Non-Interventional Post-Authorisation Safety Study (NI-PASS) as an effectiveness check of an additional Risk Minimisation Measure (aRMM) (Direct Healthcare Professional Communication [DHPC]) for Bendamustine

ISN/Protocol [6231-MA-3264]

Version [7.0]

12-Jan-2023

Procedure number: DE/H/1250/001/II/034

Additional Pharmacovigilance activity in the RMP (Category 3)

EU-PAS register number: EUPAS34255

Sponsor:

Astellas Pharma Europe B.V.

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Title	Non-Interventional Post-Authorisation Safety Study (NI-PASS) as an effectiveness check of an additional Risk Minimisation Measure (aRMM) (Direct Healthcare Professional Communication [DHPC]) for Bendamustine
Study identifier / Protocol Number	ISN: 6231-MA-3264 Clinical Trials.gov identifier: not applicable (NA) EU PAS register number: EUPAS34255
Protocol version & date of last version of protocol	Version: 7.0 Incorporating Non-substantial amendment Date: 12 Jan 2023
Active substance	Bendamustine hydrochloride
Medicinal product	Levact®, Ribovact®, Ribomustin®
Product reference	DE/H/1250/001
Procedure number	DE/H/1250/001/II/034
Marketing authorization holder(s)	zr pharma& Hietzinger Hauptstrasse 37 1130 Vienna, Austria
Joint PASS	(Select one below) ☐ Yes ☒ No

Research question and objectives	The overall goal of this study is to evaluate the effectiveness of the DHPC as an aRMM for bendamustine. This study will be descriptive in nature. Primary Objectives: 1. Outcome Indicator- To evaluate all-cause mortality and serious and fatal infections occurring in pre- and post-DHPC dissemination periods for new users of bendamustine during these periods, as well as for new users of other alkylating drugs similar to bendamustine (i.e. cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM) in populations in three European countries. 2. Process Indicator- To quantify and characterize approved- and off-label use of bendamustine and other alkylating drugs similar to bendamustine (alternative treatments) in new users in pre- and post-DHPC dissemination periods in populations from three European countries. This protocol consists of three related but independent studies to achieve the two Primary Objectives: 1. STUDY A: Retrospective cohort study of electronic healthcare databases to evaluate safety outcomes (Primary Objective 1) 2. STUDY B: Cross-sectional study of electronic healthcare databases to evaluate approved- and off-label drug use (Primary Objective 2) 3. STUDY C: Cross-sectional study of a physician survey-based database to evaluate approved- and off-label drug use (Primary Objective 2)

Countries of study	STUDY A: France, Germany, England STUDY B: France, Germany, England STUDY C: France, Germany, United Kingdom (UK)
Number of Sites or Data Sources	Four data sources in total will be used: STUDY A and STUDY B: • Three electronic healthcare databases (claims, registries) will be used i) France (French Administrative Health Care Database [SNDS] linked with the National Hospital Discharge Database [PMSI]) ii) Germany (Statutory Health Insurance Database [SHI]) iii) England (Cancer Analysis System [CAS] and Hospital Episode Statistics [HES]) STUDY C: • Oncology Dynamics (OD), an IQVIA proprietary physician-survey based database, will provide data from France, Germany and UK.
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PAS register No: EUPAS34255

Marketing Authorization Holder(s)

Marketing authorization holder(s)	zr pharma& Hietzinger Hauptstrasse 371130 Vienna, Austria
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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF KEY TERMS

Abbreviations	Description of abbreviations
aRMM	additional Risk Minimization Measure
ATC	Anatomical Therapeutic Chemical Classification System
BfArM	Bundesinstitut fűr Arzneimittel und Medizinprodukte
BMI	body mass index
CA	Competent Authorities
CAS	Cancer Analysis System
CBC	complete blood count
CDR	Cause of Death Registry
CHOP	cyclophosphamide hydroxydaunorubicin oncovin prednisone
CI	confidence interval
CIOMS	Council for International Organisations of Medical Sciences
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
COSD	Cancer Outcomes and Services Dataset
CXP	Customized eXtraction Program
DHPC	Direct Healthcare Professional Communication
DRG	diagnosis related groups
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPN	Regional Ethical Review Boards
EU	European Union
EU PAS Register	The European Union Electronic Register of Post-Authorisation Studies

Abbreviations	Description of abbreviations
FDA	Food and Drug Administration
FL	follicular lymphoma
GEP	good epidemiologic practice
GPP	good pharmacoepidemiology practice
GVP	good pharmacovigilance practice
HES	Hospital Episode Statistics
HSCIC	Health and Social Care Information Centre
ICD-10	International Classification of Diseases, 10th Revision
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEA	International Epidemiological Association
IEC	independent ethics committee
iNHL	indolent non-Hodgkin's lymphoma
INN	International nonproprietary name system
IRB	institutional review board
ISB	Information Standards Board for Health and Social Care
ISEAC	Independent Scientific Ethical Advisory Committee
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LTD	long-term diseases
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NI-PASS	non-interventional post-authorization safety study
OD	Oncology Dynamics
ODR	Office of Data Release
OPCS	Office of Population Censuses and Surveys

Abbreviations	Description of abbreviations
PAS	post-authorization study
PASS	post-authorization safety study
PHE	Public Health England
PJP	pneumocystis jirovecii pneumonia
PMSI	programme de médicalisation des systèmes d'information (French National hospital discharge database)
PRAC	Pharmacovigilance Risk Assessment Committee
PSA	prostate-specific antigen
PZN	Pharmazentralnummer
RMS	reference member state
SACT	Systemic Anti -Cancer Therapy
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SHI	Statutory Health Insurance
SmPC	summary of product characteristics
SNDS	Système National des Données de Santé (French Administrative Health Care Database)
SNIIRAM	Système National d'Information Inter-Régimes de l'Assurance Maladie (French National Health Insurance)
SOPs	standard operating procedures
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
UK	United Kingdom
VZV	varicella zoster virus

3 RESPONSIBLE PARTIES

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Regulatory Affairs Director	PPD, Astellas Pharma Europe B.V. PPD
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4 SYNOPSIS

Date and Version # of Protocol Synopsis: **12 Jan 2023 Version 7.0**
Sponsor: Astella Pharma Europe B.V. **Protocol Number ISN: 6231-MA-3264**
EU PAS # : EUPAS34255
ClinicalTrials.gov identifier : not applicable (NA)

Name of Assessed Drug(s): bendamustine

Levact®, Ribovact®, Ribomustin®

Type of Study (refer to STL-141 *Master Definition List):*
Check one below:

☒ Mandated Study

☐ Non-mandated Study

Check one below:

☐ Primary data collection

☒ Secondary data collection

☐ Mix of primary and secondary data collection

Check one below: *for categorization, see STL-2544, Algorithm Categorization PAS*

☒ Post-authorization safety study (PASS)

For PASS studies only, select the appropriate reason to perform the study:

☐ *Category 1 – Imposed as a condition of the marketing authorization*

☐ *Category 2 – Imposed as a specific obligation in the context of a marketing authorization under exceptional circumstances*

☒ *Category 3 – Required in the risk management plan to investigate a safety concern or to evaluate the effectiveness of risk minimization activities*

☐ *Category 4 – Study conducted voluntarily*

☐ Post-authorization efficacy study (PAES)

☐ Post-authorization study (PAS, non-PASS and non-PAES)

☐ *Other

**Note: "Other" category refers to non-interventional studies that do not explicitly mention any Astellas product in the title, objectives or inclusion criteria (e.g. a pre-approval study to investigate natural course of a disease history or treatment pathways might fit in this category). Provide rationale for when "Other" is selected.*

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PAS register No: EUPAS34255

Title of Study:

Non-Interventional Post-Authorisation Safety Study (NI-PASS) as an effectiveness check of an additional Risk Minimisation Measure (aRMM) (Direct Healthcare Professional Communication [DHPC]) for Bendamustine.

Study Rationale and Background:

Bendamustine hydrochloride (hereinafter referred to as bendamustine) is a nitrogen mustard compound that functions as an alkylating antineoplastic agent by cross-linking of DNA strands. Bendamustine has been approved in the European Union (EU) for the following therapeutic indications in specific clinical situations: indolent Non-Hodgkin's Lymphoma (iNHL), Chronic Lymphocytic Leukemia (CLL), Multiple Myeloma (MM).

In February 2017, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) advised new safety information related to bendamustine, including increased mortality when bendamustine was used in non-approved combination treatments or outside the approved indications; serious and fatal infections, including bacterial and opportunistic infections; reactivation of hepatitis B; and prolonged and persistent lymphocytopenia and low CD4-positive T-cell counts.

Risk minimization measures (RMMs) were implemented to revise the Summary of Product Characteristics (SmPC) to include warnings regarding these new safety concerns. Additionally, in accordance and compliance with the EMA's PRAC request, a DHPC letter was disseminated as an additional risk minimization measure (aRMM) to healthcare professionals in 22 countries in the EU by August 30th, 2017.

In line with regulatory guidance (EMA Good Pharmacovigilance Practice [GVP] XVI.B4), the effectiveness of aRMMs are required to be evaluated; in this case a DHPC dissemination. Therefore, an NI-PASS as an effectiveness check of the implementation of the DHPC and RMMs for bendamustine is proposed.

Planned Study Period:

This retrospective study consists of 3 distinct study periods: pre-DHPC dissemination period, DHPC dissemination period, and post-DHPC dissemination period. Study outcomes are not assessed during the DHPC dissemination period. The study includes data from the period 01 April 2015 (two years prior to DHPC dissemination period) to 31 August 2019 (two years after DHPC dissemination period). The individual time periods are defined as follows:

- Pre-DHPC dissemination period (24 months): 01 April 2015 – 31 March 2017
- DHPC dissemination period (5 months): 01 April 2017 – 31 August 2017
- Post-DHPC dissemination period (24 months): 01 September 2017 – 31 August 2019

Study Objective(s):

The overall goal of this study is to evaluate the effectiveness of the DHPC dissemination and aRMMs for bendamustine.

Primary Objectives:

1. Outcome Indicator- To evaluate all-cause mortality and serious and fatal infections occurring in pre- and post-DHPC dissemination periods for new users of bendamustine during these periods, as well as for new users of other alkylating drugs similar to bendamustine (i.e. cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM) in populations in three European countries.
2. Process Indicator- To quantify and characterize approved- and off-label use of bendamustine and other alkylating drugs similar to bendamustine (alternative treatments) in new users in pre- and post-DHPC dissemination periods in populations from three European countries.

Data Sources(s):

Based on the results of a feasibility study, three electronic healthcare databases (claims, registries) from France (French Administrative Health Care Database [SNDS] linked with the

National Hospital Discharge Database [PMSI]), Germany (Statutory Health Insurance Database [SHI]), and England (Cancer Analysis System [CAS] and Hospital Episode Statistics [HES]) will be used to conduct Primary Objective 1 and Primary Objective 2 as data sources.

Owing to challenges in assessing approved- versus off-label drug use in available electronic healthcare databases (Protocol section 9.1.1 STUDY A: Data Sources), Oncology Dynamics (OD) data will be used to conduct a complementary assessment of approved- and off-label drug use for Primary Objective 2. OD is an IQVIA proprietary physician survey-based database and data will be used from France, Germany, and UK.

Study Population:

This is a study of patients initiating bendamustine for the treatment of iNHL, CLL, or MM and patients initiating the alternative treatments cyclophosphamide for iNHL, chlorambucil for CLL, or melphalan for MM during the study period of 01 April 2015 to 31 August 2019.

Study Size

For study A, approximately 320 person-years of exposure by stratum (bendamustine, study period pre- and post-DHPC, and country) will enable a statistical precision for incidence of safety events of not more than 5%. For study B, approximately 385 patients by stratum (bendamustine, study period pre- and post-DHPC, and country) will enable a precision of not more than 5% around the proportion of off-label use.

Study Design Overview:

This protocol consists of three related but independent studies to achieve the two Primary Objectives:

1. STUDY A: Cohort study of electronic healthcare databases to evaluate safety outcomes (Primary Objective 1)

2. STUDY B: Cross-sectional study of electronic healthcare databases to evaluate approved- and off-label drug use (Primary Objective 2)
3. STUDY C: Cross-sectional study of a physician survey-based database (OD) to evaluate approved- and off-label drug use (Primary Objective 2)

Each Study is described separately in the Protocol.

STUDY A: Cohort study to evaluate safety outcomes (Primary Objective 1)

To evaluate all-cause mortality and serious and fatal infections occurring in pre- and post-DHPC dissemination periods associated with use of bendamustine and other alkylating drugs similar to bendamustine, a retrospective open cohort study will be conducted. Thus all participants meeting the study inclusion criteria during the study period will be included in the study. Patients initiating bendamustine for the treatment of iNHL, CLL, or MM during the pre- or post-DHPC dissemination periods will be identified and assessed for safety outcomes for the remainder of the specific study period during which they initiated bendamustine use (i.e. either pre- or post-DHPC dissemination). Patients initiating cyclophosphamide for iNHL, chlorambucil for CLL, or melphalan for MM, collectively termed the alternative treatments, will be similarly identified and assessed for safety outcomes. The primary safety event outcomes are: i) all-cause mortality and ii) serious and fatal infections. Results will be reported as incidence rates per person-time exposure. Incidence rates will be reported separately for pre- and post-DHPC dissemination periods and will be stratified by country (France, Germany, England) and disease indication.

STUDY B: Cross-sectional study to evaluate approved- and off-label use (Primary Objective 2)

To quantify and characterize approved- and off-label use of bendamustine and other alkylating drugs similar to bendamustine in new users in pre- and post-DHPC dissemination periods, a cross-sectional study of electronic healthcare databases will be conducted. Patients initiating bendamustine for the treatment of iNHL, CLL, or MM during the pre- or post-DHPC dissemination periods will be identified, and approved- versus off-label use will be assessed

throughout the specific study period during which they initiated bendamustine use (i.e. either pre- or post-DHPC dissemination). Patients initiating cyclophosphamide for iNHL, chlorambucil for CLL, or melphalan for MM, collectively termed the alternative treatments, will be similarly identified and assessed for approved- versus off-label use. The proportion of drug users (1) with any observed off-label use in the respective study periods (either pre- or post-DHPC dissemination) and (2) with off-label use at initiation of treatment will be reported. Proportions will be reported separately for pre- and post-DHPC dissemination periods and will be stratified by country (France, Germany, England) and disease indication.

STUDY C: Physician survey to evaluate approved- and off-label use (Primary Objective 2)

Owing to challenges in assessing approved- versus off-label drug use in available electronic healthcare databases, Oncology Dynamics (OD), an IQVIA proprietary physician survey-based database, will be used to conduct a complementary assessment of approved- and off-label drug use for Primary Objective 2. To quantify and characterize the approved- and off-label use of bendamustine and other alkylating drugs similar to bendamustine in new users pre- and post-DHPC dissemination, a cross-sectional study of a OD data will be conducted. Patients initiating bendamustine for the treatment of iNHL, CLL, or MM during the pre- or post-DHPC dissemination periods will be identified, and approved- and off-label use will be assessed at the time of new use. Since there is no follow-up in this data source, approved- and off-label use cannot be assessed at additional timepoints. Patients initiating cyclophosphamide for iNHL, chlorambucil for CLL, or melphalan for MM, collectively termed the alternative treatments, will be similarly identified and assessed for approved- or off-label use. The proportion of drug users with off-label use at initiation of treatment will be reported. Proportions will be reported separately for pre- and post-DHPC dissemination periods and will be stratified by country (France, Germany, UK) and disease indication.

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STUDY A Cohort study to evaluate safety outcomes

Study A Inclusion/Exclusion Criteria:

Inclusion:

1. Use of bendamustine for the treatment of iNHL, CLL, or MM, or use of alkylating drugs similar to bendamustine (cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM) during the pre- or post-DHPC dissemination periods
2. A minimum of six months of observable data available prior to the first observed use of bendamustine or alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period
3. New user of bendamustine, defined as first observed use of bendamustine during the pre- or post-DHPC dissemination period with no observed use of bendamustine in prior six months, or new user of alkylating drugs similar to bendamustine, defined as first observed use of alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period with no observed use of alkylating drugs similar to bendamustine in the prior six months. Bendamustine new users are included even if they were previously using alkylating drugs similar to bendamustine. Similarly, for new users of alkylating drugs similar to bendamustine, previous use of bendamustine is not an exclusion criterion.

Exclusion:

1. Use of bendamustine for a disease indication other than iNHL, CLL, MM
2. Use of alkylating drugs similar to bendamustine for disease indication other than cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM
3. Less than six months of observable data available prior to the first observed use of bendamustine or alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period
4. Prior use of bendamustine within six months of the new observed bendamustine use during the pre- or post-DHPC dissemination period
5. Prior use of alkylating drugs similar to bendamustine within six months of the first observed use of alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period

Study A Assessed Product(s):

Bendamustine

Study A Alternative Treatment Groups:

New user of cyclophosphamide for iNHL, chlorambucil for CLL, and melphalan for MM.

Study A Patient Selection:

All patients meeting the study inclusion criteria will be included in the study.

Study A Endpoints for Evaluation:

Primary:

Primary safety event outcomes will be assessed in two categories:

- All-cause mortality
- Serious and fatal infections, including:
    - Opportunistic infections as defined by PJP, VZV, and CMV infection as identified using the diagnosis codes listed in Annex 3: Table 5: Exposure and Outcome Codes and Table 6: ICD-10 codes for Serious Infections*
    - Serious infections as defined by hospital discharge diagnoses for any of the infection diagnosis codes listed in Annex 3: Table 6: ICD-10 codes for Serious Infections*
    - Bacterial infections (sepsis, pneumonia)

Secondary:

The secondary safety event outcomes include:

- Hepatitis B reactivation as defined through drugs as proxy using ATC codes listed in Annex 3: Table 5: Exposure and Outcome Codes
- Myelosuppression as defined using the diagnosis codes listed in Annex 3: Table 5: Exposure and Outcome Codes

Additional secondary outcomes will also assess the frequency of the following in the pre- and post-DHPC dissemination periods:

- Use of anti-infective drugs in outpatient settings
- Use of anti-infective drugs used for prophylaxis of opportunistic infections (PJP, VZV, CMV) in outpatient settings

Exploratory:

See section 9.1.9.2 STUDY A: Statistical Analysis for additional analyses.

Independent Variables:

- Approved- and off-label use of bendamustine and alkylating drugs similar to bendamustine
- Concurrent use of bendamustine with rituximab, obinutuzumab, or idelalisib
- Disease indication (iNHL, CLL, MM)

Study A Statistical Methods:

Study Size:

Data from all available patients meeting the study inclusion criteria will be used. For study A, approximately 320 persons-years of exposure by stratum (bendamustine, study period pre- and post-DHPC, and country) will enable a statistical precision for incidence of safety events of not more than 5%.

Study A Data Analysis:

The incidence rates and corresponding 95% CIs of safety event outcomes will be calculated by dividing the number of observed events by person-time exposure. Results for the pre- and post-DHPC dissemination periods will be presented separately. The main study results will be stratified by country and disease indication.

Study A Safety:

Only safety events related to the study objectives will be extracted from the databases. Data will be analyzed at an aggregate-level and results will be presented in the final study report.

Study A Interim Analyses:

An interim report will be generated for the primary objectives of studies A and B with data from 24 months pre- and 12 months post-DHPC dissemination from France, Germany, and England.

Study A Dissemination Plan:

One study (including Study A, Study B and Study C) will be registered in The European Union electronic Register of Post-Authorization Studies (EU PAS register). Interim and final study report structure will follow the GPV module VIII (EMA/813938/2011 Rev 3). Study results will be published following the International Committee of Medical Journal Editors guidelines, and communication in appropriate scientific venues, e.g. International Society for Pharmacoepidemiology (ISPE) conferences, will be considered. The appropriate STROBE checklist will be followed for study reporting.

STUDY B Cross-sectional study to evaluate approved- and off-label use

Study B Inclusion/Exclusion Criteria:

Inclusion:

1. Use of bendamustine for the treatment of iNHL, CLL, or MM or use of alkylating drugs similar to bendamustine (cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM) during the pre- or post-DHPC dissemination period
2. A minimum of six months of observable data available prior to the first observed use of bendamustine or alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period
3. New user of bendamustine, defined as first observed use of bendamustine during the pre- or post-DHPC dissemination period with no observed use of bendamustine in prior six months or new user of alkylating drugs similar to bendamustine, defined as first observed use of alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period with no observed use of alkylating drugs similar to bendamustine in prior six months

Exclusion:

1. Use of bendamustine for a disease indication other than iNHL, CLL, MM

2. Use of alkylating drugs similar to bendamustine for disease indication other than cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM
3. Less than six months of observable data available prior to the first observed use of bendamustine or alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period
4. Prior use of bendamustine within six months of the new observed bendamustine use during the pre- or post-DHPC dissemination period
5. Prior use of alkylating drugs similar to bendamustine within six months of the first observed use of alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period
6. When a patient is a new user of both bendamustine and an alternative treatment at the index date

Study B Assessed Product(s):

Bendamustine

Study B Alternative Treatment Groups:

New user of cyclophosphamide for iNHL, chlorambucil for CLL, and melphalan for MM.

Study B Patient Selection:

All patients meeting the study inclusion criteria will be included in the study.

Study B Endpoints for Evaluation:

Primary:

Approved-label drug use and off-label drug use as defined in section 9.2.6.2 STUDY B: Assessment of Approved- versus Off-label Drug Use.

Secondary:

Concurrent off-label use of bendamustine with rituximab, obinutuzumab, or idelalisib

Exploratory:

See section 9.2.9.2 STUDY B: Statistical Analysis.

Independent Variables:

- Disease indication (iNHL, CLL, MM)

Study B Statistical Methods:

Study Size:

Data from all available patients meeting the study inclusion criteria will be used. For study B, approximately 385 patients by stratum (bendamustine, study period pre- and post-DHPC, and country) will enable a precision of not more than 5% around the proportion of off-label use.

Study B Data Analysis:

The proportion of new users of bendamustine or alkylating drugs similar to bendamustine with any observed off-label use during the study period (pre- and post-DHPC dissemination separately) will be calculated by dividing the number of new users with any off-label use by the total number of new users, and 95% CI will be calculated. The proportion of new users of bendamustine or alkylating drugs similar to bendamustine with off-label use at the time of new use will be calculated together with 95% CIs. Results for the pre- and post-DHPC dissemination periods will be presented separately. The main study results will be stratified by country and disease indication.

Study B Safety:

Only safety events related to the study objectives will be extracted from the databases. Data will be analyzed at an aggregate-level and results will be presented in the final study report.

Study B Interim Analyses:

An interim report will be generated for the primary objectives of study A and B with data from 24 months pre- and 12 months post-DHPC dissemination from France, Germany, and England.

Study B Dissemination Plan

One study (including Study A, Study B and Study C) will be registered in EU PAS register. Interim and final study report structure will follow the GPV module VIII (EMA/813938/2011 Rev 3). Study results will be published following the International Committee of Medical

Journal Editors guidelines, and communication in appropriate scientific venues, e.g. ISPE conferences, will be considered. The appropriate STROBE checklist will be followed for study reporting.

STUDY C: Physician survey to evaluate approved- and off-label use

Study C Inclusion/Exclusion Criteria:

Inclusion:

1. Use of bendamustine for the treatment of iNHL, CLL, or MM or use of alkylating drugs similar to bendamustine (cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM) during the pre- or post-DHPC dissemination period
2. New user of bendamustine, defined as first observed use of bendamustine during the pre- or post-DHPC dissemination period with no observed use of bendamustine in prior six months or new user of alkylating drugs similar to bendamustine, defined as first observed use of alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period with no observed use of alkylating drugs similar to bendamustine in prior six months

Exclusion:

1. Use of bendamustine for a disease indication other than iNHL, CLL, MM
2. Use of alkylating drugs similar to bendamustine for disease indication other than cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM
3. Prior use of bendamustine within six months of the new observed bendamustine use during the pre- or post-DHPC dissemination period
4. Prior use of alkylating drugs similar to bendamustine within six months of the first observed use of alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period

Study C Assessed Product(s):

Bendamustine

Study C Alternative Treatment Groups:

New user of cyclophosphamide for iNHL, chlorambucil for CLL, and melphalan for MM.

Study C Patient Selection:

All patients meeting the study inclusion criteria will be included in the study.

Study C Endpoints for Evaluation:

Exploratory:

Approved-label drug use and off-label drug use as defined in Protocol section 9.3.6.2 STUDY C: Assessment of Approved- versus Off-label Drug Use

Concurrent off-label use of bendamustine with rituximab, obinutuzumab, or idelalisib.

See section 9.3.9.2 STUDY C: Statistical Analysis.

Independent Variables:

- Disease indication (iNHL, CLL, MM)

Study C Statistical Methods:

Study Size:

Data from all available patients meeting the study inclusion criteria will be used. Analogous to Study B, approximately 385 patients by stratum (bendamustine, study period pre- and post-DHPC, and country) will enable a precision of not more than 5% around the proportion of off-label use.

Study C Data Analysis:

The proportion of new users of bendamustine or alkylating drugs similar to bendamustine with off-label use at time of new use of these drugs will be calculated by dividing the number of new users with off-label use by the total number of new users; 95% CIs will also be calculated. Results for the pre- and post-DHPC dissemination periods will be presented separately. The main study results will be stratified by country and disease indication.

Study C Safety:

Only safety events related to the study objectives will be collected. Data will be analyzed at an aggregate-level and results will be presented in the final study report.

Study C Interim Analyses:

No interim report will be provided for Study C.

Study C Dissemination Plan

One study (including Study A, Study B and Study C) will be registered in EU PAS register. Final study report structure will follow the GPV module VIII (EMA/813938/2011 Rev 3). Study results will be published following the International Committee of Medical Journal Editors guidelines, and communication in appropriate scientific venues, e.g. ISPE conferences, will be considered. The appropriate STROBE checklist will be followed for study reporting.

4.1 Flow Chart

Not applicable.

4.2 Schedule of Assessments

Not applicable.

5 AMENDMENTS AND UPDATES

The table below summarizes modifications included in protocol version 7.0. As listed below, these modifications include updates to Sections 9.1.1.1 and 9.1.7, and Tables 1 and 4.

Number	Date	Section numbers of the protocol	Reason
1. Description of idelalisib availability in France	16 Sept 2022	Section 9.1.1.1 Section 9.1.7 Table 1 Table 4 (footnote)	To correct description of idelalisib availability in France which was based on the prior IQVIA feasibility report (2018); to align the protocol with the SAP. Updates were made to reflect that data on idelalisib is captured when dispensed in community pharmacies, delivered in retrocession (Private hospital pharmacy retails) or via Temporary Authorization for Use (ATU).
2. Update to planned timing of milestones	31 Oct 2022	Section 6 Milestones	To account for revised timing of finalization of final study report.

6 MILESTONES

The milestones listed are the initial planned dates based on data availability (see Annex 4), and are not intended to be updated in the protocol if the planned dates change. Communication regarding shifts in the planned dates stated in the protocol will be done outside of an amendment to the protocol (unless other changes to the Protocol are made at the same time).

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Milestone	Planned Periods
Registration in the EU PAS register	Q2 2020
First data extraction (Germany, France, England)	Q4 2020
Interim study report submitted to BfArM	Q2 2021
Second data extraction (all countries and OD)	Q3 2021
Final study report submitted to BfArM	Q2 2023

7 RATIONALE AND BACKGROUND

Bendamustine is a nitrogen mustard compound that functions as an alkylating antineoplastic agent. Bendamustine has been approved in the EU for the following therapeutic indications:

- Indolent non-Hodgkin's lymphoma (iNHL) as monotherapy in patients who have progressed during or within six months following treatment with rituximab or a rituximab containing regimen
- First-line treatment of chronic lymphocytic leukemia (CLL) (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate
- Front-line treatment of multiple myeloma (MM) (Durie-Salmon stage II with progress or stage III) in combination with prednisone, for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment

In February 2017, the Pharmacovigilance Risk Assessment Committee (PRAC) advised the Member States on following new safety information related to bendamustine in the framework of the Renewal procedure and as requested by the Bundesinstitut fűr Arzneimittel und Medizinprodukte (BfArM) as Reference Member State (RMS). The advice was taken over in the Final Renewal Assessment Report and the renewal procedure ended positively on 15 March 2017. The PRAC specified the following in their assessment report:

- Increased mortality was observed in recent clinical studies when bendamustine was used in non-approved combination treatments or outside of the approved indications. Fatal toxicities were mainly due to (opportunistic) infections, but also some fatal cardiac, neurological, and respiratory toxicities were reported.

- Serious and fatal infections have occurred with bendamustine, including bacterial (sepsis, pneumonia) and opportunistic infections such as PJP, varicella zoster virus (VZV) and cytomegalovirus (CMV) infection.
- Reactivation of hepatitis B in patients who are chronic carriers of this virus has also occurred. Some cases resulted in acute hepatic failure or a fatal outcome.
- Treatment with bendamustine may cause prolonged lymphocytopenia (<600 cells/µl) and low CD4-positive T-cell (T-helper cell) counts (<200 cells/µl) which may persist for at least 7–9 months after the completion of treatment, in particular when bendamustine is combined with rituximab. Patients with lymphopenia and low CD4-positive T-cell counts following treatment with bendamustine are more susceptible to (opportunistic) infections.

Risk minimization measures have been implemented to revise the SmPC to include warnings regarding these new safety concerns. Additionally, in accordance and compliance with the EMA's PRAC request, a Direct Healthcare Professional Communication (DHPC) letter was disseminated as an additional risk minimization measure (aRMM) to healthcare professionals in 22 countries in the EU by August 30, 2017.

In line with regulatory guidance (EMA Good Pharmacovigilance Practice [GVP] XVI.B4), the effectiveness of risk minimization interventions are required to be evaluated; in this case a DHPC dissemination. Therefore, an NI-PASS as an effectiveness check of an aRMM (the DHPC dissemination) for bendamustine is proposed.

8 RESEARCH QUESTION AND OBJECTIVES

The overall goal of this study is to evaluate the effectiveness of the DHPC and an aRMM for bendamustine. Primary Objectives:

1. Outcome Indicator- To evaluate all-cause mortality and serious and fatal infections (detailed in section 9.1.2 STUDY A: Endpoints) occurring in pre- and post-DHPC dissemination periods for new users of bendamustine during these periods, as well as for new users of other alkylating drugs similar to bendamustine (i.e. cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM) in populations in three European countries.

2. Process Indicator- To quantify and characterize approved- and off-label use of bendamustine and other alkylating drugs similar to bendamustine (alternative treatments) in new users pre- and post-DHPC dissemination in populations from three European countries.

This protocol consists of three related but independent studies to achieve the two Primary Objectives:

1. STUDY A: Cohort study of electronic healthcare databases to evaluate safety outcomes (Primary Objective 1)
2. STUDY B: Cross-sectional study of electronic healthcare databases to evaluate approved- and off-label drug use (Primary Objective 2)
3. STUDY C: Cross-sectional study of a physician survey-based database to evaluate approved- and off-label drug use (Primary Objective 2)

Each Study is described separately in the Protocol.

9 RESEARCH METHODS

9.1 STUDY A: Research methods

To evaluate all-cause mortality and serious and fatal infections observed in the pre- and post-DHPC dissemination periods associated with use of bendamustine and other alkylating drugs similar to bendamustine, a retrospective open cohort study will be conducted. Patients initiating bendamustine for the treatment of iNHL, CLL, or MM during the pre- or post-DHPC dissemination periods will be identified and assessed for safety outcomes for the remainder of the specific study period during which they initiated bendamustine use (i.e. either pre- or post-DHPC dissemination). Patients initiating cyclophosphamide for iNHL, chlorambucil for CLL, or melphalan for MM, collectively termed the alternative treatments, will be similarly identified and assessed for safety outcomes (i.e. either pre- or post-DHPC). The primary safety events outcomes are: i) all-cause mortality and ii) serious and fatal infections. Results will be reported as safety event incidence rates per person-time exposure. Incidence rates will reported

separately for pre- and post-DHPC dissemination periods and will be stratified by country (France, Germany, England).

9.1.1 STUDY A: Data Sources

Electronic healthcare databases (claims, registries) from France (French Administrative Health Care Database [SNDS] linked with the National Hospital Discharge Database [PMSI]), Germany (Statutory Health Insurance Database [SHI]), and England (Cancer Analysis System [CAS] and Hospital Episode Statistics [HES]), will be used to conduct this study. The databases from these countries were selected based on higher volume of bendamustine sales and utilization and results of a feasibility study informing the accessibility and size of the available patient-level data.

9.1.1.1 STUDY A: France: French Administrative Health Care Database (SNDS)[1] linked with the National Hospital Discharge Database (PMSI)

The SNDS (formerly the French National Health Insurance [SNIIRAM] database) contains individualized, anonymous and comprehensive data on all reimbursements of patients' health expenditure in France. Data are derived from the various French Health Insurance schemes, including the general scheme and the various special insurance schemes. Altogether, these schemes cover nearly the entire population residing in France (67.2 million inhabitants in 2017). Besides data on health expenditure reimbursements, demographic data are available, including the year of birth, gender, area of residence, geographical region, and date of death. The SNDS also contains information on patient eligibility for 100% health insurance coverage for long-term diseases (LTD) encoded in the International Classification of Diseases, 10th Revision (ICD-10). Similar diagnostic coding is used for the payment of disability pensions for patients of the general scheme. The SNDS is linked by a unique patient identifier to the PMSI database which provides medical information about all private and public hospital stays in France, including hospitalization dates and diagnoses coded according to ICD-10.

The SNDS contains data on patient diagnosis for iNHL, CLL, and patients with MM. Data on bendamustine is available, however, data on use of chlorambucil, cyclophosphamide, and melphalan are not in the PMSI because these drugs are not individually billed from the hospital spending. Cyclophosphamide is mainly administered as IV treatment and cannot be traced.

However, chlorambucil as well as melphalan are administered mainly orally, and can therefore be found in the outpatient part of SNDS. Obinutuzumab, rituximab, and idelalisib are available in the database. However, for idelalisib, which is prescribed only at hospitals, data are captured if idelalisib is dispensed in community pharmacies, delivered in retrocession (Private hospital pharmacy retails), or via Temporary Authorization for Use (ATU). Diagnoses are mainly available in the inpatient setting, so clinical outcomes will be estimated only during a hospital stay. Less serious infections can be estimated using proxies, using a defined list of anti-infectious agents. Staging of cancer is not available. Death and cause of death is available.

Table 1: Summary of data in French SNDS database

French SNDS database	Data Availability	Limitations
● directly and fully available ● indirectly and/or partially observable ● data not available		
iNHL indication		
Data to define approved label definition of bendamustine	●	• Disease progression unavailable but proxy with date of the next treatment evaluable
Data to define approved label definition of alkylating drugs similar to bendamustine (cyclophosphamide)	●	• Cyclophosphamide use only during hospitalization (inpatient) and unobservable in the SNDS • CD20 antigen results not available
CLL indication		
Data to define approved label definition of bendamustine	●	• Binet stage and ofatumumab not collected • 1st line identification observable by proxy • Fludarabine observable only in community pharmacies (outpatient)
Data to define approved label definition of alkylating drugs similar to bendamustine (chlorambucil)	●	• Chlorambucil observable only in community pharmacies (outpatient)
MM indication		
Data to define approved label definition of bendamustine	●	• Durie-Salmon stage not collected • Prednisone observable only in community pharmacies (outpatient)
Data to define approved label definition of alkylating drugs similar to bendamustine (melphalan)	●	• 1st line identification observable by proxy • Melphalan observable only in community pharmacies (outpatient)
Common to the three indications		
Data to evaluate the off-label measurement	●	• Drugs taken during hospitalizations which are neither costly nor innovative are not observable
Data to evaluate the clinical outcomes	●	• Clinical outcomes based on blood testing results not available (immunosuppression, myelosuppression) • Outcomes available if hospitalization and when can be specified in ICD-10 codes; not available in outpatient care • Laboratory test measurements not available

9.1.1.2 STUDY A: Germany: Statutory Health Insurance (SHI) database[2]

Approximately 90% of the population in Germany are members of statutory health insurance (SHI) and are entitled to receive healthcare benefits through SHI. The German SHI database contains anonymized medical claims data for patients covered by SHI. The full SHI database includes 5 million insured patients (i.e. approximately 7% of national population) and is representative of the entire insured German population (73 million). The updated database for 2019 will have data from 2007 to 2017. The database is updated once a year in the first quarter, so data for the pre-DHPC dissemination period (April 2015-March 2017) will be available in Q1 2019, and data for the post-DHPC dissemination period (Oct 2017-Sept 2019) will be available in Q1 2021. These data are representative with respect to age, sex, prescriptions and hospital diagnoses.

The database contains core data, hospitalization data, outpatient prescription data, and outpatient care data/diagnoses starting at January 1st, 2004. The database allows for the analysis of patient-level demographic and clinical characteristics, healthcare resource utilization (e.g. number and/or duration of inpatient and outpatient visits), and dated prescriptions. Longitudinal pre-index date and follow-up periods can also be defined according to the study requirements. Diagnoses and procedures are coded ICD-10 (German modification, GM), and include treatments that are reimbursed in accordance with the German law. Among others, the following measures are available in the German database allowing demographic characteristics, treatments, healthcare utilization and clinical outcomes to be assessed:

- Registration data including age, gender, insurance status, time insured, nationality and region of residence
- Outpatient care data including ICD-10 GM diagnoses, physician specialty, OPS-Codes
- Outpatient drug prescription data including ATC code of prescribed drugs and related costs, PZN (Pharmazentralnummer) of prescribed drugs, and date of prescription
- Inpatient care claim including ICD-10 diagnoses (up to 3 principal and 30 secondary diagnoses per stay), billed DRGs (German classification), up to 30 OPS-Codes* per stay, duration of hospitalizations, and medical department.

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**NB: The Operationen- und Prozedurenschlüssel (OPS) is the German modification of the ICPM and now the official classification of operational procedures for power control, the performance record and basis for the claims processing (for inpatient services for G-DRG) of the German hospitals and physicians. The OPS is provided on an annual basis by Deutsches Institut für Medizinische Dokumentation und Information (DIMDI).*

The German SHI database contains data on patient diagnosis for iNHL, CLL, and patients with MM. All study drugs and drugs needed to determine approved- and off-label use are available within the database, albeit may require the use of proxy measure for dates of injection. Some of the other variables for determination of approved- and off-label use such as Binet staging, disease progression, CD20 antigen results are not available and may limit drug indication definitions in this database. In Germany most of the patients receive their treatment in the outpatient setting and the office-based sector. Diagnoses related to healthcare spending, both in the outpatient or inpatient setting, which cover the complete array of clinical outcomes (including death) and comorbidities are available. Staging of cancer is not available.

Table 2: Summary of data in German SHI database

German SHI database	Data Availability	Limitations
● directly and fully available ● indirectly and/or partially observable and sample size could be a limitation		
iNHL indication		
Data to define approved label definition of bendamustine	●	• Inpatient part: date of injection missing but proxy with date of procedure • Disease progression unavailable but proxy with date of the next treatment evaluable
Data to define approved label definition of alkylating drugs similar to bendamustine (cyclophosphamide)	●	• Inpatient part: date of injection missing • CD20 antigen results not available
CLL indication		
Data to define approved label definition of bendamustine	●	• Inpatient part: date of injection missing but proxy with date of procedure • Binet stage B or C not collected
Data to define approved label definition of alkylating drugs similar to bendamustine (chlorambucil)	●	• Inpatient part: date of injection missing but proxy with date of procedure • Number of patients expected taking chlorambucil by year < 200
MM indication		
Data to define approved label definition of bendamustine	●	• Inpatient part: date of injection missing but proxy with date of procedure
Data to define approved label definition of alkylating drugs similar to bendamustine (melphalan)	●	• Inpatient part: date of injection missing but proxy with date of procedure.

		• Number of patients expected taking melphalan by year ~100
Common to the three indications		
Data to evaluate the off-label measurement	●	• Number of patients expected taking Gazyvaro or idelalisib by year < 100
Data to evaluate the clinical outcomes	●	• Including death

9.1.1.3 STUDY A: England: Cancer Analysis System (CAS) and Hospital Episode Statistics (HES)[3]

Cancer Analysis System (CAS): Public Health England (PHE) collects data on cancer patients in England. These data are stored in a database called the Cancer Analysis System (CAS). The CAS also contains the Systemic Anti-Cancer Therapy (SACT) dataset from 2012, and the Cancer Outcomes and Services Dataset (COSD), which contains detailed information about tumours and mortality. PHE data are taken from a wide range of sources including Hospital Episode Statistics (HES), the National Cancer Registration and Analysis Service (NCRAS) and the SACT dataset. According to the Health and Social Care Act, the data can only be released at row level for specific (non-commercial) analysis and for work that will improve "the provision or promotion of health and social care".

Hospital Episode Statistics (HES): The HES dataset is produced by the Health and Social care Information Centre (HSCIC), a non-departmental government body that houses and safeguards UK healthcare data. It captures reimbursement data as well as data on admissions, outpatient appointments, accident & emergency attendances, and higher cost diagnostic imaging at NHS hospitals in England. Data are collected during the patient's time at hospital (either in an outpatient, emergency department or inpatient care setting), resulting in over 125 million episodes per year, including information for all hospital-based activity in England. Certain information will differ depending on care setting. This is due to no requirement being placed on hospitals to record information for an outpatient appointment or emergency department visit to obtain reimbursement. HES uses ICD-10 codes for diagnoses and classification of surgical operations and procedures (OPCS) for classification of interventions and procedures. Studies using HES may require review by the Independent Scientific Ethical Advisory Committee (ISEAC).

The CAS+HES together contain data on patient characteristics (e.g. age, gender, race), tumor characteristics (e.g. site, TNM classification), mortality (e.g. date of death, cause of death), treatment (e.g. regimen, number of cycles), radiotherapy, surgery, hospital resource use (e.g. length of stay, number of inpatient, outpatient and attendances and emergency admissions, number of procedures performed).

In England, CAS cannot be directly accessed for feasibility counts due to data protection. Therefore, Simulacrum, which contains simulated data that models many of the properties of the data collected by CAS, but contains no real patient data was used to assess likely data availability. The England database contains data on patient diagnosis for iNHL, CLL, and patients with MM. All study drugs and drugs needed to determine approved- and off-label use are available within the database. However a few of the parameters needed for defining approved- and off-label use are not available. Outcomes are only available if the patient is diagnosed during a hospitalization.

Table 3: Summary of data in English CAS/HES databases

England CAS and HES databases	Data Availability	Limitations
● directly and fully available / quantitative column = sample size sufficient to cover the objectives ● indirectly and/or partially observable / quantitative column = sample size could be a limitation		
iNHL indication:		
Data to define approved label definition of bendamustine	●	• Number of patients expected to be <100/year • Prior use of rituximab will further limit counts
Data to define approved label definition of alkylating drugs similar to bendamustine (cyclophosphamide)	●	• Number of patients expected to be 200-300; more if CHOP/R-CHOP is included here
CLL indication		
Data to define approved label definition of bendamustine	●	• Binet stage not available • Number of patients expected to be <200/year • Appropriateness of FCR if ECOG is used
Data to define approved label definition of alkylating drugs similar to bendamustine (chlorambucil)	●	• Number of patients expected to be <200/year
MM indication		
Data to define approved label definition of bendamustine	●	• Durie-Salmon stage not available • Prednisone use needs to be assumed • Number of patients expected to be <200/year
Data to define approved label definition of alkylating drugs similar to bendamustine (melphalan)	●	• Number of patients expected to be 400-500
Common to the three indications		
Data to evaluate the off-label measurement	●	• Binet stage not available

		• Overlap of patients using bendamustine and alkylating drugs similar to bendamustine could reduce sample size
Data to evaluate the clinical outcomes	●	• Available only if the patient is diagnosed in hospital and thus captured by HES

9.1.2 STUDY A: Endpoints

All study outcomes (and the ICD-10 and ATC codes) are defined in Annex 3:

Table 12: Exposure and Outcome Codes and Table 13: ICD-10 codes for Serious Infections*.

The occurrence of safety events will be assessed in each patient following the initiation of bendamustine or alkylating drugs similar to bendamustine until the patient is censored.

The primary safety event outcomes include two categories:

- All-cause mortality
- Serious and fatal infections, including:
    - Opportunistic infections as defined by PJP, VZV, and CMV infection as identified using the diagnosis codes listed in Annex 3: Table 5: Exposure and Outcome Codes and Table 6: ICD-10 codes for Serious Infections*
    - Serious infections as defined by hospital discharge diagnoses for any of the infection diagnosis codes listed in Annex 3: Table 6: ICD-10 codes for Serious Infections*
    - Bacterial infections (sepsis, pneumonia)

The secondary safety event outcomes include:

- Hepatitis B reactivation as defined through drugs as proxy using ATC codes listed in Annex 3: Table 5: Exposure and Outcome Codes
- Myelosuppression as defined using the diagnosis codes listed in Annex 3: Table 5: Exposure and Outcome Codes

The safety event outcome incidence rates will be presented for the pre- and post-DHPC dissemination periods. Results will be presented individually by country and disease indication. The results may be further stratified by approved-label versus off-label use and concurrent off-label use of bendamustine with rituximab, obinutuzumab, and idelalisib. See section 9.1.9.2 STUDY A: Statistical Analysis. The method of assessment for approved- versus off-label drug use is detailed in section 9.1.6.2 STUDY A: Assessment of Approved- versus Off-label Drug Use.

Additional secondary endpoints will assess the frequency of the following events pre- and post-DHPC dissemination for new users of bendamustine for the treatment of iNHL, CLL, or MM:

- Use of anti-infective drugs in outpatient settings using selected ATC codes listed in Annex 3: Table 14: ATC codes for Anti-infective Drugs and Substances
- Use of anti-infective drugs used for prophylaxis of opportunistic infections (PJP, VZV, and CMV infection) in outpatient settings using selected ATC codes listed in Annex 3: Table 14: ATC codes for Anti-infective Drugs and Substances

9.1.3 STUDY A: Study Design

This retrospective study consists of three distinct study periods: pre-DHPC dissemination period, DHPC dissemination period, and post-DHPC dissemination period. Study outcomes are not assessed during the DHPC dissemination period. The study includes data from the period 01 April 2015 (two years prior to DHPC dissemination period) to 31 August 2019 (two years after DHPC dissemination period). The individual time periods are defined as follows (see Figure 1):

- Pre-DHPC dissemination period (24 months): 01 April 2015 – 31 March 2017
- DHPC dissemination period (5 months): 01 April 2017 – 31 August 2017
- Post-DHPC dissemination period (24 months): 01 September 2017 – 31 August 2019

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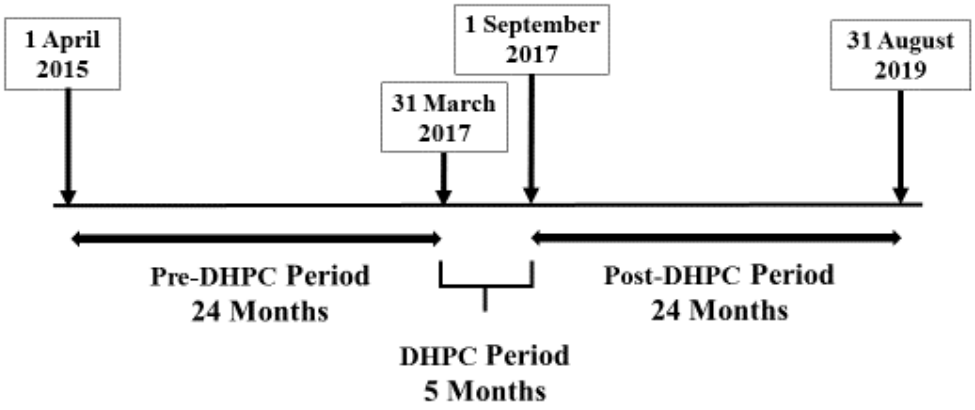

Figure 1. Study Period (not to scale)

To evaluate the incidence of safety outcomes observed in the pre- and post-DHPC dissemination periods associated with use of bendamustine and other alkylating drugs similar to bendamustine, a retrospective open cohort study will be conducted. Patients initiating bendamustine for the treatment of iNHL, CLL, or MM during the pre- or post-DHPC dissemination periods will be identified and assessed for safety outcomes for the remainder of the specific study period during which they initiated bendamustine use (i.e. pre- or post-DHPC dissemination). Patients initiating cyclophosphamide for iNHL, chlorambucil for CLL, or melphalan for MM, collectively termed the alternative treatments, will be similarly identified and assessed for safety outcomes. Results will be reported as safety event incidence rates per person-time of exposure to drug and will be stratified by country (France, Germany, England).

9.1.4 STUDY A: Study Population

This study will be conducted using retrospective analysis of existing electronic healthcare databases from France, Germany, and England. Included patients are new users of bendamustine or one of the alkylating drugs similar to bendamustine for the treatment of iNHL, CLL, or MM during the pre-DHPC dissemination period (01 April 2015 – 31 March 2017) or

the post-DHPC dissemination period (01 September 2017 – 31 August 2019). A single patient will be included in only either the bendamustine cohort or the cohort of alkylating drugs similar to bendamustine in the same pre- or post-DHPC dissemination period. Included patients are anticipated to be indicative of patients in the general population.

9.1.4.1 STUDY A: Selection of Study Population

The analysis will include all available patients meeting the study inclusion criteria.

The inclusion and exclusion criteria are applied to the pre- and post-DHPC dissemination periods separately to select two distinct groups of patients for each period. Patients may be included in both pre- and post-DHPC dissemination periods if they satisfy all other inclusion criteria.

9.1.4.2 STUDY A: Inclusion Criteria

1. Use of bendamustine for the treatment of iNHL, CLL, or MM, or use of alkylating drugs similar to bendamustine (cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM) during the pre- or post-DHPC dissemination period
2. A minimum of six months of observable data available prior to the first observed use of bendamustine or alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period
3. New user of bendamustine, defined as first observed use of bendamustine during the pre- or post-DHPC dissemination period with no observed use of bendamustine in prior six months or new user of alkylating drugs similar to bendamustine, defined as first observed use of alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination periods with no observed use of alkylating drugs similar to bendamustine in prior six months

9.1.4.3 STUDY A: Exclusion Criteria

1. Use of bendamustine for a disease indication other than iNHL, CLL or MM
2. Use of alkylating drugs similar to bendamustine for disease indication other than cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM

3. Less than six months of observable data available prior to the new use of bendamustine or alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period
4. Prior use of bendamustine within six months of the new observed bendamustine use during the pre- or post-DHPC dissemination period
5. Prior use of alkylating drugs similar to bendamustine within six months of the first observed use of alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period
6. When a patient is a new user of both bendamustine and an alternative treatment at the index date

The inclusion and exclusion criteria are illustrated in Figure 2, Figure 3, Figure 4, Figure 5 and Figure 6 in section 9.1.6.1 STUDY A: Exposure Definitions.

9.1.5 STUDY A: Treatments and Evaluation

9.1.5.1 STUDY A: Discontinuation Criteria

Censoring criteria:

1. Death
2. Loss to follow-up/Discontinuation from the data source
3. End of the pre-DHPC dissemination period if present in a pre-DHPC dissemination period cohort (new drug use occurred in the pre-DHPC dissemination period)
4. End of the post-DHPC dissemination period if present in a post-DHPC dissemination period cohort (new drug use occurred in the post-DHPC dissemination period)
5. Use of alkylating drugs similar to bendamustine for patients in the bendamustine cohort
6. Use of bendamustine for patients in the alkylating drugs similar to bendamustine cohort

Patients who are censored are not eligible to re-enter the study during the same pre- or post-DHPC dissemination period. For example, a patient cannot be included in both the bendamustine and alkylating drugs similar to bendamustine cohorts in the same pre- or post-DHPC dissemination period. The censoring criteria are illustrated in Figure 2, Figure 5, and Figure 6 in section 9.1.6.1 STUDY A: Exposure Definitions.

9.1.6 STUDY A: Variables

Codes used to identify exposures and outcomes in the study are listed in Annex 3: Table 12: Exposure and Outcome Codes.

9.1.6.1 STUDY A: Exposure Definitions

Study drugs are defined as:

- Bendamustine
- Alkylating drugs similar to bendamustine (cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM), termed alternative treatments.

'Use' of study drugs is defined as:

- Prescription
- Dispensing
- Injection

This is due to the different methods of administration and frequencies of use of the study drugs and the differences in identification of exposures in the different data sources. See Annex 3: Table 12: Exposure and Outcome Codes for the corresponding ATC codes for the study drugs.

The first drug use is defined as the first observed use of bendamustine or alkylating drugs similar to bendamustine during the study periods (pre- and post-DHPC dissemination assessed separately) that satisfies the inclusion criteria. A single patient may be included in both the pre- and post-DHPC dissemination periods if they meet all inclusion criteria. A single patient cannot be included in both the bendamustine and alkylating drugs similar to bendamustine cohorts in the same pre- or post-DHPC dissemination period (section 9.1.5.1 STUDY A: Discontinuation Criteria). The day that the patient becomes a new user is the index date.

Following the index date, patients will contribute follow-up time and safety event outcomes to their respective study drug cohorts until they are censored (section 9.1.5.1 STUDY A: Discontinuation Criteria).

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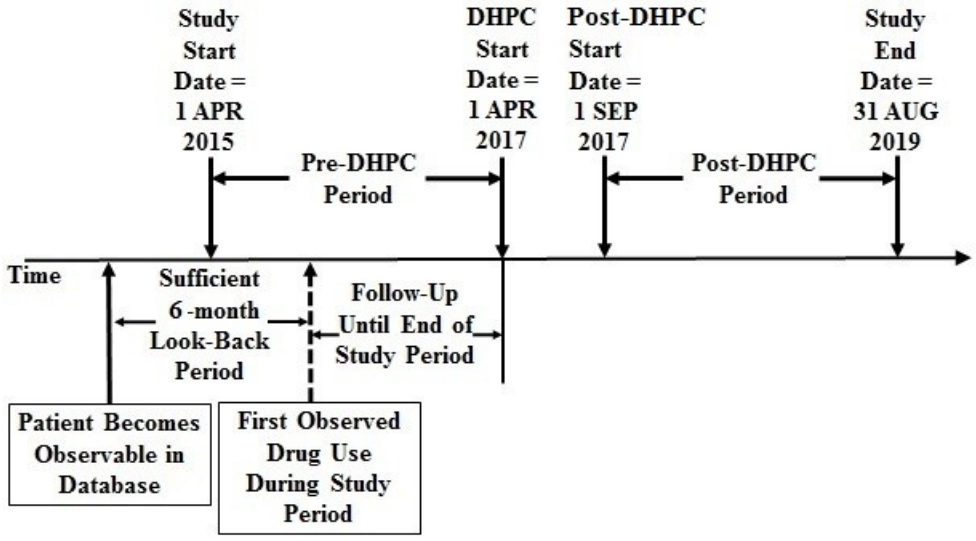

Figure 2. Example of a sufficient six-month look-back period and follow-up of new user (not to scale). The patient becomes observable six months prior to the new drug use and has no previous study drug use. The patient is included in the cohort and follow-up continues until the end of the pre-DHPC dissemination period.

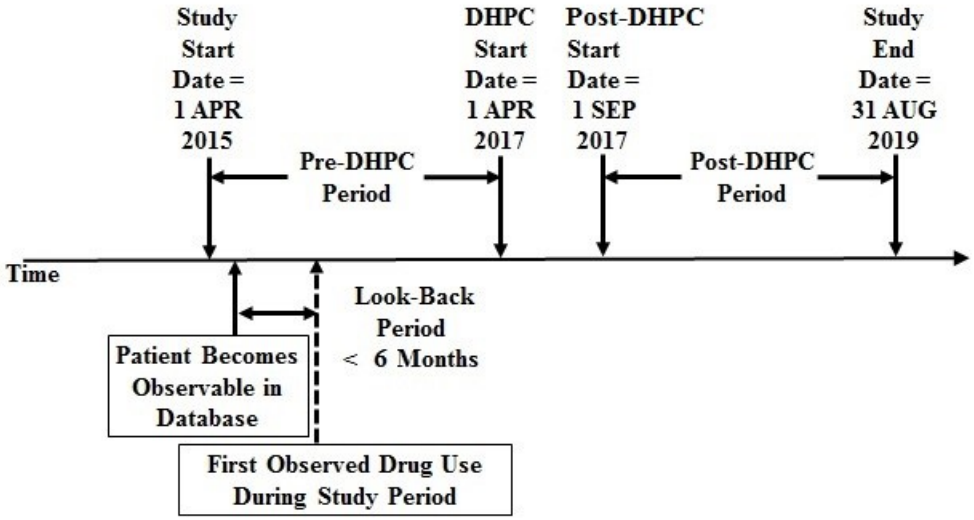

Figure 3. Example of an insufficient look-back period (not to scale). The patient becomes observable in the database less than six months prior to the new study drug use. The patient is excluded from the pre-DHPC dissemination cohort.

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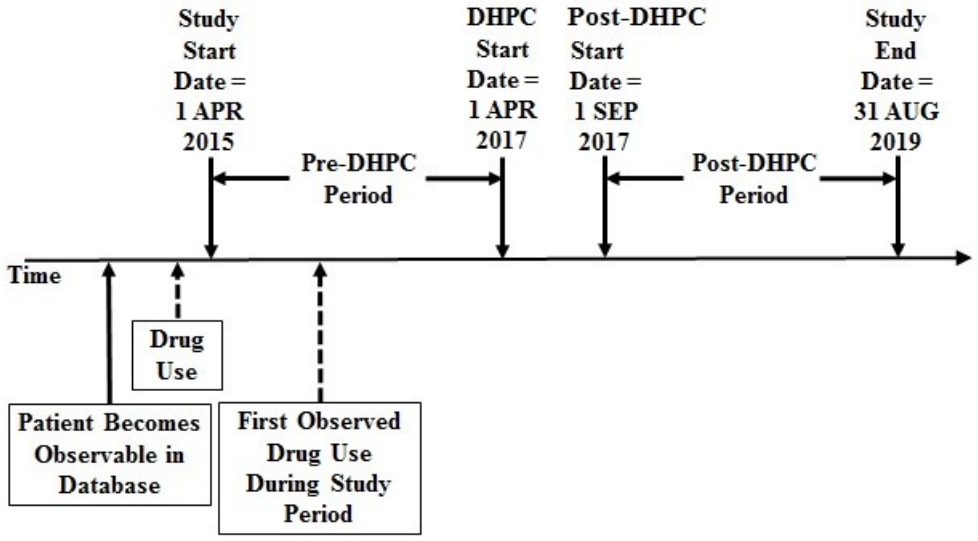

Figure 4. Example of patient exclusion due to prior drug use (not to scale). The patient used the study drug prior to the study start date but within six months of observed new use during the study period. The patient is not considered to be a new user and is excluded from the pre-DHPC dissemination cohort.

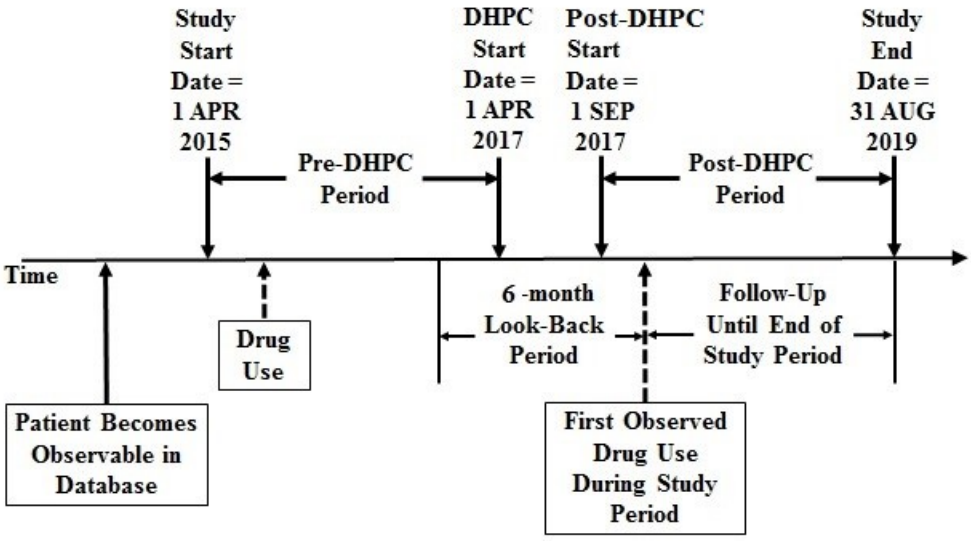

Figure 5. Example of drug use more than six months prior to first observed use during study period (not to scale). The patient has prior drug use, but it is more than six month prior to the new use during the post-DHPC dissemination period. The patient is considered to be a new user. The patient is included in the cohort and follow-up continues until the end of the post-DHPC dissemination period.

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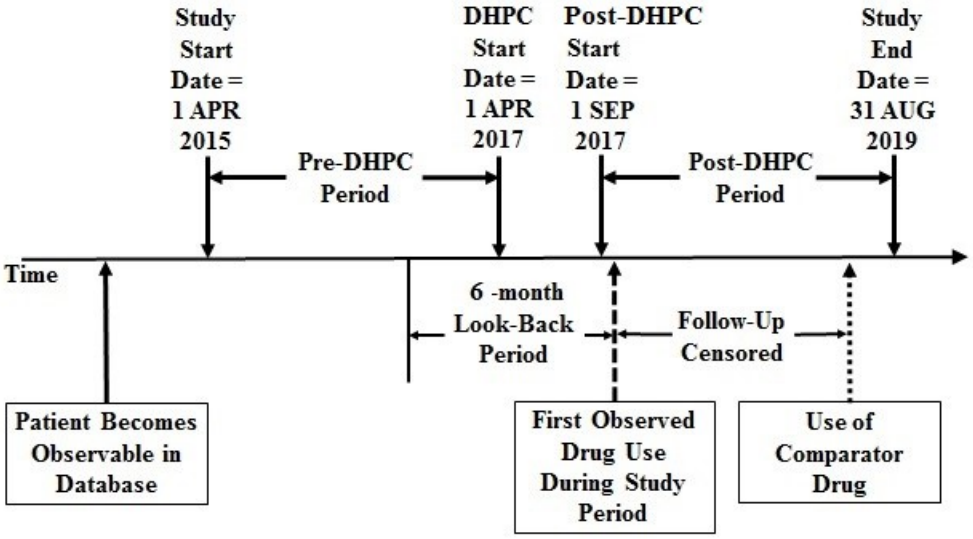

Figure 6. Example of censoring due to use of a different drug (not to scale). The new user is not a user of the drug in the prior six months. The new user is included in the post-DHPC dissemination cohort. During follow-up, the patient uses a different drug (i.e. bendamustine if present in the cohort using alkylating drugs similar to bendamustine, or an alkylating drug similar to bendamustine if present in the bendamustine cohort) and follow-up is censored. The patient is not included as a new user of the other drug group during the post-DHPC dissemination period (i.e. there is no switching between cohorts during a study period).

9.1.6.2 STUDY A: Assessment of Approved- versus Off-label Drug Use

The assessment of approved- versus off-label drug use will be made for each use of bendamustine, cyclophosphamide, chlorambucil, and melphalan. Definitions of approved-use and off-label use of bendamustine and other alkylating drugs similar to bendamustine (alternative treatments) are described in Annex 3 (Table 15). Repeated assessments of approved- versus off-label will be made because patients' clinical characteristics and concurrent drug use may change over time (i.e. patients may change status from approved-label to off-label use during the study periods).

The determination of approved- versus off-label drug use requires data dating back up to six months prior to the observation of a study drug use. For example, the approved label for bendamustine references events that may have occurred up to six months in the past.

Assessment of concurrent off-label use of bendamustine with rituximab, obinutuzumab, or idelalisib will also be made.

The assessment of approved- versus off-label use may be used to further stratify the incidence rates of safety events if meaningful differences in incidence rates are observed between the pre- and post-DHPC dissemination periods and sample sizes permit (section 9.1.9.2 STUDY A: Statistical Analysis).

9.1.6.3 STUDY A: Other Primary Variables

The following independent variables will be assessed for each patient included in the study. Their distributions will help describe the patient populations being studied:

- Demographic characteristics
    - Age (at first drug use)
    - Sex
    - Comorbidities (as reported in claims or registries) based on all available historical data (i.e. the entire medical history) of acute and chronic conditions at time of first drug use, including: NCI Comorbidity Index conditions, cardiovascular disease, autoimmune syndromes, previous cancer, renal failure, dyslipidemia, hyperlipidemia, hypertension, obesity, immunosuppression / myelosuppression, clinical neuropathies, and infections.
- Indication for study drug (i.e. diagnosis)
- Therapeutic regimen(s), including regimens for bendamustine, the alkylating drugs similar to bendamustine (cyclophosphamide, chlorambucil, melphalan), the additional drugs specified in the DHPC (rituximab, obinutuzumab, idelalisib), and any other drugs specified for use prior to, or in combination with, bendamustine or the alkylating drugs similar to bendamustine in their respective approved labels
- Other reported drug use, excluding bendamustine, the alkylating drugs similar to bendamustine (cyclophosphamide, chlorambucil, melphalan), the additional drugs specified in the DHPC (rituximab, obinutuzumab, idelalisib), and any drugs specified for use prior to, or in combination with, bendamustine or the alternative treatments in their approved labels during the study period

9.1.7 STUDY A: Study Size

Feasibility of data availability for drug exposures of interest (alkylating drugs: bendamustine, cyclophosphamide, chlorambucil, melphalan; concomitant therapies: rituximab, obinutuzumab and idelalisib) from databases used in the study for the selected countries and by disease indication were examined in the bendamustine-Astellas-Feasibility report[4] and are shown in Table 4 below. The actual numbers of study subjects will likely be lower following formal application of the study inclusion / exclusion criteria as the feasibility study was not restricted to new users of drugs.

Table 4: Number of patients identified in each data source from the feasibility study

	France PMSI (2016)	Germany SHI (2016)	England CAS and HES (2015)
Bendamustine	4163	606	1489
Rituximab	25170	2592	3931
Obinutuzumab	169	59	26 (1)
Idelalisib	0 (1)	53	50
Chlorambucil	(1)	152	490
Cyclophosphamide	0	2198	2401
Melphalan	(1)	108	790
NHL (ICD-10: C85.9)	4883	9007	682
NHL + Bendamustine	326	326	12 (24 in CAS)
NHL + Rituximab	1449	1209	36
NHL + Obinutuzumab	10	18	0 (1)
NHL + Idelalisib	0	24	0
Follicular lymphoma (ICD-10: C82.9)	2077	1147	252
CLL (ICD-10: C91.1)	11362	5204	3344
CLL + Bendamustine	842	237	28 (147 in CAS)
CLL + Chlorambucil	(1)	126	3
CLL + Chlorambucil + Obinutuzumab	(1)	35	0 (1)
CLL + Rituximab	2201	380	54
CLL+ Obinutuzumab	120	46	0 (1)
CLL + Idelalisib	0 (1)	39	10
Multiple Myeloma (ICD-10: C90)	16487	2353 (1)	4431
MM + Bendamustine + Prednisone	537 (2)	6	(2)
MM + Melphalan	(1)	2	166
MM + Rituximab	162	33	13
MM + Obinutuzumab	0	1	0 (1)
MM + Idelalisib	0 (1)	0	0
Notes	(1) Not available in PMSI, but available in the outpatient part of SNDS.	(1) Patients aged > 65 years.	(1) Obinutuzumab was approved for CLL use (with chlorambucil or bendamustine) in the UK in March 2015 Obinutuzumab was not approved for NHL or

	(2) MM+ bendamustine (prednisone is available in the outpatient part of SNDS).		MM until 2017. (2) Information on prednisone not available.

As identified in the Bendamustine-Astellas-Feasibility report[4] a number of limitations associated with the data sources to be used for the study were documented. These include:

- Some parameters which are part of the determination of on-label/off-label use for the study drugs of interest are not, or only partially available. Specifically for France, cyclophosphamide as an alkylating drug similar to bendamustine is not available. For England, not all parameters that are required to confirm bendamustine use, according to its labelled indication in CLL and MM, are available and use of chlorambucil is relatively limited. Co-treatment with prednisone in MM needs to be assumed in England and France.
- No information on staging (Binet/Durie-Salmon staging, CD20 antigen results) can be found in the data sources.
- No lab data are available in any database.
- It is difficult to find parameters such as eligibility to autologous stem cell transplantation or fludarabine treatment.

9.1.8 STUDY A: Data Management

The processes for database management differ by country. Generally the data are stored at the database site within each of the study countries. IQVIA staff of each country will be in charge of the statistical analysis in the IQVIA office with oversight by a central team not necessarily located in the country. Statistical Analysis System (SAS®) Software (Version 9.4 or later) will be utilized for access to the raw data and to manage the analytic datasets. If the study is conducted by a third party, the datasets and analytic programs will be stored according to the vendor's procedures. This study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)[5] and the International Conference on Harmonisation (ICH) guidelines for data management.

Each data source custodian will maintain any patient-identifying information securely on site for each study country according to internal standard operating procedures (SOPs). IQVIA is never granted access to raw data. Security processes are in place to ensure the safety of all systems and data. Data will be kept secure so that they cannot be accessed by anyone except selected study staff.

Data will be checked in terms of consistency in flow, range of values, units of measurement, relevance of clinical information before data analysis. Some data providers, such as IQVIA, have already integrated these checks in their data production workflow, so that the checks are conducted systematically on all incoming patient records before allowing them to be integrated into the database.

For France, the CNAM (French national health insurance) is responsible for processing the SNDS databases, making available the SNDS database to public and private companies (data source system), and data security. IQVIA obtains data through a child system for processing SNDS data that is compliant with SNDS security.

For Germany (SHI), data management for this study will be conducted using standard IQVIA processes. The process would take into consideration any data governance imposed on the data source including any plans to handle the data outside of the institution or country of origin. IQVIA will adhere to all local and regional laws on data protection and privacy.

For England (CAS/HES), the raw data is stored at Public Health England. IQVIA is never granted access to the raw data. IQVIA is provided with anonymous, aggregated outputs based on the Simulacrum code/queries that are submitted. IQVIA is never given an extract of the data. Anonymous, aggregated outputs are released via email and are password protected.

9.1.9 STUDY A: Statistical Methods

9.1.9.1 STUDY A: Sample Size Justification

The incidence rates and corresponding 95% Confidence Intervals (CIs) of the primary safety outcomes will be calculated by dividing the number of observed events by person-time. Table 5 shows the number of person-years exposure needed to provide the stated margin of error for the 95% CI (columns) given the observed incidence rate (rows). For example, if the safety event incidence rate is five per 100 person-years and 457 person-years of exposure are

observed, then the margin of error for the 95% CI would be 2%. There is not an available estimate of the incidence of safety event outcomes, so a range of expected values of from one per 100 person-years to 30 per 100 person-years is included in Table 5. Results will be stratified by drug (bendamustine and alkylating drugs similar to bendamustine), study period (pre- and post-DHPC dissemination), country, and disease indication (section 9.1.9.2 STUDY A: Statistical Analysis). The sample size estimates in Table 5 apply to each of these strata.

A recently published study of administrative claims data in the United States of patients treated with bendamustine for iNHL reported individual incident infection rates for opportunistic, bacterial, fungal, and viral infections in the range of approximately 20 to 50 infections per 100 person-years and patients experienced a mean of 2.7 infections[6].

The maximum number of persons-years of bendamustine use needed to achieve a statistical precision for the safety event incidence rate of 5% is 323, assuming the incidence of safety events does not exceed 30 per 100 persons-years (see Table 5). These estimates are calculated for each of the strata (bendamustine and alternative treatment, study period pre- and post-DHPC dissemination, country, and disease indication). The precision will increase the larger sample size.

Table 5: Number of person-years exposure needed for a given event incidence rate and desired margin of error for the 95% CI

	Margin of error for the 95% CI					
Event incidence rate	1%	2%	3%	5%	6%	10%
1 per 100 person-yrs	381	96	43	16	11	4
2 per 100 person-yrs	753	189	84	31	21	8
5 per 100 person-yrs	1825	457	203	73	51	19
10 per 100 person-yrs	3458	865	385	139	97	35
30 per 100 person-yrs	8068	2017	897	323	225	81

9.1.9.2 STUDY A: Statistical Analysis

Data analysis will be performed in accordance with IQVIA's standard operating procedures (SOPs) for statistics and clinical programming. All study specific processes and definitions will be documented.

The statistical analysis will be coordinated by the responsible biostatistician of the sponsoring organization. The Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with any specifications for tables, listings and figures to be produced. SAP will be finalized before conducting any research which informs the study objectives beyond the initial feasibility data. Any changes from the analyses after conducting any of the analyses outlined in the SAP will be captured as a revision to the SAP. All analyses will be performed using appropriate statistical software (i.e. SAS® Version 9.4). This study will follow the relevant chapters of the ENCePP[5] and the ICH guidelines for statistical analyses. A report summarizing the results of the study will be developed. All analyses will be descriptive without formal statistical hypothesis testing.

The incidence rates and corresponding 95% CIs of safety event outcomes will be calculated by dividing the number of observed events by person-time exposure. Primary safety event outcomes will consist of two categories: i) all-cause mortality; ii) serious and fatal infections. Secondary safety event outcomes will consist of hepatitis B re-activation and myelosuppression.

As sensitivity analysis for the primary outcomes, patients with a history of a prior safety event will be excluded from the analysis of this particular safety event (and in particular, patients with a serious infection prior to inclusion in the cohort will be excluded from the analysis of serious and fatal infections).

Results for the pre- and post-DHPC dissemination periods will be presented separately. The main study results will be stratified by country and disease indication (iNHL, CLL, MM). Table 6 shows a mock table shell as an example of result reporting.

Table 6: Example of a mock table shell of the presentation of results of the main analysis for Primary Objective 1: Cohort study to evaluate safety outcomes

				Incidence rate per 100 person-years [95% CI]	
Country	Disease Indication	Drug	DHPC Dissemination Period (Pre- or Post-)	Mortality	Infection
France	iNHL, CLL, MM	Bendamustine	Pre-	X.X [X.X-X.X]	X.X [X.X-X.X]
France	iNHL, CLL, MM	Bendamustine	Post-	X.X [X.X-X.X]	X.X [X.X-X.X]
France	CLL, MM	Chlorambucil, Melphalan	Pre-	X.X [X.X-X.X]	X.X [X.X-X.X]
France	CLL, MM	Chlorambucil, Melphalan	Post-	X.X [X.X-X.X]	X.X [X.X-X.X]
Germany	iNHL, CLL, MM	Bendamustine	Pre-	X.X [X.X-X.X]	X.X [X.X-X.X]
Germany	iNHL, CLL, MM	Bendamustine	Post-	X.X [X.X-X.X]	X.X [X.X-X.X]
Germany	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Pre-	X.X [X.X-X.X]	X.X [X.X-X.X]
Germany	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Post-	X.X [X.X-X.X]	X.X [X.X-X.X]
England	iNHL, CLL, MM	Bendamustine	Pre-	X.X [X.X-X.X]	X.X [X.X-X.X]

England	iNHL, CLL, MM	Bendamustine	Post-	X.X [X.X-X.X]	X.X [X.X-X.X]
England	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Pre-	X.X [X.X-X.X]	X.X [X.X-X.X]
England	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Post-	X.X [X.X-X.X]	X.X [X.X-X.X]

As secondary analyses, if meaningful differences (e.g. 50% relative difference) in safety event outcome incidence rates are observed between pre- and post-DHPC dissemination periods, then stratification by approved- versus off-label use assessed at the time of new use may be performed assuming adequate sample size. Incidence rates of safety event outcomes among patients with concurrent off-label use of bendamustine with rituximab, obinutuzumab, or idelalisib may also be calculated.

Additional secondary analyses will assess the change in frequency of physician behaviors in the outpatient setting, namely, the use of anti-infective drugs, and the use of anti-infective drugs used for prophylaxis of opportunistic infections. All patients included in the pre- and post-DHPC dissemination bendamustine cohorts will be included. The number, frequency and proportion of anti-infective prescriptions dispensed after the initiation of bendamustine for the remainder of the study period will be determined for each patient. The mean number per patient for the pre- and post-DHPC dissemination periods will be reported.

9.1.10 STUDY A: Quality Control

The study will use existing databases, which are being used widely for research. The study will be executed in line with applicable regulations and guidelines – such as best-practice guidelines applicable to non-interventional drug utilization studies, including but not limited to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology[5], the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP)[7] as well as the specific

IQVIA SOPs. All study programs, log files, and output files will be stored on the IQVIA secure server. Where elements of the study are being conducted by a third party, the datasets and analytic programs will be stored according to the vendor's procedures.

Within each research center, SOPs will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. Key programming modules written by a study analyst will, where specified, be independently reviewed by a different analyst. The programming will be done by a senior statistician. All key study documents, such as the SAP, and study reports will undergo quality-control review, senior scientific review, and editorial review as per IQVIA SOPs.

There will be no review of unstructured fields in medical records, i.e. only structured data fields will be used. Analysis data sets and program output will be checked for accuracy and integrity according to IQVIA SOPs.

None of the extracted data sets will contain data that allow identification of subjects included in the study. Each electronic record will be completely anonymized and will not contain any personal identifying data.

Procedures will be consistent with the ISPE GPP[7].

9.1.11 STUDY A: Limitations of the Research Methods

An important limitation will be related to the identification of exposure and endpoint events in the data sources. This proposed program is based on analyses of automated medical and prescription claims and medical records. Although claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, health care resource utilization, and costs, all claims databases have certain inherent limitations because the data are collected for the purpose of payment and not research. Drug exposure and effects that do not result in billed medical services will not be identifiable using administrative claims data but will be available in electronic healthcare databases. The presence of a claim for a filled prescription or a record of a prescription issued does not indicate that the drug was consumed or that it was taken as prescribed. The presence of a diagnosis code on a medical claim does

not provide positive presence of disease, as the diagnosis code may be incorrectly coded or included as a rule-out criterion rather than representing actual disease. Specific to this protocol, the data in the electronic health records may be insufficient to accurately assess the approved- versus off-label status. Note that, as per the definition of off-label use (see Protocol section 11.4.4 Definition of Off-Label Use), in this study the evaluation of off-label use focuses on the use in off-label populations (i.e. off-label combinations) rather than off-label use associated with intentional use in different indications, different route or method of administration, or different dosage than those labelled.

The limitations specific to each datasource for this study are detailed in section 9.1.1 STUDY A: Data Sources and section 9.1.7 Study A: Study Size.

9.1.12 STUDY A: Other Aspects

Not applicable.

9.2 STUDY B: Research methods

To evaluate and characterize approved- and off-label use of bendamustine and other alkylating drugs similar to bendamustine pre- and post-DHPC dissemination, a cross-sectional study will be conducted. Patients initiating bendamustine for the treatment of iNHL, CLL, or MM during the pre- or post-DHPC dissemination periods will be identified and approved- versus off-label use will be assessed throughout the specific study period during which they initiated bendamustine use (i.e. either pre- or post-DHPC dissemination). Patients initiating cyclophosphamide for iNHL, chlorambucil for CLL, or melphalan for MM, collectively termed the alternative treatments, will be similarly identified and assessed for approved- versus off-label use. The proportion of drug users with any observed off-label use during the respective study periods (pre- and post-DHPC dissemination) and with off-label use at initiation of treatment will be reported. Proportions will be reported separately for pre- and post-DHPC dissemination periods and will be stratified by country (France, Germany, England) and disease indication.

9.2.1 STUDY B: Data Sources

Data sources used for this study will be the same as for study A (see section 9.1.1 STUDY A: Data Sources).

9.2.2 STUDY B: Endpoints

All study outcomes (and the ICD-10 and ATC codes) are defined in Annex 3: Table 12: Exposure and Outcome Codes and Table 13: ICD-10 codes for Serious Infections*.

The assessment of approved- versus off-label drug use will be performed for each prescription or administration of bendamustine and the alkylating drugs similar to bendamustine that occur in patients who initiate these drugs during the pre- or post-DHPC dissemination periods. Multiple assessments of approved- versus off-label will be made because patients' clinical characteristics and concurrent drug use may change over time (i.e. patients may change status from approved-label to off-label use during the study periods).

The method of assessment for approved- versus off-label drug use is detailed in section 9.1.6.2 STUDY A: Assessment of Approved- versus Off-label Drug Use.

The assessment of approved- versus off-label use will be made throughout the study period. In addition, a sensitivity analysis will be restricted to the first observed use. The proportion of patients with any observed off-label use provides a maximum estimate of the prevalence of off-label use. This proportion can be compared to the proportion of patients with off-label use at the time of new use and this will help provide an estimate of the proportion of patients that switched from approved-label use to off-label use during the study period. The proportion of patients with approved- and off-label use will be presented for the pre- and post-DHPC dissemination periods separately. Results will be presented individually by country and disease indication (iNHL, CLL, MM). The secondary outcome of concurrent off-label use of bendamustine with rituximab, obinutuzumab, and idelalisib will also be assessed. See section 9.1.9.2 STUDY B: Statistical Analysis.

9.2.3 STUDY B: Study Design

This retrospective study consists of three distinct study periods: pre-DHPC dissemination period, DHPC dissemination period, and post-DHPC dissemination period, analogous to Study A (section 9.1.3 STUDY A: Study Design).

To evaluate and characterize approved- and off-label use of bendamustine and other alkylating drugs similar to bendamustine pre- and post-DHPC dissemination, a cross-sectional study will be conducted. Patients initiating bendamustine for the treatment of iNHL, CLL, or MM during the pre- or post-DHPC dissemination periods will be identified, and approved- versus off-label use will be assessed throughout the specific study period during which they initiated bendamustine use (i.e. either pre- or post-DHPC dissemination). Patients initiating cyclophosphamide for iNHL, chlorambucil for CLL, or melphalan for MM, collectively termed the alternative treatments, will be similarly identified and assessed for approved- versus off-label use. The proportion of drug users with any observed off-label use during the respective study periods (pre- and post-DHPC dissemination) and with off-label use at initiation of treatment will be reported. Results will be stratified by country (France, Germany, England).

9.2.4 STUDY B: Study Population

The study population of Study B will be analogous to Study A. The selection of the study population is described in section 9.1.4.1 STUDY A: Selection of Study Population.

Inclusion criteria are as described in Study A section 9.1.4.2 STUDY A: Inclusion Criteria.

Exclusion criteria are as described in Study A section 9.1.4.3 STUDY A: Exclusion Criteria.

9.2.5 STUDY B: Treatments and Evaluation

9.2.5.1 STUDY B: Discontinuation Criteria

There are no censoring criteria for the cross-sectional study.

9.2.6 STUDY B: Variables

Codes used to identify exposures and outcomes in the study are listed in Annex 3: Table 12: Exposure and Outcome Codes.

9.2.6.1 STUDY B: Exposure Definitions

Study drugs and 'use' of study drugs are defined as described in Study A section 9.1.6.1 STUDY A: Exposure Definitions.

Only patients who are new users of bendamustine or the alkylating drugs similar to bendamustine are included in the cross-sectional study (section 9.1.4.2 STUDY A: Inclusion Criteria and section 9.1.4.3 STUDY A: Exclusion Criteria). For each included patient in the pre- or post-DHPC dissemination period, all instances of medication use during that period are identified and assessed for approved- versus off-label use (section 9.1.6.2 STUDY A: Assessment of Approved- versus Off-label Drug Use).

9.2.6.2 STUDY B: Assessment of Approved- versus Off-label Drug Use

The assessment of approved- versus off-label drug use is as described in section 9.1.6.2 STUDY A: Assessment of Approved- versus Off-label Drug Use. See also Annex 3.

9.2.6.3 STUDY B: Other Primary Variables

Independent variables, which will be assessed for each patient included in the study, are as listed in section 9.1.6.3 STUDY A: Other Primary Variables.

9.2.7 STUDY B: Study Size

Feasibility of data availability for drug exposures of interest were examined in the Bendamustine-Astellas-Feasibility report[4] and are reported in section 9.1.7 STUDY A: Study Size.

9.2.8 STUDY B: Data Management

Data Management of this study is as described in section 9.1.8 STUDY A: Data Management.

9.2.9 STUDY B: Statistical Methods

9.2.9.1 STUDY B: Sample Size Justification

The outcomes of the study to evaluate approved- and off-label use will be expressed as proportions with 95% CI. Table 7 shows the number of persons needed to provide the stated margin of error for the 95% CI (columns) given the observed proportion of off-label use (rows). For example, if the proportion of off-label use is 5% and 457 persons are observed, then the margin of error for the 95% CI would be 2%.

Assuming the proportion of off-label use is 50% yields the most conservative sample size estimate i.e. the largest sample size. A sample size of 385 bendamustine users would give a precision of 5% for each of the strata (bendamustine versus alternative treatment, study period pre- versus post-DHPC dissemination, country, and disease indication). The sample size estimates are presented in Table 7.

Table 7: Number of persons needed for a given proportion of off-label use and desired 95% CI

	Margin of error for the 95% CI					
Proportion of off-label use	1%	2%	3%	5%	6%	10%
5%	1825	457	203	73	51	19
10%	3458	865	385	139	97	35
30%	8068	2017	897	323	225	81
50%	9604	2401	1066	385	267	97

9.2.9.2 STUDY B: Statistical Analysis

The overall approach to data analysis (adherence to IQVIA's SOPs, ENCePP[5] and the ICH guidelines; process of SAP creation and execution) will be as described in section 9.1.9.2 STUDY A: Statistical Analysis.

For Study B, as primary analysis, the proportion of new users of bendamustine or the alkylating drugs similar to bendamustine with any observed off-label use during the study period will be calculated by dividing the number of patients with any off-label use by the total number of new users; 95% CIs will also be calculated. As sensitivity analysis, the proportion of new users of bendamustine or the alkylating drugs similar to bendamustine with off-label use at the time of new use of the drug will be calculated with 95% CIs. Results for the pre- and post-DHPC dissemination periods will be presented separately.

The main study results will be stratified by country. Table 8 shows a mock table shell as an example of reporting of results for the pre- and post-DHPC dissemination periods.

Table 8: Example of a mock table shell of the presentation of results of the main analysis for Primary Objective 2: Cross-sectional study to evaluate approved- and off-label use

				Proportion of patients [95% CI]	
Country	Disease Indication	Drug	DHPC Dissemination Period (Pre- or Post-)	Any off-label use	Off-label use at time of new use
France	iNHL, CLL, MM	Bendamustine	Pre-	XX% [XX-XX%]	XX% [XX-XX%]
France	iNHL, CLL, MM	Bendamustine	Post-	XX% [XX-XX%]	XX% [XX-XX%]
France	CLL, MM	Chlorambucil, Melphalan	Pre-	XX% [XX-XX%]	XX% [XX-XX%]

France	CLL, MM	Chlorambucil, Melphalan	Post-	XX% [XX-XX%]	XX% [XX-XX%]
Germany	iNHL, CLL, MM	Bendamustine	Pre-	XX% [XX-XX%]	XX% [XX-XX%]
Germany	iNHL, CLL, MM	Bendamustine	Post-	XX% [XX-XX%]	XX% [XX-XX%]
Germany	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Pre-	XX% [XX-XX%]	XX% [XX-XX%]
Germany	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Post-	XX% [XX-XX%]	XX% [XX-XX%]
England	iNHL, CLL, MM	Bendamustine	Pre-	XX% [XX-XX%]	XX% [XX-XX%]
England	iNHL, CLL, MM	Bendamustine	Post-	XX% [XX-XX%]	XX% [XX-XX%]
England	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Pre-	XX% [XX-XX%]	XX% [XX-XX%]
England	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Post-	XX% [XX-XX%]	XX% [XX-XX%]

The proportion of patients with any observed concurrent off-label use of bendamustine with rituximab, obinutuzumab, or idelalisib use will also be calculated with 95% CI and stratified by country and disease indication (iNHL, CLL, MM).

9.2.10 STUDY B: Quality Control

Quality control will be as described in section 9.1.10 STUDY A: Quality Control.

9.2.11 STUDY B: Limitations of the Research Methods

Overall limitations of the research methods for Study B are as described in section 9.1.11 STUDY A: Limitations of the Research Methods.

The limitations specific to each datasource for this study are detailed in section 9.1.1 STUDY A: Data Sources.

9.2.12 STUDY B: Other Aspects

Not applicable.

9.3 STUDY C: Research methods

To evaluate and characterize approved- and off-label use of bendamustine and other alkylating drugs similar to bendamustine pre- and post-DHPC dissemination, a cross-sectional study of a physician survey-based database (Oncology Dynamics) will be conducted. Patients initiating bendamustine for the treatment of iNHL, CLL, or MM during the pre- or post-DHPC dissemination periods will be identified, and approved- versus off-label use will be assessed at the time of new use. Patients initiating cyclophosphamide for iNHL, chlorambucil for CLL, or melphalan for MM, collectively termed the alternative treatments, will be similarly identified and assessed for approved- versus off-label use. The proportion of drug users with off-label use at initiation of treatment will be reported. Proportions will be reported separately for pre- and post-DHPC dissemination periods and will be stratified by country (France, Germany, UK).

9.3.1 STUDY C: Data Sources

Owing to challenges in assessing approved- versus off-label drug use in available electronic healthcare databases, Oncology Dynamics (OD) data will be used to conduct a complementary assessment of approved- and off-label drug use for Primary Objective 2. OD is an IQVIA proprietary physician survey-based database and data will be used from France, Germany, and UK.

9.3.1.1 STUDY C: Oncology Dynamics[8] (France, Germany, UK)

OD is an IQVIA proprietary physician survey-based database comprising cross-sectional surveys that collect detailed and comprehensive patient-level data provided at one specific point in time from a representative subset of cancer-treating physicians in EU. Patient case information is generated from secondary data and through a pre-defined web-based questionnaire. The OD database is designed to be representative across all specialties involved in the pharmacological treatment and management of cancer. Data are collected in the OD database on a quarterly basis and they are projected to the country-specific estimated cancer treated prevalence.

The variables collected in the OD database are:

- Patient demographic variables: age, gender, smoking status
- Clinical and patient characteristics: cancer type, current stage/grade, stage/grade at diagnosis, histology, site of metastases, operability, disease relapse/progression, stem cell transplant eligibility, comorbidities, ECOG performance status, key diagnostic tests, key chromosomal abnormalities, PSA level, Gleason score, platinum status, castration resistance status
- Therapy and treatment attributes: current and most recent previous product name and regimen administered, ATC class, route of administration, dosing type, dose quantity, administration frequency, cycles planned, cycles given, length of cycle, days per cycle, maintenance therapy, treatment funding, side effects, reasons for treatment discontinuation, therapy context

The OD database contains data on patient diagnosis for iNHL, CLL and MM. All study drugs and drugs needed to determine approved- and off-label use are available within the database. All parameters relating to diagnosis, staging of cancer and date and dosage of drug administration can be found in OD. However, no clinical outcomes are available in the OD database. Table summarizes the data available in the OD database.

Table 9: Summary of data in Oncology Dynamics database

Oncology Dynamics database	Data Availability	Limitations
● available / quantitative column = sample size sufficient to cover the objectives ● data not available		
NHL indication		
Data to define approved label definition of bendamustine	●	• Information 100% available in France, Germany, UK
Data to define approved label definition of alkylating drugs similar to bendamustine (cyclophosphamide)	●	• Information 100% available in France, Germany,UK
CLL indication		
Data to define approved label definition of bendamustine	●	• Information 100% available in France, Germany,UK
Data to define approved label definition of alkylating drugs similar to bendamustine (chlorambucil)	●	• Information 100% available in France, Germany,UK
MM indication		
Data to define approved label definition of bendamustine	●	• Information 100% available in France, Germany,UK
Data to define approved label definition of alkylating drugs similar to bendamustine (melphalan)	●	• Information 100% available in France, Germany,UK
Common to the three indications		
Data to evaluate the off-label measurement	●	• Information 100% available in France, Germany,UK
Data to evaluate the clinical outcomes	●	• Clinical outcomes not collected

9.3.2 STUDY C: Endpoints

The assessment of approved- versus off-label drug use will be performed at the initiation of treatment with bendamustine or the alkylating drugs similar to bendamustine during the pre- and post-DHPC dissemination periods. Assessment of off-label use for each instance of drug use during the study period will not be performed because details of each instance of drug use are not recorded in the physician survey.

The method of assessment for approved- versus off-label drug use is detailed in section 9.1.6.2 STUDY A: Assessment of Approved- versus Off-label Drug Use.

The assessment of approved- versus off-label use will be restricted to the first observed use. The proportion of patients with approved- and off-label use will be presented for the pre- and post-DHPC dissemination periods. Results will be presented individually by country and disease indication. The secondary outcome of concurrent off-label use of bendamustine with rituximab, obinutuzumab, and idelalisib will also be assessed.

9.3.3 STUDY C: Study Design

This retrospective study consists of three distinct study periods: pre-DHPC dissemination period, DHPC dissemination period, and post-DHPC dissemination period. Study outcomes are not assessed during the DHPC dissemination period. The entire study begins 01 April 2015 (two years prior to DHPC dissemination period) and ends 31 August 2019 (two years after DHPC dissemination period). The individual time periods are defined analogous to Study A and B (see Figure 1):

- Pre-DHPC dissemination period (24 months): 01 April 2015 – 31 March 2017
- DHPC dissemination period (5 months): 01 April 2017 – 31 August 2017
- Post-DHPC dissemination period (24 months): 01 September 2017 – 31 August 2019

To evaluate and characterize approved- and off-label use of bendamustine and other alkylating drugs similar to bendamustine pre- and post-DHPC dissemination, a cross-sectional study will be conducted. Patients initiating bendamustine for the treatment of iNHL, CLL, or MM during the pre- or post-DHPC dissemination periods will be identified, and approved- versus off-label use will be assessed throughout the specific study period during which they initiated bendamustine use (i.e. either pre- or post-DHPC dissemination). Patients initiating cyclophosphamide for iNHL, chlorambucil for CLL, or melphalan for MM, collectively termed the alternative treatments, will be similarly identified and assessed for approved- versus off-label use. The proportion of drug users with off-label use at initiation of treatment during the respective study periods (pre- and post-DHPC dissemination) will be reported. Results will be stratified by country (France, Germany, UK).

9.3.4 STUDY C: Study Population

This study will be conducted using a retrospective analysis of existing physician survey databases from France, Germany, and UK. Included patients are new users of bendamustine or one of the alkylating drugs similar to bendamustine for the treatment of iNHL, CLL, or MM during the pre-DHPC dissemination period (01 April 2015 – 31 March 2017) or the post-DHPC dissemination period (01 September 2017 – 31 August 2019). A single patient will be included in only either the bendamustine cohort or the cohort of alkylating drugs similar to bendamustine in the same pre- or post-DHPC dissemination period. Included patients are anticipated to be indicative of patients in the general population.

9.3.4.1 STUDY C: Selection of Study Population

The analysis will include all available patients meeting the inclusion criteria.

The inclusion and exclusion criteria are applied to the pre- and post-DHPC dissemination periods separately to select two distinct groups of patients for each period. Patients may be included in both pre- and post-DHPC dissemination periods if they satisfy all other inclusion criteria.

9.3.4.2 STUDY C: Inclusion Criteria

1. Use of bendamustine for the treatment of iNHL, CLL, or MM or use of alkylating drugs similar to bendamustine (cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM) during the pre- or post-DHPC dissemination period
2. New user of bendamustine (see 9.3.11 STUDY C: Limitations of the Research Methods), defined as use of bendamustine during the pre- or post-DHPC dissemination periods with no use of bendamustine in prior six months, or new user of alkylating drugs similar to bendamustine, defined as use of alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination periods with no use of alkylating drugs similar to bendamustine in prior six months

9.3.4.3 STUDY C: Exclusion Criteria

1. Use of bendamustine for a disease indication other than iNHL, CLL, MM

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2. Use of alkylating drugs similar to bendamustine for disease indication other than cyclophosphamide for iNHL, chlorambucil for CLL, melphalan for MM
3. Prior use of bendamustine within six months of the observed new bendamustine use during the pre- or post-DHPC dissemination period (see 9.3.11 STUDY C: Limitations of the Research Methods)
4. Prior use of alkylating drugs similar to bendamustine within six months of the time of new use of alkylating drugs similar to bendamustine during the pre- or post-DHPC dissemination period (see 9.3.11 STUDY C: Limitations of the Research Methods)

Figure 7 illustrates the inclusion criteria for new users.

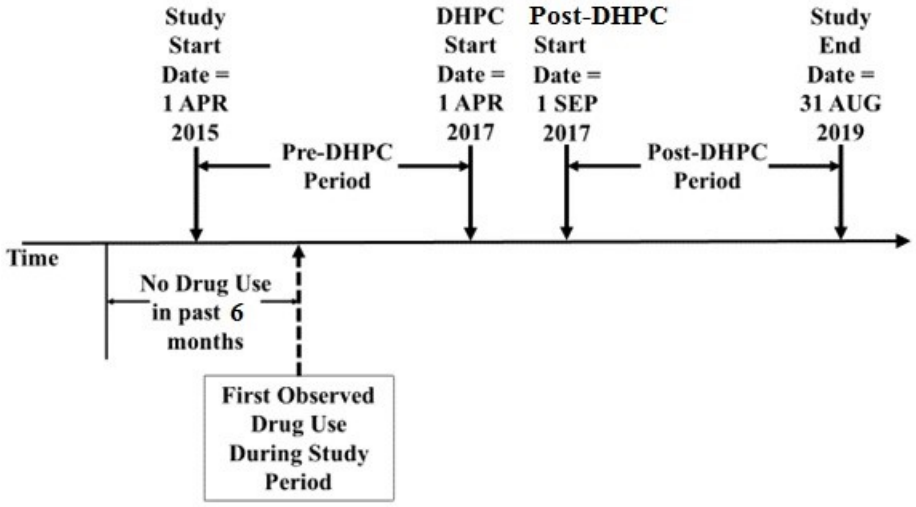

Figure 7. Example of a new user (not to scale). The patient has no study drug use in the six months before the first observed use during the study period. The patient is included in the study for the pre-DHPC dissemination period.

9.3.5 STUDY C: Treatments and Evaluation

9.3.5.1 STUDY C: Discontinuation Criteria

There are no censoring criteria for the cross-sectional study.

9.3.6 STUDY C: Variables

Codes used to identify exposures and outcomes in the study are listed in Annex 3: Table 12: Exposure and Outcome Codes. Exposures and outcomes are reported directly in the physician survey.

9.3.6.1 STUDY C: Exposure Definitions

Study drugs and 'use' of study drugs are defined as described in section 9.1.6.1 STUDY A: Exposure Definitions.

Only patients who are new users of bendamustine or the alkylating drugs similar to bendamustine are included in the cross-sectional study (section 9.1.4.2 STUDY A: Inclusion Criteria and section 9.1.4.3 STUDY A: Exclusion Criteria). For each included patient in the pre- or post-DHPC dissemination period, all instances of medication use during that period are identified and assessed for approved- versus off-label use (section 9.1.6.2 STUDY A: Assessment of Approved- versus Off-label Drug Use).

9.3.6.2 STUDY C: Assessment of Approved- versus Off-label Drug Use

The assessment of approved- versus off-label drug use is as described in section 9.1.6.2 STUDY A: Assessment of Approved- versus Off-label Drug Use. See also Annex 3.

9.3.6.3 STUDY C: Other Exploratory Variables

Independent exploratory variables, which will be assessed for each patient included in the study, are as listed in section 9.1.6.3 STUDY A: Other Primary Variables.

9.3.7 STUDY C: Study Size

Feasibility of data availability for drug exposures of interest (alkylating drugs: bendamustine, cyclophosphamide, chlorambucil, melphalan; concomitant therapies: rituximab, obinutuzumab and idelalisib) from databases used in the study for the selected countries and by disease indication were examined in the Bendamustine-Astellas-Feasibility report[4] and shown for Oncology Dynamics in Table below. The actual numbers of study subjects will likely be lower

following formal application of the study inclusion / exclusion criteria as the feasibility study was not restricted to new users of drugs.

Table 10: Number of patients available in Oncology Dynamics in pre- and post-DHPC dissemination periods

Oncology dynamics	France		Germany		UK	
	Time period		Time period		Time period	
	Pre-DHPC dissemination(1)	Post-DHPC dissemination(2)	Pre-DHPC dissemination(1)	Post-DHPC dissemination(2)	Pre-DHPC dissemination(1)	Post-DHPC dissemination(2)
Bendamustine	171	532	739	1868	189	740
Rituximab	691	2080	1157	3116	840	2560
Obinutuzumab	13	104	26	80	19	184
Idelalisib	22	48	17	64	29	108
Chlorambucil	106	284	75	72	105	424
Cyclophosphamide	1169	3600	1677	4420	1410	4364
Melphalan	191	512	129	472	76	144
NHL Indolent	184	660	357	936	294	928
NHL indolent + Bendamustine	31	144	272	712	92	344
NHL C82.X + Rituximab	146	560	317	796	228	656
NHL C82.X + Bendamustine	37	128	261	644	77	284
NHL C82X + Obinutuzumab	1	16	1	60	1	24
NHL C82.X + Idelalisib	6	16	3	16	3	14
CLL (C91 1)	298	872	471	1468	263	1064
CLL + Bendamustine	84	232	242	740	60	248
CLL + Chlorambucil	83	204	70	68	78	368
CLL + Rituximab	197	548	338	1052	182	612
CLL + Obinutuzumab	10	84	24	20	18	160
CLL+ Idelalisib	14	28	14	48	24	96
Multiple Myeloma (C90)	474	1572	562	1732	466	1324
MM + Bendamustine	6	28	58	104	6	12
MM + Melphalan	179	500	112	408	73	140
MM + Rituximab	0	0	1	0	0	0

9.3.8 STUDY C: Data Management

Data collection is conducted through a standardized online questionnaire where responses to all questions are mandatory. Clear instructions and a guide manual are provided to respondents.

Quality is ensured by consistent procedures that include:

- Using controlled code lists and choice lists to minimize manual data entry
- Filters to show questions that are only relevant to specific cancer types (e.g. HER2 test for breast and stomach cancer).
- Some responses are confirmed against previous answers (where appropriate) in order to detect inadmissible responses (e.g. absence of metastatic sites if patient with stage IV cancer)
- Dosage of each drug reported by the doctor is checked against a drug dose reference file to determine whether it is included within a range of acceptable dose levels

Standardized procedures with clear instructions are implemented to prevent errors in coding of free-text entries. Processed data are then checked by the Quality Control team and trend checks are conducted to detect errors and anomalous values. Event frequencies and mean values are compared to those in the most recent available periods. Additional data validations are conducted by contacting physicians who have participated in the study.

9.3.9 STUDY C: Statistical Methods

9.3.9.1 STUDY C: Sample Size Justification

The sample size considerations to evaluate approved- and off-label use are detailed in section 9.2.9.1 STUDY B: Sample Size Justification.

9.3.9.2 STUDY C: Statistical Analysis

The overall approach to data analysis (adherence to IQVIA's SOPs, ENCePP[5] and the ICH guidelines; process of SAP creation and execution) will be as described in section 9.1.9.2 STUDY A: Statistical Analysis.

The proportion of new users of bendamustine or the alkylating drugs similar to bendamustine with off-label use at the time of new use of drug will be calculated with 95% CIs. Results for the pre- and post-DHPC dissemination periods will be presented separately. The main study

results will be stratified by country and disease indication. Table shows a mock table shell as an example of the reporting of results for the pre- and post-DHPC dissemination periods.

Table 11: Example of a mock table shell of the presentation of results of the main analysis for Primary Objective 2: Cross-sectional study to evaluate approved- and off-label use

				Proportion of patients [95% CI]
Country	Disease Indication	Drug	DHPC Dissemination Period (Pre- or Post-)	Off-label use at time of new use
France	iNHL, CLL, MM	Bendamustine	Pre-	XX% [XX-XX%]
France	iNHL, CLL, MM	Bendamustine	Post-	XX% [XX-XX%]
France	CLL, MM	Chlorambucil, Melphalan	Pre-	XX% [XX-XX%]
France	CLL, MM	Chlorambucil, Melphalan	Post-	XX% [XX-XX%]
Germany	iNHL, CLL, MM	Bendamustine	Pre-	XX% [XX-XX%]
Germany	iNHL, CLL, MM	Bendamustine	Post-	XX% [XX-XX%]
Germany	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Pre-	XX% [XX-XX%]
Germany	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Post-	XX% [XX-XX%]

England	iNHL, CLL, MM	Bendamustine	Pre-	XX% [XX-XX%]
England	iNHL, CLL, MM	Bendamustine	Post-	XX% [XX-XX%]
England	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Pre-	XX% [XX-XX%]
England	iNHL, CLL, MM	All alkylating drugs similar to bendamustine	Post-	XX% [XX-XX%]

The proportion of patients with any observed concurrent off-label use of bendamustine with rituximab, obinutuzumab, or idelalisib use will also be calculated with 95% CI and stratified by country and disease indication.

9.3.10 STUDY C: Quality Control

Collected data are validated, processed, and thoroughly checked by qualified IQVIA teams who have a wealth of experience in the management of oncology studies. Quality checks are conducted on a daily basis. Processes are also in place to identify issues with the online data collection. In total more than 400 quality checks are performed during each data production cycle.

Most of the values in the data collection questionnaire are predefined. The participants select the appropriate pre-defined checkboxes to enter their responses. Nevertheless, some questions allow participating doctors to enter free text that requires validation by the Quality Control team. This validation consists of assessing the free text entered by the doctors and assigning the most appropriate of the available values in the system based on coding rules. If necessary new values can be integrated into the system (e.g. new therapeutics, diagnostics, etc.).

9.3.11 STUDY C: Limitations of the Research Methods

In this cross-sectional study, data collection is limited to only one timepoint for each individual patient. Information on the treatment regimen received on the day of data collection and the closest previous line of treatment are captured. However, information is not available on other lines of treatment administered prior to the current and closest previous line of treatment.

Patients may be misclassified as new user of a medication, due to the limited possibility to apply a six-month look-back period to distinguish between prevalent and new user.

Data from deceased patients are not captured in OD.

9.3.12 STUDY C: Other Aspects

Not applicable.

10 PROTECTION OF HUMAN PATIENTS

This study will be conducted in compliance with national and European Union requirements for ensuring the rights of participants in non-interventional studies.

10.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

Databases will not contain any patient identification information (e.g. name), except for a unique number assigned for the purpose of linking files.

Approval for use of encrypted and aggregated data from all databases is granted from national authorities involved in privacy protection and/or local ethic committees.

No IRB approval is required for OD for France, Germany and UK.

France (SNDS):

IQVIA will seek approval from the Independent Scientific Advisory Committee. This will require that IQVIA prepare several documents, including a version of the present protocol adapted to the required format. Historically, the approval process takes 8-12 weeks and may involve revisions of the submitted documents.

Germany (SHI):

The application procedure for studies based on statutory health insurances (SHI data) in Germany is executed by the cooperation partner handling the SHI data. IQVIA will provide the partner a short summary description of the study. The cooperation partner will review the content and confirm the content feasibility and the compliance with local legal requirements. The summary description will be provided to the individual data providers for review. In the case that no comments or concerns are addressed within a defined time period (i.e. between 2-4 weeks based on complexity of the study) by the requested individual SHI data providers, the approval will be considered as given and the study will proceed.

England (CAS/HES):

In England, IQVIA uses simulated cancer registry data (the Simulacrum) to develop analysis code on non-identifiable synthetic data. The Simulacrum is publicly available and can be used with no restrictions. Projects utilizing the Simulacrum to access CAS and HES data are logged via the Simulacrum Project Purpose form, and will be evaluated and approved by Public Health England's Office of Data Release (ODR) prior to release. Once code has been developed on simulated data, the code will be sent to PHE to be run on the actual CAS data. Analyses performed should be known to PHE to be strictly non-identifiable (fully anonymized) and releasable under an Open Government License, e.g. if it reaches the Information Standards Board for Health and Social Care (ISB) standard 1523 for anonymization of health and social care data. Aggregated data which are deemed to be anonymous will be released to IQVIA. The ODR will review the purpose of the data release to ensure that it is legal to run the submitted code on data collected for medical purposes under section 251 of the NHS Act 2006.

10.2 Ethical Conduct of the Study

This study will be conducted in compliance with national and European Union requirements for ensuring the rights of participants in non-interventional studies.

The Investigator(s) and all parties involved in this study will conduct the study in adherence to the ethical principles based on the Declaration of Helsinki (2013 or most current version available), ICH E6, and any applicable laws and regulations.

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the Guideline on Good Pharmacovigilance Practices (GVP) Module XVI-Risk Minimization Measures: Selection of Tools and Effectiveness Indicators[9], ISPE GPP[7], Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA)[10], Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[11], International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS)[12], EMA, ENCePP Guide on Methodological Standards in Pharmacoepidemiology[5] and FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment[13].

10.3 Patient Information and Consent

As this study will be conducted through secondary databases of anonymized electronic health records, there will be no patient consent sought at the study level.

10.4 Patient Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the patient to the patient's physician only or to other appropriate medical personnel responsible for the patient's well-being. The Sponsor shall not disclose any confidential information on patients obtained during the performance of their duties in this non-interventional study without justifiable reasons.

The Sponsor affirms the patient's right to protection against invasion of privacy. Only a patient identification number and/or initials will identify patient data retrieved by the Sponsor in accordance with national data privacy requirements. However, the Sponsor requires the Investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and when

necessary, representatives of the regulatory health authorities, to review and/or to copy any medical records relevant to the study.

10.5 Insurance of Patients

As there is no direct patient involvement in the study, this section is not applicable.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Only safety events related to the study objectives will be extracted from the databases. Data will be analyzed at an aggregate level and results will be presented as incidence rates in the final study report. As this is a study with secondary use of data (electronic healthcare records), it is generally not feasible to make a causality assessment at the individual case level.[15] Thus individual adverse events and adverse reactions will not be reported.

Note, according to the EMA Guidelines, Module VI and VIII:

"For non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required. All adverse events/reactions should be summarized in the final study report."[14]

11.1 Primary Data Collection

This study does not contain primary data collection.

11.2 Secondary Data Collection

For this non-interventional study using only secondary data collection, reporting of adverse events/reactions to authorities in the form of ICSRs is not required according to GVP Module VI.C.1.2.1. Data will be analyzed at an aggregate-level and results will be presented in the final study report.

11.3 Selected Secondary Data Collection Studies

Given the information available within the data sources for this study, extraction on adverse events data will not be conducted and only data related to the study objectives will be extracted.

Therefore, information about individual adverse events will not be available. Data on aggregate-level medication use only, are being analyzed.

Any adverse event encountered in the data used for this study will be listed in the final CSR.

11.4 Definitions

11.4.1 Definitions of Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a study drug, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

AE collection begins after the signing of the informed consent and will be collected until <insert appropriate timeframe after completion of study drug that accounts for the study drug's half-life> days after the last dose of study drug.

An abnormality identified during a medical test is defined as an AE per the following criteria:

- Any abnormal laboratory test result (e.g. hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g. ECGs, radiographic scans, vital signs measurements, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.
- Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.
- Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

11.4.2 Definitions of Adverse Drug Reaction

An Adverse Drug Reaction is defined as 'Any noxious and unintended response associated with the use of a drug in humans, at any dose, where a causal relationship (drug-event) is at least a reasonable possibility'. (See also section 11.5 Criteria for Causal Relationship to the (Study) Drug)

11.4.3 Definitions of Serious Adverse Events (SAEs)

An adverse event is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an adverse event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The Sponsor has a list of events that they classify as “always serious” events. If an adverse event is reported that is considered to be an event per this classification as “always serious”, additional information on the event may be requested.

11.4.4 Definition of Off-Label Use

Off-label use refers to situations where the medicinal product that is prescribed and/or administered by a healthcare professional is intentionally used for a medicinal purpose not in accordance with the authorized product information. This includes use in a different indication, a different population, a different route or method of administration or a different dosage than those described in the local product label. When a physician unintentionally prescribes the drug for an unapproved indication it is considered a medication error and not off-label use (regardless whether the patient took the drug or not).

11.5 Criteria for Causal Relationship to the (Study) Drug

As this is a secondary analysis of electronic health records study, it is not feasible to make a causality assessment at the individual level.

11.6 Procedure in Case of Pregnancy

This study of data from databases with no link to live data cannot provide data on potential pregnancies.

11.7 Notification of Adverse Drug Reactions (Serious and Non-serious) by Study Personnel to Sponsor

This section is not applicable as there is no requirement for expedited reporting of any observed adverse events to authorities by the sponsor.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

One study (including Study A, Study B and Study C) will be registered in The European Union electronic Register of Post-Authorization Studies (EU PAS register).

Interim and final study report structure will follow the GPV module VIII (EMA/813938/2011 Rev 3). The interim and final study reports will be submitted to the EU Reference Member State (BfArM).

Study results will be published following the International Committee of Medical Journal Editors[16] guidelines, and communication in appropriate scientific venues, e.g. ISPE conferences, will be considered.

The appropriate STROBE checklist[17] will be followed for study reporting.

13 REFERENCES

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2. Theidel U, Kuhlmann A, Braem A. Pneumococcal vaccination rates in adults in Germany: an analysis of statutory health insurance data on more than 850,000 individuals. Dtsch Arztebl Int. 2013 Nov 1;110(44):743-50.
3. Wong SL, Ricketts K, Royle G, Williams M, Mendes R. A methodology to extract outcomes from routine healthcare data for patients with locally advanced non-small cell lung cancer. BMC Health Serv Res. 2018 Apr 11;18(1):278.
4. Bendamustine-Astellas-Feasibility report-version 1.0. 20 December 2018.
5. Guide on Methodological Standard in Pharmacoepidemiology. European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology (ENCePP); June 2013. (http://www.encepp.eu/standards_and_guidances).
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7. International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP), Revision 3, June 2015. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed August 15, 2018.
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9. EMA- Good Pharmacoviglilance Practives (GVP) Module XVI-Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144010.pdf
10. Guidelines for Good Epidemiological Practice (GEP). International Epidemiological Association (IEA); April 2010.

11. Good Outcomes Research Practices. International Society for Pharmacoeconomic and Outcomes Research (ISPOR). http://www.ispor.org/research_initiatives/hs_initiatives.asp
12. International Ethical Guidelines for Epidemiological Studies, issued by the Council for International Organizations of Medical Sciences (CIOMS), World Health Organization (WHO) Press, Geneva Switzerland. April 2009.
13. Food and Drug Administration. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment US Dept of Health and Human Services. Food and Drug Administration. Rockville, Maryland. March 2005.
14. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VI– Management and reporting of adverse reactions to medicinal products. June 22, 2012.
15. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – post-authorisation safety studies. July 9, 2012.
16. International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. August 2013.
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14 ANNEXES

Annex 1 List of stand-alone documents

None.

Annex 2 ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Non-Interventional Post-Authorisation Safety Study (NI-PASS) as an effectiveness check of an additional Risk Minimisation Measure (aRMM) (Direct Healthcare Professional Communication [DHPC]) for Bendamustine

Study reference number: ISN: 6231-MA-3264

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

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Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.1.4, 9.2.4, 9.3.4
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1.3, 9.2.3, 9.3.3
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1.1, 9.2.1, 9.3.1
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.1.9.1, 9.2.9.1, 9.3.9.1
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☐	☐	☒	
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.1.3, 9.2.3, 9.3.3
	4.2.2 Age and sex?	☐	☒	☐	
	4.2.3 Country of origin?	☐	☒	☐	
	4.2.4 Disease/indication?	☒	☐	☐	9.1.4, 9.2.4, 9.3.4
	4.2.5 Duration of follow-up?	☒	☐	☐	9.1.3, 9.2.3, 9.3.3

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1.4, 9.2.4, 9.3.4

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.1.6.1, 9.2.6.1, 9.3.6.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4	Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.2, 9.2.2, 9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1.2, 9.2.2, 9.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	
6.4	Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
	7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.2	Does the protocol address:	☐	☐	☐	
	7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
	7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3	Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.1.1, 9.2.1, 9.3.1
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.1.1, 9.2.1, 9.3.1
	9.1.3 Covariates?	☐	☐	☒	
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.1.1, 9.2.1, 9.3.1
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.1.1, 9.2.1, 9.3.1
	9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Annex 3
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Annex 3
	9.3.3 Covariates?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.1.9, 9.2.9, 9.3.9
10.2 Are descriptive analyses included?	☒	☐	☐	9.1.9, 9.2.9, 9.3.9
10.3 Are stratified analyses included?	☒	☐	☐	9.1.9, 9.2.9, 9.3.9
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.1.7, 9.1.9, 9.2.7, 9.2.9, 9.3.7, 9.3.9

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.1.10, 9.2.10, 9.3.10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.1.10, 9.2.10, 9.3.10
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.1.7, 9.1.9, 9.2.7, 9.2.9, 9.3.7, 9.3.9

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.1
13.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: PPD

Date: 20 Jan 2023

Signature: PPD

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Annex 3 Variable Definitions

Table 12: Exposure and Outcome Codes

Variable	Definition and coding
Demographics	Year of birth: Age will be analyzed as categorical variable Male or female: Gender will be analyzed as categorical variable
Location	Country
Indication	
• Indolent non-Hodgkin's lymphoma	Follicular lymphoma: ICD-10 C82.0-C82.3, C82.5-C82.9 Marginal zone lymphoma ICD-10: C83.0, C88.4 Waldenström Macroglublinaemia: ICD-10 88.0
• Chronic lymphocytic leukemia	ICD-10: C91.1
• Multiple myeloma	ICD-10: C90.0
Exposure	
• Bendamustine	ATC code: L01AA09
• Cyclophosphamide	ATC code: L01AA01
• Chlorambucil	ATC code: L01AA02
• Melphalan	ATC code: L01AA03
Safety outcomes	
Immunosuppression/ myelosuppression	ICD-10: D50-D89
• Immunodeficiency	ICD-10: D81.0-D81.2, D81.9, D83.x, D84.9
• Anemia	ICD-10: D60-D64
• Neutropenia	ICD-10: D70.x; excluding 70.0 (congenital neutropenia)
• Lymphocytopenia	ICD-10: D72.810
• Febrile neutropenia[a]	ICD-10: Algorithm: D70.1 AND R50
Clinical neuropathies	ICD-10: G50.x-G59.x, G60.x-G65.x, M79.2

Infections	Serious/severe infections: defined by an in-hospital primary diagnosis with an ICD-10 code for infection (listed in Table 14)
Hepatitis B reactivation	Nucleotide analogs ATC: J05AF Lamivudine: ATC: J05AF05 Adefovir dipivoxil: ATC: J05AF08 entecavir hydrate :ATC: J05AF10 tenofovir disoproxil fumarate : ATC : J05AF07
• Varicella zoster virus infection	ICD-10: B01.xx, B02.xx
• Cytomegalovirus infection	ICD-10: B25.xx
• Pneumonia	ICD-10: A01.03, A37.01, A37.81, A37.11, A37.91, B01.2, B05.2, B96.0, J84.11, J84.2, J85.1, J12-J18, A54.84, J95.851
○ *Pneumocystis jirovecii* pneumonia	ICD-10: B59
Acute hepatic failure[b]	ICD-10: K72.00, K76.2, K72.90 K72.90, K72.91, B15.0, B19.0, K70.41, B19.11, B17.11, K72.11, K72.01, K72.11 K76.7 K72.10 K71.6, K71.2 K71 Z94.4
Other medications	
• rituximab	ATC: L01XC02
• obinutuzumab	ATC: L01XC15
• idelalisib	ATC: L01XX47
• cyclophosphamide	ATC: L01AA01
• hydroxy-adriamycin / doxorubicin Hydrochloride	ATC: L01DB01
• vincristine sulfate	ATC: L01CA02
• prednisone/prednisolone	ATC: H02AB07/ATC: H02AB06

• fludarabine	ATC: L01BB05
• ofatumumab	ATC: L01XC10
• thalidomide	ATC: L04AX02
• bortezomib	ATC: L01XX32
• lenalidomide	ATC: L04AX04
• ibrutinib	ATC: L01XE27
• Other anticancer therapy*	ATC codes: L01 (all drugs included) L03 (L03AB01: Interferon alfa natural; L03AB04: Interferon alfa-2a; L03AB05: Interferon alfa-2b; L03AB09 : Interferon alfacon-1; L03AB10 : Peginterferon alfa-2b; L03AB60 : Peginterferon alfa-2b, combinations; L03AC01 : Aldesleukin; L03AX01 : Lentinan; L03AX02 : Roquinimex; L03AX10 : Immunocyanin; L03AX11 : Tasonermin; L03AX15 : Mifamurtide; L03AX17 : Sipuleucel-T; L03AX18 : Cridanimod) L04 (L04AA18 : Everolimus L04AX02 : Thalidomide L04AX03 : Methotrexate L04AX04 : Lenalidomide L04AX06 : Pomalidomide)

*Other anticancer therapy includes only drugs indicated for cancer(s) (e.g. everolimus is indicated for solid tumors); other anticancer therapy does not include drugs indicated only as immunostimulants and immunosuppresants (e.g. prophylaxis of transplant rejection).

Abbreviations: ICD-10 = International classification of disease, 10th version, ICD-9= International classification of disease, 9th version, ATC: Anatomical Therapeutic Chemical (ATC) Classification System; CPT: Current Procedural Terminology (CPT) code; HCPCS: Healthcare Common Procedure Coding System. LTD: long term disease attribution code

[a]. Febrile Neutropenia :Weycker D, Sofrygin O, Seefeld K et al. Technical evaluation of methods for identifying chemotherapy-induced febrile neutropenia in healthcare claims databases. BMC Health Serv Res. 2013 Feb 13;13:6

[b]. Acute hepatic failure: adapted from: Lo Re III, V *et al*. Validity of Diagnostic Codes and Laboratory Tests of Liver Dysfunction to Identify Acute Liver Failure Events. Pharmacoepidemiol Drug Saf. 2015 July;24(7):676–683.

Table 13: ICD-10 codes for Serious Infections*

Variable	Definition and coding
Meningitis	A02.2,A39.0, A87.2, A51.4, A52.1, A54.8, G04-G05, G00, G01, G03, A39.8, B00.4, A83.0, A84.0, A85.2, A92.3
Cellulitis	A48.0, K91.4, R02, M72.6, H00.1, L03.1-L03.3, L03.8, L03.9, K12.2
Endocarditis	A39.5, A32.8, A52.0, M32.1, A54.8, I09.8, I01.1, B37.6, I39, I33.9, I40.0, A02.22, A39.51, M05.31, A18.84, A01.02, I09.1
Pneumonia	Algorithm: A01.0, and J17.9 A03.2, A37.1, A37.8, A37.9, B01.2, B05.2, B96.0, J84.1, J85.1, J12-J18, A54.8, A02.2
• *Pneumocystis jirovecii* pneumonia	B48.5
Pyelonephritis/urinary tract infection	N10, N39.0
Septic arthritis	M00-M02, A02.2, B06.8, A54.4
Osteomyelitis	A02.2, M86, K10.2, H05.0
Bacteremia/septicemia	A40-A41, A41/R57.2 A49.9, B96.8
Upper respiratory tract infection	H68, H66.0, H70, J00-J06, J09-J18, J20-22, J47, J65
Abdominal Abscess	K35.2, K61, K63.0, K65.0, K67, N15.1, N41.2, N43.1, N73.2, N30.9, L02.2
Brain Abscess	G06
Cholecystitis	K83.0, K81.0, K80.0, K80.1, K80.4
Prostate infections	N41
Gastroenteritis	A00-A08, K52, A08.4, A08.5, A09
Infectious conjunctivitis	H10,B30.9,A74.0
Device associated infections	T80.2, T82.6, T82.7, T83.5, , T84.5, T84.6, T84.7, T85.7
Local infection of skin and subcutaneous tissue	L00-L08
Gangrene	R02
Retropharyngeal abscess	J39.0, J39.1

Breast abscess	N61
Splenic abscess	D73.3
Pyogenic granuloma	L98.0
Post-traumatic wound infection	T79.8, T79.9
Post-operative wound infection	T81.4
Infective myositis	M60.0
Necrotising fasciitis	M72.6
Cytomegalovirus	B25.x
Varicella zoster virus	B01.x, B02.x
Adenovirus	B97.0, B34.0, A08.2, A85.1, A87.1, B30.0, B30.1
Herpes simplex virus	B00.x
Hepatitis B	B16.x, B17.0, B18.0, B18.1
Hepatitis C	B17.1, B18.2
Other viral hepatitis	B15.x, B17.2, B17.8, B17.9, B18.8, B18.9, B19.x, K77
Tuberculosis	A15.x – A19.x
Toxoplasmosis	B58.x
Non-tuberculous mycobacteria	A31.x
Nocardiosis	A43.x
Actinomycoses	A42.x
Candidiasis	B37.x
Coccidioidomycosis	B38.x
Histoplasmosis	B39.x
Blastomycosis	B40.x
Aspergillosis	B44.x
Cryptococcosis	B45.x
Other mycoses	B35.x, B36.x, B41.x, B42.x, B43.x, B46.x, B47.x, B48.0 - B48.4, B48.8, B49

Opportunistic mycoses	B48.7
Bacterial infection in conditions classified elsewhere	B96.x
Sepsis	A40.x, A41.x, R65.x, R65.2
Bacterial pneumonia	J13, J14, J15.x, J16.0, J17.0
Pseudomonas infection	B96.5
Staphylococcal infection	A49.0, B95.6 - B95.8, U82.1
Streptococcal infection	A49.1, B95.0 - B95.5

* adapted from: Patkar,N.M et al.Administrative Codes Combined with Medical Records-based Criteria Accurately Identified Bacterial Infections among Rheumatoid Arthritis Patients. J Clin Epidemiol. 2009 March; 62(3): 321–327 and Fung M et al. Increased risk of infectious complications in older patients with indolent non-Hodgkin lymphoma exposed to bendamustine. Clin Infect Dis. 2019 Jan;68(2):247-255.

Table 14: ATC codes for Anti-infective Drugs and Substances

Anti-infectives for systemic use	
ATC Code	**Description**
J01	Antibacterial drugs for systemic use
J02	Antimycotic drugs for systemic use
J04	Antimycobacterials for systemic use
J05AA	Direct acting antiviral drugs: Thiosemicarbazones
J05AB	Direct acting antiviral drugs: Nucleosides and nucleotides excl. reverse transcriptase inhibitors
J05AC	Direct acting antiviral drugs: Cyclic amines
J05AD	Direct acting antiviral drugs: Phosphonic acid derivatives
J05AF	Direct acting antiviral drugs: Nucleoside and nucleotide reverse transcriptase inhibitors
J05AH	Direct acting antiviral drugs: Neuraminidase inhibitors
J05AP	Direct acting antiviral drugs: Antivirals for treatment of HCV infections
J05AX	Direct acting antiviral drugs: Other antivirals
Anti-infectives for prophylaxis of opportunistic infections of interest	
	Pneumocystis jirovecii pneumonia (PJP)*
ATC Code	**Description**
J01EE01	sulfamethoxazole and trimethoprim
J04BA02	dapsone
	Varicella zoster virus (VZV)
ATC code	**Description**
J05AB01	aciclovir
J05AB11	valaciclovir
J06BB03	varicella/zoster immunoglobulin
J07BK01	varicella, live attenuated
J07BK02	zoster, live attenuated
J07BK03	zoster, purified antigen
	Cytomegalovirus (CMV)
ATC code	**Description**
J05AB01	aciclovir
J05AB06	ganciclovir
J05AB11	valaciclovir
J05AB14	valganciclovir

J05AX18	letermovir
J06BB09	cytomegalovirus immunoglobulin

*Other anti-infectives sometimes used for prophylaxis of PJP include drugs listed as antiparasitic products, insecticides, and repellents: atovaquone (P01AX06); pentamidine isethionate (P01CX01); primaquine in combination with clindamycin (P01BA03 + J01FF01)

Table 15: Definitions of Approved-use and Off-label use of Bendamustine and other Alkylating drugs similar to Bendamustine (alternative treatments)

Approved-label use	Off-label use
as per bendamustine label 1. iNHL as monotherapy in patients who have progressed during or within six months following treatment with rituximab or a rituximab-containing regimen 2. First-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. 3. Front-line treatment of MM (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib. **as per Arzerra, Imbruvica, MabThera, Gazyvaro labels** 4. **Arzerra (ofatumumab)** in combination with bendamustine is indicated for the treatment of adult patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy. 5. **Imbruvica (ibrutinib)** in combination with bendamustine and rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. 6. **MabThera (rituximab)** in combination with bendamustine is indicated for the treatment of adult patients with previously untreated and relapsed/refractory CLL. **MabThera** is indicated for the treatment of previously untreated adult patients with stage III-IV follicular lymphoma in combination with bendamustine (chemotherapy). 7. **Gazyvaro (obinutuzumab)** in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to six months after treatment with rituximab or a rituximab-containing regimen. **Gazyvaro**, in combination with chemotherapy (bendamustine), followed by Gazyvaro maintenance therapy in patients achieving a response, is also indicated for the treatment of patients with previously untreated advanced FL.	1. For iNHL patients: - Patients not using bendamustine in monotherapy, or using it prior to treatment with rituximab or a rituximab containing regimen, or using bendamustine for the treatment of aggressive lymphoma. - bendamustine use with idelalisib. - **Excluding obinutuzumab** use, in combination with bendamustine in follicular lymphoma patients who did not respond or progressed during or up to six months after treatment with rituximab or rituximab containing treatment. Also **excluding obinutuzumab** use, in combination with chemotherapy (bendamustine), followed by obinutuzumab maintenance therapy in patients achieving a response, for patients with previously untreated advanced FL. - **Excluding rituximab** use, in combination with bendamustine (chemotherapy), for the treatment of previously untreated patients with stage III-IV follicular lymphoma. 2. For CLL patients: - Patients not using bendamustine in monotherapy. - Patients not using bendamustine in first line. - bendamustine use in patients for whom fluradabine combination chemotherapy is appropriate. - bendamustine use with rituximab and/or obinutuzumab and/or idelalisib. - **Excluding ofatumumab** use, in combination with bendamustine in previously untreated adult patients ineligible for fludarabine. - **Excluding ibrutinib** use, in combination with bendamustine and rituximab in adult CLL patients who have received at least one prior therapy. - **Excluding rituximab** use, in combination with bendamustine in adult patients with previously untreated and relapsed/refractory CLL. 3. For MM patients: - not in combination with prednisone - patients ≤ 65 years - patients eligible for autologous stem cell transplant - patients who do not have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib. - use in patients with Durie-salmon stage I or stage II with no progression - bendamustine use with rituximab and/or obinutuzumab and/or idelalisib 4. Bendamustine use for any indications other than iNHL, CLL, or MM.

<u>for other Alkylating drugs similar to bendamustine (alternative treatments)</u> 1. Alternative treatment for iNHL patients: ***cyclophosphamide*** *patient population* - Patients using cyclophosphamide (as part of CHOP) used in combination with Rituximab (R-CHOP) and used for iNHL (FL, MCL). 2. Alternative treatment for CLL patients: ***chlorambucil*** *patient population* - Patients using chlorambucil in combination with obinutuzumab or ofatumumab; previously untreated patients; ≥18 years old; ineligible for fludarabine 3. Alternative treatment for MM patients: ***melphalan*** *patient population* - Patients using melphalan in combination with lenalidomide and prednisone; previously untreated; ≥18 years old; ineligible for transplant - Patients using melphlan in combination with Thalidomide Celgene and prednisone as first line treatment; previously untreated; ≥ 65 years old or ineligible for high dose chemotherapy - Patients using melphalan in combination with Velcade (bortezomib) and prednisone; previously untreated adults who cannot have high-dose chemotherapy with a haematopoietic stem-cell transplant	**<u>for other Alkylating drugs similar to bendamustine (alternative treatments)</u>** 1. Alternative treatment for iNHL patients: ***cyclophosphamide*** *patient population* - Patients using cyclophosphamide for iNHL (FL, MCL) but not as part of R-CHOP 2. Alternative treatment for CLL patients: ***chlorambucil*** *patient population* - Patients using chlorambucil for CLL but either not in combination with obinutuzumab or ofatumumab, or in combination with obinutuzumab or ofatumumab but not according to the approved drug labels 3. Alternative treatment for MM patients: ***melphalan*** *patient population* - Patients using melphalan but not in combination either with lenalidomide and prednisone, or with Thalidomide Celgene and prednisone, or with Velcade (bortezomib) and prednisone, or patients using melphalan in one of these three combinations but not according to the approved drug labels

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Annex 4 Timing of available data per country

Table 16: Availability of data per country

	Availability of data		
	Pre-DHPC dissemination period (24 months: 01 April 2015 - 31 March 2017)	Post-DHPC dissemination period (24 months: 01 September 2017 - 31 August 2019)	
Databases		First post-DHPC dissemination period (12 months: 01 Sept 2017 - 31 Aug 2018)	Second post-DHPC dissemination period (12 months: 01 Sept 2018 - 31 Aug 2019)
French SNDS	Q3 2018	Q3 2019	Q3 2020
Germany SHI	Q4 2018	Q4 2019	Q4 2020
UK CAS /HES	Q2 2019	Q3 2020	Q4 2021
Oncology Dynamics	Q3 2017	Q1 2019	Q4 2019

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15 SIGNATURES

COORDINATING INVESTIGATOR'S SIGNATURE

Project Title: Non-Interventional Post-Authorisation Safety Study (NI-PASS) as an effectiveness check of an additional Risk Minimisation Measure (aRMM) (Direct Healthcare Professional Communication [DHPC]) for Bendamustine

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator (IQVIA):

PPD

ISN 6231-MA-3264

PAS register No: EUPAS34255

PROTOCOL APPROVED BY

Project Title: Non-Interventional Post-Authorisation Safety Study (NI-PASS) as an effectiveness check of an additional Risk Minimisation Measure (aRMM) (Direct Healthcare Professional Communication [DHPC]) for Bendamustine

The following people have reviewed the protocol and given their approval:

Astellas Pharma

PPD