), consisting of CR in 22 (41%) patients, CRu in 7 (13%) patients and PR in 21 (39%) patients. The ORR in

patients with MCL (n=12) was 91.7% (95% CI: 61.5%, 99.8%), consisting of CR in 5 (42%) patients, CRu in 2 (17%) patients and PR in 4 (33%) patients.

The median DR (secondary efficacy variable) in the primary analysis set for patients with CR, CRu, or DR was 91.4 weeks (95% CI: 79.3, 06 weeks), based on 25 patients with progressive disease/death and 36 censored patients out of the 61 patients in the analysis.

The median PFS (secondary efficacy variable) in all patients in the primary analysis set (n=66) was 52.4 weeks (95% C: 30.0, 82.4 weeks), based on 29 patients with progressive disease/death and 37 censored patients.

Comment: In this study, the pre-defined endpoint of an ORR of better than 70% was met, with the lower bound 95% CI for the ORR being 83%.

6.4.2. Study 93BOP01

Study 93BOP01 was nominated by the sponsor as a "pivotal study" supporting approval of bendamustine for the treatment of relapsed/refractory indolent NHL (application letter). However, this Phase III, multicentre, randomized, open-label, parallel-group clinical trial comparing BOP (bendamustine + vincristine + prednisone) with COP (cyclophosphamide + vincristine + prednisone) for the first-line treatment of advanced low-grade NHL is considered to be neither pivotal nor supportive for the proposed indication. In this study, bendamustine was used in a first-line combination chemotherapy regimen rather than as monotherapy for relapsed or refractory disease. Patients were required to meet the following inclusion criteria; age 18-75, with histologically confirmed centrocytic or centroblastic/centrocytic NHL, or lymphoplasmacytoid- immunocytomas, and no prior chemotherapy treatment or radiotherapy.

The study was conducted at 20 centres in Germany from 8 April 1994 (first patient enrolled) to 21 October 1998 (last patient completed). The primary outcome measure was the complete remission (CR) rate, and CR was defined as complete disappearance of all clinically detectable (measurable tumours) and of all tumour symptoms for at least 4 weeks, normalization of blood counts (granulocytes > 1.5 x 10^9/L; Hb > 12.0 g/dL; platelets > 100 x 10^9 g/L). The secondary outcome measures were the partial remission (PR) rate, toxicity, duration of response and quality of life. PR was defined as a 50% decrease in tumour size and in tumour symptoms (A symptoms) for at least 4 weeks, no new lesions and no tumour progression (measurable tumours) at any site and no increase in tumour symptoms. PD was defined as appearance of new lesions and > 25% increase in size of lymphoma or > 25% increase in spleen size and appearance of B symptoms.

Patients in the BOP group (n=82) received bendamustine 60 mg/m^2 iv over 30 minutes on days 1-5 (the original dose of 70 mg/m^2 was reduced to 60 mg/m^2 after 25 patients had been enrolled in order to adjust the level of thrombocytopenia to the level observed with the comparator treatment), plus vincristine 2 mg iv on day 1 and prednisone 100 mg/m^2 iv on days 1-5. Patients in the COP group (n=80) received cyclophosphamide 400 mg/m^2 iv over 30 minutes on days 1-5, plus vincristine 2 mg iv on day 1 and prednisone 100 mg/m^2 iv on days 1-5. The treatment cycle for both regimens was 21 days.

In this study, patients were treated with 6 induction cycles and 2 consolidation cycles of chemotherapy, and patients with bulky disease after the consolidation cycles were treated with localized radiotherapy. Patients showing no improvement after 6 induction cycles were withdrawn from the study and offered alternative therapy. Switching to alternative treatment (including the other treatment arm) was allowed in case of progressive disease, no change in the disease or at the investigator's discretion.

The CR (primary efficacy endpoint) was analysed using the intent-to-treat principle, but patients who received no dose after randomization or with major protocol violations due to non-compliance with entry criteria were excluded. CR was assessed at restaging after induction cycle 6 and was to be reconfirmed after the consolidation cycles. The CR was 22% (18/82) in

the BOP group and 20% (16/80) in the COP group; p=0.812 (CMH), odds ratio = 1.103 (95% CI: 0.491, 2.478).

The PR (secondary efficacy endpoint) was 43.9% (36/82) in the BOP group and 56.3% (45/80) in the COP group. The overall remission rate (CR or PR) was 65.9% (54/82) in the BOP group and 76.3% (61/80) in the COP group.

The 5-year survival rate was 61% in the BOP group and 46% in the COP group. The median duration of survival was 22 months longer in the BOP group compared with the COP group (76 and 54 months, respectively), but there was no statistically significant difference between the two treatment groups (p=0.1947, log-rank test).

Comment: The primary objective of this study was not met (i.e., statistically significant superiority of BOP vs COP for the CR rates in the ITT population).

6.5. First-line indolent NHL and Mantle-Cell Lymphoma (MCL)

6.5.1. Clinical studies supporting the proposed indication

The sponsor is seeking approval for the following indication - "previously untreated Non-Hodgkin's Lymphoma and Mantle-Cell Lymphoma. RIBOMUSTIN should be used in combination with rituximab in CD20 positive patients". The bendamustine dosage regimen being proposed by the sponsor for first-line combination therapy with rituximab is 90 mg/m^2 on days 1 and 2 of a 4-week cycle for up to 6 cycles. Information provided in the submission indicates that at the date of application the proposed indication had not been approved in any overseas countries.

The sponsor's application letter states that literature-based data have been submitted to support the first-line indolent and MCL indication, and nominates recently published data (Rummel et al., 2013) reporting the results of StiL NHL 1-2003 as being pivotal. The submission included a copy of the published report of the pivotal Phase III StiL NHL 1-2003 study (Rummel et al., 2013), copies of previously published reports generally in abstract form authored by Rummel and colleagues providing preliminary data from StiL NHL 1-2003, an English translation from German of the initial September 2003 protocol for NHL 1-2003, a Module 2 summary of clinical efficacy addendum including a description of StiL NHL 1-2003, and a Module 2 clinical overview addendum including a description of the study. In addition, the Module 5 literature references included a Statistical Analysis Plan (SAP) for StiL NHL 1-2003 dated 5 May 2011 and authored by Chen and Li of the Biometric Operation Department, Cephalon®. Study StiL NHL 1-2005 has been fully evaluated in this CER using an integrated approach to the data provided by the sponsor.

The Clinical Overview Addendum (2.5) presented a tabulated summary of 12 Phase II/III studies identified from the literature in which bendamustine was used for the first-line treatment of indolent NHL and MCL. However, of these 12 studies the sponsor's letter identifies only StiL NHL 1-2003 (Rummel and colleagues) as supporting the indication the proposed indication. Examination of the 11 additional studies tabulated in the Clinical Overview Addendum (2.5) indicates that, for regulatory purposes, none are considered to provide pivotal or supportive data. Brief comments on the additional 11 studies are provided immediately below:

- Data from *Herold and colleagues* describe a study comparing bendamustine + vincristine + prednisone (BOP) with vincristine + prednisone + cyclophosphamide (COP) for the treatment of advanced indolent NHLs (Herold et al., 2006; Herold et al., 2002; Herold et al., 1999). Neither the bendamustine regimen nor the bendamustine dose are relevant to the proposed indication.
- Data from *Flinn et al (2012)* describe the ongoing BRIGHT study in which treatment Group 1 (bendamustine + rituximab [B-R]) is being compared with treatment Group 2 (rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone [R-CHOP] or rituximab +

cyclophosphamide + vincristine + prednisone [R-CVP]) for the treatment of advanced indolent. The data have been published only in abstract form and were presented orally at the 54th Annual Meeting of the American Society of Hematology (ASH 2012).

- Data from *Rummel et al (2012*) reporting preliminary findings of B-R induction followed by rituximab maintenance from StiL NHL 7-2008 (MAINTAIN) for patients with Waldenstrom's macroglobulinaemia. The data have been published in abstract form and were presented as a poster session at ASH 2012.
- Data from *Becker et al (2012)* reporting interim findings from a prospective observational study of patients with indolent NHL treated with bendamustine regimens (most commonly B-R). The data have been published in abstract form (poster presentation).
- Data from 7 Phase II non-comparator studies using various bendamustine regimens and identified in the Clinical Overview Addendum (2.5) as providing level IV evidence (Weidmann et al., 2009; Pennese and Di Renzo, 2011 (a & b); Finn et al., 2012; Lansigna et al., 2012; Magni et al., 2011; Salar et al., 2012; Boccomini et al., 2012).

6.5.2. Pivotal study (NHL 1-2003)

6.5.2.1. Design, objective, location, dates

6.5.2.1.1. (a) Design, location and dates

The pivotal Phase III study (StiL NHL 1-2003) is a prospective, randomized, multicentre, clinical efficacy and safety study comparing bendamustine in combination with rituximab (B-R) with rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for the first-line treatment of indolent NHL or MCL.

The report for the pivotal study was published in a recent edition of the Lancet by *Rummel et al (2013)* on behalf of the Study group indolent Lymphomas (StiL). The publication was accompanied by an editorial titled *First-line treatment of indolent-lymphoma: axing CHOP*?

The study was undertaken in 81 centres in Germany between 1 September 2003 and 31 August 2008. All patients gave written informed consent and the protocol was approved by IECS and/or IRBs at each participating centre. The study complied with the Declaration of Helsinki and amendments, and was conducted in accordance with Good Clinical Practice (GCP) guidelines. The study was funded by Roche Pharma AG and Ribosepharm/Mundipharma GmBH.

6.5.2.1.2. (b) Objectives

The **primary objective** was to compare progression-free survival (PFS) of bendamustine plus rituximab (B-R) and rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for the first-line treatment of patients with indolent NHL or MCL.

The **secondary objectives** included: determination and comparison of the remission rates; comparison of the toxicities, infectious complications, duration of the immunosuppressive effect and side effects; and comparison of the duration of overall survival. The protocol also included three additional objectives of cost effectiveness, comparison of mobilization of peripheral CD34-positive stem cells and TTNT (time to next treatment).

6.5.2.1.3. (c) Study plan

The 549 enrolled patients were randomized to receive either B-R (n=247) or R-CHOP (n=275) for a total of 6 cycles. All patients underwent standard pre-treatment screening, including physical examination; complete blood count; serum chemistry; serum immuno-electrophoresis; measurement of immunoglobulin concentrations; chest X-ray; CT scan of the chest, abdomen, and pelvis; sonography of the abdomen; and bone marrow aspiration and biopsy. If clinically relevant, endoscopy of the gastrointestinal tract was also done. Tumour responses were assessed after cycles 3 and 6 or at the end of treatment, and were classified as complete response, partial response, stable disease, or progressive disease, using standard WHO response

criteria. The duration of remission was assessed by clinical assessment and CT scan or sonography every 3 months for the first 2 years. Patients had a CT scan at least every 6 months.

6.5.2.2. Inclusion and exclusion criteria

The protocol specified criteria were:

- Patients with B-cell lymphomas histologically confirmed not more than 6 months ago:
  - grade 1 and 2 follicular lymphoma;
  - lymphoplasmocytic lymphoma/immunocytoma (including Waldenstrom's macroglobulinaemia);
  - lymphocytic lymphoma (CLL excluding leukaemia);
  - nodular and generalized (nodal and extranodal) marginal zone lymphoma;
  - mantle cell lymphoma (according to the Kiel classification);
  - low-malignant lymphomas that can not be classified further or in more detail.
- Positive histology for CD20.
- No prior treatment with cytostatic agents, interferons or monoclonal antibodies.
- Treatment is required, except for mantle cell lymphomas.
- Stage III or IV.
- Minimum age 18 years.
- WHO PS 0-2.
- Written consent.

The exclusion criteria were: patients who failed to meet the inclusion criteria; primary, potentially curative radiotherapy was a treatment option; prior treatment, except for locally delimited radiation therapy; concomitant illnesses including myocardial infarction within the past 6 months, unmanageable serious hypertension, serious cardiac disease (NYHA III/IV), serious lung disease, hepatic impairment (ALT, AST or bilirubin > 3 x normal value), renal impairment (creatinine > 2 mg/dL); active hepatitis; serious psychological impairment; pregnancy or breast feeding; and patients with a secondary malignant tumour or a history of malignant disease, unless cure by surgery could be confined. The published study report also states that patients with HIV infection or hepatitis B were ineligible. In addition, the study group recommended alternative clinical trials incorporating autologous stem cell transplantation for patients younger than 65 years with mantle-cell lymphoma.

The protocol included standard and appropriate criteria for withdrawing patients from the study.

6.5.2.3. Treatment criteria

The inclusion criteria specified that treatment was required for the treatment of Stage III/IV indolent NHL, apart from mantle-cell lymphoma for which the protocol specified that "therapy is always indicated to treat aggressive mantle cell lymphomas". The protocol specifies that therapy was required if one of the following criteria were met:

- B-symptoms (fever >38°C of unclear aetiology, night sweat, weight loss > 10% compared with baseline within 6 months).
- Haemopoietic insufficiency (peripheral cytopenia (not due to splenomegaly), granulocytes 1.5x109/L, Hb < 10 g/dL, platelets < 100x109/L).
- Verifiable rapid progression of the tumour.

- Increased number or size of lymphoma manifestations by > 50% within 6 months.
- Large tumour mass ("bulky disease").
- Lymphomas with a diameter of > 3 cm in 3 or more regions or a diameter of > 7.5 cm in one region.
- Lymphoma-related complications, including narrowing of ureters or bile ducts, relapsing splenic infarction, tumour related compression of a vital, lymphoma induced pain, etc.
- Hyperviscosity syndrome due to monoclonal gammopathy.

6.5.2.4. Study treatments

B-R: bendamustine 90 mg/m^2 administered by iv infusion over 30 to 60 minutes on days 1 and 2 of a 4-week cycle for up to 6 cycles **plus** rituximab 375 mg/m^2 iv on day 1 of each cycle

R-CHOP: CHOP consisting of cyclophosphamide 750 mg/m^2 iv, doxorubicin 50 mg/m^2 iv, vincristine 1.4 mg/m^2 iv (up to a maximum of 2 mg) on day 1, and prednisone 100 mg po per day for 5 days, every 3 weeks for up to 6 cycles **plus** rituximab 375 mg/m^2 iv on day 1 of each cycle.

The protocol stated that therapy consisted of a maximum of 6 cycles. Treatment was stopped in the event of CR or progressive disease. The published study report stated that no maintenance or consolidation treatment was given with either B-R or R-CHOP.

All patients received standard anti-emetic prophylaxis, but no antibiotic prophylaxis was given. Granulocyte-colony stimulating factors (G-CSF) was allowed, according to the guideline from the American Society of Clinical Oncology (ASCO).

WHO toxicity criteria were used to assess treatment related toxicities. Blood counts, including differentials, were done once a week. Treatment cycles were delayed for 1 week if the leucocyte count was < 100x10^9/L before a schedule cycle. If the leucocyte count was < 1x10^9/L or the platelet count was < 5x10^9/L on 2 consecutive days between cycles, the dose of bendamustine was reduced to 70 mg/m^2, and for the R-CHOP regimen the doses of cyclophosphamide and doxorubicin were reduced to 600 mg/m^2 and 40 mg/m^2, respectively. Vincristine was discontinued in cases of grade 2 or higher neurological toxic effects.

> Comment: The R-CHOP regimen is considered to be an appropriate comparator for the B-R regimen for the first-line treatment of indolent NHL and MCL. For patients younger than 65 years with MCL, the study group recommended alternative clinical trials incorporating autologous stem cell transplantation. This recommendation is consistent with Australian practice where R-HiDAC (rituximab and cytarabine) and R-Maxi-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) regimens are recommended for treatment of MCL (II-IV) disease where the intention is to proceed to autologous stem cell transplantation (eviQ, Cancer Treatments Online). The median age of patients with MCL in the study was 70 years (range: 64.5, 74), suggesting that patients with MCL enrolled in the study were considered unsuitable for autologous stem cell transplantation.

The published study report stated that the maximum number of treatment cycles was 6, and that no patients in received maintenance or consolidation treatment. Rituximab is approved in Australia for the treatment of CD20, previously untreated, Stage III/IV follicular, B-cell NHL. The rituximab (MabThera®) PI indicates that for treatment of this condition the drug should be administered at a dose of 375 mg/m^2 in combination with chemotherapy for up to 8 cycles as induction therapy. R-CHOP 21 is a regimen recommended by Australian oncologists for the treatment of CD20 positive NHL (eviQ, Cancer Treatments Online). The US National Comprehensive Cancer Network (NCCN) Guidelines (V 2.2013) recommend R-CHOP as a first-line therapy for follicular lymphoma (grade 1-2), and also recommend B-R as a first line therapy for this condition. In Australia, there are no drugs approved for the first-line treatment of MCL.

Temsirolimus is approved for the treatment of relapsed and/or refractory MCL, but this would not be an appropriate control for the B-R regimen which is being proposed for the first-line treatment of MCL.

6.5.2.5. Randomization and blinding methods

Patients were centrally randomly assigned (1:1) by the StiL Head Office according to a pre-specified randomization list to receive B-R or R-CHOP. Randomization was stratified by subtype of histological lymphoma ("follicular", "immunocytoma", "lymphocytic", "marginal zones", "unclassifiable" and "mantle cell"). Patients, treating physicians, and individuals assessing outcomes and analyzing data were not masked to treatment allocation.

> Comment: This study was open-label and all key participants in the trial were unblinded making it subject to the well known biases associated with clinical trials of this design.

6.5.2.6. Efficacy variables and outcomes

(a) The primary efficacy endpoint in *Rummel et al (2013)* was progression-free survival (PFS), defined as the time between first-treatment and progressive disease, relapse after response, or death from any cause, whichever occurred first. This was the protocol pre-specified primary efficacy endpoint.

(b) The secondary efficacy endpoints in *Rummel et al (2013)* were:

- rates of overall and complete response;
- overall survival;
- time to next anti-lymphoma treatment; and
- event free survival with any event defined as progression of disease, death from any cause, patients not achieving at least a partial response after three treatment cycles or start of subsequent salvage treatment.

The author's stated that subsequent treatment not specified in the protocol, such as a rituximab maintenance therapy in ongoing remission, was not counted as an event for event-free survival, but was censored at the time of treatment. All subsequent treatments in the analysis of time to next anti-lymphoma treatment were counted as events, irrespective of the reason for initiation. At the cut-off date for the analysis of 31 October 2011, data were censored for patients who had no reported events at the most recent assessment.

Remission was evaluated according to the WHO criteria based on investigator assessment. The following definitions were provided in the protocol.

Complete remission (CR): Complete reversal of all verifiable findings of symptoms including infiltration of the bone marrow at the time of restaging with complete reversal of pre-existing swelling of lymph nodes and pre-existing hepatomegaly and/or splenomegaly for at least 4 weeks. The complete reversal of pre-existing lymphoma infiltration of the bone marrow must be verified by means of histological analysis. Normalization of the haemogram with a granulocyte count of > $1.5x10^9$/L, platelet count of > 10^9/µL, and a hemoglobin value of > 11 g/dL. Confirmation of the CR by means of immunology or molecular biology was not planned.

Partial remission (PR): Decrease of measurable and recordable tumor parameters by at least 50%, decrease of the infiltration of the bone marrow by at least 50% for at least 4 weeks after the completion of the chemotherapy, without the occurrence of any new manifestations.

Stable disease (SD): No reversal of the verifiable findings of the illness (patients who failed to go into remission and who do not meet the conditions for a progression of the disease). New tumour manifestations with simultaneous reversal of pre-existing tumour parameters (mixed response) were considered a progression of the disease.

Progressive disease (PD): Increase of one or more tumor parameters by at least 25% or occurrence of new tumour manifestations. Increased frequency and severity of symptoms.

6.5.2.7. Analysis populations

The final SAP defined three analysis sets:

Randomized patients set - The set of randomized patients included all patients who were randomized to a treatment group, regardless of whether or not a patient received any study drug (i.e., the ITT population). The SAP stated that the randomized set was to be used for all efficacy analyses unless otherwise stated.

Safety analysis set - The safety analysis set included those randomized patients who received 1 or more doses of any component of combination therapy in any treatment arm. All summaries using the safety analysis set were presented by actual treatment received.

Evaluable patients set - The evaluable patient set includes patients from the safety analysis set but excluding: patients for whom access to clinical sites was not possible, and thus clinical monitoring of source documents was not done; patients for whom informed consent can not be retrieved or patients for whom informed consent was not obtained prior to a study specific procedure; patients whose malignant disease is not one defined in the inclusion criterion (the qualifying disease must be confirmed histologically within 6 months of the screening visit); patients without positive histology for CD20; patients who received prior treatment with cytostatic agents (including chemotherapy), interferons or monoclonal antibodies; patients who received prior radiation therapy, except for one-time locally delimited radiation therapy (radiation field not exceeding two adjacent lymph node regions); patients whose need to treat is not demonstrated at baseline as per protocol; patients aged less than 18 years; patients with WHO performance status greater than 2; patients with a secondary malignant tumor or a history of malignant illnesses, without confirmation of curative surgery; patients who received initial study chemotherapy from the treatment arm that they were not randomized to.

6.5.2.8. Sample size

The initial sample size calculation described in the protocol was based on a non-inferiority design for event-free-survival (EFS). However, the final SAP states that the primary efficacy endpoint was changed in October 2007 from EFS to PFS, but no sample size adjustment was made as a result of this amendment. Consequently, the sample size calculations for this study were based on EFS, but the results are applicable to PFS.

In *Rummel et al (2013)*, the provided data indicates a sample size of 224 patients per treatment with a recruitment time of 4 years was sufficient to reject the null hypothesis (i.e., B-R is inferior to R-CHOP) with a power of 80%, and an α set at 5% (one-sided). The assumptions used to make the sample size calculation were based on the null hypothesis that the B-R arm would have an inferior PFS survival rate after 3 years follow-up of 40% compared with 50% in the R-CHOP arm, corresponding to a non-inferiority margin of 10% and a non-inferiority hazard ratio [B-R/R-CHOP] of 1.32.

> Comment: The non-inferiority margin of 10% is considered to be appropriate. The initial non-inferiority margin specified in the protocol was 15%, but this was subsequently amended to 10% following market authorizations in indolent lymphoma and other incurable diseases that considered a difference in EFS of 2 months as clinically relevant. The number of randomized patients in each treatment arm was larger than the estimated sample size needed to ensure that the study would be adequately powered. The final SAP indicates that it was assumed that there was an exponential progression of EFS curves, and that there would be a drop out rate of 10% within the first 3-years of the study, and that recruitment would take 4-years. Therefore, the number of patients required in this study was calculated to be 237 per arm. Due to the group sequential design, an alpha-spending approach was used to adjust for any interim analyses. Using

this approach, the sample size was adjusted leading to a projected maximum sample size of 244 to 249 per group (which was achieved).

6.5.2.9. Statistical methods

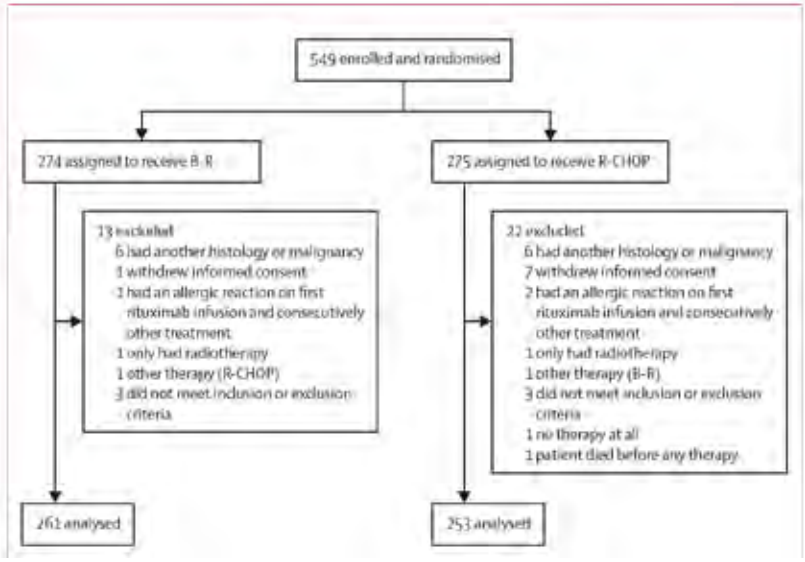
The Kaplan-Meier (KM) method was used to estimate survival curves, with the log-rank test being applied for comparison between the two treatment arms. The Cox proportional hazards model with a stepwise backward variable selection approach ($p<0.1$) was used for multivariate analysis, and to obtain hazard ratios with confidence intervals. Fisher's exact or chi-square tests were used to compare toxic effects and rates of G-CSF use for the two treatment arms. Except for the primary endpoint, all statistical tests that included subgroup and interaction analyses were exploratory and not prospectively defined. No statistical adjustments were made for multiplicity. All tests were two-sided. The final SAP stated that only the observed data for all variables was to be used in the statistical analyses and missing data was not be estimated.

The protocol outlined procedures for interim evaluations based on a group-sequential design using the "α error spending function" according to *Lan and DeMets (1983)* to approximate the termination limits established by *O'Brien and Fleming (1979)*. Consequently, termination was possible due to prematurely proven superiority of the standard arm with respect to the therapeutic efficacy (rejection of H_1), or to premature proof of non-superiority of the standard arm at the specified extent (rejection of H_0). The final SAP indicated that three interim analyses were conducted and the results presented at "conventions" (Rummel et al 2007; Rummel et al 2008; Rummel et al 2009).

6.5.2.10. Participant flow

The participant flow from *Rummel et al (2013)* is summarized below in Figure 4.

Figure 4: NHL first-line treatment (Rummel et al 2013) - Trial profile.



Comment: The total number of enrolled and randomized patients was 549, and 514 were evaluable. The proportion of patients enrolled and randomized to B-R who were evaluable was greater in the B-R arm than in the R-CHOP arm (95% vs 92%, respectively). The main difference between the two treatment arms related to a greater number of patients withdrawing consent in the R-CHOP arm compared with the B-R arm (7 vs 1 patient, respectively). Overall, it is considered that the two evaluable populations are comparable.

6.5.2.11. Baseline data

The age distribution was similar in both treatment and the median age was 64 (range: 34, 83 years) in the B-R arm and 63 years (range: 31, 82 years) in the R-CHOP arm. The NHL stage was

consistent with the inclusion criteria (i.e., 96% of patients with stage III/IV disease, and the staging distribution (II, III or IV) was similar for the two treatment arms. The majority of patients in both treatment groups had intermediate or poor prognostic risk according to FLIPI criteria, with 46% of patients in the B-R arm being in the poor-risk category (3-5 risk factors) compared with 48% of patients in the R-CHOP arm.

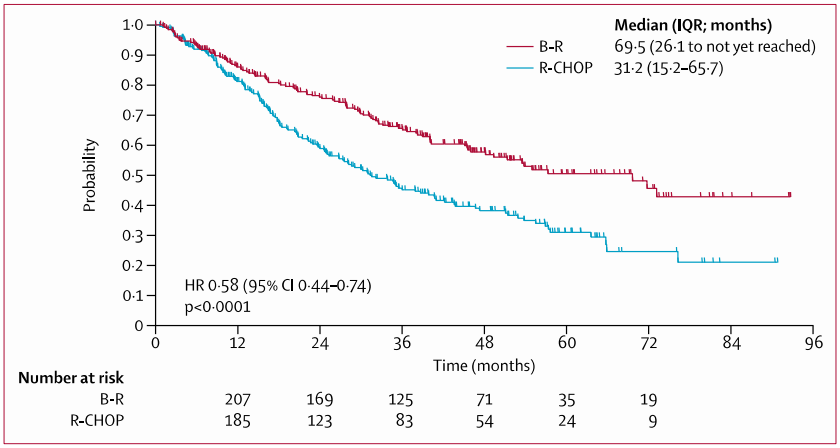
The distribution of the lymphoma subtypes, based on histology, was similar in both treatment arms. In the total population, the majority of lymphomas were follicular cell (54%) followed by MCL (18%), marginal-zone (13%), lymphoplasmacytic (Waldenstrom's macroglobulinaemia) (8%), small lymphocytic (4%), and low grade, unclassifiable (2%). Within the histological sub-groups, the median age of patients was 60 years (IQR 51–67) for those with follicular lymphoma, 70 years (64.5–74) for those with mantle-cell lymphoma, 66 years (61–70) for those with marginal-zone lymphoma, and 64 years (56–69) for those with Waldenstrom's macroglobulinaemia.

> Comment: The median baseline ages of the patients in the study were 63 years (B-R arm) and 64 years (R-CHOP). The median ages of patients in the study are consistent with the estimated mean age of onset of 64.7 years (63.8, males; 66.0, females) in Australian patients with NHL based on 2009 data (Cancer in Australia, 2012). There were no demographic data for the sex or race distribution of the population in the study. The Australian data (Cancer in Australia, 2012) indicate that the incidence of NHL is higher in males compared with females (22.5 vs 15.5 persons/100,000 population, respectively). The baseline characteristics indicate that nearly all patients had Stage III or IV disease and that approximately 50% of patients had poor-prognostic risk (FILIP categorization). The age range of patients with MCL is older than that of patients who might be offered treatment with autologous stem cell transplantation following chemotherapy.

6.5.3. Primary efficacy outcome (progression-free survival)

In *Rummel et al 2013*, the primary efficacy endpoint was stated to be PFS, and the median time to follow-up was 45 months (IQR: 25, 57). PFS was significantly longer in the B-R arm than in the R-CHOP arm (HR = 0.58 [95% CI: 0.44, 0.74]; p< 0.0001), with the median PFS being approximately 38 months longer in the B-R arm than in the R-CHOP arm (69.5 months [IQR: 26.1, NR] vs 31.2 months [IQR: 15.2, 65.7], respectively). The KM analysis indicates that the PFS survival curves appeared to separate in favour of the B-R arm compared with the R-CHOP arm at about 6 months after initiation of treatment (see Figure 5, below).

Figure 5: Rummel et al 2013 - Progression-Free Survival; evaluable population.

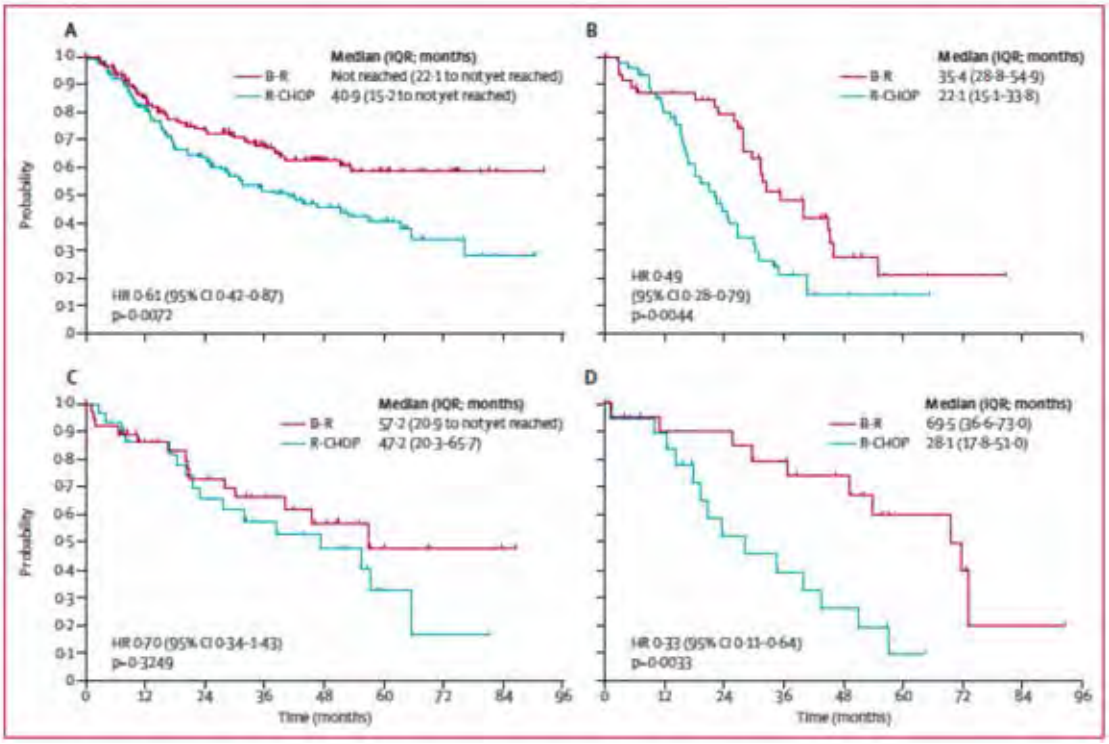


Source: Rummel et al 2013, Figure 2.

In a pre-planned analysis of PFS stratified by histological sub-type, the median PFS was significantly improved in patients treated with B-R compared with R-CHOP for follicular NHL

(p=0.0072), MCL (p=0.0044) and Waldenstrom's macroglobulinaemia (p=0.0033), but not for marginal-zone lymphoma (p=0.3249). The results are summarized in below in Figure 6.

Figure6: Rummel et al 2013 - Progression-Free Survival in the NHL by histological sub-types, follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia.



Source: Rummel et al 2013, Figure 3.

In exploratory subgroup analyses, PFS significantly favoured patients treated with B-R compared with R-CHOP irrespective of age (≤ 60 or > 60 years), and irrespective of FILIP subgroup (favourable or unfavourable), while for patients with normal LDH PFS significantly favoured B-R over R-CHOP but for patients with elevated LDH there was no difference between the two treatment arms.

In a multivariate analysis with backward selection, mantle-cell histology (HR = 1·84 [95% CI: 1·37, 2·48]; p<0·0001) and LDH concentrations of more than 240 U/L (HR = 1·40 [95% CI: 1.08, 1.82]; p=0.010) were independent negative predictors of poor PFS outcome. However, in this adjusted analysis B-R showed a significant PFS benefit compared with R-CHOP (HR = 0.56 [95% CI: 0.43, 0.72]; p<0.0001), which was similar to the outcome for the adjusted analysis (HR = 0.58 [95% CI: 0.44, 0.74]; p< 0.0001).

6.5.4. Secondary efficacy outcomes

6.5.4.1. (a) Overall Remission Rate (ORR) and Complete Response (CR)

In *Rummel et al 2013*, the ORR and CR were both stated to be secondary efficacy endpoints. The ORR was defined as the proportion of patients who achieved a best response of CR or PR. ORR results indicated no significant difference between the B-R and the R-CHOP treatment arms (93% [242/261] vs 91% [231/253], respectively). However, the rate for CR was significantly higher in patients in the B-R arm compared with the R-CHOP arm (40% [104/261] vs 30% [76/253], respectively, p=0.021).

6.5.4.2. (b) Overall Survival (OS)

OS was defined as secondary efficacy endpoint in *Rummel et al (2013)*, and in the original protocol survival was defined as the time between randomization and death. OS results

provided in *Rummel et al 2013* showed that 43 patients had died in the B-R arm compared with 45 patients in the R-CHOP arm, and that median overall survival had not been reached in either group.

6.5.4.3. (c) Time To Next anti-lymphoma Treatment (TTNT)

TTNT was defined as a secondary efficacy endpoint in *Rummel et al (2013).* TTNT results provided in *Rummel et al (2013)* showed that the TTNT was significantly longer in the B-R arm compared with the R-CHOP arm (HR = 0.52 [95% CI: 0.39, 0.69]; p<0.0001). The median TTNT was not reached for the B-R arm (IQR: 35.1 months, not reached), while in the R-CHOP arm the median TTNT was 42.3 months (IQR: 18.2 months, not reached). At the time of the analysis, 74 salvage treatments had been started by patients in the B-R arm compared with 116 in the R-CHOP arm.

6.5.4.4. (d) Event-Free Survival (EFS)

EFS was defined as a secondary efficacy endpoint, and the Cephalon® SAP (final) indicated that it had been downgraded from the primary efficacy objective in the original protocol to a secondary efficacy endpoint in a subsequent protocol amendment. In the original protocol, EFS was defined as the time elapsed between randomization and the occurrence of one of the following events (whichever occurs first): objective progression of the disease according to the criteria established by the WHO; non-achievement of at least partial remission after three therapy cycles; the occurrence of a secondary tumour; and death due to any cause. No results for EFS were provided in *Rummel et al (2013).*

6.6. Evaluators summary of efficacy

6.6.1. Chronic lymphocytic leukaemia

The submission included one pivotal, multinational, multicentre, open-label, Phase III study (02CLLIII) supporting the application to register bendamustine for the first-line treatment of CLL (Binet stage B or C). The study included 319 treatment-naive patients with B-CLL (Binet Stage B or C) randomized sequentially to bendamustine 100 mg/m^2 administered by iv infusion over 30 minutes on days 1 and 2 every 4 weeks (n=162), or chlorambucil 0.8 mg/kg (Broca's normal weight) administered po on days 1 and 15 or, if necessary given as divided doses on days 1/2 and days 15/16, every 4 weeks (n=157). All patients who received the study drug started at least 1 cycle and received up to 6 cycles. The proportion of patients in the safety population receiving treatment for 6 cycles was 64.0% (104/161) in the bendamustine arm and 62.9% (95/151) in the chlorambucil arm. The mean (SD) number of treatment cycles in both treatment arms was 4.9 (1.7).

The first primary efficacy endpoint was the overall response rate (ORR), and response included patients with CR plus PR plus nPR. The response criteria were required to be met for at least 8 weeks. The ORR (ICRA assessment) was statistically significantly greater in the bendamustine arm than in the chlorambucil arm (67.9%, 110/162 vs 30.6%, 48/157, respectively; p<0.0001). The CR was notably greater in the bendamustine arm compared with the chlorambucil arm (30.9%, 50/162 vs 1.9%, 3/157, respectively), while the PR was similar in the two treatment arms (26.5%, 43/162 vs 26.1%, 41/157, respectively). The treatment effect (difference between the two treatment arms in the proportion of patients with overall response) was 37.3% (95% CI: 21.7%, 47.4%) in favour of the bendamustine arm, after adjusting for Binet stage. The ORR based on the investigator assessment (sensitivity analysis) was consistent with results of the ORR based on the primary ICRA analysis. The ORR was significantly greater in the bendamustine arm compared with the chlorambucil arm irrespective of whether patients were categorized as Binet stage B or C. Similarly, the benefit of bendamustine compared with chlorambucil as regards the ORR was observed in both male and female patients, and in patients aged < 65 years and ≥ 65 years.

The second primary efficacy endpoint was progression free survival (PFS), defined as the time from the date of randomization to the date of first PD, or relapse after intercurrent remission, or death from any cause. Median PFS (ICRA assessment) was 13.3 months longer in the bendamustine arm than in the chlorambucil arm (21.6 months [95% CI: 18.6, 31.0 months] vs 8.3 months [95% CI: 5.9, 11.3 months]; p<0.0001). According to KM estimates, the proportion of patients free of progression 12 months after randomization was notably greater in the bendamustine arm than in the chlorambucil arm (78.6% vs 34.9%, respectively). The HR CLB/BEN was 4.37 (95% CI: 3.14, 4.37), indicating that there was a significant approximately 4.4-fold increased risk of experiencing an event in the chlorambucil arm compared with the bendamustine arm. PFS based on investigator assessment (sensitivity analysis) was consistent with PFS based on the primary ICRA analysis. Median PFS was longer in the bendamustine arm than in the chlorambucil arm irrespective of whether patients were categorized as Binet stage B or C, and there was no statistically significant difference between Binet B and C categories as regards the proportion of patients experiencing an event. Similarly, the PFS benefit of bendamustine compared with chlorambucil was observed in both male and female patients, and in patients aged < 65 years and aged ≥ 65 years.

The first primary efficacy endpoint (ORR) was tested first (two-sided p<0.0001<0.016 Pocock critical bound for a 5 stage sequential design). The first primary endpoint was analysed by the CMH test stratified by Binet group for each individual sequence and combined using the inverse-phi method). As the p-value for the first primary efficacy was < 0.016, testing of the second primary efficacy (PFS) could proceed (two sided p< 0.0001< 0.016 Pocock critical bound for a 5 stage sequential design). The second primary endpoint was analysed by the log-rank test stratified by Binet stage for each individual sequence and combined using the inverse phi method. Based on the observed results for both primary efficacy endpoints, the null hypothesis was rejected as the final p values for both endpoints remained under the critical value of α_1 = 0.016.

The secondary efficacy endpoints of time to progression and duration of remission both significantly favoured the bendamustine arm compared with the chlorambucil arm, and supported the results of two primary efficacy endpoint analyses. However, no significant difference in the secondary efficacy endpoint of overall survival (OS) between the bendamustine and the chlorambucil arms was observed, based on the data available at the cut-off date. The OS data showed no statistically significant difference between the bendamustine and chlorambucil arms (HR CLB/BEN = 1.45 (95% CI: 0.91, 2,31); p=0.1623). However, due to the immaturity of the OS data, the KM estimate of median duration of survival was available only for patients in the chlorambucil arm (65.4 months [95%: 55.1, NA months). A total of 72 patients died during the observational period, 31 (19.3%) in the bendamustine arm and 41 (26.1%) in the chlorambucil arm. As regards the secondary efficacy endpoint of quality of life, bendamustine did not provide a quality of life benefit compared with chlorambucil.

The limitations of the submitted efficacy data provided to support the registration of bendamustine for the first-line treatment of CLL (Binet stage B or C) are:

- The submission included only one pivotal Phase III study supporting registration of bendamustine for the proposed indication (02CLLIII). However, the results of this study were robust, with both primary efficacy endpoints (overall response and PFS) statistically significantly favouring bendamustine compared with chlorambucil. Support for the primary efficacy endpoints were provided by the secondary efficacy outcomes of time to progression and duration of remission, but there was no evidence from the pivotal study that bendamustine provides an overall survival benefit or improves quality of life compared with chlorambucil. There is a TGA adopted EU guideline for submissions that include only one pivotal Phase III study supporting approval (CPMP/EWP/2330/99). This guideline states that where confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling" and lists a number of criteria which "the regulatory evaluation will need to consider". In general, it is considered that the submitted pivotal

Phase III study meet the criteria listed in the guideline. It is considered that the application to register bendamustine for CLL should not be precluded simply on the basis that only one pivotal study was submitted supporting the application,

- The pivotal study (02CLLIII) was open-label in design and, consequently, is subject to the well known biases associated with studies of this design. However, the two primary efficacy endpoints were assessed by independent evaluators (ICRA) blinded to treatment allocation. The results of the study were robust and the sensitivity analyses of the two primary efficacy endpoints supported the ICRA primary analyses of these endpoints. The subgroup analyses of the two primary efficacy endpoints supported the primary analyses of both endpoints. It is considered that the data should not be rejected due to the open-label design of the study.
- The patient population in the pivotal study (02CLLIII) was relative young and the majority of patients were categorized as WHO PS 0. In Australia, it is likely that this patient population might have been offered combination treatment with fludarabine/cyclophosphamide/rituximab as first-line treatment for CLL rather than chlorambucil. The sponsor states that fludarabine was not approved as first-line treatment for CLL when the study was planned, and that chlorambucil is still likely to be a first-line treatment option for elderly patients. In the EU, bendamustine is approved as first-line treatment for CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. Overall, it is considered that registration of bendamustine as first-line treatment for CLL (Binet stage B or C) should not be precluded on the basis that a more appropriate control treatment arm might have been fludarabine combination chemotherapy. In addition, it is considered that the indication should not limit bendamustine to those patients for whom fludarabine combination chemotherapy is not appropriate.
- The pivotal study (02CLLIII) excluded patients older than 75 years, and the mean age (range) of patients in the ITT population for bendamustine and chlorambucil was 63.0 years (47, 77 years) and 63.6 (35, 78 years). Consequently, the study population is younger than Australian patients with CLL for whom bendamustine might be a treatment option. Reassurance concerning the efficacy of bendamustine in older patients comes from the subgroup analyses of the two primary efficacy endpoints (ORR and PFS) showing that treatment with bendamustine was significantly superior compared with treatment with chlorambucil independent of age (< 65 years, ≥ 65 years). However, there were no efficacy data on patients aged ≥ 75 years and the availability of such data from the pivotal study are likely to be negligible, given that patients > 75 years were excluded and the upper age range for the total population was 77 years. It is considered that the lack of efficacy data in patients aged ≥ 75 years is a deficiency in the submission, but should not preclude registration of bendamustine for the CLL indication.
- In the pivotal study (02CLLIII), no significant difference in OS between the bendamustine and the chlorambucil arm was observed. While a significant difference between the two treatment arms might emerge following a longer period of follow-up, future assessment of OS will be confounded by the high proportion of patients receiving other antineoplastic therapy after the last dose of the study drug. In the follow-up analysis (safety population), 79 (49%) patients in the bendamustine arm received antineoplastic therapy after the last dose of the study drug compared with 99 (63%) patients in the chlorambucil arm. Of particular note, 41 (27.2%) patients in the chlorambucil arm received bendamustine as a single agent, and 5 (3.1%) patients received bendamustine in combination with other agents. It is considered that the absence of data demonstrating an OS benefit for patients treated with bendamustine should not preclude registration of the drug for the CLL indication.
- In the pivotal study (02CLLIII), the second primary efficacy endpoint of PFS was defined as the time from randomization to progression, relapse, or death. In the submitted data, while

the total number of patients with PFS events could be identified, the number of patients with each of the three events contributing to the total number could not be clearly identified. While this deficiency should not preclude registration, the sponsor should provide this data for evaluation as part of the second round assessment procedure.

6.6.2. Relapsed/refractory indolent NHL

The submission is considered to include one, pivotal Phase III study (SDX-105-03). In this study, 100 patients in the primary analysis set aged at least 18 years with indolent B-cell NHL refractory to rituximab were evaluable for efficacy. Patients were considered to be refractory to rituximab if the disease had progressed during treatment (i.e., no response) or within 6 months of treatment (i.e., time to progression < 6 months) with rituximab or a rituximab-containing regimen. Patients were treated with bendamustine 120 mg/m^2 via iv infusion over 30 to 60 minutes on days 1 and 2 every 3 weeks for at 6 least cycles (i.e., consistent with the proposed regimen), and could receive a further 2 cycles up to a maximum of 8 cycles based on continued clinical benefit. Follow-up of each patient was to progression of disease, death, start of a new anti-cancer therapy, or up to 2 years from the last dose of bendamustine.

The pivotal study was single-arm and open-label. Consequently, it is subject to the well known biases associated with studies of this design. However, all patients in the treated population (n=100) had disease that was refractory to rituximab, and nearly all (99%) of the treated population had been previously treated with chemotherapy (92% ≤ 3 prior courses, 8% > 3 prior courses). In addition, 25% of patients had received previous radio-immunotherapy, 20% had received previous radiation therapy, and 8% had undergone cancer surgery. Therefore, in this heavily pre-treated patient population with indolent NHL refractory to rituximab it can be reasonably inferred that significant benefits following treatment with single-arm bendamustine are likely to be due to the drug rather than to chance alone. Furthermore, there appears to be no "gold-standard" active control treatment that could have reasonably been used as a comparator for monotherapy bendamustine in this patient population.

The sponsor claims that tumour regression following bendamustine monotherapy in the pivotal study in patients with refractory NHL can be attributed to active treatment with the drug. Consequently, ORR (CR, CRu or PR) can be considered to be a satisfactory outcome measure of efficacy in the context of this single-agent therapy study in this patient population. The sponsor considered that it was not scientifically necessary for the pivotal study to include a comparison group in order to determine the anti-tumor effect and clinical benefit of bendamustine monotherapy, as the occurrence of a high response rate with a durable response would reflect patient benefit due to bendamustine treatment regimen. The sponsor stated that its view relating to a single-arm study is consistent with the FDA guidance for industry document concerning clinical trial endpoints for the approval of cancer drugs and biologicals published in 2007, and with agreements between the FDA and sponsor regarding the pivotal study. The sponsor stated that the FDA advised that a single-arm study in the absence of a randomized trial against approved therapy in a rituximab-refractory patient population might be sufficient for approval if the clinical results were convincing. It is noted that the FDA has approved an indication for indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen based on the single pivotal study (SDX-105-01) (CDER, application number 22-203, Summary Review).

The results for the primary efficacy endpoints of ORR (IRC assessment) of 75% (95% CI: 65%, 83%; p<0.0001), and median DR (IRC assessment) of 40 weeks (95% CI: 31, 47 weeks) are statistically significantly greater than the protocol-defined measures of minimal meaningful clinical efficacy (i.e., null hypothesis of less than 40% for ORR and less than 4 months [17 weeks] for DR). The median DR for patients with CR, CRu, and PR was 45, 59, and 36 weeks, respectively, showing that response was durable for patients with each of the response outcomes contributing to the overall response. The results for the ORR and DR observed in the primary analysis (IRC assessment) were consistent with the results in the subgroup analyses (IRC assessment) for these two endpoints based on baseline disease characteristics. In addition,

the results for the primary analyses of the ORR and DR based on IRC assessments and investigator assessments were consistent.

Treatment with bendamustine in patients refractory to prior-alkylator and prior chemotherapy therapy resulted in meaningful improvements in ORR and DR. In patients with disease refractory to prior alkylator therapy the ORR was 60% (18/30 patients) (95% CI: 41%, 77%), and in patients with disease refractory to the last prior chemotherapy regimen the ORR was 64% (23/36 patients) (95% CI: 46%, 79%). In patients with disease refractory to prior-alkylator therapy the median DR was 33.3 weeks (95% CI: 21.4, NA weeks), and in patients with disease refractory to the last prior chemotherapy regimen the median DR was 27.3 weeks (95% CI: 214, NA weeks).

In the pivotal study, the median PFS (secondary efficacy endpoint) based on IRC assessment was 40.3 weeks (95% CI: 35.0, 41.9 weeks), and was primarily driven by disease progression (47 patients) followed by death (5 patients) and change of therapy (5 patients). PFS was 51, 65, and 42 weeks for patients with CR, CRu, and PR, respectively. Meaningful improvement in PFS was seen in all subgroups based on baseline disease characteristics.

Support for the pivotal study was provided by the results from an exploratory Phase II, multicentre, open-label, single-arm study in patients with indolent or transformed B-cell NHL refractory to rituximab (SDX-105-01). This study was of similar design to the pivotal study and was undertaken prior to that study. The bendamustine treatment regimen in this study was identical to the pivotal study (SDX-105-03). Of the 76 patients included in this study, 61 (80%) had indolent NHL (predominantly follicular lymphoma, 46 patients), and 15 (20%) patients had transformed NHL (predominantly follicular lymphoma, 11 patients).

In study SDX-105-01, all 76 patients in the primary analysis set had received previous rituximab-containing regimens, and their lymphoma was deemed refractory to rituximab treatment. The median and mean number of previous rituximab-containing courses was 2, ranging from 1 to 4. In this study, a patient could have been refractory to rituximab treatment in a previous single agent or combination regimen, but have responded to a subsequent rituximab-containing regimen and have been included in the study. Consequently, 23 (30%) of the patients included in the study had responded to their most recent rituximab regimen. When the worst response to any rituximab-containing regimen was assessed, 53 (70%) patients treated with a rituximab-containing regimen showed stable disease or disease progression. Of the 23 patients with a CR, PR or unknown as their worst response, 10 patients had an interval of less than 180 days between the last dose of rituximab and disease progression or recurrence. Six (6) patients had an interval of less than 180 days between the last dose of rituximab and the first dose of a subsequent regimen or bendamustine, consistent with an early relapse, and for 7 patients the rituximab-refractory status of their lymphoma was unclear.

In the primary analysis set of study SDX-105-01 (n=76), the ORR was 76.3% (95% CI: 65.2%, 85.3%). Of the 76 patients in the primary analysis set, 58 (76%) achieved a response (11, 14%, CR; 14, 18%, CRu; 33, 43%, PR), while SD was reported in 3 (4%) and PD in 13 (17%) with missing/unknown results for 2 (3%). The lower bound 95% CI of the ORR was > 35%, and in this study bendamustine was considered to be a promising treatment for the proposed indication if the pre-specified true overall response rate was ≥ 35%.

The median DR for patients with a response (CR, CRu or PR) in study SDX-105-01 was 29.0 weeks (95% CI: 22.1, 43.1 weeks), based on 38 patients with a response and 20 censored patients out of the 58 patients in the analysis. The median PFS for all patients in the primary analysis was 31.0 weeks (95% CI: 26.1, 38.7 weeks), based on 55 patients with an event and 21 censored patients out of the 76 patients in the analysis. The KM estimate of the proportion of patients in the primary analysis set remaining progression-free after 48 weeks was 21%.

In study SDX-105-01, the ORR was 66.67% (95% CI: 38.3%, 88.18%) in patients with transformed disease (i.e., 10 patients out of 15, including Cr = 0, Cru = 2, and PR = 8), and

78.69% (95% CI: 66.32%, 88.1%) in patients without transformed disease (i.e., 48 patients out of 61, including Cr = 11, CRu = 12, PR =25).

There were no survival data from study SDX-105-03 (pivotal) or study SDX-105-01 (exploratory/supportive) for patients with indolent NHL refractory to rituximab. However, survival benefit in this patient population are likely to be particularly difficult to show. Consequently, the results for the ORR based on CR, CRu, or PR and the durability of response (DR) in this patient population demonstrated in both the pivotal and exploratory/supportive studies are considered to be clinically meaningful.

Studies SDX-105-02 and 93BOP01 were both nominated by the sponsor as being pivotal for the proposed indication. However, both studies are considered to be neither pivotal nor supportive for the proposed indication of relapsed/refractory indolent NHL. Both studies included bendamustine in combination with other agents rather than as monotherapy, and in both studies patients were not required to be refractory to treatment with rituximab. Furthermore, in study 93BOP01 patients were included only if they had received no prior chemotherapy or radiotherapy.

6.6.3. First-line treatment of indolent NHL and mantle-cell lymphoma

The submission included the results from one pivotal Phase III study supporting the application to register bendamustine in combination with rituximab for the first-line treatment of indolent NHL and MCL in patients with stage III/IV CD20 positive disease (Rummel et al., 2013). The pivotal study was undertaken in multiple centres in Germany (81 centres) and 274 patients were randomized to open-label treatment with B-R (261 analyzed) and 275 patients randomized to open-label treatment with R-CHOP (275 analyzed). The two treatments were administered for up to a maximum of 6 cycles. Neither treatment arm was followed by maintenance or consolidation therapy.

The study was designed to show that B-R was non-inferior to R-CHOP, based on PFS (investigator assessment). The median time to follow-up was 45 months (IQR: 25, 75). PFS (primary efficacy endpoint) was significantly longer in the B-R arm than in the R-CHOP arm (HR = 0.58 [95% CI: 0.44, 0.74]; p< 0.0001), with the median PFS being approximately 38 months longer in the B-R arm than in the R-CHOP arm (69.5 months [IQR: 26.1, NR] vs 31.2 months [IQR: 15.2, 65.7], respectively). The results indicate that B-R is non-inferior to R-CHOP, based on PFS, as the HR for this endpoint was ≤ 1.32.

In a pre-planned analysis, PFS was significantly improved in patients treated with B-R compared with R-CHOP for histological subtypes of follicular lymphoma (p=0.0072), MCL (p=0.0044) and Waldenstrom's macroglobulinaemia (p=0.0033), but not for marginal-zone lymphoma (p=0.3249). In exploratory subgroup analyses, clinically significant improvement in PFS in the B-R arm compared with the R-CHOP arm was found to be independent of age (≤ 60 and > 60 years) and FLIPI subgroup (favourable and unfavourable risk). In a multivariate analysis with backward selection, mantle-cell histology and LDH concentrations greater than 240 IU/L were independent predictors of poor PFS outcome. However, in this adjusted analysis treatment B-R still showed a significant PFS benefit compared with R-CHOP (HR = 0.56 [95% CI: 0.43, 0.72]; p<0.0001), and the results were similar to the unadjusted analysis (HR = 0.58 [95% CI: 0.44, 0.74]; p< 0.0001).

The secondary efficacy endpoints of ORR (CR + PR) were similar for the two treatment arms, while the CR rate significantly favoured B-R compared with R-CHOP. The secondary efficacy endpoint of TTNT significantly favoured the B-R arm compared with the R-CHOP arm, but the median TTNT had not been reached in the B-R arm at the date of the data cut-off. No differences were observed in OS between the B-R arm and the R-CHOP arm (43 vs 45 deaths), and median OS had not been reached at the date of the data cut-off for the analysis.

Overall, *Rummel et al 2013* is considered to show that first-line induction treatment with B-R is non-inferior to R-CHOP as regards PFS in patients with CD20 positive stage III or IV indolent

NHL and MCL. However, no follow-up maintenance therapy was administered to patients responding to induction treatment with B-R. It is noted (Rummel et al., 2003) that there is an ongoing study comparing the effects of rituximab maintenance therapy (every 2 months for 2 or 4 years) in patients who initially respond (CR or PR) to B-R induction (StiL study MAINTAIN). However, this study includes only rituximab treatment arms (2 and 4 years) and no "observation only" comparator treatment arm. Rituximab maintenance therapy for up to a maximum of 2 years is approved in Australia for patients with follicular NHL lymphoma who have responded to an R-CHOP induction regimen, and data show that maintenance treatment for this period significantly improves PFS compared with observation.

The limitations of the submitted data supporting the proposed indication are:

- The absence of efficacy data establishing that rituximab can maintain efficacy in patients achieving a response to induction treatment with B-R is considered to be a significant limitation of the submitted data. It is currently unknown whether the significant PFS benefit seen with B-R induction therapy will be maintained, with or without subsequent maintenance treatment with rituximab.
- No randomized, controlled, double-blind data supporting the proposed indication. However, given the difference between the two treatment regimens it would be difficult to implement a double-blind study comparing the two treatments. Furthermore, the study was well designed and the results showing that B-R was at least non-inferior to R-CHOP were statistically robust.
- Treatment outcomes were determined by investigators using WHO criteria for response. In order to reduce bias associated with subjective differences in investigator assessment it would have been preferable to have used a small number of centralized independent assessors blinded to treatment allocation.
- The data supporting the proposed indication (Rummel et al 2013) included patients from only one country (Germany), although 81 centres were involved. This limits the generalizability of the study results to other patient populations. Furthermore, no data could be identified in the pivotal study describing the racial background of the study population. Despite these limitation, the results in the study population are likely to be generalizable to the Australian population.
- The data supporting the proposed indication included only one pivotal study (Rummel et al 2013). However, there is a TGA adopted EU guideline for submissions that include only one pivotal Phase III study supporting approval (CPMP/EWP/2330/99). This guideline states that where confirmatory evidence is provided by one pivotal study only, this study will have to be "exceptionally compelling" and lists a number of criteria to which the "regulatory evaluation will need to consider". In general, it is considered that the efficacy data from the submitted pivotal Phase III study meets the criteria listed in the guideline.

7. Clinical safety

7.1. Chronic lymphocytic leukaemia - study 02CLIII

7.1.1. Exposure

Bendamustine 100 mg/m^2 was administered by iv infusion over 30 minutes on days 1 and 2 every 4 weeks (n=161, safety population), and chlorambucil 0.8 mg/kg (Broca's normal weight) was administered po on days 1 and 15 or, if necessary given as divided doses on days 1/2 and days 15/16, every 4 weeks (n=151, safety population). The duration of treatment for both treatment arms depended on response. Patients with partial or complete remission were to receive two consolidating cycles with a maximum of six cycles. Patients with no change in

disease received at least three cycles. Patients experiencing progressive disease despite treatment discontinued the study. The median observation time in patients at the time of the follow-up analysis was 35 months (range: 1, 68) (Knauf et al., 2009).

All patients in the bendamustine (n=161) and the chlorambucil (n=151) arms received 1 cycle. The proportions of patients (bendamustine vs chlorambucil) treated for more than 1 cycle were: 93.8% (n=151) vs 94.7% (n=143) for 2 cycles; 81.4% (n=131) vs 86.8% (n=131) for 3 cycles; 75.2% (n=121) vs 73.5% (n=111) for 4 cycles; 70.9% (n=114) vs 67.6% (n=102) for 5 cycles; and 64.0% (n=104) vs 62.9% (n=95) for 6 cycles.

The mean (SD) number of cycles was 4.9 (1.7) in both the bendamustine and chlorambucil arms, and the median number of cycles and range was 6.0 (range: 1, 6.0) in both treatment arms. The mean (SD) overall dose per cycle was 337.5 (86.0) mg in the bendamustine arm (median 360.9; range 40, 480), and 103.5 (26.2) mg in the chlorambucil arm (median 108; range 8, 216). The mean (SD) relative dose per cycle was 89.4% (21.0%) in the bendamustine arm (median 98.7%; range 9.3%, 108.8%), and 94.7% (20.8%) in the chlorambucil arm (median 100.0%; range 9.3%, 225.0%). The mean dose was reduced from cycle 1 to cycle 6 in the bendamustine arm (369.0 to 334.9 mg) and in the chlorambucil arm (111.3 to 98.5 mg)

The treatment duration was calculated as the number of days between the first and last study medication. The mean (SD) treatment duration in the bendamustine arm was 116.2 (51.8) days, and treatment duration ranged from 2 to 112 days. The mean (SD) treatment duration in the chlorambucil arm was 124.4 (50.5) days, and treatment duration ranged from 1 to 199 days.

The study duration was calculated as the number of days between the first and last visit. The mean (SD) study duration in the bendamustine arm was 147.7 (51.5) days, and study duration ranged from 6 to 254 days. The mean (SD) study duration in the chlorambucil arm was 143.9 (47.9) days, and study duration ranged from 8 to 239 days.

At least one dose modification was undertaken in 54 patients in the bendamustine and 46 patients in the chlorambucil arm, and the main reasons in both treatment arms were thrombocytopenia and neutropenia (see Table 21, below).

Table 21: Study 02CLLIII - Dose modifications

	BEN (N = 161)	CLB (N = 151)	Total (N = 312)
Patients with dose modification	54 (33.5%)	46 (30.5%)	100 (32.1%)
Reasons[1]			
Anemia	2 (1.2%)	2 (1.3%)	4 (1.3%)
Fever	7 (4.3%)	0 (0.0%)	7 (2.2%)
Fever and non hematological AE	1 (0.6%)	0 (0.0%)	1 (0.3%)
Hepato-toxocity	1 (0.6%)	0 (0.0%)	1 (0.3%)
Investigators decision	7 (4.3%)	14 (9.3%)	21 (6.7%)
Leukopenia	4 (2.5%)	0 (0.0%)	4 (1.3%)
Multiple reasons (hematological)	4 (2.5%)	6 (4.0%)	10 (3.2%)
Neutropenia	17 (10.6%)	13 (8.6%)	30 (9.6%)
Non hematological AE	5 (3.1%)	6 (4.0%)	11 (3.5%)
Thrombocytopenia	16 (9.9%)	18 (11.9%)	34 (10.9%)
Other	4 (2.5%)	1 (0.7%)	5 (1.6%)

[1] More than 1 reason can be documented per patient if more than one modification was performed the same reason is only counted once.

7.1.2. Adverse events

7.1.2.1. Background

Adverse events (AEs) were defined as any untoward medical happening (clinical or laboratory) experienced by a subject in association with the clinical trial, including any signs and symptoms as well as intercurrent diseases and accidents and any clinically relevant change in a laboratory value (as assessed by the investigator), regardless of a causal relationship to the treatment under study.

AEs were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), Version 2, and infections were additionally graded according to NCI-CTC (Version 3). Haemoglobin, platelets, and neutrophils were graded as proposed by *Cheson et al (1996).* Decreases in platelets and haemoglobin were only toxicities if values drop below normal ranges (see Table 22 below).

Table 22: 02CLLLIII - Toxicities for haemoglobin and platelets

Decrease in platelets* or hemoglobin** (nadir) from baseline value (%)	Grade	ANC: 10^9/L (nadir)***
0% - 10%	0	≥ 2.0
11% - 24%	1	≥ 1.5 and < 2.0
25% - 49%	2	≥ 1.0 and < 1.5
50% - 74%	3	≥ 0.5 and < 1.0
≥ 75%	4	< 0.5

* Platelet counts of < $20x10^9$/L will be considered grade 4 toxicity, unless a decrease in the initial platelet count ≤ $20x10^9$/L was present at baseline, in which case the patient is not evaluable for toxicity referable to platelet counts. ** Baseline and subsequent Hb determinations must be performed before any given transfusions. *** If the absolute neutrophil count was less than (<) $1.0x10^9$/L prior to therapy (at baseline), the patient is not evaluable for toxicity referable to the ANC.

7.1.2.2. Overall adverse event profiles

AEs in all summary categories occurred more frequently in patients in the bendamustine arm compared with the chlorambucil arm (see Table 23 below).

Table 23: Study 02CLLIII - Summary of adverse events

Category	Number (%) of patients		
	BEN (N = 161)	CLB (N = 151)	Total (N = 312)
Any adverse event	143 (88.8%)	122 (80.8%)	265 (84.9%)
Number of adverse events	660	385	1045
Severe adverse events (grade 3 or grade 4 / Cheson or CTC)	85 (52.8%)	47 (31.1%)	132 (42.3%)
Number of severe adverse events	175	72	247
Severe hematologic adverse events with (grade 3 or grade 4)	54 (33.5%)	28 (18.5%)	82 (26.3%)
Number of severe hematologic adverse events	62	31	93
Severe nonhematologic adverse events (grade 3 or grade 4)	66 (41.0%)	26 (17.2%)	92 (29.5%)
Number of severe nonhematologic adverse events	113	41	154
Treatment-related adverse events[1]	132 (82.0%)	97 (64.2%)	229 (73.4%)
Number of treatment-related adverse events[1]	471	225	696
Serious adverse event	31 (19.3%)	19 (12.6%)	50 (16.0%)
Number of serious adverse event	38	22	60
Infections	66 (41.0%)	45 (29.8%)	111 (35.6%)
Number of infections	112	67	179
Withdrawals due to unacceptable toxicity or risk/benefit assessment no longer acceptable	18 (11.2%)	5 (3.3%)	23 (7.4%)
Patients who died	31 (19.3%)	41 (27.2%)	72 (23.1%)

[1] Possibly, probably, definitely related to study drug, including missing relationship

7.1.2.3. Most frequently reported adverse events (SOC and PT)

AEs were reported more frequently in patients in the bendamustine arm than in the chlorambucil arm (88.8%, 143/161, 660 events vs 80.8%, 385/151, 385 events). AEs occurring in ≥ 5% of patients in either treatment arm by system organ class (SOC) and preferred term (PT) are summarized below.

Blood and lymphatic disorders were the most frequently reported conditions reported in either treatment arm and occurred more commonly in the bendamustine arm than in the chlorambucil arm (57.1%, 92/161 vs 35.8%, 54/151, respectively). AEs reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) were neutropenia (27.3%, 44 vs 13.9%, 21), thrombocytopenia (24.8%, 40 vs 20.5%, 31), anaemia (21.7%, 35 vs 13.9%, 21), leukopenia (17.4%, 28 vs 3.3%, 5), and lymphopenia (6.2%, 10 vs 0.7%, 1).

Gastrointestinal disorders occurred more commonly in patients in the bendamustine arm than in the chlorambucil arm (30.4%, 49 vs 27.2%, 41), and AEs reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) were nausea (19.3%, 31 vs 13.9%, 21), vomiting (15.5%, 25 vs 6.6%, 10), and diarrhoea (9.9%, 16 vs 4.0%, 6).

General disorders and administration sites conditions occurred more commonly in patients in the bendamustine arm than in the chlorambucil arm (37.3%, 60/161 vs 15.2%, 23/151), and AEs reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) were pyrexia (24.8%, 40 vs 5.3%, 8), asthenia (8.7%, 14 vs 4.6%, 7), fatigue (8.7%, 14 vs 4.6%, 7), and chills (5.6%, 9 vs 1.3%, 2).

Immune system disorders occurred more commonly in patients in the bendamustine arm than in the chlorambucil arm (6.2%, 10 vs 4.0%, 6), and the only AE reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) was hypersensitivity (5.0%, 8 vs 2.0%, 3).

Infections and infestations occurred more commonly in patients in the bendamustine arm compared with the chlorambucil arm (30.4%, 49/161 vs 25.2%, 38/151), and AEs reported in ≥

5% of patients in either treatment arm (bendamustine vs chlorambucil) were nasopharyngitis (6.8%, 11 vs 7.3%, 11) and infection (6.2%, 10 vs 1.3%, 2).

Investigations occurred more commonly in patients in the bendamustine arm compared with the chlorambucil arm (16.8%, 27 vs 13.2%, 20), and the only AE reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) was weight decreased (5.6%, 9 vs 3.3%, 5).

Metabolism and nutrition disorders occurred more commonly in patients in the bendamustine arm than in the chlorambucil arm (15.5%, 25 vs 6.0%, 9), and the only AE reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) was hyperuricaemia (7.5%, 12 vs 1.3%, 2).

Respiratory, thoracic and mediastinal disorders occurred more commonly in the bendamustine arm than in the chlorambucil arm (13.0%, 21 vs 9.9%, 15), and the only AE reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) was cough (6.2%, 10 vs 4.6%, 7).

Skin and subcutaneous tissue disorders occurred more commonly in patients in the bendamustine arm than in the chlorambucil arm (26.1%, 42 vs 12.6%, 19), and the AEs reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) were rash (9.3%, 15 vs 4.6%, 7) and pruritis (5.0%, 8 vs 2.6%, 4).

7.1.2.4. Drug related adverse events (SOC and PT)

Treatment-related AEs (possibly, probably/definitely related including missing information on relationship) were reported notably more frequently in patients in the bendamustine arm than in the chlorambucil arm (82.0%, 132/161, 471 events vs 64.2%, 97/151, 225 events). AEs occurring in ≥ 5% of patients in either treatment arm by system organ class (SOC) and preferred term (PT) and summarized below.

Blood and lymphatic disorders (treatment-related) were the most frequently reported treatment-related conditions reported in either treatment arm and occurred more commonly in the bendamustine arm than in the chlorambucil arm (52.8%, 85, vs 32.2%, 49). Treatment-related AEs reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) were neutropenia (26.7%, 43 vs 13.9%, 21), thrombocytopenia (23.0%, 37 vs 17.9%, 27), anaemia (17.4%, 28 vs 9.9%, 15), leukopenia (17.4%, 28 vs 3.3%, 5), and lymphopenia (6.2%, 10 vs 0.7%, 1).

Gastrointestinal disorders (treatment-related) occurred more commonly in patients in the bendamustine arm than in the chlorambucil arm (29.2%, 47/161 vs 22.5%, 34/151), and treatment-related AEs reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) were nausea (19.3%, 31 vs 13.9%, 21), vomiting (14.9%, 24 vs 6.0%, 9), and diarrhoea (8.1%, 13 vs 2.6%, 4).

General disorders and administration sites conditions (treatment-related) occurred more commonly in patients in the bendamustine arm than in the chlorambucil arm (30.4%, 49/161 vs 9.9%, 151), and treatment-related AEs reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) were pyrexia (21.1%, 24 vs 2.0%, 3), asthenia (7.5%, 12 vs 4.6%, 7), fatigue (6.2%, 10 vs 2.6%, 4), and chills (5.0%, 8 vs 0.7%, 1).

Infections and infestations (treatment-related) occurred more commonly in patients in the bendamustine arm compared with the chlorambucil arm (15.5%, 25/161 vs 7.9%, 12/151), and the only treatment-related AE reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) was infection (5.0%, 8 vs 0.7%, 1).

Metabolism and nutrition disorders (treatment-related) occurred more commonly in patients in the bendamustine arm than in the chlorambucil arm (11.8%, 19 vs 3.3%, 5), and the only treatment-related AE reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) was hyperuricaemia (5.6%, 9 vs 0.7%, 1).

Skin and subcutaneous tissue disorders (treatment-related) occurred more commonly in patients in the bendamustine arm than in the chlorambucil arm (22.4%, 36 vs 7.9%, 12), and the only treatment-related AEs reported in ≥ 5% of patients in either treatment arm (bendamustine vs chlorambucil) was rash (8.1%, 13 vs 3.3%, 8).

7.1.2.5. Adverse events of special interest

7.1.2.5.1. Haematological AEs grade 3 or 4 (CTC or Cheson).

The most commonly reported AEs grade 3 or 4 (CTC or Cheson) occurring in patients in both treatment arms were *blood and lymphatic system disorders, SOC* (39.8%, 64/161, bendamustine vs 18.5%, 28/151, chlorambucil). Drug-related haematological AEs (PTs) grade 3 or 4 from blood *and lymphatic system disorders (SOC, PTs)* combined with *investigations (SOC, PTs)* were reported notably more commonly in patients in the bendamustine arm than in the chlorambucil arm (39.8%, 64/161 vs 17.2% , 26/151); see Table 24 below.

Table 24: Study 02CLLLIII - Drug-related haematological AEs grade 3 or 4 (CTC or Cheson et al., 1996)

Group Subgroup	BEN (N = 161)	CLB (N = 151)	Total (N = 312)
Hematologic adverse event	**64 (39.8%)**	**26 (17.2%)**	**90 (28.8%)**
Neutropenia (including granulocytopenia)	37 (23.0%)	16 (10.6%)	53 (17.0%)
Leukopenia	23 (14.3%)	2 (1.3%)	25 (8.0%)
Thrombocytopenia (including platelet count decreased)	19 (11.8%)	11 (7.3%)	30 (9.6%)
Lymphopenia	10 (6.2%)	0 (0.0%)	10 (3.2%)
Anaemia (including haemoglobin decreased)	5 (3.1%)	0 (0.0%)	5 (1.6%)
Anaemia haemolytic autoimmune (including haemolysis, haemolytic anaemia)	1 (0.6%)	0 (0.0%)	1 (0.3%)

Neutropenia grade 3 or 4 (CTC) was reported in 115 (15.4%) of a total of 748 treatment cycles with bendamustine, and 51 (7.5%) of a total of 684 treatment cycles with chlorambucil, and the corresponding numbers for grade 1 or 2 (CTC) events were 209 (27.9%) and 144 (21.1%).

The *mean duration of neutropenia* grade 3 or 4 (CTC) was 20.5 days (median 13 days, range 3-162 days) in the bendamustine arm (n=55) and 33.7 days (median 13.5 days, range 3-171 days).

The *first occurrence of neutropenia grade 3 or 4* is summarized below in Table 25 *for Cheson et al (1996)* events. The duration of neutropenia was not calculated for *Cheson et al (1996)* events.

Table 25: 02CLLLIII - First occurrence of neutropenia grade 3 or 4 (Cheson et al., 1996)

	BEN (N = 161)	CLB (N = 151)	Total (N = 312)
Patients with neutropenia	37 (23.0%)	16 (10.6%)	53 (17.0%)
First occurrence of neutropenia			
Cycle 1	17 (10.6%)	5 (3.3%)	22 (7.1%)
Cycle 2	11 (6.8%)	5 (3.3%)	16 (5.1%)
Cycle 3	5 (3.1%)	3 (2.0%)	8 (2.6%)
Cycle 4	0 (0.0%)	3 (2.0%)	3 (1.0%)
Cycle 5	1 (0.6%)	0 (0.0%)	1 (0.3%)
Cycle 6	3 (1.9%)	0 (0.0%)	3 (1.0%)

Haemoglobin reduced grade 3 or 4 (CTC) was reported in 24 (3.2%) of a total of 748 treatment with bendamustine and 20 (2.9%) of a total of 684 treatment cycles for chlorambucil, and the corresponding numbers for grade 1 and 2 (CTC) events were 232 (31.0%) and 165 (25.5%).

Thrombocytopenia grade 3 or 4 (CTC) was reported in 19 (2.5%) of a total of 748 treatment cycles with bendamustine and 22 (3.4%) of total of 684 treatment cycles with chlorambucil, and the corresponding numbers for grade 1 or 2 (CTC) events were 187 (25.0%) and 195 (28.5%).

Granulocyte simulating factors were administered to 10 (6.2%) patients in the bendamustine arm (ITT population) and 1 (0.6%) patient in the chlorambucil arm, while *erythropoietic growth factors* were administered to 4 (2.5%) patients in the bendamustine arm (ITT population) and 2 (1.3%) patients in the chlorambucil arm (ITT population).

7.1.2.5.2. Infections

Infections (all CTC grades; all relevant SOCs) were reported in 41.0% (66/161, 112 events) of patients in the bendamustine arm and 29.8% (45/151, 67 events) of patients in the chlorambucil arm. AEs (PT) reported in ≥ 2% of patients in either treatment arm and in ≥ 2% more patients in the bendamustine arm vs the chlorambucil arm were pyrexia (19.9%, 32 vs 5.3%, 8) and infection (6.2%, 10 vs 1.4%, 2). No events meeting these criteria were reported in the chlorambucil arm.

Infections (CTC grade 3 or 4; all relevant SOCs) were reported in 8.7% (14/161) of patients in the bendamustine arm and 3.3% (5/151) of patients in the chlorambucil arm. AEs (PT) Grade 3 or 4 AEs (PT) reported in ≥ 2 patients in either treatment arm and more commonly in the bendamustine arm vs the chlorambucil arm were pneumonia (4, 2.5% vs 0%), pyrexia (3, 1.9% vs 2, 1.3%) and infection (3, 1.9% vs 0%). No events meeting this criteria were observed in the chlorambucil arm. There was only one patient with a grade 4 CTC event (pneumonia in the bendamustine arm).

7.1.2.5.3. Allergic and hypersensitivity reactions

Immune system disorders (SOC) were reported in 6.2% (10/161) of patients in the bendamustine arm and 4.0% (6/161) of patients in the chlorambucil arm. The only AE (PT), all CTC grades, occurring in ≥ 2 patients in either treatment was hypersensitivity (5.0%, 8, bendamustine vs 2.0%, 3, chlorambucil). Skin and subcutaneous tissue disorders (SOC) were reported in 26.1% (42/161) of patients in the bendamustine arm and 12.6% (19/151) of patients in the chlorambucil arm. AE (PT), all grades, considered to be potentially allergic or hypersensitivity reactions and occurring in ≥ 2 patients in either treatment arm (bendamustine vs chlorambucil) were: rash (9.3%, 15 vs 4.6%, 7); pruritis (5.0%, 8 vs 2.6%, 4); urticaria (4.3%, 7 vs 1.3%, 2); allergic dermatitis (1.9%, 3 vs 0%); and skin reaction (0% vs 1.3%, 2).

Immune system disorders (SOC) grade 3 or 4 were reported in 1.2% (2/161) patients in the bendamustine arm (both AE [PT] of hypersensitivity) and 0% (0/151) of patients in the chlorambucil arm. Skin and subcutaneous tissue disorders (SOC) grade 3 or 4 events were reported in 4.3% (7/161) of patients in the bendamustine arm and 3.3% (5/151) of patients in the chlorambucil arm. The AEs (PT) reported in patients in this SOC (bendamustine vs chlorambucil) were rash (2.5%, 4 vs 2.0%, 3), rash generalized (0.6%, 1 vs 0.7%, 1) and urticaria (0.6%, 1 vs 0%).

7.1.2.6. Deaths, SAEs and other significant AEs

7.1.2.6.1. Deaths

Death occurred in 19.3% (31/161) of patients in the bendamustine arm and 27.7% (41/151) of patients in the chlorambucil arm. Of the 72 deaths, 4 patients died up to 30 days after the last treatment with the study drug (1, 0.6%, bendamustine; 3, 2.0%, chlorambucil), and 68 patients died after study treatment. Of the 4 patients who died up to 30 days after the last treatment with the study drug, the reasons for the death were CLL (n=1, chlorambucil), haemorrhage (n=1, chlorambucil), COPD/dyspnoea/acute heart and pulmonary insufficiency (n=1, bendamustine), and heart failure (n=1, chlorambucil).

Of the 72 deaths, 34 (10.9%) were considered to be due to CLL (13, 8.1%, bendamustine; 21, 13.9%, chlorambucil). The only deaths considered to be unrelated to CLL and occurring in ≥ 2

patients in the two treatment arms (bendamustine vs chlorambucil) combined were unknown (4, 2.5% vs 6, 3.2%), "insultis cerebri" (2, 1.2% vs 0%), sepsis (1, 0.6% vs 1, 0.7%), and sudden cardiac death (0% vs 2, 1.3%).

7.1.2.6.2. Serious adverse events (SAEs)

SAEs were defined as fatal or life-threatening events; events resulting in persistent disability or incapacity; events requiring in-patient hospitalization or prolongation of existing hospitalization; events resulting in congenital anomalies; and/or secondary malignancies. All SAEs that occurred within 30 days of the last dose of the study drug were to be reported and to be handled in the same way as SAEs occurring while on study drug.

SAEs (PT), other than death, were reported more commonly in patients in the bendamustine arm than in patients in the chlorambucil arm (19.3%, 31/161, 38 event vs 12.8%, 19/151, 22 events). *Blood and lymphatic disorders (SOC)* SAEs occurred more frequently in patients in the bendamustine arm (3.1%, n=5) than in the chlorambucil arm (0.7%, n=1), and the following SAEs (PT) were reported only in patients in the bendamustine arm: anaemia (n=2), anaemia haemolytic anaemia (n=1), autoimmune thrombocytopenia (n=1), haemolysis (n=1), and pancytopaenia (n=1) Gastrointestinal disorder (SOC) SAEs occurred with similar frequency in both the bendamustine and the chlorambucil arms (1.2%, 2 vs 1.3%, 2, respectively).

SAEs (PT) occurring in ≥ 2 patients in either treatment arm and more commonly in the bendamustine arm compared with the chlorambucil arm were hypersensitivity (3, 1.9% vs 1, 0.7%), pneumonia (3, 1.9%), anaemia (2, 1.2% vs 0%), vomiting (2, 1.2% vs 0%), pyrexia (2, 1.2% vs 1, 0.7%), and tumour lysis syndrome (2, 1.2% vs 0%). The only SAE occurring in ≥ 2 patients in the chlorambucil arm and more commonly than in the bendamustine arm was herpes zoster (2, 1.3% vs 1, 0.6%).

7.1.2.7. Other significant AEs

- Secondary neoplasms occurring after randomization were reported in 2 patients in the ITT bendamustine arm: 1 x bronchial carcinoma ~ 1 year after end of treatment; and 1 x lung cancer ~ 1 month after start of treatment and resulting in withdrawal from the study.
- Other significant AEs listed in CSR2 and stated to be related to bendamustine were: tumour lysis syndrome (2 patients, both SAEs); anaemia CTC grade 4 requiring hospitalization (1 patient); pulmonary infection requiring hospitalization and antibiotics (1 patients); CTC grade 3 tracheobronchitis (1 patient). No other significant AEs occurring in patients in the bendamustine arm were listed in CSR2.
- No other significant AEs (related or unrelated to treatment) associated with chlorambucil were listed in the CSR2.

7.1.2.8. AEs resulting in treatment discontinuation

There were 23 patients who withdrew from the study due to unacceptable toxicity (20 patients) or due to the risk/benefit becoming unacceptable (3 patients). Of these 23 patients, 18 (11.2%) patients were from the bendamustine arm and 5 (3.3%) were from the chlorambucil arm. For an additional 6 patients, comments were documented stating that AEs did contribute to study drug discontinuation, but the primary reason for termination was classified as "other" (3 patients) or "subject refusal" (3 patients).

The most frequently reported AEs resulting in withdrawal from the study due to unacceptable toxicity or risk/benefit in ≥ 2 patients were (bendamustine vs chlorambucil), hypersensitivity (1.9%, 3 vs 0.7%, 1), pyrexia (1.2%, 2 vs 0.7%, 1), neutropenia (0.7%, 1 vs 0.7%, 1) and rash (1.2%, 2 vs 0%). All other events occurred in a total of 1 patient each and nearly all in the bendamustine arm. Haematological AEs leading to withdrawal occurred in 3 (1.9%) patients in the bendamustine arm and 1 (0.7%) patient in the chlorambucil arm and were, respectively, anaemia haemolytic autoimmune including haemolysis, haemolytic anaemia (1, 0.6% 0%), leukopenia (1, 0.6%, 1 vs 0%), neutropenia including granulocytopenia (1, 0.6% vs 1, 0.7%),

and thrombocytopenia including platelet count decreased (1, 0.6% vs 0%). The only AE resulting in discontinuation that could be identified in CSR2 as not being related to treatment was paraplegia (CTC grade 3) in 1 patient in the bendamustine arm, and surgery confirmed the paraplegia to be due to infiltrating tumour cells.

7.1.3. Laboratory tests

7.1.3.1. Haematology

Haematology laboratory parameters were extensively summarized in CSR2. Assessment of laboratory values in relation to their normal ranges and classification according to the Common Toxicity Criteria (CTC) and Cheson (where available) were summarized for each parameter. The results for number of cycles with haematology laboratory parameters (baseline adjusted) CTC grades 3 and 4 are summarized below in Table 26. The results in the table is adjusted for baseline values, and cycles with a CTC grade lower or equal to baseline CTC grade are ignored.

Table26: Study 02CLLIII - Haematology, number of cycles with CTC grade 3 or 4, baseline adjusted

	BEN (n=782)	CLB (n=733)	BEN (n=733)	CLB (n=733)
	CTC 3	CTC 3	CTC 4	CTC4
Haemoglobin	14 (1.8%)	17 (2.3%)	11 (1.4%)	3 (0.4%)
Leucocytes	71 (9.1%)	4 (0.5%)	5 (0.6%)	0 (0.0%)
Lymphocytes	200 (25.6%)	9 (1.2%)	0%	0%
Neutrophils	77 (9.8%)	35 (4.8%)	42 (5.4%)	17 (2.3%)
Platelets	19 (2.4%)	19 (2.6%)	1 (0.1%)	3 (0.4%)

7.1.3.2. Clinical chemistry laboratory values

Clinical chemistry laboratory parameters were summarized in a similar fashion to haematology laboratory parameters. The number of cycles with clinical chemistry CTC graded 1-4 laboratory abnormalities (baseline adjusted) was notably less than for haematology CTC grade 1-4 laboratory abnormalities. There were a total of 782 bendamustine cycles and 733 chlorambucil cycles, and the number of cycles with clinical chemistry CTC 1-4 abnormalities (baseline adjusted) was summarized. The majority of clinical chemistry CTC laboratory abnormalities (baseline adjusted) in the cycles were grade 1-2. Clinical chemistry CTC (grade 3-4) laboratory abnormalities occurring in ≥ 1% of cycles in both treatment arms combined were (bendamustine vs chlorambucil), hyperglycaemia (7, 0.9% vs 10, 1.4%), hyperbilirubinaemia, (9, 1.1% vs 6, 0.8%), and hyperkalaemia (10, 1.2% vs 6, 0.8%). Clinical chemistry CTC laboratory abnormalities grade 4 were reported for hyperbilirubinaemia 1 (0.1%) cycle for bendamustine, increased creatinine 2 (0.3%) cycles for bendamustine, and hyperkalaemia 5 (0.6%) cycles for bendamustine and 2 (0.3%) cycles for chlorambucil.

7.1.3.3. Urinalysis

In the bendamustine arm (n=161), ~ 45% of patients had one or more urinalysis abnormalities over the course of the studies compared with ~ 47% of patients in the chlorambucil arm. Examination of the results by visit and treatment for leucocytes, protein, and haemoglobin showed no noteworthy differences between the two treatment arms.

7.1.3.4. Vital signs

Changes from baseline in body weight, body surface area, systolic and diastolic blood pressure, pulse rate and temperature were summarized using descriptive statistics. Frequency

distribution for the WHO PS was tabulated and compared between groups. There were no noteworthy differences in vital signs between the two treatment arms over the course of 6 cycles.

7.1.3.5. Electrocardiogram (ECG)

The results of the ECG at baseline and termination visit were summarized for 298 patients in the safety population (154, bendamustine; 144, chlorambucil). At the termination visit, 7 (4.3%) patients in the bendamustine arm had an abnormal ECG finding compared with 11 (7.3%) patients in the chlorambucil arm. Only 2 abnormalities detected at the termination visit were recorded as being clinically relevant (1 in each of the two treatment arms). Examination of the reported abnormalities at the termination visit did not show a particular pattern for either the bendamustine or the chlorambucil treatment arm.

7.2. Relapsed/refractory indolent NHL

7.2.1. Studies with clinical safety data

The evaluation of clinical safety for the relapsed/refractory indolent NHL indication is based on the data from the 100 patients in the primary analysis set of the pivotal study (SDX-105-103), the 76 patients in the primary analysis set of the supportive study (SDX-105-101), and the 176 patient for the combined pivotal and supportive studies. In the pivotal and supportive studies, patients with indolent NHL refractory to rituximab were treated with bendamustine monotherapy 120 mg/m^2 administered over 30 to 60 minutes by iv infusion on days 1 and 2, every 3 weeks for 6 to 8 cycles.

7.2.2. Exposure

7.2.2.1. Basic exposure data

In the pivotal study, all 100 patients received between 1 and 8 cycles, with a mean of 5.3 and a median of 6 cycles. There were 39 (39%) patients treated for 6 cycles, and 21 (21%) patients treated for > 6 cycles. The mean and median total dose received was 1225 mg/m^2 and 1410 mg/m^2, respectively, and the total dose ranged from 240 to 1920 mg/m^2. The mean duration of treatment was 105 days, ranging from 2 to 233 days. The mean absolute dose intensity was 71 mg/m^2/week, which is equivalent to a mean relative dose intensity of 88%. Bendamustine dose reductions from 120 to 90 mg/m^2 were required for 20 (20%) patients and from 120 to 90 to 60 mg/m^2 for 4 (4%) patients.

In the supportive study, all 76 patients received between 1 and 9 cycles, with a mean of 4.8 and a median of 5 cycles. There were 20 (26%) patients treated for 6 cycles and 14 (18%) patients treated for > 6 cycles. The mean and median total doses received were 1094 mg/m^2 and 1200 mg/m^2, respectively, and the total dose ranged from ranged 240 to 2160 mg/m^2. The mean absolute dose intensity was 70 mg/m^2/week, which is equivalent to a relative dose intensity of 87%. Bendamustine dose reductions from 120 to 90 mg/m^2 were required for 15 (20%) patients and from 120 to 90 to 60 mg/m^2 for 4 (5%) patients.

> Comment: The basic exposure parameters for both the pivotal and supportive study were comparable.

7.2.2.2. Cycle characteristics

In the pivotal study, the median average cycle length was 22.4 days. The number of patients completing all cycles per protocol was 32 (23%) (i.e., per-protocol defined as 2 doses/cycle with no delays > 2 days and no reductions), and 68 (68%) patients had a least 1 dose delay/reduction/ incomplete cycle (7, 7%, did not get 2 doses in any cycle; 65, 65%, had dose delay/ reduction in any cycle). The reasons for dose delay/reduction were (patients, %), neutropenia (30, 30%), thrombocytopenia (19, 19%), other AEs (27, 27%), other (14, 14%), and missing (1, 1%).

Of 533 patient-cycles administered, 466 (87%) were administered at 120 mg/m^2, 59 (11%) at 90 mg/m^2, and 8 (2%) at 60 mg/m^2. Of the 533 patient-cycles administered, 88 (17%) were delayed (36, 7%, for 3-7 days; 28, 5%, for 8-14 days; 11, 2%, for 15-21 days; 12, 2%, for 22-28 days; and 1, <1%, for > 28 days).

In the supportive study, the median average cycle length was 23.1 days. The number of patients completing all cycles per protocol was 30 (39%) (i.e., defined as for the pivotal study), and 46 (61%) had a least 1 dose delay/reduction/incomplete cycle (1, 2% did not get 2 doses in any cycle; 46, 61%, patients had dose delay/reduction in any cycle). Of the 368 patient-cycles administered, 72 (20%) were delayed (32, 44%, for 3-7 days; 22, 31%, for 8-14 days; 10, 14%, for 15-21 days; 5, 7%, for 22-28 days; and 3, 4 %, for > 28 days).

Comment: The cycle characteristics were similar for the two treatment groups.

7.2.3. Adverse events

7.2.3.1. Overview of adverse events

Adverse events (AEs) were defined as any untoward medical occurrence that developed or worsened in severity during the study, and not necessarily having a causal relationship to the study drug. For the purpose of AE recording, the study period was defined as the time period from signature of the informed consent form through to the end-of-study evaluation (performed 28 days after the last dose of study drug treatment). All patients who experienced non-serious adverse events unrelated to study drug were monitored for 28 days after the end-of-treatment visit. Patients who experienced any study drug-related AEs that were ongoing at the time of the end-of-study evaluation were monitored. Patients were asked to specifically describe any signs, symptoms, or AEs that they had noticed before the start of the study through to the end-of-study evaluation (performed 28 days after the last dose of study drug). At a minimum, during the study, patients were asked to report adverse events on day 1 of each cycle. The severity of adverse events was determined using the CTCAE version 3.0. For each adverse event, the relationship to the study drug was required to be recorded as definite, probable, possible, unlikely, or not related. The overview of AEs in the primary analysis sets are summarized below in Table 27.

Table 27: Relapsed/refractory NHL - Overview of adverse events, studies SDX-105-01 and SDX 105-103; primary analysis set

	SDX-105-01 (n=76)	SDX-105-03 (n=100)	Total (n=176)
Any adverse event	76 (100%)	100 (100%)	176 (100%)
Severe AEs (grades 3 and 4)	48 (63%)	77 (77%)	125 (71%)
Treatment-related AEs	71 (93%)	98 (98%	169 (96)
Deaths	3 (4%) [a]	11 (11%)	14 (8%)
Serious AEs (including death)	26 (34%)	39 (39%)	65 (37%)
Discontinuation due to AEs	30 (39%)	31 (31%)	61 (35%)

[a] In addition, 1 patient had progressive disease, progressive lymphoma, which was reported as an AE with outcome of death.

Comment: The pattern of AEs occurring during the treatment period was similar in both the pivotal and supportive studies. All patients in both studies had at least 1 AE reported during treatment, and the majority of events were considered to be treatment-related.

7.2.3.2. Commonly occurring adverse events

AEs occurring in ≥ 20% of patients in the total population (n=176) in descending order of frequency were nausea 75%, fatigue 57%, vomiting 40%, neutropenia 38%, diarrhoea 37%, anaemia 35%, pyrexia 34%, thrombocytopenia 31%, constipation 29%, anorexia 23%, and headache 21%.

In the pivotal study, AEs consistent with mucosal inflammation or stomatitis were reported in 21% of patients, and alopecia (grade 1 and 2) was reported in 3% of patients. In the supportive study, AEs consistent with mucosal inflammation or stomatitis were reported in 15% of patients, and alopecia (grade 1 and 2) was reported in 5% of patients.

7.2.3.3. Grade 3 or 4 adverse events

In the pivotal study, 77 (77%) patients experienced at least one grade 3 AE (31, 31%) or grade 4 AE (46, 46%). The *SOCs* with grade 3 or 4 AEs occurring in ≥ 20% of patients were *blood and lymphatic system disorders* (56%), *general disorders and administration site conditions* (21%), *infections and infestations* (21%), and *metabolism and nutrition disorders* (20*%). In the supportive study*, 48 (63%) patients had at least one grade 3 AE (33, 43%) or grade 4 AE (15, 20%). The only *SOC* with grade 3 or 4 AEs occurring in ≥ 20% of patients was *blood and lymphatic system disorders* (37%). Grade 3 or 4 AEs occurring *blood and lymphatic system disorders (SOC)* in the pivotal and supportive studies are summarized below in Table 28.

Table 28: Relapsed/refractory indolent NHL - blood and lymphatic system disorders (SOC, PT) in studies SDX-105-01 and SDX-105-03; primary analysis sets

	SDX-105-01 (n=76)			SDX-105-03 (n=100)		Total
	Grade 3	Grade 4	Total	Grade 3	Grade 4	(n=176)
Blood and lymphatic system disorders	18 (24)	10 (13)	28 (37)	28 (28)	28 (28)	56 (32)
Neutropenia	10 (13)	7 (9)	17 (22)	23 (23)	28 (28)	42 (24)
Thrombocytopenia	8 (11)	3 (4)	11 (14)	12 (12)	4 (4)	16 (12)
Anaemia	7 (9)	0	7 (9)	10 (10)	0	10 (6)
Febrile neutropenia	5 (7)	0	5 (7)	5 (5)	1 (1)	6 (3)
Leukopaenia	1 (1)	1 (1)	2 (3)	8 (8)	4 (4)	12 (7)
Monocytosis	0	1 (1)	1 (1)	-	-	-
Lymphopenia	-	-	-	1 (1)	2 (2)	3 (2)
Anaemia	-	-	-	1 (1)	0	1 (0.6)

	SDX-105-01 (n=76)			SDX-105-03 (n=100)		Total
	Grade 3	Grade 4	Total	Grade 3	Grade 4	(n=176)
haemolytic autoimmune						
Haemolytic anaemia	-	-	-	0	(1)	1 (0.6)
Pancytopaenia	-	-	-	1 (1)	0	1 (0.6)

In the pivotal study, the following *non-blood and lymphatic disorders (SOC)* preferred term grade 3 or 4 AEs were reported in ≥ 1 patient (in descending order of frequency): fatigue (14, 14%) (G3 = 12, 12%; G4 = 2, 2%); hypokalaemia (6, 6%) (G3 = 5, 5%; G4 = 1, 1%); dehydration (6, 6%) (all G3); pneumonia (5, 5%) (G3 = 3, 3%; G4 = 2, 2%); diarrhoea (5, 5%) (all G3); nausea (4, 4%) (all G3); asthenia (4, 4%) (all G3); herpes zoster (4, 4%) (all G3); cytomegalovirus infection (3, 3%) (all G3); urinary tract infection (3, 3%) (all G3); weight decreased (3, 3%) (all G3); anorexia (3, 3%) (all G3); back pain (3, 3%) (all G3); pleural effusion (3, 3%) (all G3); myocardial infarction (3, 3%) (G3 = 1, 1%; G4 = 2, 2%); blood uric acid increased (2, 2%) (both G4); hypomagnesaemia (2, 2%) (G3 = 1, 1%; G4 = 1, 1%); pain in extremity (2, 2%) (both G3); shoulder pain (2, 2%) (both G3); tumour lysis syndrome (2, 2%) (G3 = 1, 1%; G4 = 1, 1%); respiratory failure (2, 2%) (both G4); pulmonary embolism (2, 2%) (both G4); vomiting (2, 2%) (both G3); infection (2, 2%) (G3 = 1, 1%; G4 = 1, 1%); neutrophil count decreased (2, 2%) (G3 = 1, 1%; G4 = 1, 1%); white blood cell count decreased (2, 2%) (both G3); hyperkalaemia (2, 2%) (both G3); NHL (2, 2%) (G3 = 1, 1%; G4 = 1, 1%); syncope (2, 2%) (both G3); dyspnoea (2, 2%) (both G3); dyspnoea exacerbated (2, 2%) (both G3); hypotension (2, 2%) (G3 = 1, 1%; G4 = 1, 1%); and cardiorespiratory arrest (2, 2%) (both G4);

In the pivotal study, the following *non-blood and lymphatic disorders (SOC, PT)* grade 3 or 4 AEs were reported in ≥ 1 patient (in descending order of frequency): fatigue (5, 7%) (all G3); pneumonia (4, 5%) (all G3); nausea (3, 4%) (all G3); vomiting (3, 4%) (all G3); hypokalaemia (3, 4%) (all G3); back pain (2, 3%) (both G3); dehydration (2, 3%) (both G3); myelodysplastic syndrome (2, 3%) (both G4); pyrexia (2, 3%) (both G3); oral candidiasis (2, 3%) (both G3); and sepsis (2, 3%) (G3 = 1, 1%; G4 = 1, 1%).

7.2.3.4. Treatment-related adverse events

In the pivotal study, 98 (98%) patients had at least 1 treatment-related AE. *Blood and lymphatic system disorders (SOC, PT)* treatment-related AEs reported in ≥ 10% of patients were neutropenia (45%), thrombocytopenia (35%), anaemia (34%); and leukopenia (15%). *Non-blood and lymphatic system (SOC, PT)* treatment-related AEs reported in ≥ 10% of patients in descending order of frequency were: nausea (73%); fatigue (63%); diarrhoea (31%); vomiting (28%); pyrexia (28%); constipation (21%); anorexia (21%); stomatitis (20%); chills (14%); weight decreased (14%); headache (14%); dyspepsia (13%); asthenia (12%); decreased appetite (12%); rash 12%); dysgeusia (11%); dyspnoea (11%); abdominal pain (10%); herpes zoster (10%); and dehydration (10%).

In the supportive study, 71 (93%) patients had at least 1 treatment-related AE. *Blood and lymphatic system disorders (SOC, PT)* treatment-related AEs reported in ≥ 10% of patients were anaemia (32%), neutropenia (25%), and thrombocytopenia (22%). *Non-blood and lymphatic system disorders (SOC, PT)* treatment-related AEs reported in ≥ 10% of patients in descending order of frequency were: nausea (66%); fatigue (43%); vomiting (32%); diarrhoea (17%); anorexia (17%);pyrexia (13%); rash 13%; constipation (12%); and chills (12%).

7.2.3.5. Deaths, serious adverse events and other significant adverse events

7.2.3.5.1. Deaths

In the pivotal study, there were 11 (11%) deaths during the study: 2 considered to be definitely related to the study drug (1 x CMV infection with normal ANC; 1 x diffuse inter-alveolar haemorrhage); 2 considered to be probably related to the study drug (1 x respiratory failure/pneumonia; 1 x pneumonia/septic shock/cardiomyopathy); 2 considered to be possibly related to the study drug (1 x respiratory failure; 1 x worsening of COPD); 1 considered unlikely to be related to the study drug (1 x unknown/disease progression); and 4 considered to be unrelated to the study drug (1x generalized deterioration due to NHL progression; 1 x progressive disease due to NHL; 1 x cardiopulmonary arrest; 1 x progression of disease).

In the supportive study, 8 deaths were reported during the study, including 3 patients with AEs leading to death (1 x myelodysplastic syndrome considered to be possibly related for the study drug; 1 x renal failure considered to be unlikely to be related to the study drug; 1 x chronic myelomonocytic leukaemia considered to be possibly related to the study drug). In addition, there was 1 patient with progressive disease/progressive lymphoma reported as an AE with an outcome of death. There were 4 patients who died due to disease progression, rather than due to AEs resulting in death. Only 1 patient died within 30 days of receiving the last dose of the study drug (acute renal failure), 2 patients died between 30 and 60 days of receiving the last dose of the study drug, 4 patients died more than 60 days afar receiving the last dose of study drug, and the exact date of death was unknown for 1 patient.

7.2.3.5.2. Serious adverse events

Serious AEs were defined in the protocol as: death; life-threatening AE; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; congenital anomaly or birth defect; and an important medical event that did not result in death, was not life-threatening, or did not require hospitalization, but jeopardized the patient and required medical intervention to prevent one of the outcomes listed in this definition. Any SAES or deaths which occurred during the study or within 28 days after the end-of-treatment visit were to be reported to the sponsor or CRO within 24 hours.

In the pivotal study, the reported SAEs were stated by the sponsor to be overstated as the CRF included a check-box where the investigator indicated whether an AE was considered serious, irrespective of the protocol definition. In the pivotal study, 39 (39%) patients had at least one SAE (including 8 SAEs resulting in death) as determined by the investigator. Therefore, 31 (31%) patients had SAEs other than death. The most common SAEs occurring in ≥ 5% of patients were febrile neutropenia (6, 6%), and pneumonia (5, 5%). SAEs of myelodysplastic syndrome and squamous cell carcinoma were each reported in 1 patient, and were considered to be new emerging neoplasms other than a recurrence of lymphoma.

In the supportive study, 26 (34%) patients had at one least SAE (including 3 deaths) during the study. Therefore, 22 (29%) patients had SAEs other than death. The most common serious adverse events (those occurring in 4% or more patients overall) were anemia (4, 5%), and febrile neutropenia, pneumonia, and dehydration occurring in 4% (n=3) of patients each. Two patients had myelodysplastic syndrome (SAE) and 1 patient chronic myelomonocytic leukaemia (SAE).

7.2.3.6. Other significant adverse events

7.2.3.6.1. Acute drug reactions/hypersensitivity events:

In the pivotal study, the sponsor undertook a *post-hoc* clinical review of all preferred terms included in the AE category of acute drug reactions/hypersensitivity events (CTCAE version 3.0). There were 14 (14%) patients with 1 or more acute drug reactions/hypersensitivity events occurring with 24 hours of treatment with bendamustine. Of the 14 patients, 12 patients had grade 1 or 2 events, and 2 patients had grade 3 or 4 events (1 patient with grade 4 sinus

tachycardia, grade 4 infusion-related reaction, grade 2 thrombocytopenia, and grade 2 chills considered by the investigator to be treatment-related and resulting in study drug treatment discontinuation; 1 patient with grade 3 back pain, grade 3 shoulder pain, and grade 1 chills considered by the investigator to be treatment-related and resulting is study drug treatment discontinuation). No cases of anaphylaxis were reported. No cases of angioedema were reported, although there was 1 case in which the patient reported pharyngolaryngeal pain and throat tightness.

In the supportive study, the sponsor undertook a *post-hoc* clinical review of all preferred terms included in the AE category of acute drug reactions/hypersensitivity events and identified 21 (27.6%) patients with events. Eight (5.3%) patients had a grade 1 or 2 rash associated with study drug administration without other features of a hypersensitivity reaction. While most reports of rash were isolated events, 1 patient had rash reported in several cycles. Three (3.9%) patients had acute drug reactions resulting in discontinuation of study drug, and in 2 of these patients the events were consistent with a drug hypersensitivity reaction. The remaining events were generally mild and were typical of the reactions associated with the infusion of cytotoxic agents. The tabulated summary provided for acute drug reactions/hypersensitivity events occurring with 24 hours of treatment reported in the pivotal study are considered to reflect the events reported in the supportive study.

7.2.3.6.2. Cardiac-related events

In the pivotal study, cardiac-related AEs were reported in 16 (16%) patients. The most common cardiac-related events were grade 1 tachycardia (5 [5%] patients) and grade 1 palpitations (3 [3%] patients). Five (5%) patients had cardiac events considered possibly related to study drug treatment (palpitations grade 1, cyanosis, grade 1 tachycardia grade 1, and sinus tachycardia grade 1). The remaining cardiac-related adverse events were considered by the investigators to be either unlikely to be related or not to be related to study drug treatment. There were 9 (9%) patients with grade 3 or 4 cardiac-related AEs (3 x myocardial infarction; 2 x cardio-respiratory arrest; 1 each for acute myocardial infarction, cardiac failure congestive, sinus tachycardia, cardiomyopathy, ventricular dysfunction). With the exception of 1 patient, all patients with grade 3 or 4 cardiac-related AEs had a previous history of cardiac disease. The sponsor concludes that "while a role for bendamustine in [grade 3 or 4 cardiac-related AEs] cannot be excluded there is no conclusive evidence for cardiotoxicity in association with bendamustine treatment".

In the supportive study, cardiac-related AEs were reported in 15 (20%) patients, and none were considered to be severe or life-threatening (grade 3 or 4). The only preferred term cardiac-related disorders reported in ≥ 2 patients were tachycardia (8, 11%) and cardiac murmur (5, 7%). The tabulated summary provided for cardiac-related AEs reported in the pivotal study are considered to reflect the events reported in the supportive study.

7.2.3.6.3. Infections

In the pivotal study, infections were reported in 69 (69%) patients, and most were grade 1 (20%) or 2 (28%) in severity and resolved with no residual effect. Fifteen (15%) patients had grade 3 infections, and 6 (6%) patients had grade 4 infections consisting of pneumonia, sepsis, clostridial infection, infection systemic, septic shock, mycobacterial infection, and tuberculosis. One patient had grade 4 septic shock with a fatal outcome, and one patient had grade 3 lung infection considered definitely related to bendamustine treatment which resolved with no residual effect. Overall, 20 patients had fever or infection with grade 3 or 4 neutropenia, and most events resolved and were considered to be not related to study drug treatment.

In the supportive, 30 (39%) patients had documented infection in the absence of neutropenia and 13 (17%) patients had infection with neutropenia. The most commonly reported infections occurring in ≥ 2 patients with documented neutropenia were urinary tract infection (3, 4%) and 2 (3%) patients each for oral candidiasis, rectal abscess, sinusitis and an upper respiratory tract infection. In addition, 5 (6.6%) patients had events classified as febrile neutropenia (grade 3).

The most commonly reported infections without documented neutropenia occurring in ≥ 5% of patients were upper respiratory tract infection (9%, 7 patients), herpes zoster (8%, 6 patients), sinusitis (7%, 5 patients), and pneumonia (5%, 4 patients). The tabulated summary provided for infections reported in the pivotal study are considered to reflect the events reported in the supportive study.

7.2.3.6.4. Secondary neoplasms

In the pivotal study, emerging neoplasms other than lymphoma were reported in 2 patients (1 x myelodysplastic syndrome considered to be drug-related; 1 x squamous cell carcinoma considered to be unrelated to the study drug). *In the supportive study*, emerging neoplasms other than lymphoma considered to be related to bendamustine treatment were reported in 3 patients (2 x myelodysplastic syndrome; 1 x chronic myelomonocytic leukaemia).

7.2.3.7. Withdrawals due to adverse events

In the pivotal study, 31 (31%) patients discontinued study drug treatment due to AEs, and 27 (27%) of these patients discontinued due to drug-related AEs. Discontinuations of study drug treatment due to AEs reported in ≥ 2 patients were thrombocytopenia (9, 9%), fatigue (6, 6%), and neutropenia (4, 4%). All other AEs leading to discontinuation of study drug treatment were reported for 1 patient each.

In the supportive study, 30 (39%) patients discontinued treatment. The primary reason for discontinuation in 27 of the 30 patients was considered to be AEs, while in 3 of the 30 patients the primary reason was considered to be disease progression. Discontinuations of study drug treatment due to AEs in ≥ 2 patients were thrombocytopenia (13, 17%), neutropenia (5, 7%), and anaemia (2, 3%). All other AEs leading to discontinuation of study drug treatment were reported for 1 patient each.

7.2.4. Laboratory tests

7.2.4.1. Haematology

7.2.4.1.1. (a) Pivotal study

The proportion of patients with worst CTCAE grades or haematology test results overall (up to 8 cycles) is summarized below in Table 29, and the results in terms of patient-years are summarized below in Table 30.

Table 29: Refractory/relapsed indolent NHL - study SDX-105-03 worst CTCAE grade value for haematology results overall (up to 8 cycles) for patients, n (%) in the primary analysis set

	WBC, 10^9/L (n=100)	Hemoglobin, g/L (n=100)	ANC, 10^9/L (n=97)	Platelets, 10^9/L (n=100)	ALC, 10^9/L (n=97)
Grade 0	8 (8)	6 (6)	4 (4)	12 (12)	1 (1)
Grade 1	10 (10)	40 (40)	10 (10)	39 (39)	2 (2)
Grade 2	26 (26)	44 (44)	12 (12)	24 (24)	0
Grade 3	45 (45)	7 (7)	38 (38)	19 (19)	21 (21)
Grade 4	11 (11)	3 (3)	23 (23)	6 (6)	73 (73)

Note: ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; ALC=absolute lymphocyte count; WBC=white blood cell. ANC and ALC were calculated and summarized from the differentials as ANC=(%neutrophils+%bands)xWBC/100, ALC=%lymphocytes x WBC/100. If multiple laboratory tests were performed within a cycle, the worst grade was summarized.

Table 30: Refractory/relapsed indolent NHL - study SDX-105-03 sum of worst grades in haematology laboratory test results across cycles; patients, n (%), in the primary analysis set

	WBC, 10^9/L (n=531 cycles)	Hemoglobin, g/L (n=531 cycles)	ANC, 10^9/L (n=513 cycles)	Platelets, 10^9/L (n=531 cycles)	ALC, 10^9/L (n=513 cycles)
Grade 0	151 (28)	128 (24)	220 (41)	177 (33)	16 (3)
Grade 1	127 (24)	273 (51)	102 (19)	258 (48)	20 (4)
Grade 2	151 (28)	111 (21)	87 (16)	55 (10)	58 (11)
Grade 3	89 (17)	15 (3)	74 (14)	35 (7)	180 (34)
Grade 4	13 (2)	4 (1)	30 (6)	6 (1)	239 (45)

Note: ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; ALC=absolute lymphocyte count; WBC=white blood cell. ANC and ALC were calculated and summarized from the differentials as ANC=(%neutrophils+%bands)xWBC/100, ALC=%lymphocytes x WBC/100. If multiple laboratory tests were performed within a cycle, the worst grade was summarized.

Comment: *Significant neutropenia occurred* with bendamustine treatment (38%, grade 3 and 23%, grade 4), but in relatively few patient-cycles (grade 3 in 14% [74/513] and grade 4 in 6% [30/513] of patient cycles). Prophylactic use of granulocyte growth factors were discouraged in the first cycle. However, granulocyte growth factors (any cycle) were administered during the study to 38% of patients following neutropenia, and there was an increase in the number of patients receiving these factors over the course of the study. Documented neutropenic infections and febrile neutropenia occurred in 1% and 6% of patients, respectively.

Significant thrombocytopenia occurred with bendamustine treatment (grade 3 in 19% of patients, grade 4 in 6% of patients), but in relatively few patient-cycles (grade 3 events in 7% [35/531] and grade 4 in 1% [6/513] of patient-cycles). Thrombocytopenia was the most frequent AE leading to treatment discontinuation and the second most frequent AE leading to dose delay. One (1) patient received platelet transfusions because of thrombocytopenia. There were no significant events of haemorrhage related to thrombocytopenia. The frequency of thrombocytopenia did not change significantly as the number of cycles increased.

Significant lymphopenia occurred with bendamustine treatment in most patients (grade 3 in 21% of patients, and grade 4 in 73% of patients), and occurred in a notable number of patient-cycles (grade 3 events in 34% [180/513] and grade in 45% [239/513] of patient cycles).

7.2.4.1.2. (b) Supportive study

The results for patients with worst CTCAE grades for haematology laboratory results were similar to those for pivotal study (see Table 31 below), and the results in terms of patient-years are summarized below in Table 32.

Table 31: Refractory/relapsed indolent NHL - study SDX-105-101 worst CTCAE grade value for haematology results overall (1-8 cycles) for patients, n (%) in the primary analysis set

	WBC, 10^9/L (n=76)	Hemoglobin, g/L (n=76)	ANC, 10^9/L (n=76)	Platelets, 10^9/L (n=76)	ALC, 10^9/L (n=76)
Grade 0	2 (3)	5 (7)	11 (14)	12 (16)	1 (1)
Grade 1	11 (14)	27 (36)	7 (9)	27 (36)	3 (4)
Grade 2	21 (28)	35 (46)	17 (22)	18 (24)	4 (5)
Grade 3	35 (46)	9 (12)	23 (30)	12 (16)	20 (26)
Grade 4	7 (9)	0	18 (24)	7 (9)	48 (63)

Note: ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; ALC=absolute lymphocyte count; WBC=white blood cell. ANC and ALC were calculated and summarized from the differentials as ANC=(%neutrophils+%bands)xWBC/100, ALC=%lymphocytes x WBC/100. If multiple laboratory tests were performed within a cycle, the worst grade was summarized.

Table 32: Refractory/relapsed indolent NHL - study SDX-105-03 sum of worst grades in haematology laboratory test results across cycles; patients, n (%), in the primary analysis set

	WBC, 10^9/L (n=368 cycles)	Hemoglobin, g/L (n=368 cycles)	ANC, 10^9/L (n=368 cycles)	Platelets, 10^9/L (n=368 cycles)	ALC, 10^9/L (n=368 cycles)
Grade 0	91 (25)	101 (27)	174 (47)	162 (44)	31 (8)
Grade 1	105 (29)	163 (44)	51 (14)	131 (36)	28 (8)
Grade 2	89 (24)	76 (21)	66 (18)	35 (10)	49 (13)
Grade 3	59 (16)	13 (4)	41 (11)	17 (5)	142 (39)
Grade 4	9 (2)	0	21 (6)	8 (2)	103 (28)

Note: ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; ALC=absolute lymphocyte count; WBC=white blood cell. ANC and ALC were calculated and summarized from the differentials as ANC=(%neutrophils+%bands)xWBC/100, ALC=%lymphocytes x WBC/100. If multiple laboratory tests were performed within a cycle, the worst grade was summarized.

Comment: S*ignificant neutropenia occurred* with bendamustine treatment (30%, grade 3 and 24%, grade 4), but in relatively few patient-cycles (grade 3 in 11% [41/368] and grade 4 in 6% [21/368] of patient cycles). While use of prophylactic granulocyte growth factors was not allowed, 36% of patients received these factors following neutropenia. Documented neutropenic infections and febrile neutropenia occurred in 17% and 12% of patients, respectively.

S*ignificant thrombocytopenia* occurred with bendamustine treatment (grade 3 in 16% of patients, grade 4 in 9% of patients), but in relatively few patient-cycles (grade 3 in 5% [17/368] and grade 4 in 2% [8/368] of patient-cycles). Thrombocytopenia was the

single most frequent AE leading to treatment discontinuation and causing dose delay. One (1) patient received platelet transfusions because of thrombocytopenia. There were no significant events of haemorrhage related to thrombocytopenia. The frequency of thrombocytopenia did not change significantly as the number of cycles increased.

Significant lymphopenia occurred with bendamustine treatment in most patients (grade 3 in 26% of patients, and grade 4 in 63% of patients), and occurred in a notable number of patient-cycles (grade 3 events in 39% [142/368] and grade 4 events in 28% [103/368] of patient cycles).

7.2.5. Clinical chemistry

In the pivotal study, the number (%) of patients with worst grades for clinical chemistry laboratory values overall (up to 8 cycles) are summarized below in Table 33.

Table 33: Refractory/relapsed indolent NHL - study SDX-105-103 worst CTCA grade value for clinical chemistry tests overall (up to 8 cycles) for patients, n (%) in the primary analysis set

		Number (%) of patients					
		Bendamustine (N=100)					
Serum chemistry variable		Unknown	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Sodium (mmol/L)	low values	0	80 (80)	18 (18)	0	1 (1)	1 (1)
	high values	0	89 (89)	9 (9)	2 (2)	0	0
Potassium (mmol/L)	low values	0	75 (75)	19 (19)	0	5 (5)	1 (1)
	high values	0	89 (89)	7 (7)	2 (2)	2 (2)	0
Glucose (mmol/L)	low values	0	91 (91)	7 (7)	2 (2)	0	0
	high values	0	34 (34)	43 (43)	18 (18)	5 (5)	0
Creatinine (µmol/L)		0	80 (80)	12 (12)	5 (5)	2 (2)	1 (1)
Calcium (mmol/L)	low values	0	75 (75)	17 (17)	5 (5)	3 (3)	0
	high values	0	96 (96)	3 (3)	0	1 (1)	0
Albumin (g/L)		1 (1)	59 (59)	28 (28)	10 (10)	2 (2)	0
SGOT (AST) (U/L)		1 (1)	64 (64)	26 (26)	8 (8)	1 (1)	0
SGPT (ALT) (U/L)		1 (1)	73 (73)	24 (24)	2 (2)	0	0
Alk phos (U/L)		1 (1)	73 (73)	26 (26)	0	0	0
Total bilirubin (µmol/L)		1 (1)	86 (86)	9 (9)	3 (3)	1 (1)	0

Note: If multiple laboratory tests were performed within a cycle, the worst grade was summarized.

In the supportive study, the results for the proportion of patients with worst CTCAE grades for clinical chemistry laboratory results were similar to those for the pivotal study. Grade 3 or 4 AEs were reported for the following events: hyponatraemia (1%, 1 patient [grade 3]); hypokalaemia (4%, 3 patients [all grade 3]); hyperkalaemia (3%, 2 patients [both grade 3]); hyperglycaemia (3%, 2 patients [both grade 3]); and hypercalcaemia (1%, 1 patient [grade 4]).

7.2.6. Other safety results

No significant changes in vital signs of pulse, blood pressure (systolic, diastolic), temperature, or weight gain occurred from baseline over the course of the pivotal and supportive studies. Urinalysis was not performed in the pivotal or supportive studies.

In *the pivotal study*, there were 56 (56%) patients with weight loss from baseline over the course of the study (42 [42%] grade 1; 15 (15%) grade 2; 3 [3%] grade 3]), and in *the supportive study* there were 38 (50%) patients with weight loss from baseline over the course of study (27 [36%] grade 1; 9 [12%] grade 2; 2 [2%] grade 3).

In both the pivotal and supportive studies, 12-lead ECGs were performed at baseline and at the end-of-treatment evaluation, but only qualitative interpretation of ECGs as normal or abnormal was reported. *In the pivotal study*, of the 97 patients with baseline ECG recordings, 42 had normal findings and 55 had abnormal findings (not clinically significant). At end-of-treatment,

34 patients had no post-baseline ECG evaluation, 33 patients had normal ECG findings, and 33 patients had abnormal ECG findings (not clinically significant). In the *supportive study*, of the 76 patients with baseline ECG recordings, 31 had abnormal findings (not clinically significant) and 5 had abnormal clinically significant ECG findings at baseline (none preventing entry into the study). In 11 patients with normal ECG findings at baseline, at endpoint the ECG shifted to abnormal (clinically significant) and to abnormal (not clinically significant) in 2 patients.

In the pivotal study, of the 50 patients with WHO PS of 0 at baseline, 26, 21, 1, and 1 patients had endpoint scores of 0, 1, 2 or 3, respectively, and of the 45 patients with WHO PS of 1 at baseline, 9, 24, 6, 4, and 1 had endpoint scores of 0, 1, 2, 3 or 4, respectively*. In the supportive study,* of the 41 patients with WHO PS of 0 at baseline, 18, 18, 4, and 1 patients had endpoint scores of 0, 1, 2 or 3, respectively, and of the 30 patients with WHO PS of 1 at baseline, 10, 13, 3, and 2 patients had endpoint scores or 0, 1, 2 or 3 respectively.

During the course of the pivotal study, 33 (33%) patients received erythropoietin agonists (primarily darbepoetin alfa), 38 (38%) patients received granulocyte growth factors (mostly pegfilgrastim or fligrastim), and 18 (18%) patients received at least one blood product (12 x RBC concentrate; 5 x RBCs; 1 x whole blood; 1 x plasma; 1 x platelets). *During the course of the supportive study*, 28 (37%) patients received erythropoietin agonists (approximately equally split between darbepoetin alfa and epoetin alfa), 27 (36%) patients received granulocyte growth factors (mostly pegfilgrastim or fligrastim), and 23 (30%) patients received at least one blood product (22 x RBC concentrate; 1 x blood and related products; 1 x plasma; 1 x platelets).

7.3. First-line treatment indolent NHL and mantle-cell lymphoma

7.3.1. Overview

The safety data for B-R for the first-line treatment of indolent NHL and MCL in patients with CD20 positive stage III/IV disease are limited to the published information from the pivotal study (Rummel et al 2013). In this study, patients were treated with B-R or R-CHOP for a maximum of 6 cycles. The safety analysis set consisted of 267 patients in the B-R arm and 252 patients in the R-CHOP arm, and included patients who received at least one dose of study treatment. The median follow-up period for patients in the study was 45 months (IQR: 25, 75 months).

7.3.2. Haematological adverse events

Haematological toxic events reported in patients receiving at least one dose of study drug are summarized below in Table 34.

Table 34: Rummel et al., 2013 - Haematological toxic events

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 3–4	
	R-CHOP	B-R	R-CHOP	B-R	R-CHOP	B-R	R-CHOP	B-R	R-CHOP	B-R
Leucocytopenia	13 (5%)	52 (19%)	39 (15%)	80 (30%)	110 (44%)	85 (32%)	71 (28%)	13 (5%)	181 (72%)*	98 (37%)*
Neutropenia	6 (2%)	30 (11%)	19 (8%)	61 (23%)	70 (28%)	53 (20%)	103 (41%)	24 (9%)	173 (69%)*	77 (29%)*
Lymphocytopenia	12 (5%)	14 (5%)	72 (29%)	38 (14%)	87 (35%)	122 (46%)	19 (8%)	74 (28%)	106 (43%)	196 (74%)
Anaemia	115 (46%)	102 (38%)	84 (33%)	44 (16%)	10 (4%)	6 (2%)	2 (<1%)	2 (<1%)	12 (5%)	8 (3%)
Thrombocytopenia	89 (35%)	104 (39%)	20 (8%)	19 (7%)	11 (4%)	15 (6%)	5 (2%)	2 (<1%)	16 (6%)	13 (5%)

B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab. *p<0·0001 between groups.

Table 3: **Haematological toxic events in patients receiving at least one dose of study treatment**

Comment: The most notable difference between the two treatment arms was the higher incidence of grade 3-4 leukopenia and neutropenia in patients in the R-CHOP arm compared with the B-R arm. However, Grade 1-2 leukopenia occurred more commonly in patients in the B-R arm than in the R-CHOP arm (49% vs 20%, respectively) as did neutropenia (34% vs 10%, respectively). Lymphopenia grade 3-4 occurred notably more commonly in patients in

the B-R than in the R-CHOP arm, while grade 1-2 lymphopenia occurred more commonly in patients in the R-CHOP arm than in the B-R arm. The authors of the pivotal study commented that there no "relevant cases of thrombocytopenia or anaemia in either group, but GSF use was significantly reduced in the bendamustine plus rituximab group compared with R-CHOP group (58 cycles [4%] vs 282 cycles [20%]; p<0.0001)". Most reports of anaemia in both treatment arms were Grade 1-2 events, while most reports of thrombocytopenia in both treatment arms were Grade 1 events.

7.3.3. Non-haematological adverse events

7.3.3.1. (a) Commonly occurring non-haematological adverse events (SOC, PT)

The most commonly reported non-haematological AEs reported in ≥ 10% of patients in either treatment arm (B-R vs R-CHOP) in decreasing order of frequency in the B-R arm were: vomiting (42% [113/267] vs 46% [115/252]); pyrexia (21% [56/267] vs 22% [56/252]); fatigue (16% [42/267] vs 12% [31/252]); diarrhoea (15% [41/267] vs 16% [40/ 252]); and lung disorder (11% [29/267] vs 16% [40/252])

Non-haematological AEs occurring in ≥ 5% of patients in either treatment and in ≥ 2% more patients in the B-R arm than in the R-CHOP arm were: fatigue (16% [42/267] vs 12% [31/252]); chills (5% [13/267] vs 2% [5/252]); and cough (5% [13/252] vs 3% [8/267]).

Non-haematological AEs occurring in ≥ 5% of patients in either treatment and in ≥ 2% more patients in the R-CHOP arm than in the B-R arm were vomiting (46% [115/252] vs 42% [113/267]); lung disorders (16% [40/252] vs 11% [29/267]); arrhythmias (6% [14/252] vs 4% [11/267]), cardiac disorders (5% [13/252] vs 3% [9/267]); and hypotension (5% [12/252] vs 3% [9/267].

> Comment: The most notable feature of the non-haematological commonly occurring AEs in the two treatment arms was the greater incidence of the cardiovascular events of arrhythmias, cardiac disorders and hypotension in the R-CHOP arm compared with the B-R arm. Overall, there was no evidence from the provided data that patients treated with B-R are at a greater risk of experiencing commonly occurring non-haematological AEs than patients treated with R-CHOP.

7.3.3.2. (b) Statistically significant non-haematological adverse events

Non-haematological AEs occurring statistically more commonly in one of the treatment arms compared with the other are summarized below in Table 35. This table was presented in the text of *Rummel et al (2013)*, and although not stated in the text appears to consist of groups of preferred terms for most events.

Table 35: Rummel et al 2013 - Non-haematological toxicities occurring statistically significantly more frequently in one treatment arm compared with the other

	B-R (n=261)	R-CHOP (n=253)	p value
Alopecia	0	245 (100%)*	<0·0001
Paresthesia	18 (7%)	73 (29%)	<0·0001
Stomatitis	16 (6%)	47 (19%)	<0·0001
Skin (erythema)	42 (16%)	23 (9%)	0·024
Skin (allergic reaction)	40 (15%)	15 (6%)	0·0006
Infectious episodes	96 (37%)	127 (50%)	0·0025
Sepsis	1 (<1%)	8 (3%)	0·019

B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab. *Includes only patients who received three or more cycles.

Table 4: **All grades of non-haematological toxic events in patients receiving at least one dose of study treatment**

Comment: Skin reactions were reported more commonly in patients in the B-R arm compared with the R-CHOP arm, but no cases of Steven-Johnson syndrome or toxic epidermal necrolysis were reported in either arm. Drug associated erythematous skin reactions (urticaria, rash) were observed more commonly in patients in the B-R arm than in the R-CHOP arm, as were skin irritations occurring in combination with fever and assessed as allergic skin reactions. Infectious episodes and sepsis both occurred more commonly in patients in the R-CHOP arm than in the B-R arm, and severe complications with fatal outcome occurred more frequently in the R-CHOP arm than in the B-R arm (5 vs 1, respectively). Neurotoxic effects, specifically peripheral neuropathy, occurred significantly less frequently in patients in the B-R arm compared with the R-CHOP arm. No cases of alopecia were observed in patients in the B-R arm who received three or more cycles, while alopecia occurred in all patients in the R-CHOP arm who received three or more cycles. Stomatitis occurred significantly less frequently in patients in the B-R arm compared with the R-CHOP arm.

7.3.3.3. (c) Non-haematological AEs (WHO grade 3 and 4) by SOC and PT

Non-haematological AEs (WHO grade 3 or 4) reported in ≥ 2% of patients in either treatment arm and more commonly in the B-R arm than in the R-CHOP arm were chills (1% [n=3] vs < 1% [n=1]), pyrexia (6% [n=15] vs 5% [n=12]); and pulmonary embolism (1% [n=3]) vs 0%). Most of the non-haematological AEs (WHO grade 3 or 4) reported in ≥ 2% of patients in either treatment arm occurred more frequently in the R-CHOP arm than in the B-R arm, with two events occurring with the same incidence in both treatment arms.

Comment: Severe non-haematological AEs (WHO grade 3 or 4) occurred notably less frequently in patients in the B-R arm than in the R-CHOP arm. Of note, 3 (1%) patients in the B-R arm experienced grade 4 pulmonary embolism compared with no patients in the R-CHOP arm, 10 (4%) patients in the B-R arm experienced grade 4 pyrexia compared with 7 (3%) patients in the R-CHOP arm, and 3 (1%) patients in the B-R arm experienced grade 4 chills compared with 1 (<1%) patient in the R-CHOP arm.

7.3.3.4. (d) CTCAE grade 3 or 4 serum chemistry results

CTCAE grade 3 or 4 serum chemistry laboratory test results were summarized.

Comment: The number of patients in both treatment groups with events was small. The results suggest no significant difference between the two treatment groups as regards CTCAE grade 3 or 4 serum chemistry results. In particular, treatment with B-R was not associated with hepatic or renal toxicity.

7.3.3.5. (e) Worst CTCAE grades for serum chemistry laboratory test results

Worst CTCAE grades for serum chemistry laboratory test results overall for both treatment arms were summarized.

Comment: There were no marked differences between the two treatment groups as regards overall worst CTCAE grades for serum chemistry results. However, Grade 1-4 worst CTCAE grades for AST, ALT, and total bilirubin occurred 2-3% more frequently in the B-R arm than in the R-CHOP arm, and 4% more frequently for alkaline phosphatase.

7.3.4. Secondary malignancies

Secondary malignancies were reported in 20 (7.5%) patients in the B-R group and 23 (9.1%) patients in the R-CHOP group, with one haematological malignancy in each group (1 x myelodysplastic syndrome in the B-R group and 1 x acute myeloid leukaemia in the R-CHOP group).

7.3.5. Deaths

There was no discussion of deaths in the safety analysis population, apart from reference to a greater number of deaths in the R-CHOP group compared with the B-R group due to severe

infections resulting in death. However, the overall survival analysis showed that 43 (16.5%) patients died in the B-R group compared with 45 (17.8%) patients in the R-CHOP group.

7.4. Post-marketing experience

7.4.1. Provided post-marketing data

The post-marketing data included two periodic safety up date reports in ICH format for bendamustine covering the periods 01 April 2007 through 06 July 2010 (PSUR 1), and 07 July 2010 to 07 July to 06 January 2011 (PSUR 2). In addition, the post-marketing data included a document written in German dated 11/1998 which appears to be a post-marketing report, a PSUR identified as number 1 (Bulgaria) for the period 01 January 1994 to 30 April 2004, and an Overall Safety Update Report (SUR) for the period 01 January 1994 to 31 March 2007 that appears to have been prepared for the EU decentralized evaluation procedure. The post-marketing data from the two PSURs in ICH format have been reviewed.

7.4.2. PSUR1 and PSUR2 - ICH format

The PSUR/ICH format documents indicate that the international birth date (IBD) of bendamustine HCl is 10 November 1971 in the former German Democratic Republic. In addition, the documents indicate that by European Commission Decision of 7 July 2010, bendamustine as powder for concentrate for solution for infusion was recommended for approval in EU Member States.

PSUR2 states that the formulation for iv administration is currently approved in 17 countries, and marketed in 14. The PSUR also indicates that a new oral formulation (liquid filled hard capsules, containing 55.10 mg bendamustine per capsule) is being investigated.

PSUR2 indicates that cumulative market exposure to bendamustine since 1994 has been approximately 104,375 patients (42,974 exposed to 100 mg/m^2/day and 61,401 exposed to 120 mg/m^2/day). No sales data are available for the time period from 1971 to 1994.

In Europe, estimated post-marketing exposure from 2007 through to 2010 was 9,594 CLL patients, 8,934 NHL patients, 5,294 MM patients, and 9,265 other patients. In the USA, estimated post-marketing exposure from 2008 through to 2012 was 14,300 CLL patients and 16,200 NHL patients.

PSUR2 indicates that Astellas has received 1,471 medically confirmed cases describing adverse events since 01 April 2007 through to 06 January 2011 (1,071 in PSUR1 plus 401 in PSUR2)

In PSUR2, the following events of interest requiring monitoring were identified (same as PSUR1):

- Secondary malignancies
- Steven-Johnson syndrome / Toxic epidermal necrolysis
- Opportunistic infections
- Cardiac events
- Hepatic events
- Renal events
- Pulmonary embolism (including symptoms of dyspnoea, tachypnoea, and pleuritic pain), which the sponsor considered to be possibly due to silicon oil contamination and required temporarily monitoring until all batches contaminated with silicon oil have expired.

7.5. Evaluator's overall conclusions on clinical safety

7.5.1. Chronic lymphocytic leukaemia

In the pivotal study (02CLLIII), the safety population included 161 patients in the bendamustine arm and 151 patients in the chlorambucil arm. Based on the "rule of three", the upper limit of the 95% CI for the rate of adverse reactions associated with bendamustine is approximately 2%. Consequently, it is unlikely that adverse reactions associated with bendamustine occurring with an incidence of < 2% have been detected in the pivotal study. The mean (SD) number of treatment cycles in each arm was identical at 4.9 (1.7) cycles, as was the range of treatment cycles (1-6). The mean (SD) relative dose per cycle was 89.4% (21.0%) in the bendamustine arm, and 94.7% (20.8%) in the chlorambucil arm. The difference in the planned dose between the two treatment arms reflects the higher percentage of dose reductions due to toxicity in the bendamustine arm than in the chlorambucil arm (33.5% vs 30.5%). The median observation time in patients at the time of the follow-up analysis was 35 months (range: 1, 68) (Knauf et al., 2009).

Overall, the safety profile of bendamustine for the treatment of CLL was notably inferior to that of chlorambucil. In the bendamustine arm, 88.8% (n=143) of patients experienced at least one AE (660 events) compared with 80.8% (n=122) of patients in the chlorambucil arm (385 events), and the majority of AEs in both treatment arms were considered to be treatment-related or to have missing causality information (82.0%, 132 patients, 471 events vs 64.2%, 97 patients, 225 events, respectively).

Severe AEs (grade 3 or 4 CTC/Cheson) occurred more frequently in patients in the bendamustine arm than in the chlorambucil arm (52.8%, 85 patients, 175 events vs 31.1%, 47 patients, 72 events), and both severe haematological AEs and severe non-haematological AEs occurred notably more commonly in the bendamustine arm than in the chlorambucil arm.

Severe haematological AEs (grade 3 or 4 CTC/Cheson) were reported in 40.4% (n=65) patients in the bendamustine arm and 19.2% (n=40.4%) of patients in the chlorambucil arm. The most commonly reported severe haematological AE (grade 3 or 4 CTC/Cheson) in both the bendamustine and chlorambucil treatment arms was neutropenia, including granulocytopenia (23.0%, 37 patients vs 10.6%, 16 patients, respectively). Severe infections (grade 3 or 4 CTC/Cheson) were reported notably more commonly in the bendamustine arm than in chlorambucil arm (8.7%, 14 patients vs 3.3%, 5 patients), and severe allergic reactions (grade 3 or 4 CTC/Cheson) occurred more commonly in the bendamustine than in the chlorambucil arm (5.6%, 9 patients vs 5, 3.3%).

Serious adverse events (other than death) occurred more frequently in patients in the bendamustine arm than in the chlorambucil arm (19.3%, 31 patients, 38 events vs 12.6%, 19 patients, 22 events), and there were 31 (19.3%) deaths in the bendamustine arm and 41 (27.2%) deaths in the chlorambucil arm.

Withdrawals due to unacceptable toxicity or risk/benefit assessment occurred notably more frequently in the bendamustine arm than in the chlorambucil arm (11.2%, 18 patients vs 3.3%, 5 patients), while dose modifications due to AEs occurred in a similar proportion of patients in the two treatment arms (33.5%, 54 patients vs 30.5%, 46 patients, respectively).

The changes in haematology laboratory parameters have been discussed above. There were no marked differences between the two treatment arms in clinical chemistry laboratory changes or urinalysis changes over the course of the study. There were no notable differences between the two treatment arms relating to vital signs of changes from baseline in weight, BSA, blood pressure, pulse rate or temperature. There were not notable changes in WHO PS over the course of the study in the two treatment arms. ECG changes remained largely unchanged over the course of the study in both treatment arms, but no systematic assessment of changes in the QT interval were undertaken.

7.5.2. Refractory/relapsed indolent NHL

The safety of bendamustine for the treatment of indolent NHL refractory to rituximab has been assessed in 176 patients (100 patients in the pivotal study SDX-105-03 and 76 patients in the supportive study SDX-105-01). The safety assessment is based on open-label bendamustine data. Consequently, the interpretation of the data is limited due to the absence of a control group. However, selection of an appropriate control treatment would have been problematic in this population of heavily pre-treated patients with indolent relapsed/refractory NHL.

In the *pivotal study* (n=100), the median number of treatment cycles was 6 and the mean relative dose intensity was 88%, and in the *supportive study* (n=76) the median number of treatment cycles was 5 and the mean relative dose intensity was 87%. The safety profile of bendamustine was similar in both studies, and was consistent with the safety profile of the drug in patients with CLL. In the total population (n=176), all patients experienced at least one AE and nearly all of these events (96%) were considered to be treatment-related.

In the *pivotal study* (n=100), the median cycle length was 22.4 days and 68% (n=68) of patients had dose reductions or delays or did not receive both doses in the cycle at some point during the course of treatment. In the *supportive study* (n=76), the median cycle length was 23.1 days, and 61% (n=46) of patients had dose reductions or delays or did not receive both doses in the cycle at some during the course of treatment.

The major safety concern with the use of bendamustine in patients with relapsed/refractory indolent NHL relate to haematological toxicity. In the total population, "blood and lymphatic disorders" (SOC) occurred in 62% (109/176) of patients. Haematological AEs reported in ≥ 20 % of patients in the total population were neutropenia (38%), anaemia (35%), and thrombocytopenia (31%). Of note, grade 3 or 4 haematological AEs occurring in ≥ 10% of patients in the total population were neutropenia (32%), thrombocytopenia (24%) and anaemia (12%). The SAE of febrile neutropenia was reported in 5% (n=9) of patients in the total population, while the SAEs of anaemia and neutropenia were reported in 3% (n=5) and 2% (n=3) of patients, respectively.

In both the *pivotal and supportive studies*, haematological AEs were the most commonly reported events leading to discontinuation of study drug treatment. In the *pivotal study*, discontinuations of study drug treatment due to thrombocytopenia occurred in 9% (n=9) of patients, followed by neutropenia in 4% (n=4). In the *supportive study*, discontinuations of study drug treatment due to thrombocytopenia occurred in 17% (n=13) of patients followed by neutropenia and anaemia in 7% (n=5) and 3% (n=2), respectively. In the *pivotal study*, dose delays occurred in 30% (n=30) of patients due to neutropenia and 19% (n=19) of patients due to thrombocytopenia.

In the *pivotal study*, haematology laboratory test results showed that lymphopenia was the most commonly observed abnormality associated with worst case grade 3 or 4 CTCAEs over all treatment cycles (419 [82%] of 513 patient-cycles), with most patients experiencing worst grade 3 or 4 lymphopenia following bendamustine (97% [94/97]). Neutropenia worst grade 3 or 4 CTCAE was observed in 20% (104/513) of patient-cycles, with 63% (61/97) of patients experiencing worst grade 3 or 4 neutropenia following bendamustine. Overall, thrombocytopenia worst grade 3 or 4 CTCAE was observed in 8% (41/531) of patient-cycles and 25% (25/100) of patients, while anaemia worst grade 3 or 4 CTCAE was observed in 4% (19/531) of patient-cycles and 10% (10/100) of patients. The haematology laboratory results for the *supportive study* were consistent with those for the pivotal study.

Of the non-haematological AEs, those occurring in ≥ 20% of patients in the total population (n=176) were nausea (75%), fatigue (57%), vomiting (40%), diarrhoea (37%), pyrexia (34%), constipation (29%), anorexia (23%), cough (22%), and headache (21%). Non-haematological grade 3 or 4 AEs occurred in 53% of patients, and grade 3 or 4 AEs reported in ≥ 2% of patients were fatigue (11%), febrile neutropenia (6%), pneumonia (5%), dehydration (5%), hypokalaemia (5%), nausea (4%), vomiting (3%), diarrhoea (3%), herpes zoster (3%), back

pain (3%), pyrexia (2%), asthenia (2%), urinary tract infection (2%), weight decreased (2%), anorexia (2%), and dyspnoea (2%).

In the *pivotal study,* SAEs occurred in 39 (39%) patients including death in 11 (11%) patients, while in the supportive study SAEs occurred in 26 (34%) of patients including death in 3 (4%) patients. In the *pivotal study*, the most common SAEs occurring in ≥ 5% of patients were febrile neutropenia (6%, 6 patients), and pneumonia (5%, 5 patients). In the *supportive study*, SAEs occurring in 4% of patients were anemia (5%, 4 patients), and febrile neutropenia, pneumonia, and dehydration each occurring in 4% (3 patients) of patients.

In the *pivotal study*, 31 (31%) patients discontinued study drug treatment due to AEs, and 27 (27%) of these patients discontinued treatment due to drug-related AEs. Discontinuations of study drug treatment due to AEs reported in ≥ 2 patients were reported for thrombocytopenia (9 [9%] patients), fatigue (6 [6%] patients), and neutropenia (4 [4%] patients). *In the supportive study*, 30 (39%) patients discontinued study drug treatment due to AEs. Discontinuations of study drug treatment due to AEs in ≥ 2 patients were thrombocytopenia (13 [17%] patients), neutropenia (5 [7%] patients), and anaemia (2 [3%] patients).

Clinical chemistry laboratory abnormalities observed during both the *supportive and pivotal studies* do not give rise to concern. Similarly, changes in the vital signs of pulse rate, blood pressure, temperature and weight gain do not give rise to concern. However, weight loss over the course of treatment was observed in a notable proportion of patients in both the *pivotal and supportive studies.* There appears to have been only a small number of patients with clinically abnormal ECG recordings the pivotal and supportive studies, but there was no systematic assessment of QT interval changes in either study.

7.5.3. First-line indolent NHL and MCL

The safety data for the proposed first-line treatment of indolent NHL and MCL are from one study *Rummel et al.,* 2013. The safety data from this study includes information on 267 patients who received at least one "dose" of B-R and 252 patients who received at least one "dose" of R-CHOP. It was not clear whether the one "dose" referred to one cycle. The safety data from *Rummel et al (2013)* showed that B-R was generally better tolerated than R-CHOP. However, while the data are promising it is considered that they are not sufficient to make a definitive assessment of the safety of B-R for the proposed indication.

In order for a definitive assessment of the safety of B-R for the proposed indication to be made the sponsor should provide conventional safety data included in a CSR. Evaluation of conventional safety data is considered to be particularly important for the proposed indication, given that B-R has not been approved in any country for first-line treatment of indolent NHL or MCL in treatment-naive patients. Consequently, there are no safety data based on extensive overseas experience with the B-R combination for the proposed indication that would support approval in the absence of conventional safety data.

The limitations of the submitted safety data include:

- No data on the extent of exposure relating to number of patients per cycle, mean number of cycles per patient, overall dose per cycle (mean and relative dose), and mean total dose per cycle. The extent of exposure in the two treatment groups needs to be known in order to meaningfully compare their safety profiles. Significant imbalance in the extent of exposure between two treatment groups might complicate interpretation of the safety data.
- No data on the proportion of patients requiring dose modifications due to AEs, or on the nature of the AEs resulting in dose modifications. Data on dose modifications include patients requiring downward dose adjustments because of toxicity, and patients requiring temporary treatment discontinuations due to toxicity. Significant imbalance in dose modification data between the two treatment groups might impact on benefit-risk assessment.

- No data on the total number of AEs experienced by patients in the two treatment groups (overall, and individual events). Significant imbalance in the number of clinically significant AEs between the two treatment groups might impact on benefit-risk assessment.
- No data on the incidence of AEs by treatment cycle.
- No data on AEs considered to be treatment-related.
- No data on conventional defined serious adverse events (i.e., fatal or life threatening, resulting in persistent disability or incapacity, requiring in-patient hospitalization or prolongation of existing hospitalization, resulting in congenital and/or causing secondary malignancies). Limited data on secondary malignancies were provided (total number and haematological), but no case narratives of the two patients with secondary haematological malignancies were provided and no information on the nature of secondary non-haematological malignancies were provided. No case narratives of patients experiencing SAEs were provided. No data were provided on suspected unexpected serious adverse reactions (SUSARs).
- No comprehensive data on deaths in the safety analysis population (i.e., causes of death and case narratives). Significant imbalance in the nature of the deaths between the two treatment groups might impact on benefit-risk assessment.
- No data on permanent treatment discontinuation of the study-drugs due to AEs. Significant imbalance in permanent treatment discontinuation between the two treatment groups might impact on benefit-risk assessment.
- No data on the nature of the infections reported in the two treatment groups.
- No data on the proportion of patients requiring treatment with erythropoietin agonists, or transfusions with blood products for anaemia or thrombocytopenia.
- No data on changes in vital signs or the ECG during the course of the study were provided.
- No data safety data based on age differences (e.g., ≥ 65 years vs < 65 years).

8. First round benefit-risk assessment

8.1. First round assessment of benefits

8.1.1. Chronic lymphocytic leukaemia

It is considered that the pivotal study (02CLLIII) has satisfactorily demonstrated that the benefits of bendamustine (n=162) for the treatment of patients with CLL (Binet stage B or C) at the dose proposed for registration were significantly superior to chlorambucil (n=157). The duration of treatment depended on response. Patients with complete or partial remission received two consolidation cycles with a maximum of 6 cycles. Patients with no change in their disease status received at least 3 cycles. Patients in whom the disease progressed discontinued study treatment. The benefits described below relate to the outcome assessments undertaken by the ICRA.

The overall response rate (ORR = CR+PR=nPR) was significantly greater in patients treated with bendamustine compared with chlorambucil (67.9% vs 30.6%, respectively, p<0.0001). The treatment effect (difference in ORR between the two treatment arms) significantly favoured patients treated with bendamustine compared with chlorambucil (37.3% [95% CI: 21.7%, 47.4%]; p<0.001), after adjusting for Binet stage. The treatment effect in favour of bendamustine was also seen in patients with CLL Binet stage B or C, and was similar in the two stages (36.5% and 39.1%, respectively). The CR was notably greater in patients treated with bendamustine compared with chlorambucil (30.9% vs 1.9%, respectively). The benefits of

bendamustine were also observed in both male and female patients, and patients < 65 years of age and ≥ 65 years of age (with no data on patients > 75 years of age).

The median duration of progression free survival was 13.3 months longer in bendamustine treated patients compared with chlorambucil treated patients (21.6 months [95% CI: 18.6, 31.0 months] vs 8.3 months [95% CI: 5.9, 11.3 months]; p<0.0001). According to KM estimates, the proportion of patients free of progression 12 months after randomization was notably greater in the bendamustine arm than in the chlorambucil arm (78.6% vs 34.9%, respectively). The HR CLB/BEN was 4.37 (95% CI: 3.14, 4.37), indicating that patients treated with chlorambucil had a 4.4-fold significantly increased risk of experiencing an event compared with patients in the bendamustine arm. The benefits of bendamustine compared with chlorambucil relating to PFS were also observed in patients with CLL Binet stage B or C, both male and female patients, and patients < 65 years of age and ≥ 65 years of age (with no data on patients > 75 years of age).

The median time to progression from the start of therapy to PD, or relapse after intercurrent remission, or CLL related death was 15.6 months greater in bendamustine treated patients compared with chlorambucil treated patients (23.9 months [95% CI: 20.7, 31.5 months] vs 8.3 months [95% CI: 6.0, 11.4 months]; p<0.0001). According to KM estimates, 81.2% of patients in the bendamustine arm and 35.4% of patients in the chlorambucil arm were free of progression 12 months after randomization. The HR CLB/BEN was 4.70 (95% CI: 3.36, 6.58), indicating that patients treated with chlorambucil had a 4.7-fold significantly increased risk of experiencing an event compared with patients in the bendamustine arm.

The median duration of overall response from the time of maximum response (CR, nPR, PR) to PD or death was 13.8 months longer in patients treated with bendamustine compared with chlorambucil (21 months [95% CI: 17.4, 27.0 months] vs 8.0 [95% CI: 6.3, 9.3], respectively, p<0.0001). According to KM estimates, 75.6% of patients in the bendamustine arm and 24.1% of patients in the chlorambucil group were still responding 12 months after randomization. The HR CLB/BEN was 4.46 (95% CI: 2.89, 6.88), indicating that patients treated with chlorambucil had a 4.5-fold significantly increased risk of experiencing an event compared with patients in the bendamustine arm.

For patients treated with bendamustine compared with chlorambucil, the median duration of CR was 21.3 months longer (29.3 vs 8.0 months), the median duration of nPR was 7.7 months longer (18.6 vs 10.9 months), and the median PT was 10.9 months longer (17.4 vs 6.5 months).

Patients treated with bendamustine did not demonstrate a significant overall survival benefit compared with patients treated with chlorambucil, with no marked differences between the two treatment arms being observed at the date of data cut-off for the analysis. Patients treated with bendamustine did not demonstrate a significant improvement in quality of life compared with patients treated with chlorambucil, with no marked differences between the two treatment arms being observed in these parameters in the third interim analysis.

8.1.2. Relapsed/refractory indolent NHL

The benefits of bendamustine as monotherapy for the treatment of indolent B-cell NHL refractory to rituximab have been satisfactorily demonstrated in one pivotal Phase III study (SDX-105-03) in 100 patients. Limited supportive efficacy data is provided by the Phase II study (SDX-105-01) in 76 patients. However, it should be noted that the Phase II study included 15 (20%) patients with transformed NHL rather than indolent NHL, and 23 (30%) patients had responded to their most recent rituximab-regimen while 8 (11%) patients had an unknown response to this regimen.

The bendamustine regimen used in the both the pivotal and supportive studies was 120 mg/m^2 on days 1 and 2 every 3 weeks for at least 6 cycles, and this is the dosage regimen being proposed by the sponsor for the treatment of indolent NHLs refractory to rituximab. In both the pivotal and supportive studies, the benefits of bendamustine were demonstrated in open-label, single-dose studies. However, in heavily pre-treated patients with indolent NHL refractory to

rituximab and/or chemotherapy it is reasonable to infer that the benefits seen with bendamustine as monotherapy relate to the effects of the drug on the disease.

In the pivotal study, the ORR and the DR were co-primary efficacy endpoints, and the results for both endpoints were required to be statistically significant in order for the study to have established a treatment benefit for bendamustine. PFS in this study was a secondary efficacy endpoint.

In the pivotal study, the ORR (IRC assessment) in the primary analysis set (n=100) was 75% (95% CI: 65%, 83%), and was statistically significant ($p<0.0001$) as the ORR was ≥ 40%. It had been pre-specified that the null hypothesis was to be rejected if the ORR was ≥ 40%. It is noted that both the point estimate for the ORR and the lower bound 95% CI of the estimate are well above 40%. The ORR was based on the best-response of CR, CRu or PR. Overall response was achieved by 75 out of the 100 patients in the primary analysis set, and included 14 (14%) patients with CR, 3 (3%) patients with CRu, and 58 (58%) patients with PR. In the 25 (25%) patients in the primary analysis set not meeting the response criteria for inclusion in the ORR analysis, 16 (16%) had SD, 7 (7%) had PD and 2 (2%) had an unknown response.

In the pivotal study, the median DR (IRC assessment) in the primary analysis set with a best overall response of CR, CRu, or PR was 40.1 weeks (95% CI: 31.0, 46.9 weeks), based on 39 (52%) patients with PD/death/change of therapy and 36 (48%) censored patients out of a total of 75 patients included in the analysis. The results were significant as it had been pre-specified that the null hypothesis was to be rejected if the median DR was > 6 months (26 weeks) and the lower bound 95% CI was > 4 months (17 weeks). Patients who responded had durable responses (medians of 45, 59, and 36 weeks for patients with CR, CRu, and PR, respectively).

In the pivotal study, the median PFS (IRC assessment) in all patients in the primary analysis set was 40.3 weeks (95% CI: 35.0, 51.9), based on 57 (57%) patients with PD/death/change of therapy and 43 (43%) censored patients out of a total of 100 patients in the analysis. The analysis was primarily driven by disease progression (47 patients) followed by death (5 patients) and change of therapy (5 patients).

In the supportive study (SDX-105-01), the ORR (investigator assessment) in the primary analysis set (n=76) was 76.3% (95% CI: 65.2%, 85.3%). It had been pre-specified that bendamustine was considered to be "promising" if the ORR was 35% or higher. Of the 76 patients in the primary analysis set, 58 (76%) achieved a response (11, 14%, CR; 14, 18%, CRu; 33, 43%, PR).

The ORR was 67% (95% CI: 38%, 88%) in patients with transformed disease (i.e., 10 patients out of 15, including Cr = 0, Cru = 2, and PR = 8), and 79% (95% CI: 66%, 88%) in patients without transformed disease (i.e., 48 patients out of 61, including Cr = 11, CRu = 12, PR =25).

In the supportive study, the median DR (investigator assessment) in the primary analysis for patients who had achieved CR, CRu, or PR was 29.0 weeks (95% CI: 22.1, 43.1 weeks), based on 38 patients with progressive disease/death/change of therapy and 20 censored patients out of the total 58 patients in the analysis. The median PFS in the primary analysis for all patients was 31.0 weeks (95% CI: 26.1, 38.7 weeks), based on 55 patients with progressive disease/death/change of therapy and 21 censored patients out of the total 76 patients in the analysis.

Overall, the data from the pivotal and supportive studies are considered to show that bendamustine at the proposed dose for the treatment of patients with indolent NHL refractory to rituximab results in a clinically meaningful benefit in the ORR, DR and PSF. However, there are no data from the pivotal or supportive studies indicating that bendamustine at the proposed dose will provide a survival benefit in this patient population.

8.1.3. First-line treatment of indolent NHL and mantle-cell lymphoma.

The benefits of treatment with bendamustine in combination with rituximab (B-R) for the treatment of first-line treatment of indolent NHL and MCL in patients with CD20 positive stage III/IV disease have been satisfactorily established in one pivotal study (StiL NHL 1-2003) with published results (Rummel et al 2013). In the pivotal study, bendamustine 90 mg/m^2 administered by iv infusion over 30 to 60 minutes on days 1 and 2 of a 4-week cycle for up to 6 cycles plus rituximab 375 mg/m^2 iv on day 1 of each cycle 1 was compared with R-CHOP for up to 6 cycles (an Australian approved regimen for first line treatment of CD20 positive stage III/IV follicular B-cell lymphoma) The median duration of patient follow-up in the study was 45 months (IQR: 25, 75 months), and 261 patients were assessed in the B-R arm and 275 patients were assessed in the R-CHOP arm.

The pivotal study established that B-R was at least non-inferior to R-CHOP, as assessed by PFS (the primary efficacy endpoint). PFS was significantly longer in patients treated with B-R compared with R-CHOP (HR = 0.58 [95% CI: 0.44, 0.74]; p< 0.0001). The median duration of PFS for patients treated with B-R was 38.3 months longer than for patients treated with R-CHOP (69.5 months [IQR: 26.1, NR] vs 31.2 months [IQR: 15.2, 65.7], respectively), and this difference is considered to be clinically meaningful. In a pre-planned analysis, PFS was significantly improved in patients treated with B-R compared with R-CHOP for histological subtypes of follicular lymphoma (p=0.0072), mantle-cell lymphoma (p=0.0044) and Waldenstrom's macroglobulinaemia (p=0.0033), but not for marginal-zone lymphoma (p=0.3249).

The secondary efficacy endpoints of ORR (CR + PR) were similar for the two treatment arms, 93% (242/261) in the B-R arm compared with 91% (231/253) in the R-CHOP arm. However, the CR was significantly higher in the B-R arm compared with the R-CHOP arm (40% [104/261] vs 30% [76/253]), respectively, p=0.021).

The secondary efficacy endpoint of TTNT was significantly longer in the B-R arm compared with the R-CHOP arm (HR = 0.52 [95% CI: 0.39, 0.69]; p<0.0001). The median TTNT was not reached for the B-R arm (IQR: 35.1 months, not reached), while in the R-CHOP arm the median TTNT was 42.3 months (IQR: 18.2 months, not reached). At the time of the analysis, 74 salvage treatments had been started by patients in the B-R arm compared with 116 in the R-CHOP arm.

There was no difference between the two treatment arms in OS, with 43 deaths being reported in the B-R compared with 45 deaths in the R-CHOP arm. The median duration of OS had not been reached in either treatment arm.

The were no data assessing whether the beneficial effect on PFS of the B-R induction regimen can be maintained with or without follow-up rituximab maintenance/consolidation treatment.

8.1.4. First round assessment of risks

8.1.4.1. Chronic lymphocytic leukaemia

The data from the pivotal study (02CLLIII) indicates that the risks associated with bendamustine for the treatment of CLL are notably greater than the risks associated with chlorambucil. The risk of experiencing at least one AE occurred more frequently in the bendamustine arm than in the chlorambucil arm (88.8%, 143/161, 660 events vs 80.8%, 385/151, 385 events), and the majority of these events were considered to be treatment-related or to have a missing causality assessment (82.0%, 132/161, 471 events vs 64.2%, 97/151, 225 events, respectively). Unless otherwise stated, the risks reviewed below are based on all causality events in the safety population.

Disorders (SOC) reported in ≥ 10% of patients in either treatment arm in descending of order of frequency in the bendamustine arm (n=161) vs the chlorambucil arm (n=151) were: blood and lymphatic system disorders (57.1% vs 35.8%); general disorders and administrative site conditions (37.3% vs 15.2%); gastrointestinal disorders (30.4% vs 27.2%); infections and infestations (30.4% vs 25.2%); skin and subcutaneous tissue disorders (26.1% vs 12.6%);

investigations (16.8% vs 13.2%); metabolism and nutrition disorders (15.5% vs 6.0%); respiratory, thoracic and mediastinal disorders (13.0% vs 9.9%); and nervous system disorders (10.6% vs 10.6%).

AEs reported in ≥ 5% of patients in either treatment arm and in ≥ 2% more patients in the bendamustine arm (n=161) compared with the chlorambucil arm (n=151), in descending order of frequency in the bendamustine arm were: neutropenia (27.3% vs 13.9%); pyrexia (24.8%, vs 5.3%); thrombocytopenia (24.8% vs 20.5%); anaemia (21.7% vs 13.9%); nausea (19.3% vs 13.9%); leukopenia (17.4% vs 3.3%); vomiting (15.5% vs 6.6%); diarrhoea (9.9% vs 4.0%); rash (9.3% vs 4.6%); asthenia (8.7% vs 4.6%); fatigue (8.7% vs 4.6%); hyperuricaemia (7.5% vs 1.3%); lymphopenia (6.2% vs 0.7%); infection (6.2% vs 1.3%) chills (5.6% vs 1.3%); weight decreased (5.6% vs 3.3%); pruritis (5.0% vs 2.6%); and hypersensitivity (5.0% vs 2.0%). There were no AEs occurring in ≥ 5% of patients in either treatment arm and in ≥ 2% more patients in the chlorambucil arm compared with the bendamustine arm.

The risk of experiencing a severe AE (grade 3 or 4/CTC or Cheson) was greater in patients in the bendamustine arm than in the chlorambucil arm (52.8%, 85 patients, 175 events vs 31.1%, 47 patients, 72 events), and both severe (grade 3 or 4 CTC) haematological and non-haematological AEs occurred notably more commonly in the bendamustine arm than in the chlorambucil arm.

Severe haematological AEs (grade 3 or 4/CTC or Cheson) were reported in 40.4% (n=65) patients in the bendamustine arm and 19.2% (n=29) of patients in the chlorambucil arm. Severe haematological AEs appeared to be manageable by dose modification and/or symptomatic treatment rather than withdrawal from treatment. In the ITT population, GSFs were administered to 10 (6.2%) patients in the bendamustine arm and 1 (0.6%) patient in the chlorambucil arm, while erythropoietic growth factors were administered to 4 (2.5%) patients in the bendamustine arm and 2 (1.3%) patients in the chlorambucil arm. Haematological AEs resulting in treatment withdrawal were reported in 3 (1.9%) patients in the bendamustine arm (1x event each of anaemia, leukopenia, neutropenia, and thrombocytopenia) and 1 (0.7%) patient in the chlorambucil arm (1x event of neutropenia).

The most commonly reported severe haematological AE (grade 3 or 4/CTC or Cheson) in both the bendamustine and chlorambucil arms was neutropenia, including granulocytopenia (23.0%, 37 patients vs 10.6%, 16 patients, respectively). Neutropenia resulted in dose modifications in 10.6% (n=17) of patients in the bendamustine arm and 8.6% (n=13) patients in the chlorambucil arm, and permanent withdrawal from treatment in 1 (0.7%) patient in each of the two treatment arms. Other severe haematological AEs (grade 3 or 4/CTC or Cheson) in the bendamustine vs chlorambucil arms were leukopenia (14.3%, 23 patients vs 1.3%, 2 patients), thrombocytopenia, including platelet count decreased (11.8%, 19 patients vs 8.6%, 13 patients), lymphopenia (6.2%, 10 patients vs 0%), anaemia, including haemoglobin decreased (3.1%, 5 patients vs 0.7%, 1 patient), haemolytic autoimmune anaemia (0.6%, 1 patient vs 0.7%, 1 patient), and autoimmune thrombocytopenia (0.6%, 1 patient vs 0%). The results for severe haematological AEs indicates that the risk of myletoxicity is notably greater in patients treated with bendamustine compared with chlorambucil.

Severe non-haematological AEs (CTC 3 or 4) were reported in 41.0% (n=66) of patients in the bendamustine arm (113 events) and 17.2% (n=26) patients in the chlorambucil arm. The most commonly occurring severe grouped non-haematological events (grade 3 or 4 CTC) were infections, reported notably more commonly in the bendamustine arm than in chlorambucil arm (8.7%, 14 patients vs 3.3%, 5 patients), and severe allergic reactions, reported more commonly in the bendamustine arm than in the chlorambucil arm (6.5%, 9 patients vs 3.3%, 5 patients).

Severe non-haematological AEs (grade 3 or 4/CTC or Cheson) occurring in ≥ 2 patients in the combined treatment groups by SOCs were (bendamustine vs chlorambucil): gastrointestinal disorders - diarrhoea (2, 1.2% vs 0%), vomiting (2, 1.2% vs 0%), and nausea (1, 0.6% vs 1, 0.7%); general disorders and administration site conditions - pyrexia (3, 1.9% vs 2, 1.3%) and fatigue (2, 1.2% vs 0%); immune system disorders - hypersensitivity (2, 1.2% vs 0%); infections

and infestations - pneumonia (4, 2.5% vs 0%) and infection (3, 1.9% vs 0%); investigations - LDH increased (2, 1.2% vs 0%); metabolism and nutrition disorders - hyperuricaemia (3, 1.9% vs 0%) and hyperkalaemia (1, 0.6% vs 1, 0.7%); neoplasms benign, malignant and unspecified - tumour lysis syndrome (2, 1.2% vs 0%); renal and urinary disorders - renal impairment (2, 1.2% vs 0%); respiratory, thoracic and mediastinal disorders - dyspnoea (2, 1.2% vs 2, 1.3%), pleural effusion (2, 1.2% vs 1, 0.7%), and cough (1, 0.6% vs 1, 0.7%); skin and subcutaneous tissue disorders - rash (4, 2.5% vs 3, 2.0%) and rash generalized (1, 0.6% vs 1, 0.7%); and vascular disorders - hypertensive crisis (3, 1.9% vs 0%) and hypertension (2, 1.2% vs 0%).

Serious AEs (other than death), were reported more commonly in patients in the bendamustine arm compared with patients in the chlorambucil arm (19.3%, 31 patients, 38 event vs 12.8%, 19 patients, 22 events). Blood and lymphatic disorder (SOC) SAEs occurred more frequently in patients in the bendamustine arm (3.1%, n=5) than in the chlorambucil arm (0.7%, n=1), and the following SAEs (PT) were reported only in patients in the bendamustine arm anaemia (n=2), anaemia haemolytic anaemia (n=1), autoimmune thrombocytopenia (n=1), haemolysis (n=1), and pancytopaenia (n=1). Gastrointestinal disorder (SOC) SAEs occurred with similar frequency in both the bendamustine and the chlorambucil arms (1.2%, 2 vs 1.3%, respectively). SAEs occurring in ≥ 2 patients in either treatment arm and more commonly in the bendamustine arm compared with the chlorambucil arm were hypersensitivity (3, 1.9% vs 1. 0.7%), pneumonia (3, 1.9%), anaemia (2, 1.2% vs 0%), vomiting (2, 1.2% vs 0%), pyrexia (2, 1.2% vs 1, 0.7%), tumour lysis syndrome (2, 1.2% vs 0%). The only SAE occurring in ≥ 2 patients in the chlorambucil arm and more commonly than in the bendamustine arm was herpes zoster (2, 1.3% vs 0.6%).

Death occurred in 19.3% (n=31) of patients in the bendamustine arm and 27.7% (n=41) of patients in the chlorambucil arm. Of the 72 deaths, 4 patients died up to 30 days after the last study drug (1, 0.6%, bendamustine; 3, 2.0%, chlorambucil) and 68 patients died after study treatment. Of the 4 patients who died up to 30 days after last study drug, the reasons for the death were CLL (n=1, chlorambucil), haemorrhage (n=1, chlorambucil), COPD/dyspnoea/acute heart and pulmonary insufficiency (n=1, bendamustine), and heart failure (n=1, chlorambucil). Approximately 50% of the total number of deaths in both treatment arms were considered to be related to CLL.

Treatment withdrawals due unacceptable toxicity of risk/benefit occurred notably more frequently in the bendamustine arm than in the chlorambucil arm (11.2%, 18 patients vs 3.3%, 5 patients). The most frequently reported AEs resulting in withdrawal in ≥ 2 patients due to unacceptable toxicity or risk/benefit were (bendamustine vs chlorambucil), hypersensitivity (1.9%, 3 vs 0.7%, 1), pyrexia (1.2%, 2 vs 0.7%, 1), neutropenia (0.7%, 1 vs 0.7%, 1) and rash (1.2%, 2 vs 0%). All other events each occurred 1 patient, and nearly all patients were in the bendamustine arm.

Other significant AEs of interest (apart from the 2 patients with tumour lysis in the bendamustine arm noted above) were 2 cases of secondary neoplasm in patients in the bendamustine arm (1 x bronchial carcinoma; 1 x lung cancer).

8.1.4.2. Relapsed/refractory indolent NHL

The risks of bendamustine for the treatment of relapsed/refractory indolent NHL are based on open-label data on 176 patients exposed to the drug for up to 8 cycles (*pivotal study* - median of 6 cycles, mean relative dose intensity of 88% in 100; *supportive study* - median of 5 cycles, mean relative dose intensity of 87% in 76 patients). Of the 176 patients with indolent NHL refractory to rituximab treated with bendamustine at the proposed dose, all patients (100%) experienced at least one AE and in nearly all patients (96%) the AEs were considered to be related to treatment with the study drug.

The risks of greatest clinical concern associated with bendamustine treatment relate to haematological AEs. In the total population (n=176), haematological AEs reported in ≥ 20 % of patients were neutropenia (38%), anaemia (35%), and thrombocytopenia (31%). Of note, severe and life-threatening haematological AEs (grade 3 or 4) occurring in ≥ 10% of patients

were neutropenia (32%), thrombocytopenia (24%) and anaemia (12%). SAEs of febrile neutropenia were reported in 5% (n=9) of patients, while SAEs of anaemia and neutropenia were reported in 3% (n=5) and 2% (n=3) of patients, respectively.

In *both the pivotal and supportive studies*, haematological AEs were the most commonly reported events leading to discontinuation of study drug treatment. In the *pivotal study*, discontinuations of study drug treatment due to thrombocytopenia occurred in 9% (n=9) of patients, followed by neutropenia in 4% (n=4) of patients. In the *supportive study*, discontinuations of study drug treatment due to thrombocytopenia occurred in 17% (n=13) of patients followed by neutropenia and anaemia in 7% (n=5) and 3% (n=2), respectively. In the pivotal study, dose delays occurred in 30% (n=30) of patients due to neutropenia and 19% (n=19) of patients due to thrombocytopenia. The most commonly reported AEs resulting in dose delays were neutropenia in the *pivotal study* and thrombocytopenia in the *supportive study*.

GSFs were administered to 38% of patients in the *pivotal study*, and to 36% of patients in the *supportive study*, while the proportions of patients treated with erythropoietin agonists were 33% and 37%, respectively. Blood product transfusions were administered to 18% of patients in the *pivotal study* and 30% of patients in the *supportive study*. Only 1 patient in each of the *pivotal and supportive studies* required a platelet transfusion, while 18 and 23 patients, respectively, required transfusion with a RBC containing product.

The risks of experiencing a non-haematological AE were high, but the majority of these events were mild or moderate in severity (grade 1 or 2) and appear to have been manageable by symptomatic therapy and/or dose reduction/dose delay. Of the non-haematological AEs, those occurring in ≥ 20% of patients in the total population (n=176) were nausea (75%), fatigue (57%), vomiting (40%), diarrhoea (37%), pyrexia (34%), constipation (29%), anorexia (23%), cough (22%), and headache (21%). Non-haematological grade 3 or 4 AEs reported in ≥ 2% of patients were fatigue (11%), febrile neutropenia (6%), pneumonia (5%), dehydration (5%), hypokalaemia (5%), nausea (4%), vomiting (3%), diarrhoea (3%), herpes zoster (3%), back pain (3%), pyrexia (2%), asthenia (2%), urinary tract infection (2%), weight decreased (2%), anorexia (2%), and dyspnoea (2%).

In the *pivotal study*, SAEs occurred in 39 (39%) patients including death in 11 (11%) patients, while in the *supportive study* SAEs occurred in 26 (34%) of patients including death in 3 (4%) patients. In the *pivotal study*, the most common SAEs occurring in ≥ 5% of patients were febrile neutropenia (6%) and pneumonia (5%). In the *supportive study*, the most common SAEs occurring in ≥ 4% of patients were anaemia (5%) and 4% for each of febrile neutropenia, pneumonia, and dehydration;

In the *pivotal study*, of the 11 deaths reported during the study, 2 were considered to be definitely related to the study drug (1 x CMV infection with normal ANC; 1 x diffuse inter-alveolar haemorrhage), 2 were considered to be probably related to the study drug (1 x respiratory failure/pneumonia; 1 x pneumonia/septic shock/cardiomyopathy), 2 were considered to be possibly related to the study drug (1 x respiratory failure; 1 x worsening of COPD), and 5 were considered to be unrelated to the study drug (disease progression). In the *supportive study*, the 3 deaths due to AEs were myelodysplastic syndrome considered to be possibly related to the study drug in 1 patient, renal failure considered to be unlikely to be related to the study drug in 1 patient, and chronic myelomonocytic leukaemia considered to be possibly related to the study drug in 1 patient.

In the *pivotal study*, 31 (31%) patients discontinued study drug treatment due to AEs. Discontinuations of study drug treatment due to AEs reported in ≥ 2% of patients were thrombocytopenia (9%), fatigue (6%), and neutropenia (4%). In the *supportive study*, 30 (39%) patients discontinued study drug treatment due to AEs. Discontinuations of study drug treatment due to AEs in ≥ 2 % patients were thrombocytopenia (17%), neutropenia (7%), and anaemia (3%).

In the *pivotal study* (n=100), 24 (24%) patients had dose reductions as specified in the protocol, and 68 (68%) patients had dose reductions or dose delays, or did not received both doses in a cycle at some point during their treatment. The most common reason for dose delay was neutropenia. In the *supportive study* (n=76), 19 (25%) patients had dose reductions as specified in the protocol, and 46 (61%) patients had dose reductions or dose delays, or did not received both doses in a cycle at some point during their treatment. The most common reason for dose delay was thrombocytopenia.

Infections were reported in 61% (107/176) of patients in the total population. In the *pivotal study*, 15% of patients had grade 3 infections, and 6% patients had grade 4 infections consisting of pneumonia, sepsis, clostridial infection, infection systemic, septic shock, mycobacterial infection, and tuberculosis. One patient had grade 4 septic shock with a fatal outcome, and one patient had grade 3 lung infection considered definitely related to bendamustine treatment which resolved with no residual effect. Overall, in the *pivotal study* 20 patients had fever or infection with grade 3 or 4 neutropenia, and most events resolved and were considered to be not related to study drug treatment. In the *supportive study*, 20% (n=15) of patients had grade 3 infections and 1% (n=1) had a grade 4 infection (sepsis). The only grade 3 infections occurring in more than 1 patient was pneumonia (4, 5%). Overall, in the *supportive study* 21% (n=16) of patients had febrile neutropenia/neutropenia with infection, and 39% (n=30) of patients had infection without documented neutropenia.

Acute drug reactions/hypersensitivity events within 24 hours of the bendamustine infusion were reported in 20% (35/176) of patients in the total population, and most of the events were mild or moderate in severity (grade 1 or 2). No cases of anaphylaxis were reported. The nature of the reactions and events were typical of those expected to be seen with drug infusion. Cardiac-related disorders were reported in 18% (31/176) of patients in the total population. There is no conclusive evidence that bendamustine is associated with cardiotoxicity. Secondary neoplasms were reported in 3% (5/176) of patients in the total population (3 x myelodysplastic syndrome, 1 x chronic myelomonocytic leukaemia, and 1 x squamous cell carcinoma).

The haematological laboratory abnormalities observed in the *pivotal and supportive studies* have been discussed above. The clinical chemistry laboratory abnormalities observed in the *pivotal and supportive studies* were similar and do not give rise to significant concern. In the *pivotal study*, grade 3 clinical chemistry abnormalities over the course of the 8 treatment cycles occurring in ≥ 2 patients were hyperglycaemia (5 [5%] patients), hypokalaemia (5 [5%] patients), hypocalcaemia (3 [3%] patients), hyperkalaemia (2 [2%] patients), increased serum creatinine (2 [2%] patients), and Hypoalbuminaemia (2 [2%] patients), while grade 4 events were reported for hyponatraemia (1 [1%] patient), hypokalaemia (1 [1%] patient) and increased serum creatinine (1 [1%] patient). In the *supportive study*, grade 3 clinical chemistry results over the course of the 8 cycles occurring in ≥ 2 patients were hypokalaemia (3 [4%] patients), hyperkalaemia (2 [3%] patients) and hyperglycaemia (2 [3%] patients), while grade 4 events were reported for hypercalcaemia in 1 (1%) patient.

In the *pivotal study* there were no grade 3 or 4 AST or ALT clinical chemistry laboratory abnormalities over the course of the 8 treatment cycles, but grade 1 or 2 events occurred commonly for both enzymes (32% [AST]; 26% [ALT]). Similarly, in the *supportive study* there were no grade 3 or AST or ALT clinical chemistry abnormalities occurring over the course of the 8 treatment cycles, but grade 1 or 2 events occurred commonly for both enzymes (40% [AST]; 16% [ALT]).

The observed changes in vital signs of pulse rate, blood pressure, temperature or weight gain over the course of the *pivotal and supportive studies* do not give rise to concern. However, weight loss over the course of the study occurred in 56% of patients in the *pivotal study* and 50% of patients in the *supportive study*, but the majority of events in both studies were mild (grade 1) in severity. The number of clinically significant abnormalities in the ECG recordings over the course of the *pivotal and supportive studies* was small and does not give rise to concern.

However, there was no systematic assessment of QT interval change in bendamustine treated patients in either the *pivotal or supportive study*.

8.1.4.3. First-line indolent NHL and MCL

The safety data from the single-pivotal study (Rummel et al., 2013) are promising and suggest that the risks of treatment with B-R for the proposed indication are similar to those for R-CHOP. However, in the absence of conventional safety data for the proposed indication a definitive assessment of the risks of treatment with B-R for the proposed indication can not be made.

8.1.5. First round assessment of benefit-risk balance

8.1.5.1. Chronic lymphocytic leukaemia

The benefit/risk balance for bendamustine for the treatment of CLL at the proposed dose is considered to be acceptable. However, while the benefits of bendamustine for CLL are greater than those of chlorambucil, the risks of treatment with bendamustine are notably greater than those of chlorambucil. Consequently, although the benefit/risk balance for bendamustine for the treatment of CLL is considered to be acceptable, the benefits are considered to only marginally outweigh the risks. The risks of treatment with bendamustine appear to be manageable by dose reduction, and prophylactic and symptomatic treatment of toxicities rather than treatment discontinuation. There appears to be no difference in overall survival between the two treatment regimens.

8.1.5.2. Refractory/relapsed indolent NHL

The benefit/risk balance for bendamustine for the treatment of patients with indolent relapsed/refractory NHL refractory to rituximab at the proposed dose is considered to be acceptable.

8.1.5.3. First-line indolent NHL and MCL

The benefit/risk balance is promising for bendamustine in combination with rituximab for first-line treatment of indolent NHL and MCL in patients with CD20 positive stage III/IV disease, based on published data from *Rummel et al 2013*. However, in the absence of confirmatory conventional safety data no definitive assessment of the benefit/risk balance of the proposed B-R regimen for the proposed indication can be made.

9. First round recommendation regarding authorisation

9.1. Chronic lymphocytic leukaemia

It is recommended that bendamustine HCl (Ribomustin®) **be approved** for the "first line treatment of chronic lymphocytic leukaemia (Binet stage B or C)".

9.2. Relapsed refractory indolent NHL

It is recommended that bendamustine HCl (Ribomustin®) **be approved** for the treatment of "indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen".

The recommended indication differs from that proposed by the sponsor. It is considered that the recommended indication reflects the patient population in the pivotal Phase III study (SDX-105-03), and aligns with the dosage regimen stated in the proposed PI (i.e., monotherapy for indolent NHL refractory to rituximab).

9.3. First-line indolent NHL and MCL

It is recommended that the proposed regimen of bendamustine HCl (Ribomustin®) in combination with rituximab **be rejected** for "previously untreated indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma. RIBOMUSTIN should be used in combination with rituximab in CD20 positive patients".

The reason for rejection is the absence of conventional safety data confirming that the proposed treatment regimen of bendamustine is safe for the proposed indication. The specific deficiencies in the submitted safety data are:

- No data on the extent of exposure relating to number of patients per cycle, mean number of cycles per patient, overall dose per cycle (mean and relative dose), and mean total dose per cycle.
- No data on the proportion of patients requiring dose modifications (dose reductions or temporary treatment discontinuations) due to AEs, or on the nature of the AEs resulting in dose modifications.
- No data on the total number of AEs experienced by patients in the two treatment groups (overall, and individual events).
- No data on the incidence of AEs by treatment cycle.
- No data on AEs considered to be treatment-related.
- No data on conventionally defined serious adverse events (i.e., fatal or life threatening, resulting in persistent disability or incapacity, requiring in-patient hospitalization or prolongation of existing hospitalization, resulting in congenital and/or causing secondary malignancies). Limited data on secondary malignancies were provided (total number and haematological), but no case narratives of the two patients with secondary haematological malignancies were provided and no information on the nature of secondary non-haematological malignancies were provided. No case narratives of patients experiencing serious adverse events were provided. No data were provided on suspected unexpected serious adverse reactions (SUSARs).
- No comprehensive data on deaths in the safety analysis population (i.e., causes of death and case narratives).
- No data on permanent treatment discontinuation of the study-drugs due to AEs.
- No data on the nature of the infections reported in the two treatment groups.
- No data on the proportion of patients requiring treatment with erythropoietin agonists, or transfusions with blood products for anaemia or thrombocytopenia.
- No data on changes in vital signs or the ECG during the course of the study.
- No data safety data based on age differences (e.g., ≥ 65 years vs < 65 years).

10. Clinical questions

10.1. Paediatric development program

1. No paediatric data have been submitted to the TGA. However, the relevant document relating to the Paediatric Development Program (M1.12) indicates that paediatric data have been submitted to the EU and the FDA. Please indicate the specific indications being sought for the paediatric population (and relevant age ranges) in the EU and the FDA. Please justify why paediatric data has not been submitted to the TGA, but has been provided to the EU and USA drug regulatory authorities.

10.2. Pharmacokinetics

1. The study report for SDX-105-03 indicates that this study included a population pharmacokinetic analysis (CP-07-002) and a pharmacokinetic/pharmacodynamic analysis (CP-07-003). These analyses could not be identified in the submission. Please provide copies of both analyses.
2. In Preiss (M5.3.3.2 Humboldt University Berlin 1987) a tentative bendamustine HCl metabolite was identified as β-hydroxy-bendamustine according to the HPLC analytical method used in this study. This metabolite accounted for about 25% of the iv bendamustine dose. However, this metabolite does not appear to have been identified in subsequent PK studies using validated HPLC/FC methods. Was the metabolite an artefact of the analytical method used in the study? Please clarify this matter.
3. The mean half life of bendamustine was notably longer following 120 mg/m^2 infused over 60 minutes (SDX-105-03) than 100 mg/m^2 infused over 30 minutes (98B03) (i.e., 4.9 hours vs 28.2 minutes, respectively). Please comment on the reasons for this difference.
4. In the study report DP-2007-043 on bendamustine PKs from study SDX-105-03, the mean (SD) Vz (L) is given as 208.2 (167.1) L and the Vss is given as 25.3 (28.6) L (see DP-2007-043). Please comment on the apparent inconsistency between the two values.
5. There were no PK studies assessing the role of active transporters in bendamustine distribution. Does the sponsor have results from such studies? If not, does the sponsor plan to undertake such studies? If not, please justify.
6. *In vitro* data indicate that bendamustine is metabolized by CYP 1A2. Does the sponsor intend to undertake *in vivo* drug-drug PK interaction studies between bendamustine and CYP 1A2 inducers and inhibitors? If not, please justify?
7. Please comment on the relative contributions of non-renal and renal clearance to the total clearance of bendamustine in patients with normal renal and hepatic function. Please provide estimates of hepatic and renal clearance in patients with normal renal and hepatic function. Does the sponsor propose to undertake a mass balance study of bendamustine in humans? If not please justify.
8. Does the sponsor intend to undertake PK studies in patients with renal and hepatic impairment that meet current standards of best-practice for such studies (see relevant EU guidelines). If not, please justify?

10.3. Efficacy

1. CLL: The pivotal study (02CLLIII) excluded patients older than 75 years, and the mean age (range) of patients in the ITT population for bendamustine and chlorambucil was 63.0 years (47, 77 years) and 63.6 (35, 78 years). Consequently, the study population appears to be younger than Australian patients with CLL for whom bendamustine might be a treatment option. Subgroup analyses of the two primary efficacy endpoints (overall response and PFS) showed that treatment with bendamustine was significantly superior to treatment with chlorambucil independent of age (< 65 years, ≥ 65 years). However, there were no specific efficacy data on patients aged ≥ 75 years and the availability of such data from the pivotal study are likely to be negligible, given that patients aged > 75 years were excluded from the study and the upper age range for the total population was 77 years. Please comment on the generalizability of the data from the pivotal study population to the Australian population of patients with treatment-naive CLL for whom bendamustine might be a treatment option.
2. CLL: In the Canadian monograph the results for response for study 02CLIII summarized in Table 38 (below) notably differ from the ICRA results provided in the submission in the second CSR (see Table 39 below), and from those presented in the proposed Australian PI.

The differences are particularly marked for the CR and PR assessments. Please account for these differences.

3. CLL: In the second CSR for study 02CLIII it is stated that one of the methods used to assess the response involved the electronic CRF (eCRF) calculating the overall response according to a programmed algorithm based on the NCI-WG Criteria for response assessment (Cheson, 1996). Please provide the results for this analysis using the data provided in the second CSR.
4. CLL: The break-down of PFS into its components could not be identified for any of the analyses (i.e., no separate patient numbers for progression, relapse or death contributing to the total number of events). Please provide the break-down of PFS events for the primary analysis (ICRA), the sensitivity analysis (investigator assessment), Binet B and C assessments, males and females, and patients < 65 years of age and ≥ 65 years of age.
5. CLL: No information on the median duration of follow-up could be identified in the submitted data. However, in *Knauf et al (2009)* it is stated that median observation time in patients in the follow-up analysis was 35 months (range: 1, 68 months). Please confirm the median observation time in patients in the follow-up analysis.
6. Relapsed/refractory indolent NHL: Please provide separate ORRs for the 31 patients from study SDX-105-01 who were either sensitive to their most recent rituximab-containing treatment regimen (n=23) or had an unknown response (n=8) to their most recent rituximab-containing regimen, and the 45 patients who were refractory to their most recent rituximab-containing regimen.
7. Relapsed/refractory indolent NHL: Has all long-term follow-up data for study SDX-105-103 accrued? If so, please provided the results for the efficacy outcomes of ORR, DR, and PFS.
8. First-line indolent NHL and MCL - The application for the proposed indication for bendamustine in combination with rituximab for the first line treatment of indolent NHL and MCL is supported by one pivotal study (StiL NHL 1-2003), and published results for this study are provided in *Rummel et al (2013)*. The submission included an English translation from German of the initial protocol for this study identified as StiL NHL 1-2003 (September 2003). However, it is obvious from *Rummel et al (2013)*, and from a document included in the Module 5 literature references (Chen and Li, Cephalon Statistical Analysis Plan for StiL NHL 1-2003, 5 May 2011), that the initial protocol underwent a number of amendments. Please provide the final protocol for StiL NHL 1-2003, indicating all amendments, and the final statistical analysis plan for this study. In addition, please explain why the Cephalon final statistical analysis plan for StiL NHL 1-2003 was provided in the M5 literature references rather than in the relevant M5 studies for evaluation section.
9. First-line indolent NHL and MCL - Why were the final Complete Study Report (CSR) and the final Biometric Report for study StiL NHL 1-2003 not provided? Presumably the published study *Rummel et al (2013)* were based on these reports. In the absence of conventional safety data, a comprehensive regulatory assessment of the safety of bendamustine in combination with rituximab for the proposed indication can not be undertaken.
10. First-line indolent NHL and MCL - Does the sponsor have the results from *Rummel et al (2013)* of efficacy analyses in the ITT population? If so, please provide these results.

10.4. Safety

1. Relapsed/refractory indolent NHL: In study SDX-105-01, it is stated that thrombocytopenia was the most common AE resulting in dose delay. How many patients (n [%]) experienced a dose delay due to thrombocytopenia?
2. In the post-marketing data (PSUR 2), reference was made to pulmonary embolism (including symptoms of dyspnoea, tachypnoea, and pleuritic pain), being possibly due to

silicone oil contamination. Consequently, PSUR 2 indicates that these events are being temporarily monitored until all batches bendamustine potentially contaminated with silicon oil have expired. Please provide updated information on cases of pulmonary embolism reported in association with bendamustine, and on the sponsor's plans for continuing monitoring of pulmonary embolism (including symptoms of dyspnoea, tachypnoea, and pleuritic pain). Please comment on procedures undertaken to prevent future recurrence of silicon oil contamination.

11. Second round evaluation of clinical data submitted in response to questions

11.1. Overview

The sponsor provided an s31 Response, dated 26 February 2014, to the clinical questions raised in the first round clinical evaluation report. The s31 Response has been evaluated based on the clinical data relating to the questions raised in the first round clinical evaluation. The sponsor's 31 Response was provided in electronic NeeS format on DVD (1 disc). The sponsor responded to each of the questions raised in the first round clinical evaluation report. The approach adopted in preparing the second round evaluation of the sponsor's s31 Response has been to repeat each question in full, using the sponsor's numbering, followed by the sponsor's response, either in full or abridged and/or edited, and clinical comment on the response. The first round clinical evaluation report, the second round clinical evaluation of the s31 Response, and the second round clinical evaluation report have all been prepared by the same clinical evaluator.

11.2. Paediatric development program

11.2.1. Question 1

No paediatric data have been submitted to the TGA. However, the relevant document relating to the Paediatric Development Program (M1.12) indicates that paediatric data have been submitted to the EU and the FDA. Please indicate the specific indications being sought for the paediatric population (and relevant age ranges) in the EU and the FDA. Please justify why paediatric data has not been submitted to the TGA, but has been provided to the EU and USA drug regulatory authorities.

11.2.1.1. Sponsor's response (abridged/edited)

The study Cephalon C18083/2046 PK was a multicenter, open label, non-randomised study in 43 paediatric patients with relapsed/refractory acute leukemia.

The first part of the study (the phase I portion) determined the recommended dose and dose limiting toxicities (DLTs) of bendamustine in this patient population. The second part (the phase II portion) evaluated the efficacy and safety of bendamustine in this patient population. Eleven patients were enrolled in phase 1 and 32 patients in phase 2 of the study.

The PK/PD efficacy analysis population was a subset of the total study population and included 38 patients randomized to receive 120 mg/m^2 who had PK exposure estimates.

These studies were not submitted to TGA since these data were not aligned with our proposed indication.

Of the 43 patients enrolled in the study, 14 (32.6%) patients were 1 through 6 years old; 13 (30.2%) patients were 7 through 11 years old; and 16 (37.2%) patients were 12 to 20 years.

The results of this study do not support efficacy as monotherapy in the treated study population. However, the study provided safety and dosage information for the pediatric

population that could be included in the package insert. Therefore the study data were submitted both in the US and EU to update the product information with respect to the pediatric population.

11.2.1.2. Clinical evaluator's comment

The sponsor's response is satisfactory. The data from the study in paediatric patients with relapsed/refractory acute leukemia (ALL and AML) are not directly relevant to the indications being proposed for approval in Australia.

11.3. Pharmacokinetics

11.3.1. Question 1

The study report for SDX-105-03 indicates that this study included a population pharmacokinetic analysis (CP-07-002) and a pharmacokinetic/pharmacodynamic analysis (CP-07-003). These analyses could not be identified in the submission. Please provide copies of both analyses.

11.3.1.1. Sponsor's response (complete)

Please refer to Module 5.3.5.2.3 for copies of the pharmacokinetic (CP-07-002) and the pharmacokinetic/ pharmacodynamic (CP-07-003) analysis.

11.3.1.2. Clinical evaluator's comment

The sponsor's response is satisfactory. The two reports referred to in the sponsor's response have been evaluated and are discussed below.

11.3.1.2.1. Population Pharmacokinetic Report (CP-07-002) - Dated 27 November 2007

The objectives of the PopPK analysis were:

- to develop separate population pharmacokinetic (PK) models for bendamustine, N-desmethyl-bendamustine (M4), and γ-hydroxy-bendamustine (M3), and to describe the PK disposition of each analyte in patients with non-Hodgkin's lymphoma (NHL);
- to perform covariate analysis of selected patient factors and laboratory values to explore sources of inter-patient variability in bendamustine PK parameters, and to assess the PK disposition of bendamustine in special population groups;
- to graphically assess the influence of selected concomitant medications on the disposition of bendamustine; and
- to evaluate the dose proportionality of bendamustine PK within the administered dose range.

Data for the analysis were obtained from study SDX-105-03, which was the Phase III, multicentre, open-label, 6-treatment cycle, single-agent study designed to investigate the safety, efficacy, and pharmacokinetic profile of bendamustine in patients with indolent NHL refractory to rituximab. Bendamustine was administered as a 60 minute IV infusion at a dose of 120 mg/m^2 on Days 1 and 2 of 6 consecutive 21-day treatment cycles. If a patient continued to experience clinical benefit at cycle 6, the patient received up to 2 additional cycles of bendamustine.

The PK data from this study has been reviewed in Section 4.2.3 of the Final CER. PK samples were drawn in cycles 1 and 2 only. Patients in the General Clinical Research Center (GCRC) group had a full PK profile on Day 1 of cycle 1. Blood samples were collected before the start of the infusion (pre-dose), at the midpoint of the infusion, at the end of the infusion, and at 15, 30, and 45 minute, and 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after the end of the infusion. In addition, PK samples were collected on Day 1 of cycle 2 pre-dose, and then between 0.25 and 0.5 hours, and 1 and 3 hours after the start of the infusion. Sparse data were collected from the

non-GCRC patients, up to 4 samples per patient.

The total dataset included a total or 576 PK sample records (100 patients) from study SDX-105-103. After exclusions and imputations, 347 bendamustine sample records (78 patients), 254 M4 sample records (73 patients), and 302 M3 sample records (77 patients) were included in the total dataset. Overall, the mean age of the patients in the three analyte groups in the total dataset was approximately 59 years (range: 31, 84 years), approximately 64% were male, the mean BSA was approximately 2.0 m^2 (range: 1.3, 2.7), and approximately 90% were Caucasian.

Nonlinear mixed effects modeling was used to develop separate population PK models for bendamustine, M4 and M3. Bendamustine, M3 and M4 exposures were estimated for each individual patient included in the analysis based on Bayesian model parameter values. The Bayesian PK parameter estimates were obtained by using the final population PK model from the total dataset and the population mean PK parameter estimates (fixed and random effects) as prior information in conjunction with the individual dosing and concentration data. The predicted concentration-time profile for each patient was used to compute systemic exposure as assessed by the area under the concentration-time curve (AUC) and the maximum concentration (Cmax) for bendamustine, M4, and M3 for each patient. AUC values were calculated using the linear trapezoidal rule. Covariate analysis was performed using forward selection and backward elimination procedures for bendamustine only. The PopPK analysis was comprehensively reported and was consistent with the relevant TGA adopted EU guidelines (CHMP/EWP/185990/06).

11.3.1.2.2. Results

- The final population PK model for bendamustine in patients indolent NHL refractory to rituximab was a 3-compartment open model with 0-order input, 1st-order elimination. The final model for bendamustine is provided schematically below in the Figure 7, and the mean fixed effect parameters for the final population model are summarized below in Table 36.

Figure 7: Final bendamustine population PK model; total dataset

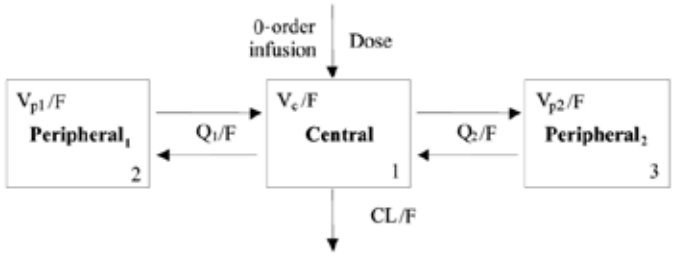


Table 36: Parameter estimated and standard errors from the bendamustine final model; total dataset

	Final parameter estimate		Magnitude of interindividual variability (%CV)	
Parameter	Population mean	%SEM	Final estimate	%SEM
CL (L/h)	31.7	6.6	33.32	21.9
V_c (L)	14.1	5.7	15.56	69.4
V_{p1} (L)	0.920	8.0	22.29	40.8
V_{p2} (L)	25.2	33.6	66.78	51.6
Q_1 (L/h)	0.989	9.2	NE	NA
Q_2 (L/h)	0.159	24.5	NE	NA
RV (%CV)	35.64	18.2	NA	NA
Minimum value of the objective function=3009.938				

CL = central clearance; Vc = central volume of distribution; Vp1 = peripheral volume of distribution 1; Vp2 = peripheral volume of distribution 2; Q1 = inter-compartmental clearance 1; Q2v = inter-compartmental 2; RV = residual variability.

- The residual variability (RV) for the final bendamustine model was 36%. The median total AUC for bendamustine was 13,635 ng·h/mL. Estimates of t1/2α, t1/2β, and t1/2γ for bendamustine were 0.29, 0.7 and 110 hours, respectively. The AUC for the terminal phase accounted for less than 1% of the total AUC. Therefore, the t1/2 of the β phase is considered to be the best estimate of bendamustine elimination half-life (i.e., 0.7 hours). Furthermore, the predicted concentration at 12 hours (C(0-12h)) after the first dose was 0.272 ng/mL. The mean predicted Cmax was 5,813 ng/mL. The ratio of C(0-12h) to Cmax had a mean value of 0.00004. Consequently, accumulation is not expected following multiple dosing and the single dose PK profile is representative of the multiple PK dose profile.
- The effects of sex, age, race, weight, BSA, hepatic function (ALT, albumin, AST, total bilirubin), and renal function (estimated creatinine clearance) on central clearance (CL), central volume of distribution (Vc), peripheral volume of distribution 1 (Vp1), and peripheral volume of distribution 2 (Vp2) were tested as covariates in the final bendamustine model. However, none of the tested covariates had statistically significant effects on the selected PK parameters in the final bendamustine model.
- The PK profile of M4 plasma concentrations declined from peak in a mono-exponential manner. A 1-compartment model with 0-order input and 1st-order elimination adequately described the data for M4. Typical value parameter estimates for M4 apparent clearance (CL/F) and apparent volume of distribution (V/F) were 3,890 L/h and 3,490 L, respectively. The estimated half-life was 0.622 hours, which was similar to that of the α phase of bendamustine. The CL/F and V/F values were each approximately 100-fold larger than the estimates for bendamustine and resulted in exposure to M4 (median AUC=115 ng·h/mL) approximately 100-fold less than that of bendamustine.
- The PK profile of M3 plasma concentrations declined from peak in a biphasic manner. A 2-compartment model with 0-order input, 1st-order elimination, and a metabolite-formation lag time adequately described the data for M3. Typical value parameter estimates for M3 CL/F, Q/F, Vc/F, and Vp/F were 347 L/h, 6.60 L/h, 209 L and 26.1 L, respectively. The estimated M3 values for t1/2α and t1/2β were 0.408 hours and 2.8 hours, respectively. The median estimated M3 value for AUC was 1,252 ng·h/mL, which was approximately 10-fold lower than that of bendamustine.
- Based on the corresponding PK models, the inter-individual variability (IIV) of AUC was 33.10 %CV, 44.10 %CV, and 16.73 %CV for bendamustine, M4, and M3, respectively. Inter-individual variability of Cmax was 23.53 %CV, 48.97 %CV, and 16.63 %CV for bendamustine, M4, and M3, respectively. Residual variability (RV) for the three PK models was similar for bendamustine, M4 and M3 (i.e., 36 %CV, 35 %CV, and 37 %CV).
- Individual patient exposures were estimated using the final population PK model. Though none of the covariates were found to be statistically significant in the population PK model, these exposures were stratified in categories of various covariates and special populations in order to evaluate potential trends or differences in estimated exposures between groups. No notable differences between groups were present for sex, age, race, hepatic function, or renal function.
- Individual estimates of bendamustine AUC and Cmax were summarized across quartiles of BSA. A trend for increasing exposure with increasing BSA was observed, with maximum differences in median values across the BSA categories being approximately 30% for both AUC and Cmax. Of note, the central 80% of the BSA values were within the range of 1.61 m^2 to 2.40 m^2. Within this narrow range, the AUC to BSA relationship was very flat. Therefore, although a trend was present across the full range of BSA values, the influence of inter-

individual variability (IIV) on PK parameter estimates did not reach the pre-specified level of significance for the population analysis.

- Individual estimates of bendamustine AUC and Cmax values were summarized by hepatic function category. Median bendamustine AUC and Cmax showed little difference between the normal (N=52) and mild (N=26) dysfunction groups. Patient with mild hepatic dysfunction were defined as having total bilirubin ≤ ULN, ALT ≥ ULN to 2.5 x ULN, and/or SAP ≥ ULN to 5.0 x ULN. No patients with PK data were classified as having moderate or severe hepatic dysfunction.
- Individual estimates of bendamustine AUC and Cmax values were summarized by renal function category. Median bendamustine AUC and Cmax showed little difference between the normal (N=47), mild (N=23) and moderate (N=8) dysfunction groups. Normal renal function, mild renal impairment, and moderate renal impairment were defined as CrCL > 80 mL/min, 50 mL/min < CrCL ≤ 80 mL/min, and 30 mL/min < CrCL ≤ 50 mL/min, respectively. No patients with PK data were classified as having severe renal dysfunction.
- The data do not allow for conclusive assessment of dose proportionality. Exposure estimates were obtained only for the 120 mg/m^2 dose.
- The data did not allow for conclusive assessment of CYP1A2 related drug interaction potential. Only two bendamustine samples were collected in the presence of an inhibitor or substrate of CYP1A2.

11.3.1.2.3. Population Pharmacokinetic/Pharmacodynamic Report (CP-07-003) - Dated 07 December 2007

The objectives of the PK/PD analyses were:

- to develop a model, including the evaluation of covariates, to describe the correlation between bendamustine exposure and responder status in patients who are refractory to rituximab therapy;
- to explore graphically the correlation between bendamustine exposure and duration of response (DR) in patients who are refractory to rituximab therapy;
- to explore graphically the correlation between bendamustine exposure and the duration of progression-free survival (PFS) in patients who are refractory to rituximab therapy; and
- to develop a model, including the evaluation of covariates, to describe the correlation between bendamustine exposure and the occurrence of selected adverse events of interest.

The data from the PK/PD analyses were obtained from study SDX-105-03 in patients with indolent NHL refractory to rituximab. Baseline assessment of NHL was performed within 28 days before Cycle 1, Day 1. Assessments of patient response to bendamustine treatment were performed at Week 6 (Day 42) and Week 12 (Day 84), and then every 12 weeks thereafter, with a window of ±3 days around each timepoint, until the patient completed or discontinued treatment. Assessments continued up to 2 years from the last dose of bendamustine. After a patient completed or discontinued treatment for any reason, an end-of-treatment assessment was performed within 28 days after the last dose of study drug, unless the patient had experienced a treatment delay due to toxicity, in which case the assessment was performed within 2 weeks of the decision to discontinue the patient from treatment.

The exploration of potential PK/PD relationships for bendamustine included graphical evaluation of 3 efficacy endpoints (responder status, DR, and PFS) and 3 safety adverse events (fatigue, nausea, and vomiting). In addition, laboratory data for neutropenia was evaluated graphically. These adverse events were selected due to the fact that they are known to be frequently associated with bendamustine treatment. The relationships between these endpoints and individual estimates of exposure (i.e., Cycle 1 bendamustine AUC and Cmax and Cycle 1 composite AUC and Cmax) were assessed for possible trends.

A population PK model was used to generate Bayesian estimates of model parameters for each patient. These parameter values were used to compute appropriate measures of Cycle 1 AUC for bendamustine and its 2 active metabolites, M4 and M3, for each patient. The key exposure parameter was the composite AUC, which was based on the sum of the AUC for bendamustine plus its 2 active metabolites weighted for the relative potency of each of the analytes. Cumulative AUC values for bendamustine, M4, and M3 were calculated as the sum of all cycle AUCs. In addition, the cycle 1 Cmax of bendamustine was evaluated for each patient as a predictor of efficacy and safety.

A PK/PD model was developed for responder status using logistic regression to characterize the exposure-response relationship, as well as the influence of select patient covariates. In addition, the safety profile of bendamustine was evaluated by developing PK/PD models using logistic regression for the relationship between individual estimates of bendamustine exposure and the occurrence of the adverse events fatigue, nausea, and vomiting. The efficacy analyses of DR and PFS were exploratory analyses, and no formal statistical models were developed for these efficacy endpoints.

The following demographic and clinical covariates analysed in the final population PK model were determined at baseline and were assumed to remain constant throughout the study: sex; age; race; BSA; number of prior treatment courses; indolent NHL subtypes; baseline WHO performance grade; and antiemetic use (only in the safety analyses).

11.3.1.2.4. PK/PD results - efficacy

Responder status: Of the 80 patients in the PK/PD efficacy analysis, 68 patients (85%) were responders after treatment with bendamustine. Response to bendamustine appeared to be correlated with sex, and baseline WHO performance. Male patients had a higher rate of response than female patients (90% vs 77%, respectively). The observed response rate for baseline WHO performance status 0, 1, and 2 was 92%, 81%, and 33% respectively. However, no correlation existed between the responders and age, BSA, indolent NHL subtype, and number of prior treatment courses. The relationship between responder status and race could not be evaluated because nearly 90% of patients were Caucasian.

Responder status: Exploratory graphical analyses demonstrated that responders and non-responders had similar Cycle 1 bendamustine and composite exposure values. The logistic regression analysis of responder status included the evaluation of Cycle 1 bendamustine AUC and Cmax, Cycle 1 composite AUC and Cmax, cumulative bendamustine AUC, and cumulative composite AUC. Cumulative bendamustine AUC and cumulative composite AUC were statistically significant predictors of responder status (p-value < 0.05), with values being greater in responders than in non-responders.

Responder status: Because no Cycle 1 exposure parameters were significant predictors of responder status, the number of cycles completed was also analyzed to determine if the significance of the cumulative AUC measures was related to time alone. The number of completed cycles was more significant than cumulative exposure (p-value <0.0001), and there was no additional benefit to the inclusion of Cycle 1 exposure once the number of cycles was included in the model. Therefore, the number of completed exposures (i.e., time) was a confounder for the observed relationship between cumulative exposure and responder status. Consequently, response status was deemed to be unrelated to cumulative exposure. Since no exposure parameters were found to be both clinically and statistically significant predictors of responder status, no further covariate analyses were performed.

Duration of response (DR): The mean (SD) DR was 31.60 (18.27) weeks and ranged from 0.1 to 77 weeks. Exploratory graphical analyses demonstrated no significant relationship between DR and exposure. Kaplan-Meier analysis resulted in no statistically significant relationship between DR and cycle 1 bendamustine AUC, composite AUC, cycle 1 bendamustine Cmax, or composite Cmax (p-value = 0.5246, 0.9712, 0.5572, and 0.8748, respectively). In summary, no significant correlation between bendamustine exposure and DR was observed.

Progression-free-survival (PFS): The mean (SD) PFS was 35.79 (18.42) weeks and ranged from 2.9 to 83 weeks. Exploratory graphical analyses demonstrated an initial trend for a relationship between PFS and Cycle 1 bendamustine Cmax up to 60 weeks, followed by no difference in PFS after 60 weeks of treatment with bendamustine. However, Kaplan-Meier analysis resulted in no statistically significant relationship between PFS and Cycle 1 bendamustine AUC, Cycle 1 composite AUC, Cycle 1 bendamustine Cmax or Cycle 1 composite Cmax (p-value = 0.3025, 0.2870, 0.1563, and 0.5135, respectively). In summary, no significant correlation between bendamustine exposure and PFS was observed.

11.3.1.2.5. PK/PD results - safety

Fatigue: Of the 80 patients in the PK/PD safety analyses, 45 patients (56%) had at least 1 occurrence of fatigue during the treatment period. Exploratory graphical analyses of the data demonstrated no relationships between the occurrence of fatigue and measures of bendamustine exposure. Logistic regression analysis confirmed that no exposure measures or covariates were statistically significant predictors of the probability of fatigue.

Nausea: A total of 59 patients (74%) had at least 1 occurrence of nausea during the treatment period. Exploratory graphical analyses of the data indicated potential relationships between the occurrence of nausea and both Cycle 1 bendamustine Cmax and Cycle 1 composite Cmax. Logistic regression analysis showed that Cycle 1 bendamustine Cmax and Cycle 1 composite Cmax were both statistically significant predictors of the probability of nausea (p=0.013; for each parameter). Since both exposures were equally significant, Cycle 1 bendamustine Cmax was deemed to be the more appropriate exposure measure, given that Cycle 1 composite Cmax is composed mostly of bendamustine, and because the 2 measures were highly correlated (r>0.99). The final exposure-response model for nausea included a statistically significant linear relationship between Cycle 1 bendamustine Cmax and the probability of nausea. At the Cycle 1 bendamustine median Cmax value of 5,839 ng/mL for the 120 mg/m^2 dose of bendamustine, the model-predicted probability of nausea was 0.753. In summary, Cycle 1 bendamustine exposure (Cmax) was a statistically significant predictor of nausea. No covariates were significant predictors of nausea.

Vomiting: A total of 25 patients (31%) had at least 1 occurrence of vomiting during the treatment period. No relationship between bendamustine exposure and vomiting was observed. However, the covariates of sex and the number of prior treatment courses were found to be statistically significant predictors of the probability of vomiting. For a male patient with a median of 3 prior treatment courses, the model predicted probability of vomiting was 0.224. For a female patient with a median of 3 prior treatment courses, the model predicted probability of vomiting was 0.547. As the number of prior treatment courses increased, the model predicted probability of vomiting decreased. In summary, no significant correlation between bendamustine exposure and vomiting was observed. The covariates of sex and number of prior treatment cycles were statistically significant predictors of vomiting.

Neutropenia: Boxplots of bendamustine AUC measures at each cycle demonstrated that patients with neutropenia had slightly higher bendamustine AUC measures during Cycles 1 through 3. However, during Cycles 4 through 6, similar bendamustine AUC measures were observed in patients with and without neutropenia.

11.3.2. Question 2

In Preiss (M5.3.3.2 Humboldt University Berlin 1987) a tentative bendamustine HCl metabolite was identified as β-hydroxy-bendamustine according to the HPLC analytical method used in this study. This metabolite accounted for about 25% of the iv bendamustine dose. However, this metabolite does not appear to have been identified in subsequent PK studies using validated HPLC/FC methods. Was the metabolite an artefact of the analytical method used in the study? Please clarify this matter.

11.3.2.1. Sponsor's response (complete)

In terms of structure the postulated β-hydroxy-bendamustine was later identified as gamma-hydroxy-bendamustine (M3 metabolite).

In terms of quantity M3 was accounting for 3.2% of the AUC and 2.4% of Cmax of the mother compound in patients of study 20BEN D1 (M5.3.3.2.3 BioProof 2002 - refer to the registration dossier). These values are regarded as representative for the amount of the M3 metabolite at therapeutic dose levels.

This percentage of M3 compared to bendamustine is also confirmed in the Japanese patient population in study Symbio 2006001. The data is shown in the table below.

Table 37. Mean ±SD pharmacokinetic parameters for bendamustine and its M3 and M4 metabolites in Japanese cancer patients after 60-minute iv infusion of bendaustine HCl at 90 and 120 mg/m² on day 1 of cycle 1.

		Dose Cohort	
Analyte	**Parameter**	**90 mg/m² (n=3)**	**120 mg/m² (n=6)**
Bendamustine	C_{max} (ng/mL)	7250 ± 3303	8616 ± 4488
	AUC_{0-all} (ng•h/mL)	8327 ± 3626	10212 ± 5759
M3 Metabolite	C_{max} (ng/mL)	246 ± 72	381 ± 50
	AUC_{0-all} (ng•h/mL)	361 ± 109	640 ± 94

This percentage is further confirmed by the results of the US population PK study. The results show a median M3 AUC was 1252 ng*h/mL, or approximately 1-tenth of bendamustine exposure (SDX-105-03 population pharmacokinetic analysis report CP-07- 002).

The value of 25% for the suspected β-hydroxy-bendamustine is not reproducible. Missing details and validation data of the analytical method make a closer assessment of this value impossible.

11.3.2.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.3.3. Question 3

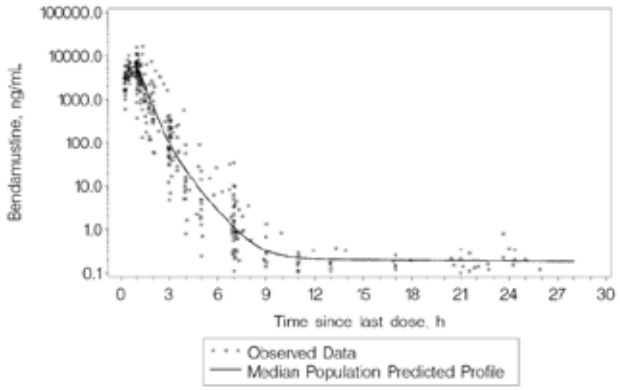
The mean half-life of bendamustine was notably longer following 120 mg/m² infused over 60 minutes (SDX-105-03) than 100 mg/m² infused over 30 minutes (98B03) (i.e., 4.9 hours vs 28.2 minutes, respectively). Please comment on the reasons for this difference.

11.3.3.1. sponsor's response (complete)

The t1/2 value of the 98B03 study is used in EU for the elimination half-life. The design of study 98B03 is a pharmacokinetic study and the number of patients in each group is adequate to assess inter-individual deviations.

The population PK analysis of study SDX 105-03 resulted in estimates of half-lives (t1/2), (t1/2 alpha, t1/2 beta, t1/2 gamma) for bendamustine were 0.29 h, 0.7 h, and 110 h, respectively. The AUC for the terminal phase accounted for less than 1% of the total AUC. Therefore, the t1/2 of the beta phase of 0.7 h is considered to be reflective of bendamustine elimination half-life (page 22 report CP-07-002). [The plasma concentration time curve of the population PK study is shown below in Figure 8 (page 23 report CP-07- 002)].

Figure 8: Measured plasma bendamustine concentration versus time since last dose with Bendamustine Final Model Typical Value Median Population-Predicted Profile Overlaid: Total Dataset



The 28.2 minutes are in line with the 42 minutes (0.7 h) of the population PK study for the t1/2 beta. The US label states an elimination half-life of "approximately 40 minutes" for the 60 minutes infusion time.

The mentioned value of 4.9 hours could not be identified.

11.3.3.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.3.4. Question 4

In the study report DP-2007-043 on bendamustine PKs from study SDX-105-03, the mean (SD) Vz (L) is given as 208.2 (167.1) L and the Vss is given as 25.3 (28.6) L (see DP-2007-043). Please comment on the apparent inconsistency between the two values.

11.3.4.1. Sponsor's response (complete)

The Vss is the steady-state (equilibrium) volume of distribution, whereas the Vz represents the volume of distribution only during the terminal elimination phase.

The Vss is always numerically smaller than Vz. The extent of the difference between the two parameters is generally larger for drugs that follow multi-exponential disposition kinetics. Bendamustine follows a 3-compartment model.

The larger Vz value for bendamustine is consistent with its much longer half-life during the terminal phase relative to the other two dispositional phases. The large Vz suggests that at least some portion of the dose is more extensively distributed beyond the vascular space. After intravenous application of bendamustine the AUC for the terminal phase accounted for less than 1% of the total AUC. Therefore the fraction of the dose that is represented by this larger volume of distribution Vz is small.

11.3.4.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.3.5. Question 5

There were no PK studies assessing the role of active transporters in bendamustine distribution. Does the sponsor have results from such studies? If not, does the sponsor plan to undertake such studies? If not, please justify.

11.3.5.1. Sponsor's response (complete)

In the context of the investigation of resistance mechanisms and bendamustine treatment the role of active transporters has been studied to some extent.

Resistance mechanisms related to the ABC transporter family (P-glycoprotein, MRP and MXR/BCRP), to dihydrofolate reductase (DHFR), to reduced folate carrier (RFC) and to beta-tubulin were investigated. *In vitro* data suggest that bendamustine may be a substrate for P-glycoprotein.

No further studies investigating the role of active transporters in bendamustine distribution are available. During the long clinical experience there was no cause to investigate the role of active transporters in more detail. Therefore no further studies are planned.

11.3.5.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.3.6. Question 6

In vitro *data indicate that bendamustine is metabolized by CYP 1A2. Does the sponsor intend to undertake in vivo drug-drug PK interaction studies between bendamustine and CYP 1A2 inducers and inhibitors? If not, please justify?*

11.3.6.1. Sponsor's response (complete)

The major routes of oxidative bendamustine metabolism are N-demethylation and γ-hydroxylation. The CYP1A2 isozyme is responsible for the formation of both phase I metabolites in humans (M5 S5.4.200). In vitro cytotoxicity has been shown for both metabolites, only those for γ-hydroxy bendamustine was comparable to the parent compound, whereas that for N-desmethyl bendamustine was up to tenfold lesser.

To assess the contribution of phase I metabolism to overall bendamustine elimination, the AUC ratio of γ-hydroxy bendamustine and N-desmethyl bendamustine to total bendamustine (sum of parent drug and hydrolysis products) was calculated for 36 subjects of study 98B03 (M5 S5.3.3.3.1) and 15 subjects of study 20BEND1 (M5 S5.3.3.2.7). Chemical hydrolysis products of bendamustine were included in the calculation because its formation may occur during sampling, storage, sample preparation, and analyses. Subjects of study 98B03 including patients with impaired renal as well as hepatic function received bendamustine hydrochloride 120 mg/m^2, subjects of study 20BEN D1 were doses administered ranging from 160 to 280 mg/m^2. A mean AUC ratio of 0.046 ± 0.023 (0.008 – 0.096, median 0.051, n = 36) and 0.085 ± 0.044 (0.031 – 0.162, median 0.067, n = 15), respectively, leads to assume that this pathway is a quantitatively minor one. There were no statistically significant differences for the mean AUC ratios between the three patient groups of study 98B03.

Since there is a minor contribution of both phase I metabolites to overall bendamustine elimination in humans, there is a low probability of significant metabolism-based interactions with drugs that may induce or inhibit CYP1A2.

Data on the cumulative urinary excretion further support this assumption. The mean 24-h cumulative amount of the sum of γ-hydroxy bendamustine and N-desmethyl bendamustine excreted in the urine of 12 cancer patients of study 98B03 with unimpaired renal function was 0.13% of the administered dose.

11.3.6.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.3.7. Question 7

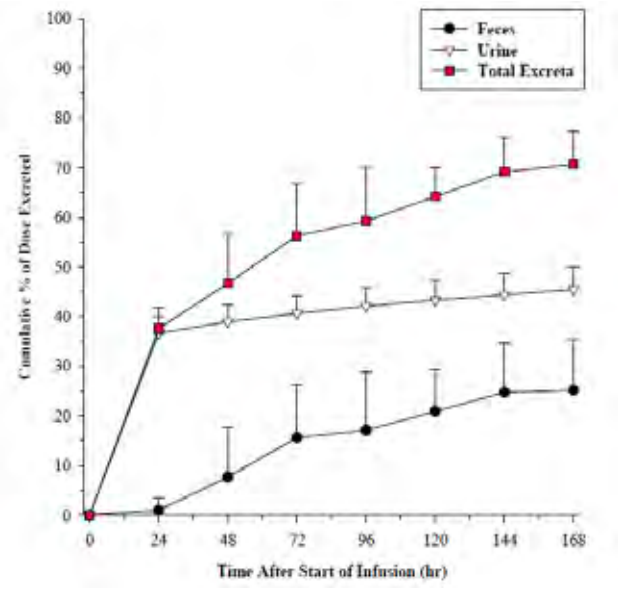
Please comment on the relative contributions of non-renal and renal clearance to the total clearance of bendamustine in patients with normal renal and hepatic function. Please provide estimates of hepatic and renal clearance in patients with normal renal and hepatic function. Does the sponsor propose to undertake a mass balance study of bendamustine in humans? If not please justify.

11.3.7.1. Sponsor's response (complete)

A mass balance study with the title "An Open-Label Study to Investigate the Pharmacokinetics (Distribution, Metabolism, and Excretion) of Bendamustine Hydrochloride Following Intravenous Infusion of [14C]Bendamustine Hydrochloride in Patients With Relapsed or Refractory Malignancy (Hematologic or Nonhematologic)" was performed by the US license partner Cephalon (Study C18083/1039/PK/NL). Please refer to Module 5.3.3.1 for a copy of this report.

The figure below shows the renal and non-renal excretion of bendamustine.

Figure 9: Cumulative daily urinary and fecal excretion of total radioactivity in 168 hours (expressed as mean plus standard deviation percent of bendamustine dose) in patients with cancer (n=6) following the initial intravenous infusion of 120 mg/m2 of [^{14}C] bendamustine hydrochloride on Day 1 Of Cycle 1.



11.3.7.2. Clinical evaluator's comment

The sponsor's response is satisfactory. The sponsor's s31 Response included a copy of the mass-balance study C18083/1039/PK/NL. This study has been evaluated and is discussed below. The study was of good quality and reporting of the results was comprehensive.

11.3.7.2.1. Study C18083/1039/PK/NL

This study was performed to satisfy a post-approval commitment in the US to characterize the distribution, metabolism, and elimination of [^{14}C]-bendamustine and its metabolites. Cephalon obtained FDA approval for the design of the protocol on March 18, 2009. The results of this study were also intended to determine the need for additional studies to satisfy post-approval commitments related to special populations (eg, patients with renal or hepatic impairment) or potential interactions with drugs or substances known to inhibit or induce cytochrome P450 enzyme 1A2 (CYP1A2), an enzyme which is involved in bendamustine metabolism. The study was initiated on 27 May 2009 and completed on 3 February 2010. The approval date for the CSR was 23 November 2010. The study was undertaken in a single-centre in the Netherlands and was conducted in compliance with Good Clinical Practice (GCP).

The **primary objective** of the study was:

- to quantitatively determine the pharmacokinetics (distribution, metabolism, and excretion) of [^{14}C]-bendamustine and its metabolites in patients with confirmed, relapsed or refractory malignancy (hematologic or non-haematologic).

The **secondary objectives** were to evaluate the following:

- occurrence of adverse events throughout the study;
- clinical laboratory (haematology, serum chemistry, and/or urinalysis) test results at specified time points during assessment periods A and B, at discharge from assessment period A, and at the final assessment;
- vital signs (systolic and diastolic blood pressures, pulse, and body temperature) measurements at each visit;
- 12-lead electrocardiogram (ECG) findings at specified time points during assessment period A (on day 1 of cycle 1), at discharge from assessment period A, and at the final assessment;
- physical examination findings during assessment period B (on day 1 of cycles 2 through 6), at discharge from assessment period A, and at the final assessment;
- body weight measurements during assessment period A (on day 1 of cycle 1) and assessment period B (on day 1 of cycles 2 through 6), at discharge from assessment period A, and at the final assessment; and
- concomitant medication usage throughout the study.

This Phase 1, single-centre, open-label, non-randomized study was **designed** to determine the PKs (distribution, metabolism, and excretion) of bendamustine and its metabolites following a dose of 120 mg/m^2 in adult patients with confirmed, relapsed or refractory malignancy (haematologic or non-haematologic). The study consisted of a screening period up to 28 days, followed by up to six 28-day open-label treatment cycles and a final assessment to occur approximately 28±7 days after the end of the last treatment cycle.

After completion of all screening procedures, eligible patients received treatment with bendamustine at a dose of 120 mg/m^2 on days 1 and 2 of each cycle. Assessment period A consisted of days 1 through 8 of cycle 1 and assessments were conducted on an in-patient basis. On day 1 of cycle 1 only, each patient received a 60 minute iv infusion of bendamustine 120-mg/m^2 containing approximately 80 to 95 microcuries (µCi) of radio-labelled carbon. To avoid any potential retention of drug-associated radioactivity in the elimination organs, patients received a high fibre diet (at least 25 g/day) and adequate fluid intake (at least 2 L/day) during cycle 1 for 8 days to ensure rapid intestinal transit and flow.

The **study population** included 6 Caucasian patients (3 males, 3 females) of mean age 64.2 years (range: 48, 75). The mean weight was 72.7 kg (range: 59, 54), the mean height was a 173.2 cm (range: 155, 181), and the mean BSA was 1.9 m^2 (range: 1.6, 2.2). The mean time since first diagnosis of cancer was 4.7 years (range: 2, 13); the primary cancer sites were breast (n=1), colorectal (n=2), renal (n=1) and other (n=2); all 6 patients had received prior cancer drug therapy and all 6 patients had undergone prior cancer surgery; 4 patients had received prior anticancer radiotherapy; baseline WHO PS was 0 for 4 patients and 1 for 2 patients.

11.3.7.2.2. Results

- The mean total radioactivity recovery of the administered radiochemical dose in the excreta was approximately 76%. The sponsor speculates that the incomplete recovery is suggestive of the presence of long-lived materials, which are slowly degraded and excreted. These may include materials that are released during the catabolism of alkylated protein molecules such as cysteine adducts.
- Of the total radioactive dose administered, approximately half of the dose (45.5%) was recovered in the urine and approximately a quarter of the dose (25.2%) was recovered in the feces.
- Urinary excretion was confirmed as a relatively minor pathway of elimination of bendamustine, with approximately 3.3% of the dose recovered in the urine as

bendamustine. Less than 1% of the dose was recovered in the urine as M3 and M4, and less than 5% of the dose was recovered in the urine as HP2.

- The results of the urinary metabolite profiling and investigation of the identities of the 25 most prominent metabolites in the current study indicate that bendamustine is extensively metabolized via hydrolytic, oxidative, and conjugative pathways. The active circulating metabolites of bendamustine (M3 and M4) are present in low concentrations relative to parent indicating that the CYP1A2 pathway, which is responsible for their formation, has a minor role in the metabolism of bendamustine.
- The mean volume of distribution (Vss) of bendamustine in this study was small (20.1 L [SD=7.14]), and the mean terminal half life (t1/2) was short (0.65 hours [SD=2.86]). These results are consistent with the data from previously submitted studies. Consistent with its limited volume of distribution, the plasma to blood ratio of total radioactivity was approximately 1, indicating no preferential association of the total bendamustine derived materials with the cellular components of the blood.
- Also consistent with the previous data, the M3 and M4 metabolites were present in very low concentrations relative to parent drug. Although not measured in previous studies, the HP2 metabolite was quantified in the current study. This metabolite was longer lived than the others, but was also present in very low concentrations relative to parent (maximum concentrations comparable to those of M4). It was not possible to reliably quantify plasma concentrations of the HP1 metabolite.
- The sustained levels of radioactivity in the plasma as compared with plasma concentrations of bendamustine, M3, and M4 observed in this study suggest that, despite the rapid clearance of bendamustine and its active metabolites, 1 or more longer-lived [^{14}C]-bendamustine derived materials remain in the plasma.

11.3.8. Question 8

Does the sponsor intend to undertake PK studies in patients with renal and hepatic impairment that meet current standards of best-practice for such studies (see relevant EU guidelines). If not, please justify?

11.3.8.1. Sponsor's response (complete/edited)

11.3.8.1.1. Hepatic impairment

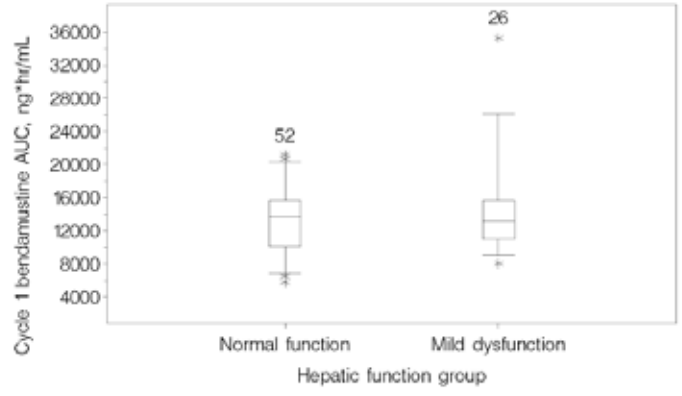
The study investigating the PK and safety of bendamustine in patients with renal or hepatic impairment (ribosepharm 98B03) started enrolment in 1998 and last patient out was March 2002.

The Guideline On The Evaluation Of The Pharmacokinetics Of Medicinal Products In Patients With Impaired Hepatic Function came into operation in October 2005. Indeed study 98B03 did not classify patients according to The Child-Pugh classification recommended by the EU guideline.

In the US study SDX-105-03 a population PK analysis was performed. PK of patients was investigated depending of the hepatic function (Figure 10). Hepatic function was classified as follows:

- normal hepatic function (normal total bilirubin range and normal SGOT range and normal alkaline phosphatase range); and
- mild hepatic dysfunction (total bilirubin < ULN, SGOT > ULN to 2.5 x ULN, and/or alkaline phosphatase > ULN to 5.0 x ULN).

Figure 10. Boxplots of bendamustine AUC versus hepatic function group: total dataset



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range.

11.3.8.1.2. Renal Impairment

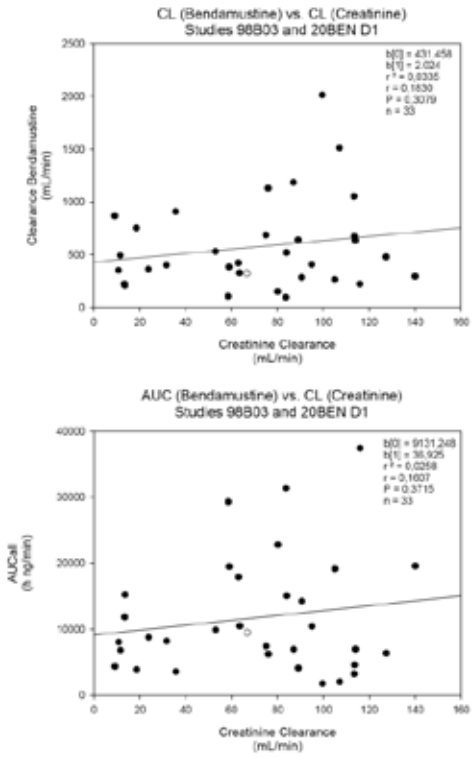
The study investigating the PK and safety of bendamustine in patients with renal or hepatic impairment (ribosepharm 98B03) started enrolment in 1998 and last patient out was March 2002.

The Guideline On The Evaluation Of The Pharmacokinetics Of Medicinal Products In Patients With Impaired Renal Function came into operation in December 2004.

The applicant performed an analysis on correlation of Clearance and AUC of bendamustine versus creatinine clearance in patients of studies 98B03 and 20 BEN D1.

The results are shown below.

Figure 11. Clearance and AUC of bendamustine versus creatinine clearance in studies 98B03 and 20BEND1



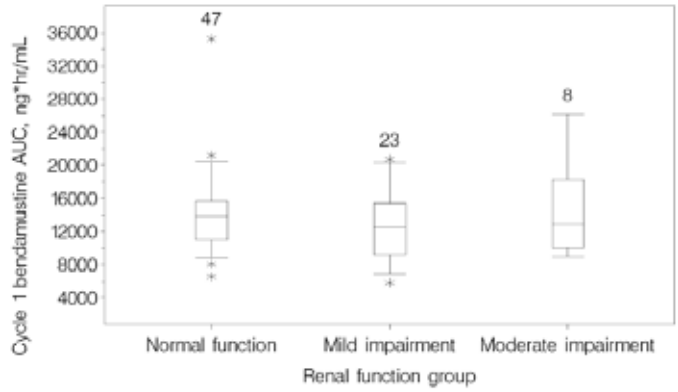
The results presented in the figure provide evidence that both, AUC and total body clearance of bendamustine do not significantly correlate with creatinine clearance as determined for a broad

range of creatinine clearance (9 – 140 mL/min).

Individual estimates of bendamustine AUC and Cmax values were summarized by renal function category (Figure 12). Median bendamustine AUC and Cmax showed little difference between patients with normal renal function (n=47) and those with mild (n=23) or moderate (n=8) renal dysfunction. No patients with pharmacokinetic data were classified as having severe renal dysfunction. The classification was as follows:

- normal renal function (CrCL > 80 mL/min);
- mild renal impairment (50 mL/min< CrCL < 80 mL/min); and
- moderate renal impairment (30 mL/min < CrCL < 50 mL/min).

Figure12. Boxplots of cycle 1 plasma bendamustine area under the plasma drug concentration by time curve versus renal function group.



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range.

This assessment suggests the lack of significance of mild or moderate renal dysfunction as a predictor of pharmacokinetic variability.

Due to the consistent body of evidence no further studies are planned for this patient population.

11.3.8.2. Clinical evaluator's comment

The sponsor's response is satisfactory. However, there are no satisfactory data on the PKs of bendamustine in patients with severe renal impairment or in patients with moderate or severe hepatic impairment.

11.4. Efficacy

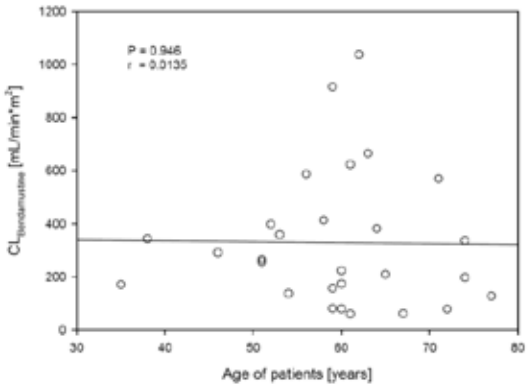
11.4.1. Question 1

CLL: The pivotal study (02CLLIII) excluded patients older than 75 years, and the mean age (range) of patients in the ITT population for bendamustine and chlorambucil was 63.0 years (47, 77 years) and 63.6 (35, 78 years). Consequently, the study population appears to be younger than Australian patients with CLL for whom bendamustine might be a treatment option. Subgroup analyses of the two primary efficacy endpoints (overall response and PFS) showed that treatment with bendamustine was significantly superior to treatment with chlorambucil independent of age (< 65 years, ≥ 65 years). However, there were no specific efficacy data on patients aged ≥ 75 years and the availability of such data from the pivotal study are likely to be negligible, given that patients aged > 75 years were excluded from the study and the upper age range for the total population was 77 years. Please comment on the generalizability of the data from the pivotal study population to the Australian population of patients with treatment-naive CLL for whom bendamustine might be a treatment option.

11.4.1.1. Sponsor's response (abridged/edited)

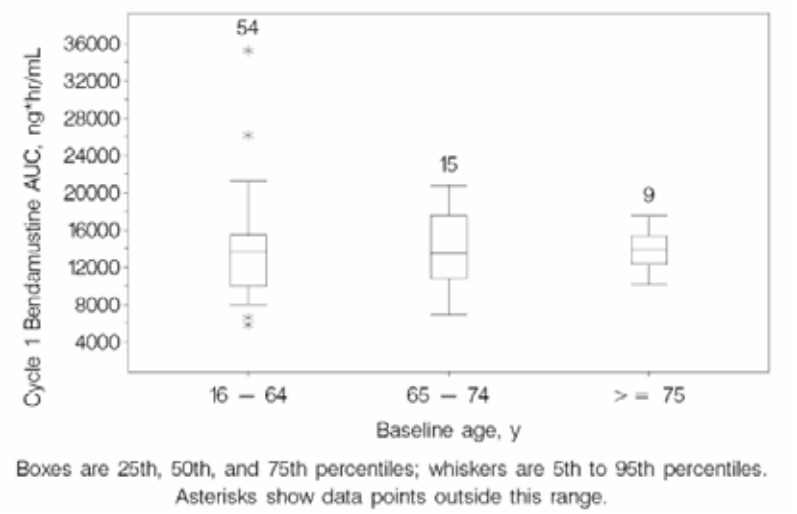
In adult patients the EU pharmacokinetic studies with bendamustine HCl included female and male patients with an age of the patients ranging from 35 to 84 years. There was no indication that advanced age of the patients changed the pharmacokinetic behaviour of bendamustine HCl (Figure 13).

Figure 13: Regression analysis between age of patients and clearance of bendamustine HCl in 28 tumour patients (Studies 98B02, 98B03, 20BEN D1)



The US study SDX-105-03 investigated bendamustine monotherapy in patients with indolent NHL. Patients with B-cell CLL were enrolled in the study and constituted 21% (n=21) of the study population. The study included a population PK investigation. The age of patients of the population PK investigation ranged from 36 to 84 years, with median age between 56 and 56.5 years (SDX 105-03; report CP-07-002). Individual estimates of bendamustine AUC and Cmax values were summarized across categories of age (16 to 64 years, 65 to 74 years, and greater than or equal to 75 years). Median bendamustine AUC (Figure 14) and Cmax showed little difference between age groups (less than 6%). This assessment supports the lack of significance of age as a predictor of PK parameter variability in the population analysis.

Figure 14: Boxplots of Plasma Bendamustine AUC Versus Baseline Age: Total Dataset



Both the EU and US investigations showed no influence of age on the PK of bendamustine. The US study SDX-105-03 for which the population PK investigation was performed included 21% of patients with CLL. Therefore the results achieved in study 02CLL III (ITT population bendamustine 47-77 years) are generalizable for patients > 75 years of age.

11.4.1.2. Clinical evaluator's comment

The sponsor's response is satisfactory. However, there are limited clinical efficacy and safety data relating to treatment of CLL with bendamustine in patients aged ≥ 65 years. The sponsor has provided data from the PopPK study (CP-07-002) based on study SDX-105-03 indicating that exposure (AUC) to bendamustine is similar irrespective of age. However, the PK/PD study (CP-07-003) showed that exposure to bendamustine was not a significant predictor of responder status or duration of response based on data from study SDX-105-03.

11.4.2. Question 2

CLL: In the Canadian monograph the results for response for study 02CLIII summarized in Table 38 notably differ from the ICRA results provided in the submission in the second CSR (see Table 39), and from those presented in the proposed Australian PI. The differences are particularly marked for the CR and PR assessments. Please account for these differences.

11.4.2.1. Sponsor's response (complete)

The data in the Canadian monograph (see Table 38) is the Overall Response Rate based on calculated response. Calculated responses are the result of an algorithmic application of the NCI-WG criteria to the primary data of the ITT analysis set. These are the results from a sensitivity analysis to explore the robustness of the effect of ORR.

Table 38: ORR data in Canadian monograph of Treanda of study 02CLL III.

	TREANDA (N=162)	**Chlorambucil (N=157)**	
	Response Rate n(%)	Response Rate n(%)	p-value
Overall response rate (95% CI)	110 (68) (60.7, 75.1)	51 (33) (25.2, 39.8)	<0.0001
Complete response (CR)*	14 (9)	1 (<1)	
Nodal partial response (nPR)**	6 (4)	0	
Partial response (PR)†	90 (56)	50 (32)	

* CR was defined as peripheral lymphocyte count ≤ 4.0 x 10^9/L, neutrophils ≥ 1.5 x 10^9/L, platelets >100 x 10^9/L, hemoglobin > 110g/L, without transfusions, absence of palpable hepato-splenomegaly, lymph nodes ≤ 1.5 cm, < 30% lymphocytes without nodularity in at least a normo-cellular bone marrow and absence of "B" symptoms. The clinical and laboratory criteria were required to be maintained for a period of at least 56 days. ** nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules. † PR was defined as ≥ 50% decrease in peripheral lymphocyte count from the pretreatment baseline value, and either ≥50% reduction in lymphadenopathy, or ≥50% reduction in the size of spleen or liver, as well as one of the following hematologic improvements: neutrophils ≥ 1.5 x 10^9/L or 50% improvement over baseline, platelets >100 x 10^9/L or 50% improvement over baseline, haemoglobin >110g/L or 50% improvement over baseline without transfusions, for a period of at least 56 days.

The Overall Response Rate based on calculated response is the Sensitivity Analysis B performed by the US license partner for the FDA submission. The US license partner compiles a separate CSR for submission to the US FDA. The tables below show the ORR based on ICRA for ITT analysis set (Table 39) compared to the ORR based on calculated response for the ITT analysis set (Table 40) as shown in the study report of the US license partner submitted to the FDA.

Table 39: Primary analysis: Overall response rate based on adjudicated responses from the independent committee for response assessment by treatment group (intent-to-treat analysis set)

	Number (%) of patients		
ICRA Response	Bendamustine (N=162)	Chlorambucil (N=157)	p-value[a]
Total number of patients overall	162	157	
Complete response	50 (31)	3 (2)	
Nodular partial response	17 (10)	4 (3)	
Partial response	42 (26)	41 (26)	
Unconfirmed response	5 (3)	5 (3)	
Stable disease	19 (12)	32 (20)	
Progressive disease	15 (9)	53 (34)	
Not examined	14 (9)	19 (12)	
Overall response rate	109 (67)	48 (31)	<0.0001
(95% CI)[b]	(60.06, 74.51)	(23.37, 37.78)	

Table 40: Sensitivity analysis B: Overall response rate based on calculated responses by treatment group (intent-to-treat analysis set)

	Number (%) of patients		
Calculated response	Bendamustine (N=162)	Chlorambucil (N=157)	p-value[a]
All patients	162	157	
Complete response	14 (9)	1 (<1)	
Nodular partial response	6 (4)	0	
Partial response	90 (56)	50 (32)	
Stable disease/Progressive disease/NE	52 (32)	106 (68)	
Overall response rate	110 (68)	51 (32)	<0.0001
(95% CI)[b]	(60.71, 75.09)	(25.16, 39.81)	

The Table 41 of the second CSR (see table below) of the study sponsor and EU license partner Mundipharma/ribosepharm shows the ORR of the ICRA for the ITT analysis set (this is equivalent to Table 39 above). These data are the basis for the text proposal for the labeling in Australia.

Table 41: Overall remission rate according to ICRA-intent-to-treat population

ICRA	BEN (N = 162)	CLB (N = 157)	p-value[1]
Number of patients overall	162	157	
Complete response	50 (30.9%)	3 (1.9%)	
Nodular partial response	17 (10.5%)	4 (2.5%)	
Partial response	43 (26.5%)	41 (26.1%)	
Unconfirmed response	4 (2.5%)	5 (3.2%)	
Stable disease	19 (11.7%)	32 (20.4%)	
Progressive disease	15 (9.3%)	53 (33.8%)	
Not examined	14 (8.6%)	19 (12.1%)	
Overall response rate	**110 (67.9%)**	**48 (30.6%)**	**<0.0001**

11.4.2.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.4.3. Question 3

CLL: In the second CSR for study 02CLIII it is stated that one of the methods used to assess the response involved the electronic CRF (eCRF) calculating the overall response according to a programmed algorithm based on the NCI-WG Criteria for response assessment (Cheson, 1996). Please provide the results for this analysis using the data provided in the second CSR.

11.4.3.1. Sponsor's response (complete)

The Addendum 02 to the CSR "Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naïve Patients

With (Binet Stage B/C) B-CLL Requiring Therapy" is provided as attachment in Module 5.3.5.1. The original report approval date is 5 September 2007 and the approval data of Addendum 02 is 3 June 2009.

Table 42: Primary analysis: Overall response rate based on adjudicated responses from the Independent Committee for Response Assessment by treatment group (intent-to-treat set)

	Number (%) of patients		
ICRA Response	Bendamustine (N=162)	Chlorambucil (N=157)	p-value[a]
Total number of patients overall	162	157	
Complete response	50 (31)	3 (2)	
Nodular partial response	17 (10)	4 (3)	
Partial response	42 (26)	41 (26)	
Unconfirmed response	5 (3)	5 (3)	
Stable disease	19 (12)	32 (20)	
Progressive disease	15 (9)	53 (34)	
Not examined	14 (9)	19 (12)	
Overall response rate	109 (67)	48 (31)	<0.0001
(95% CI)[b]	(60.06, 74.51)	(23.37, 37.78)	

11.4.3.2. Clinical evaluator's comment

The table in the response does not provide the requested analysis as it summarizes the results for the primary analysis (ORR based on adjudicated responses from the ICRA). However, from the sponsor's response to Question 2 it appears that the data for the requested analysis are included in Tables 38 and 40 provided in the Q2 Response. The data from these two tables shows that the ORR for the requested analysis is consistent with the ORR according to ICRA (ITT) provided in Table 41 (Q2), but that the compete, nodal partial response, and partial response rates that contribute to the ORR differ between the sensitivity analysis and the primary analysis.

11.4.4. Question 4

CLL: The break-down of PFS into its components could not be identified for any of the analyses (i.e., no separate patient numbers for progression, relapse or death contributing to the total number of events). Please provide the break-down of PFS events for the primary analysis (ICRA), the sensitivity analysis (investigator assessment), Binet B and C assessments, males and females, and patients < 65 years of age and ≥ 65 years of age.

11.4.4.1. Sponsor's response (complete)

The requested break-down of PFS into its components for the primary analysis (ICRA) and the sensitivity analysis (investigator) is provided in Module 5.3.5.1 - 02CLLIII PFS components. The break-down is presented for the 319 patients of the analysis with cut-off May 31, 2008.

11.4.4.2. Clinical evaluator's comment

The sponsor's response is satisfactory. The tabulated results relating to the PFS component analysis based on ICRA assessment are summarized below.

Table 43: Study 02CLIII - ICRA assessment (primary analysis); all patients

	BEN (N = 162) N (%)	CLB (N = 157) N (%)	Total (N = 319) N (%)
PFS component			
Censored	76 (46.9%)	56 (35.7%)	132 (41.4%)
Death	4 (2.5%)	3 (1.9%)	7 (2.2%)
Progression	18 (11.1%)	59 (37.6%)	77 (24.1%)
Relapse	64 (39.5%)	39 (24.8%)	103 (32.3%)
Total	162 (100.0%)	157 (100.0%)	319 (100.0%)

Table 44: Study 02CLIII - ICRA assessment; female patients

	BEN (N = 60) N (%)	CLB (N = 62) N (%)	Total (N = 122) N (%)
PFS component			
Censored	27 (45.0%)	27 (43.5%)	54 (44.3%)
Death	0 (0.0%)	2 (3.2%)	2 (1.6%)
Progression	5 (8.3%)	18 (29.0%)	23 (18.9%)
Relapse	28 (46.7%)	15 (24.2%)	43 (35.2%)
Total	60 (100.0%)	62 (100.0%)	122 (100.0%)

Table 45. Study 02CLIII - ICRA assessment; male patients

	BEN (N = 102) N (%)	CLB (N = 95) N (%)	Total (N = 197) N (%)
PFS component			
Censored	49 (48.0%)	29 (30.5%)	78 (39.6%)
Death	4 (3.9%)	1 (1.1%)	5 (2.5%)
Progression	13 (12.7%)	41 (43.2%)	54 (27.4%)
Relapse	36 (35.3%)	24 (25.3%)	60 (30.5%)
Total	102 (100.0%)	95 (100.0%)	197 (100.0%)

Table 46: Study 02CLIII - ICRA assessment; patients aged < 65 years

	BEN (N = 88) N (%)	CLB (N = 74) N (%)	Total (N = 162) N (%)
PFS component			
Censored	39 (44.3%)	25 (33.8%)	64 (39.5%)
Death	1 (1.1%)	2 (2.7%)	3 (1.9%)
Progression	7 (8.0%)	31 (41.9%)	38 (23.5%)
Relapse	41 (46.6%)	16 (21.6%)	57 (35.2%)
Total	88 (100.0%)	74 (100.0%)	162 (100.0%)

Table 47: Study 02CLIII - ICRA assessment; patients aged ≥ 65 years

	BEN (N = 74) N (%)	CLB (N = 83) N (%)	Total (N = 157) N (%)
PFS component			
Censored	37 (50.0%)	31 (37.3%)	68 (43.3%)
Death	3 (4.1%)	1 (1.2%)	4 (2.5%)
Progression	11 (14.9%)	28 (33.7%)	39 (24.8%)
Relapse	23 (31.1%)	23 (27.7%)	46 (29.3%)
Total	74 (100.0%)	83 (100.0%)	157 (100.0%)

Table 48: Study 02CLIII - ICRA assessment; patients with Binet B

	BEN (N = 116) N (%)	CLB (N = 111) N (%)	Total (N = 227) N (%)
PFS component			
Censored	51 (44.0%)	38 (34.2%)	89 (39.2%)
Death	2 (1.7%)	1 (0.9%)	3 (1.3%)
Progression	14 (12.1%)	41 (36.9%)	55 (24.2%)
Relapse	49 (42.2%)	31 (27.9%)	80 (35.2%)
Total	116 (100.0%)	111 (100.0%)	227 (100.0%)

Table 49: Study 02CLIII - ICRA assessment; patients with Binet C

	BEN (N = 46) N (%)	CLB (N = 46) N (%)	Total (N = 92) N (%)
PFS component			
Censored	25 (54.3%)	18 (39.1%)	43 (46.7%)
Death	2 (4.3%)	2 (4.3%)	4 (4.3%)
Progression	4 (8.7%)	18 (39.1%)	22 (23.9%)
Relapse	15 (32.6%)	8 (17.4%)	23 (25.0%)
Total	46 (100.0%)	46 (100.0%)	92 (100.0%)

The sponsor also provided the PFS component analyses based on investigator assessment. The tabulated results of these analyses have been inspected and were generally consistent with the analyses based on ICRA assessment.

11.4.5. Question 5

CLL: No information on the median duration of follow-up could be identified in the submitted data. However, in Knauf et al (2009) it is stated that median observation time in patients in the follow-up analysis was 35 months (range: 1, 68 months). Please confirm the median observation time in patients in the follow-up analysis.

11.4.5.1. Sponsor's response (complete)

In addition to the follow-up published by Knauf et al. (2009) a further follow-up was performed in 2010 02CLIII Follow-up report 2010). The median observation time of this follow-up was 54 months.

Table 50: Median observation time of study 02CLL III at 2010 follow-up

Observation time in months	Bendamustine	Chlorambucil	total
n	162	157	319
Mean (SD)	49.5 (22.5)	48.4 (23.9)	49.0 (23.2)
95% CL	[46.1; 53.0]	[44.6; 52.2]	[46.4; 51.5]
Min-Max	0.0 - 90.2	0.0 - 89.6	0.0 - 90.2
Median	54.1	53.6	53.9
Q1-Q3	35.3 - 66.1	34.2 - 64.5	34.2 - 65.5

Until May 2010 132 patients died, 62 patients (38%) within the BEN group and 70 patients (45%) within the CLB group (P = 0.257, Cochran-Mantel-Haenszel statistic adjusted for Binet B and C). The results of the 2010 follow-up are given in the table below.

Table 51: Results of study 02CLL III at 2010 follow-up

Survival status	Bendamustine n=162	Chlorambucil n=157	p-value
Alive	100 (61.7%)	87 (55.4%)	0.257
Dead	62 (38.3%)	70 (44.6%)	

11.4.5.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.4.6. Question 6

Relapsed/refractory indolent NHL: Please provide separate ORRs for the 31 patients from study SDX-105-01 who were either sensitive to their most recent rituximab containing treatment regimen (n=23) or had an unknown response (n=8) to their most recent rituximab-containing regimen, and the 45 patients who were refractory to their most recent rituximab-containing regimen.

11.4.6.1. Sponsor's response (abridged/edited)

The ORR (CR + CRu + PR) of the 31 patients who were sensitive or had unknown response to their most recent rituximab containing treatment is 80.65% [see table below].

Table 52: Response rates of the 31 patients who were sensitive or had unknown response to their most recent rituximab containing treatment

Category, n (%)	Bendamustine (N=31)
Complete response (CR)	3 (10)
Complete response /unconfirmed (CRu)	6 (19)
Partial response (PR)	16 (52)
Stable disease (SD)	2 (6)
Progressive disease (PD)	3 (10)
Unknown	1 (3)
Overall response rate (CR + CRu + PR)	25 (80.65)
95% confidence interval	(62.53, 92.55)

The ORR (CR + CRu + PR) of the 45 patients who were refractory to their most recent rituximab containing treatment is 73.33% [see table below].

Table 53: Response rate of the 45 patients who were refractory to their most recent rituximab containing treatment

Category, n (%)	Bendamustine (N=45)
Complete response (CR)	8 (18)
Complete response /unconfirmed (CRu)	8 (18)
Partial response (PR)	17 (38)
Stable disease (SD)	1 (2)
Progressive disease (PD)	10 (22)
Unknown	0
Missing	1 (2)
Overall response rate (CR + CRu + PR)	33 (73.33)
95% confidence interval	(58.06, 85.40)

11.4.6.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.4.7. Question 7

Relapsed/refractory indolent NHL: Has all long-term follow-up data for study SDX-105- 103 accrued? If so, please provide the results for the efficacy outcomes of ORR, DR, and PFS.

11.4.7.1. Sponsor's response (complete)

Follow-up data of study SDX-105-03 is reported in the CSR and has been published by Kahl et al. in 2010. An ORR of 75% (a 14% complete response rate, a 3% unconfirmed complete response rate, and a 58% partial response rate) was observed.

The median DOR was 9.2 months. On the basis of a median follow-up of 11.8 months the median PFS was 9.3 months.

No further follow-up data are available.

11.4.7.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.4.8. Question 8

First-line indolent NHL and MCL - The application for the proposed indication for bendamustine in combination with rituximab for the first line treatment of indolent NHL and MCL is supported by one pivotal study (StiL NHL 1-2003), and published results for this study are provided in Rummel et al (2013). The submission included an English translation from German of the initial protocol for this study identified as StiL NHL 1- 2003 (September 2003). However, it is obvious from Rummel et al (2013), and from a document included in the Module 5 literature references (Chen and Li, Cephalon Statistical Analysis Plan for StiL NHL 1-2003, 5 May 2011), that the initial protocol underwent a number of amendments. Please provide the final protocol for StiL NHL 1-2003, indicating all amendments, and the final statistical analysis plan for this study. In addition, please explain why the Cephalon final statistical analysis plan for StiL NHL 1- 2003 was provided in the M5 literature references rather than in the relevant M5 studies for evaluation section.

11.4.8.1. Sponsor's response (complete)

In agreement with the TGA, the supporting data for First line indolent NHL is based on a published paper (STiL) and other publicly available information. Beyond the information provided in this dossier Janssen are not in a position to supply any information not in the public domain, which includes the final protocol and Clinical Study Report.

Although Janssen are aware that the data to support iNHL is limited, an unmet clinical need was identified by clinicians in relation to this setting and submission of this data was in support of those clinicians who approached the company requesting access to bendamustine in this setting.

The provision of the statistical analysis plan should have been included with the M5 studies for evaluation instead of the M5 literature references, this was an oversight and Janssen apologises for any confusion this may have cause.

11.4.8.2. Clinical evaluator's comment

The sponsor's response is noted.

11.4.9. Question 9

First-line indolent NHL and MCL - Why were the final Complete Study Report (CSR) and the final Biometric Report for study StiL NHL 1-2003 not provided? Presumably the published study Rummel et al (2013) were based on these reports. In the absence of conventional safety data, a comprehensive regulatory assessment of the safety of bendamustine in combination with rituximab for the proposed indication cannot be undertaken.

11.4.9.1. Sponsor's response (complete)

In agreement with the TGA, the supporting data for First line indolent NHL is based on a published paper (Rummel) and other publicly available information. Beyond the information provided in this dossier Janssen are not in a position to supply any information not in the public domain, which includes the final protocol and Clinical Study Report.

Although Janssen are aware that the data to support iNHL is limited, an unmet clinical need was identified by clinicians in relation to this setting and submission of this data was in support of those clinicians who approached the company requesting access to bendamustine in this setting.

11.4.9.2. Clinical evaluator's comment

The sponsor's response is noted. However, the fact remains that in the absence of comprehensive safety data from a CSR, a definitive regulatory assessment of the safety of bendamustine in combination with rituximab for the proposed indication cannot be undertaken.

11.4.10. Question 10

First-line indolent NHL and MCL - Does the sponsor have the results from Rummel et al (2013) of efficacy analyses in the ITT population? If so, please provide these results.

11.4.10.1. Sponsor's response (complete)

In agreement with the TGA, the supporting data for First line indolent NHL is based on a published paper (Rummel) and other publicly available information. Beyond the information provided in this dossier Janssen are not in a position to supply any information not in the public domain, which includes the final protocol and Clinical Study Report.

11.4.10.2. Clinical evaluator's comment

The sponsor's response is noted.

11.5. Safety

11.5.1. Question 1

Relapsed/refractory indolent NHL: In study SDX-105-01, it is stated that thrombocytopenia was the most common AE resulting in dose delay. How many patients (n [%]) experienced dose delay due to thrombocytopenia?

11.5.1.1. Sponsor's response (abridged)

A total of 46 patients (61%) had dose reductions or dose delays, or did not receive both doses in the cycle at some point in their treatment. The most common reason for dose delay was thrombocytopenia. The patients with thrombocytopenia given as reason in the listing are shown below. For 5 (7%) of the patients thrombocytopenia is listed as the reason for dose delay [and for 4 of these patients the event occurred on Day 1, Cycle 2 while for 1 of these patients 2 events occurred (1 on Day 1, Cycle 2 and 1 on Day 1, Cycle 4)].

For study SDX-105-03 the number (%) of patients with dose delay or reduction in cycle due to thrombocytopenia is 19 (19%).

11.5.1.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.5.2. Question 2

In the post-marketing data (PSUR 2), reference was made to pulmonary embolism (including symptoms of dyspnoea, tachypnoea, and pleuritic pain), being possibly due to silicone oil contamination. Consequently, PSUR 2 indicates that these events are being temporarily monitored until all batches bendamustine potentially contaminated with silicon oil have expired. Please provide updated information on cases of pulmonary embolism reported in association with bendamustine, and on the sponsor's plans for continuing monitoring of pulmonary embolism (including symptoms of dyspnoea, tachypnoea, and pleuritic pain). Please comment on procedures undertaken to prevent future recurrence of silicon oil contamination.

11.5.2.1. Sponsor's response (complete)

Applicant Response:

- There were no other cases reported (PSUR 3-7); shows no mention of pulmonary embolism.
- If necessary please provide an official request for the CAPA report. The sponsor (Astellas) can provide the report to the specified TGA assessor to the TGA address specified.

Table 54: CAPA - implementation

Capa	Implementation
Visual control of the freeze dryer after CIP between batch production	Description in the SOP Attachment of the batch documentation (Tool list) - amendment of SOP ONC-AW 034 Employee Training
100 % visual inspection of the freeze dried vials	Explicit check "no oily vials" in the protocol – immediate information to the head of production and the QP - Classification of defects, deviation report, if defect rate >1% - evaluation and differentiation of defects (QP) during batch record review - documentation of defects with sample catalogue (picture data base)
	- Employee Training
more often maintenance of the freeze dryer	Quarterly – Inspection of stressed equipment Add in the maintenance program

11.5.2.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.6. Second round benefit-risk assessment

11.6.1. Chronic lymphocytic leukaemia

After consideration of the responses to the clinical questions, the positive benefits of bendamustine for the treatment of CLL (Binet stage B or C) remain unchanged from those identified in Section 9.1.1.

11.6.2. Relapsed/refractory indolent NHL

After consideration of the responses to the clinical questions, the positive benefits of bendamustine for the treatment of indolent B-cell NHL refractory to rituximab remain unchanged from those identified in Section 9.1.2.

11.6.3. First-line treatment of indolent NHL and mantle-cell lymphoma

After consideration of the responses to the clinical questions, the positive benefits of bendamustine for the first-line treatment of indolent NHL and mantle-cell lymphoma remain unchanged from those identified in Section 9.1.3.

11.7. Second round assessment of risks

11.7.1. Chronic lymphocytic leukaemia

After consideration of the responses to the clinical questions, the risks of bendamustine for the treatment of chronic lymphatic leukaemia remain unchanged from those identified in Section 9.2.1.

11.7.2. Relapsed/refractory indolent NHL

After consideration of the responses to the clinical questions, the risks of bendamustine for the treatment of relapsed/refractory indolent NHL remain unchanged from those identified in Section 9.2.2.

11.7.3. First-line indolent NHL and MCL

The safety data from the single-pivotal study (Rummel et al., 2013) are promising and suggest that the risks of treatment with B-R for the proposed indication are similar to those for R-CHOP. However, in the absence of comprehensive safety data from a CSR a definitive assessment of the risks of treatment with B-R for the proposed indication cannot be made.

The sponsor's s31 Response confirms that the data supporting the first line indolent NHL indication are based on a published paper (Rummel et al., 2013) and other publicly available information. The sponsor states that it is not in a position to supply any information not in the public domain, which includes the final protocol and CSR for the pivotal study. The sponsor acknowledges that the data to support the first line indolent NHL indication are limited. However, the sponsor considers that there is an unmet clinical need for medicines to treat this condition and refers to approaches from clinicians requesting access to bendamustine for treatment of the condition. Nevertheless, for regulatory purposes it is considered that comprehensive safety data from a CSR are required in order to satisfactorily establish the safety of bendamustine for the proposed indication.

11.8. Second round assessment of benefit-risk balance

11.8.1. Chronic lymphatic leukaemia

The benefit-risk balance for the treatment of chronic lymphatic leukaemia is favourable. However, while the benefits of bendamustine for CLL are greater than those of chlorambucil, the risks of treatment with bendamustine are notably greater than those of chlorambucil. Consequently, although the benefit/risk balance for bendamustine for the treatment of CLL is considered to be favourable, the benefits are considered to only marginally outweigh the risks. The risks of treatment with bendamustine appear to be manageable by dose reduction, and prophylactic and symptomatic treatment of toxicities rather than treatment discontinuation. There appears to be no difference in overall survival between the bendamustine and chlorambucil treatment regimens for the treatment of CLL.

11.8.2. Refractory/relapsed indolent NHL

The benefit-risk balance for bendamustine for the treatment of patients with indolent relapsed/refractory NHL refractory to rituximab is considered to be favourable.

11.8.3. First-line indolent NHL and MCL

Based on published data from *Rummel et al 2013*, the benefit-risk balance is promising for bendamustine in combination with rituximab (B-R) for first-line treatment of indolent NHL and MCL in patients with CD20 positive stage III/IV disease. However, in the absence of confirmatory safety data from a CSR it is considered that no conclusive assessment of the benefit-risk balance of the proposed B-R treatment regimen for the proposed indication can be made.

11.9. Second round recommendation regarding authorisation

11.9.1. Chronic lymphocytic leukaemia

It is recommended that bendamustine HCl (Ribomustin®) **be approved** for the "first line treatment of chronic lymphocytic leukaemia (Binet stage B or C)".

11.9.2. Relapsed refractory indolent NHL

It is recommended that bendamustine HCl (Ribomustin®) **be approved** for the treatment of "indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen".

The recommended indication differs from that proposed by the sponsor. It is considered that the recommended indication reflects the patient population in the pivotal Phase III study (SDX-105-03), and aligns with the dosage regimen stated in the proposed PI (i.e., monotherapy for indolent NHL refractory to rituximab).

11.9.3. First-line indolent NHL and MCL

It is recommended that the proposed regimen of bendamustine HCl (Ribomustin®) in combination with rituximab **be rejected** for "previously untreated indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma. RIBOMUSTIN should be used in combination with rituximab in CD20 positive patients".

The reason for rejection is the absence of confirmatory safety data from a Complete Study Report (CSR) confirming that the proposed treatment regimen of bendamustine is safe for the proposed indication. The specific deficiencies in the submitted safety data are:

- No data on the extent of exposure relating to number of patients per cycle, mean number of cycles per patient, overall dose per cycle (mean and relative dose), and mean total dose per cycle.
- No data on the proportion of patients requiring dose modifications (dose reductions or temporary treatment discontinuations) due to AEs, or on the nature of the AEs resulting in dose modifications.
- No data on the total number of AEs experienced by patients in the two treatment groups (overall, and individual events).
- No data on the incidence of AEs by treatment cycle.
- No data on AEs considered to be treatment-related.
- No data on conventionally defined serious adverse events (i.e., fatal or life threatening, resulting in persistent disability or incapacity, requiring in-patient hospitalization or prolongation of existing hospitalization, resulting in congenital and/or causing secondary malignancies). Limited data on secondary malignancies were provided (total number and haematological), but no case narratives for the two patients with secondary haematological malignancies were provided and no information on the nature of secondary non-haematological malignancies were provided. No case narratives of patients experiencing serious adverse events were provided. No data were provided on suspected unexpected serious adverse reactions (SUSARs).
- No comprehensive data on deaths in the safety analysis population (i.e., causes of death and case narratives).
- No data on permanent treatment discontinuation of the study-drugs due to AEs.
- No data on the nature of the infections reported in the two treatment groups.
- No data on the proportion of patients requiring treatment with erythropoietin agonists, or transfusions with blood products for anaemia or thrombocytopenia.

- No data on changes in vital signs or the ECG during the course of the study.
- No data safety data based on age differences (e.g., ≥ 65 years vs < 65 years).

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