| | |
|---|---|
| **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<br>Clinical Trials.gov identifier: study not registered<br>EU PAS register number: to be confirmed |
| **Protocol version & date of last version of protocol** | Version: 3.0<br>Date: 14 November 2019 |
| **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)** | Astellas Pharma GmbH<br>Ridlerstraße 57<br>80339 München<br>Germany |
| **Joint PASS** | (Select one below)<br>☐ Yes<br>☒ 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.<br><br>Primary Objectives:<br><br>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 four European countries.<br><br>2. Process Indicator- To quantify and characterise 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 four European countries.<br><br>This protocol consists of three related but independent studies to achieve the two Primary Objectives:<br><br>1. STUDY A: Retrospective cohort study of electronic healthcare databases to evaluate safety outcomes (Primary Objective 1)<br><br>2. STUDY B: Cross-sectional study of electronic healthcare databases to evaluate approved- and off-label drug use (Primary Objective 2)<br><br>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, Sweden, England<br><br>STUDY B: France, Germany, Sweden, England<br><br>STUDY C: France, Germany, United Kingdom (UK) |

| | |
|---|---|
| **Number of Sites or Data Sources** | Five data sources in total will be used:<br>STUDY A and STUDY B:<br>• Four electronic healthcare databases (electronic medical records (EMR), claims, registries) will be used<br>i) France (French National Board of Health and Welfare [SNIIRAM] linked with the National Hospital Discharge Database [PMSI])<br>ii) Germany (Statutory Health Insurance Database [SHI])<br>iii) Sweden (National Board of Health and Welfare [NBHW] database and EMRs from selected hospitals)<br>iv) England (Cancer Analysis System [CAS] and Hospital Episode Statistics [HES])<br>STUDY C:<br>• [redacted] an [redacted] proprietary physician-survey based database, will provide data from France, Germany and UK. |
| **Author** | [redacted]<br>France |

ISN 6231-MA-3264
PAS register No: TBC

# Marketing Authorization Holder(s)

| | |
|---|---|
| **Marketing authorization holder(s)** | Astellas Pharma GmbH<br>Ridlerstraße 57<br>80339 München<br>Germany |
| **MAH contact person** | [redacted] |

# 1 TABLE OF CONTENTS

# 2 LIST OF ABBREVIATIONS AND DEFINITIONS OF KEY TERMS

| Abbreviations | Description of abbreviations |
|---|---|
| aRMM | additional Risk Minimisation 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 |
| [redacted] | [redacted] |
| DHPC | Direct Healthcare Professional Communication |
| DRG | diagnosis related groups |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |
| EMR | Electronic Medical Record |
| 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 |
| FDA | Food and Drug Administration |
| FL | follicular lymphoma |

| Abbreviations | Description of abbreviations |
|---|---|
| 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 |
| 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 Authorisation Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MM | multiple myeloma |
| NBHW | National board of Health and Welfare |
| NCRAS | National Cancer Registration and Analysis Service |
| NHS | National Health Service |
| NI-PASS | non-interventional post-authorization safety study |
| NPD | National Prescription Prescribed Drug Register |
| NPR | National Patient Registers |
| [redacted] | [redacted] |
| ODR | Office of Data Release |
| OPCS | Office of Population Censuses and Surveys |

| Abbreviations | Description of abbreviations |
|---|---|
| PAS | post-authorisation study |
| PASS | post-authorisation 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 |
| 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 |

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PAS register No: TBC

# 3 RESPONSIBLE PARTIES

| | |
|---|---|
| [redacted] | |
| Project advisor and Principal Investigator | [redacted] |
| Project Leader | [redacted] |
| Medical writer | [redacted] |

| **Astellas** | |
|---|---|
| Epidemiology Executive Director, Head | [redacted] |
| Associate Medical Director and Product Responsible Person | [redacted] |
| Risk Management Director | [redacted] |
| Regulatory Affairs Director | [redacted] |
| Project Coordinator | [redacted] |

# 4 SYNOPSIS

**Date and Version # of Protocol Synopsis: 14 Nov 2019 Version 3.0**

**Sponsor: Astella Pharma Europe B.V.**

**Protocol Number ISN: 6231-MA-3264**
**EU PAS #: TBC**
**ClinicalTrials.gov identifier: not applicable**

**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.*

**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 minimisation 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 minimisation measure (aRMM) to healthcare professionals in 22 countries in the EU by August 30$^{th}$, 2017.

In line with regulatory guidance (EMA Good Pharmacovigilance Practice [GVP] XVI.B4), the effectiveness of aRRMs 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 dessimination period) to 31 August 2019 (two years after DHPC dessimination 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 four European countries.
2. Process Indicator- To quantify and characterise 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 four European countries.

**Data Sources(s):**

Based on the results of a feasibility study, four electronic healthcare databases (electronic medical records (EMR), claims, registries) from France (French National Board of Health and Welfare [SNIIRAM] linked with the National Hospital Discharge Database [PMSI]), Germany (Statutory Health Insurance Database [SHI]), Sweden (National Board of Health and Welfare [NBHW] database and EMRs from selected hospitals) 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), [redacted] data will be used to conduct a complementary assessment of approved- and off-label drug use for Primary Objective 2. [redacted] 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 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%. 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 [redacted] 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, Sweden, England).

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

To quantify and characterise 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, Sweden, England).

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, [redacted] 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 characterise 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 [redacted] 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 can not 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).

**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 13: Exposure and Outcome Codes and Table 14: 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 14: 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 13: Exposure and Outcome Codes
- Myelosuppression as defined using the diagnosis codes listed in Annex 3:
- Table 13: 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
- Frequency of laboratory testing for CD-4 positive T-cell levels 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.

**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-Authorisation 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.

**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:**

[redacted]

**Independent Variables:**

- [redacted]

**Study C Statistical Methods:**

**Study Size:**

[redacted]

**Study C Data Analysis:**

[redacted]

**Study C Safety:**

[redacted]

**Study C Interim Analyses:**

[redacted]

ISN 6231-MA-3264
PAS register No: TBC

## Study C Dissemination Plan

[redacted]

## 4.1 Flow Chart

Not applicable.

## 4.2 Schedule of Assessments

Not applicable.

# 5 AMENDMENTS AND UPDATES

The table summarises modifications included in version 3.0, based on the BfArM 2nd Draft Final Variation Assessment Report (FVAR), Variation Number DE/H/1250/001/II/034, dated 07 November 2019.

| Number | Date | Section numbers of the protocol | Reason |
|---|---|---|---|
| 1. Updates to content of Table 15 (ATC codes) | 14 Nov 2019 | Annex 3<br>Table 15 | To address recommendations included in BfArM's 2nd Draft FVAR, dated 07 November 2019. |

# 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).

| **Milestone** | **Planned Periods** |
|---|---|
| Registration in the EU PAS register | Q2 2020 |
| First data extraction (Germany, France, UK) | Q2 2020 |
| Interim study report | Q4 2020 |
| Second data extraction (all countries and [redacted] | Q3 2021 |
| Final report of study results | Q4 2022 |

# 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 minimisation 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 minimisation 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 minimisation 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 four European countries.
2. Process Indicator- To quantify and characterise 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 four 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, Sweden, England).

### 9.1.1 STUDY A: Data Sources

Electronic healthcare databases (electronic medical records (EMR), claims, registries) from France (French National Board of Health and Welfare [SNIIRAM] linked with the National

Hospital Discharge Database [PMSI]), Germany (Statutory Health Insurance Database [SHI]), Sweden (National Board of Health and Welfare [NBHW] database and EMRs from selected hospitals) 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 utilisation 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 National Health Insurance database (SNIIRAM)[1] linked with the National hospital discharge database (PMSI)

The SNIIRAM database contains individualised, 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 SNIIRAM 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 SNIIRAM database 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 hospitalisation dates and diagnoses coded according to ICD-10.

The French SDNS 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 (SNIIRAM). Both obinutuzumab and rituximab are available in the database. Idelalisib is not available in France. 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<br>● indirectly and/or partially observable<br>● 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 hospitalisation (inpatient) and unobservable in the SNIIRAM<br>• CD20 antigen results not available |
| **CLL indication** | | |
| Data to define approved label definition of bendamustine | ● | • Binet stage and ofatumumab not collected<br>• 1st line identification observable by proxy<br>• 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<br>• 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<br>• Melphalan observable only in community pharmacies (outpatient) |
| **Common to the three indications** | | |
| Data to evaluate the off-label measurement | ● | • Idelalisib not collected but withdrawn from the French market in 2014<br>• Drugs taken during hospitalisations 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)<br>• Outcomes available if hospitalization and when can be specified in ICD-10 codes; not available in outpatient care<br>• 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 anonymised medical claims data for patients covered by SHI. The full SHI database includes 5 million insured patients (ie 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, hospitalisation 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 utilisation (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 utilisation 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 hospitalisations, and medical department.

**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<br>● 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<br>• 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<br>• 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<br>• 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<br>• 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.<br>• 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: Sweden: National board of Health and Welfare (NBHW) databases[3] and EMR data

The total Population Register in Sweden includes all individuals living in the country with individual-level information on the date of birth, country of birth, place of residence, dates of any emigration and immigration, and date of death.

All prescribed and dispensed drugs to the individual patient may be tracked in the National Prescribed Drug Register (NPDR) covering all pharmacy transactions back until the year 2005. There are details on gender, age and residency of the patients included in the register. Drug-specific data can be captured on dispensed prescription drugs (ATC code, INN etc.), prescription date, pack size, health care practitioner issuing the prescription and costs associated with the drug prescription.

Data from in- and out-patient care in all hospitals in Sweden can be collected from the National Patient Registers (NPR). In Sweden, the Patient Registry dates back to 1964, and from 1987 there is information on all completed in-patient admissions in publicly operated hospitals. The collection of out-patient care data began in 1997. The key variables available are diagnosis (coded to ICD-10), medical and surgical procedure (procedure codes), external causes of injury (E-codes), sex, gender, age, residence, hospital, specialty, and information related to hospital admissions and discharges (dates, diagnoses, mode of discharge, etc.). The Registry is updated annually.

Cause of Death Registry (CDR) includes statistics on causes of death, comprises all deaths covering all residents in the country, whether the person in question was a Swedish citizen or not and irrespective of whether the deaths occurred in Sweden or not. The quality of the cause of death statistics varies, due to the examinations made to define the underlying cause of death or the changes in the classification system or the processing methods. The main variables included in the register are: Personal Identity Number (PIN, This is given at birth and to individuals resident in Sweden. This number is used each time a person receives care from any health care provider in Sweden, home district, sex, date of death, underlying cause of death, nature of the injury, multiple causes of death, marked if autopsied or not, and if so what kind, marked if operated within four weeks before death, marked if injury/poisoning, marked if alcohol-related, marked if narcotic related, and code for diabetes.

With the unique EMR-software [redacted] (the vendor) can identify, extract and analyse large amounts of additional complementary longitudinal EMR data from primary or secondary care in Sweden, which can be combined with data from the above-mentioned registries. With this, a cohort of patients based on their real-time medical records and clinical characteristics directly collected from the

EMR, which are generally not available in the health registers (e.g. weight, height, BMI, smoking, lab test values, etc.) at selected primary care centers and/or hospital clinics, can be generated. Patients identified in the EMRs will then be linked to the national healthcare registers described above, for follow-up and to capture additional variables (hospitalisations, concomitant drugs, hospital diagnoses, and death). By enriching the data with information from EMRs, it is possible to obtain more detailed data on e.g. potential confounders and outcomes of interest for a sample of the study population. It is then possible to assess this sample against the entire study population with regards to age and sex distribution etc.

The number of hospitals that can be recruited into the study will depend on the scientific interest of local key opinion leads for each indication to participate as well as the willingness of hospital administrations to share data. In this study, the EMR data from Sweden will be sought from between three and five hospitals, depending on sample size and other factors. These hospitals are selected from a sample of 10 hospitals with a large volume of cancer patients, covering approximately 65% iNHL, 32% CLL, and 34% MM of the nationally reported cases in the given time periods of the study.

In Sweden, all variables needed for both the cohort and cross-sectional studies are available. Outcome data are available within hospital EMRs, and diagnoses and all heath care consumption, death and cause of death are also available. However, precise staging and drugs administered in the hospital are only accessible through hospital EMRs.

**Table 3: Summary of data in Swedish NBHW Registries**

| Sweden National registries and EMR database | Data Availability | Limitations |
|---|---|---|
| ● directly and fully available | | |
| **iNHL indication** | | |
| Data to define approved label definition of bendamustine | ● | • All data available in EMR (incl. Case notes)<br>• Follicular lymphoma diagnosis also in Cancer Registry |
| Data to define approved label definition of alkylating drugs similar to bendamustine (cyclophosphamide) | ● | • Most data available in EMR<br>• Prednisone variables available in Rx Registry |
| **CLL indication** | | |
| Data to define approved label definition of bendamustine | ● | • Data available in EMR (incl. Case notes)<br>• Binet stage also in CLL Quality Registry |
| Data to define approved label definition of alkylating drugs similar to bendamustine (chlorambucil) | ● | • Data available in EMR<br>• Chlorambucil variables also in Rx Registry |
| **MM indication** | | |
| Data to define approved label definition of bendamustine | ● | • Most data available in EMR (incl. Case notes)<br>• MM diagnosis also available in Cancer Registry<br>• Prednisone and thalidomide variables available in Rx Registry<br>• Durie-Salmon stage not used in Sweden (ISS instead) |
| Data to define approved label definition of alkylating drugs similar to bendamustine (melphalan) | ● | • Most data available in EMR and Rx Registry |
| **Common to the three indications** | | |
| Data to evaluate the off-label measurement | ● | • Data available in EMR |
| Data to evaluate the clinical outcomes | ● | • Most data in EMR and NPR<br>• Death variables available in CDR |

#### 9.1.1.4 STUDY A: England: Cancer Analysis System (CAS) and Hospital Episode Statistics (HES)[5]

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), tumour 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, [redacted], 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 hospitalisation.

**Table 4: 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<br>● 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<br>• 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<br>• Number of patients expected to be <200/year<br>• 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<br>• Prednisone use needs to be assumed<br>• 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<br>• 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 13: Exposure and Outcome Codes and Table 14: 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 13: Exposure and Outcome Codes and Table 14: 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 14: 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 13: Exposure and Outcome Codes
- Myelosuppression as defined using the diagnosis codes listed in Annex 3:
- Table 13: 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. 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. The results may also be stratified by disease indication (iNHL, CLL, MM). 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 15: 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 15: ATC codes for Anti-infective Drugs and Substances
- Frequency of laboratory testing for CD-4 positive T-cell levels in outpatient settings using specific laboratory test codes

### 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 dessimination period) to 31 August 2019 (two years after DHPC dessimination 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

ISN 6231-MA-3264
PAS register No: TBC

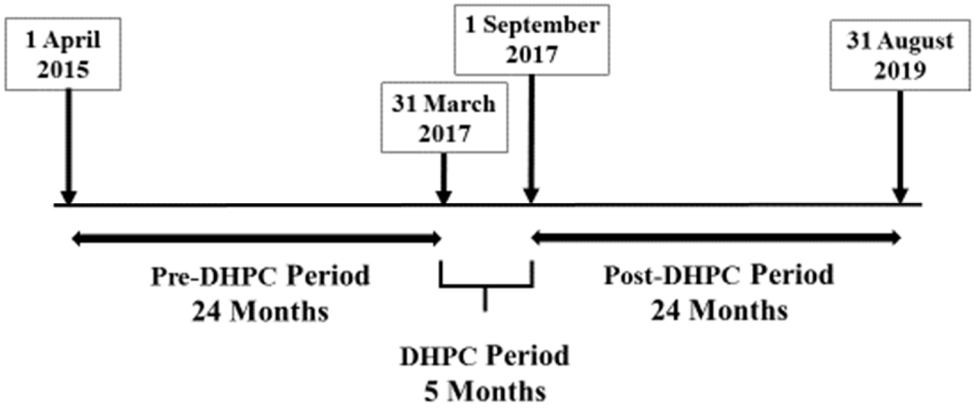


**Figure 1. Study Period** (not to scale)

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, Sweden, England).

### 9.1.4 STUDY A: Study Population

This study will be conducted using retrospective analysis of existing electronic healthcare databases from France, Germany, Sweden, 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 13: 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 13: 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).

ISN 6231-MA-3264
PAS register No: TBC

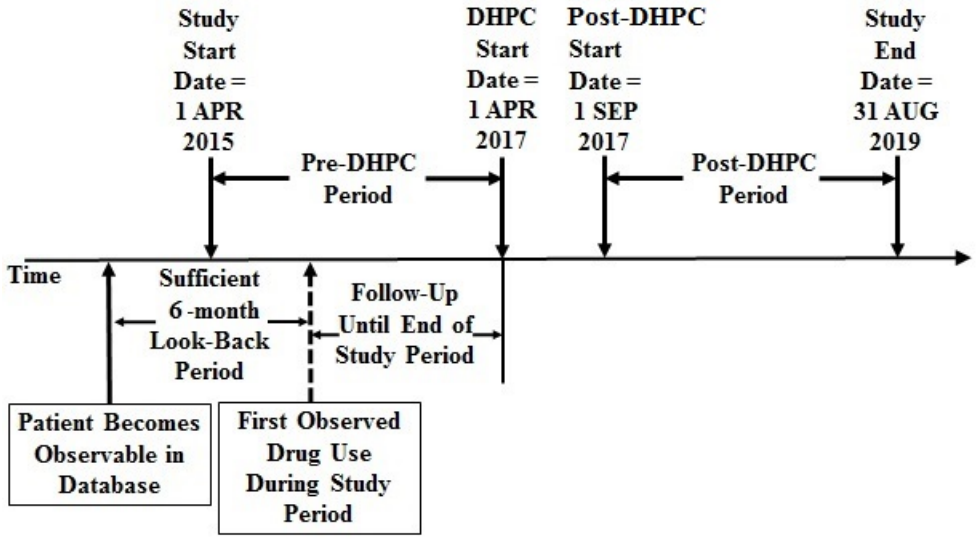


**Figure 2. Example of a sufficient six-month look-back period and follow-up of new user** (not to scale). The patient becomes observable six months prior to the new drug use and has no previous study drug use. The patient is included in the cohort and follow-up continues until the end of the pre-DHPC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

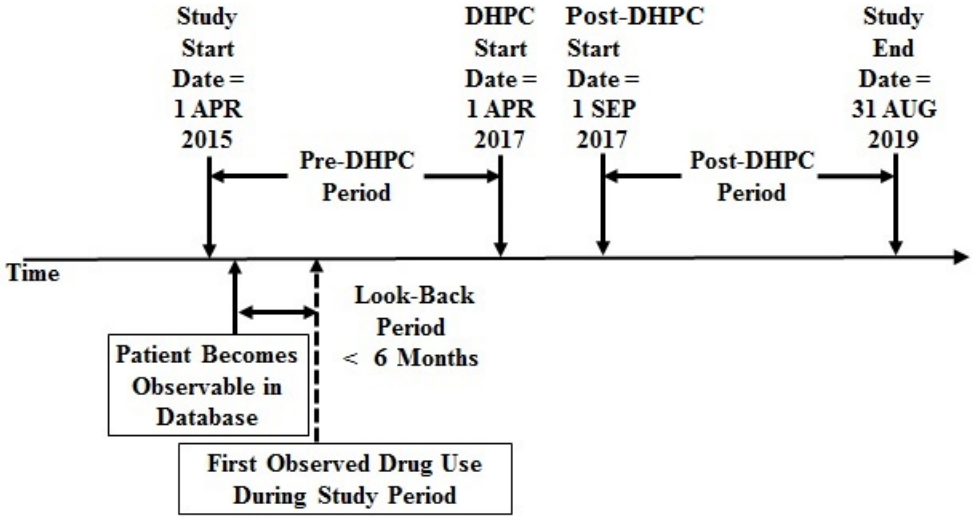


**Figure 3. Example of an insufficient look-back period** (not to scale). The patient becomes observable in the database less than six months prior to the new study drug use. The patient is excluded from the pre-DHPC dissemination cohort.

ISN 6231-MA-3264
PAS register No: TBC

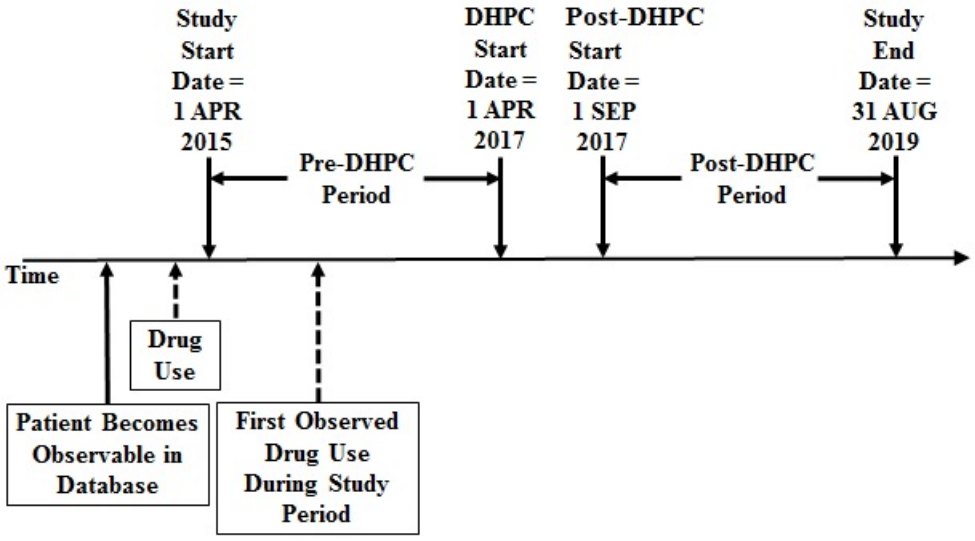


**Figure 4. Example of patient exclusion due to prior drug use** (not to scale). The patient used the study drug prior to the study start date but within six months of observed new use during the study period. The patient is not considered to be a new user and is excluded from the pre-DHPC dissemination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

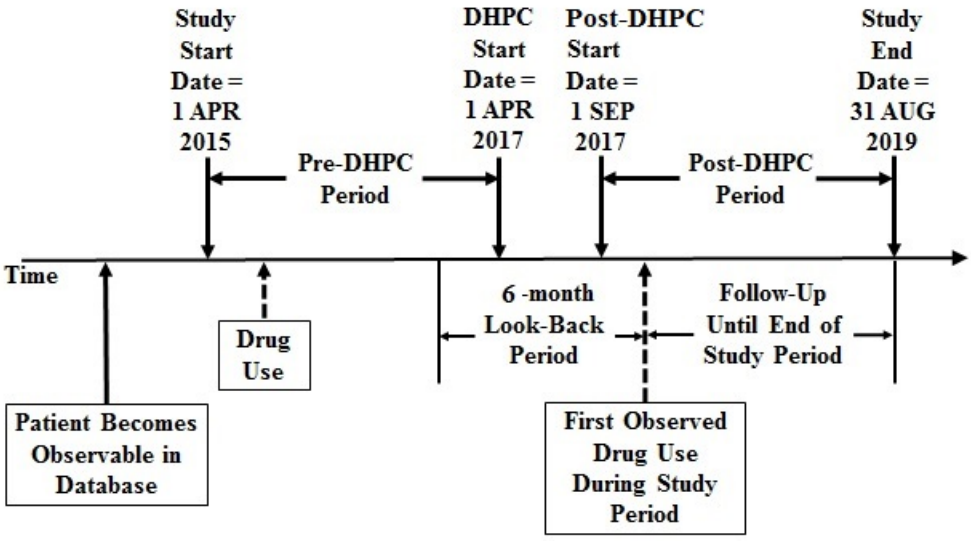


**Figure 5. Example of drug use more than six months prior to first observed use during study period** (not to scale). The patient has prior drug use but it is more than six month prior to the new use during the post-DHPC dissemination period. The patient is considered to be a

new user. The patient is included in the cohort and follow-up continues until the end of the post-DHPC dissemination period.

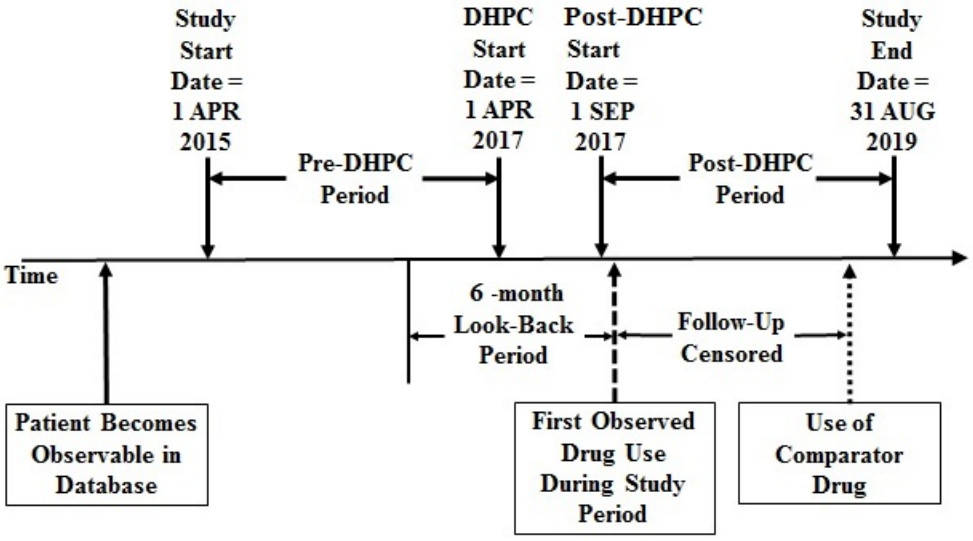


**Figure 6. Example of censoring due to use of a different drug** (not to scale). The new user is not a user of the drug in the prior six months. The new user is included in the post-DHPC dissemination cohort. During follow-up, the patient uses a different drug (i.e. bendamustine if present in the cohort 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 16). 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 historical 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 EMRs, claims or registries) at time of first drug use
- 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[6] and are shown in Table 5 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 5: Number of patients identified in each data source from the feasibility study**

| | Germany SHI (2016) | France PMSI (2016) | Sweden NBHW registries* | England CAS and HES (2015) |
|---|---|---|---|---|
| Bendamustine | 606 | 4163 | _ | 1489 |
| Rituximab | 2592 | 25170 | _ | 3931 |
| Obinutuzumab | 59 | 169 | _ | 26 (4) |
| Idelalisib | 53 | 0### | _ | 50 |
| Chlorambucil | 152 | # | _ | 490 |
| Cyclophosphamide | 2198 | 0 | _ | 2401 |
| Melphalan | 108 | # | _ | 790 |
| | | | | |
| NHL (C85.9) | 9007 | 4883 | 250(2) | 682 |
| NHL + Bendamustine | 326 | 326 | _ | 12 (24 in CAS) |
| NHL + Rituximab | 1209 | 1449 | _ | 36 |
| NHL + Obinutuzumab | 18 | 10 | _ | 0 (4) |
| NHL + Idelalisib | 24 | 0 | _ | 0 |
| Follicular lymphoma (C82.9) | 1147 | 2077 | _ | 252 |
| | | | | |
| CLL (C91.1) | 5204 | 11362 | 4599(1) | 3344 |
| CLL + Bendamustine | 237 | 842 | _ | 28 (147 in CAS) |
| CLL + Chlorambucil | 126 | # | _ | 3 |
| CLL + Chlorambucil + Obinutuzumab | 35 | # | _ | 0 (4) |
| CLL + Rituximab | 380 | 2201 | _ | 54 |
| CLL+ Obinutuzumab | 46 | 120 | _ | 0 (4) |
| CLL + Idelalisib | 39 | 0### | _ | 10 |
| | | | | |
| Multiple Myeloma (C90) | 2353[T] | 16487 | 3519 (1) | 4431 |
| MM + Bendamustine + Prednisone | 6 | 537## | _ | (3) |
| MM + Melphalan | 2 | # | _ | 166 |
| MM + Rituximab | 33 | 162 | _ | 13 |
| MM + Obinutuzumab | 1 | 0 | _ | 0 (4) |
| MM + Idelalisib | 0 | 0### | _ | 0 |
| | [T] Patients with age > 65 years | -# available in outpatient part<br>-# # MM+ bendamustine (prednisone is available in outpatient part)<br>-# # # not available | *data from literature and cancer registries<br>(1) Persons living with the diagnosis at the end of 2015 (prevalence), (2) year incident cases | (4) Obinutuzumab was approved for CLL use (with chlorambucil or bendamustine) in the UK in March 2015. Obinutuzumab was not approved for NHL or MM until 2017. |

As identified in the Bendamustine-Astellas-Feasibility report[6] 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 and for the other concomitant medicines of interest idelalisib is also not available (not commercialised in France). 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.
- Apart from potentially the Swedish NBHW registries (if hospital recruitment is confirmed), 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 except Sweden (if hospital recruitment is confirmed).
- 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. [redacted] staff of each country will be in charge of the statistical analysis in the [redacted] 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 utilised 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)[7] 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). [redacted] 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 [redacted], 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 (SNIIRAM), 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. [redacted] 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 [redacted] processes. The process would take in to consideration any data governance imposed on the data source including any plans to handle the data outside of the institution or country of origin. [redacted] will adhere to all local and regional laws on data protection and privacy. Specifically, all patient counts ≤ 5 cannot be displayed and instead will simply be reported as "≤ 5".

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

For Sweden (NBHW, and EMR from between three and five hospitals, depending on sample size and other factors), the linked data are stored in a secure room at [redacted] in accordance to the terms of the agreement. EMR data are extracted in two files: a Key file and an Analysis file. The Key file (with patient identifier) is handled and stored by the Principal Investigator. The Analysis file (with pseudonymised data and without patient identifier) is stored by a third-party called [redacted]. The linkage of EMR data and NBHW data is performed by the NBHW. EMR data are extracted with [redacted]

### 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 6 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 6. Results will be stratified by drug (bendamustine and alkylating drugs similar to bendamustine), study period (pre- and post-DHPC dissemination), and country (section 9.1.9.2 STUDY A: Statistical Analysis). The sample size estimates in Table 6 apply to each of these 16 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[8].

The required number of persons-years of bendamustine use to achieve a statistical precision for the the safety event incidence rate of at least 5% is 323, considering the incidence of safety events is expected to range from 1 to 30 per 100 persons-years (see Table 6). These estimates are calculated for each of the 16 strata (bendamustine and alternative treatment, study period pre- and post-DHPC dissemination, and country). The precision will increase the larger sample size.

**Table 6: 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 [redacted] 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 organisation. 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 finalised 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[7] and the ICH guidelines for statistical analyses. A report summarising 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. Table 7 shows a mock table shell as an example of result reporting.

**Table 7: 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 | CLL, MM | Bendamustine | Pre- | X.X [X.X-X.X] | X.X [X.X-X.X] |
| France | 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 | All | Bendamustine | Pre- | X.X [X.X-X.X] | X.X [X.X-X.X] |

| | | | | | |
|---|---|---|---|---|---|
| Germany | All | Bendamustine | Post- | X.X [X.X-X.X] | X.X [X.X-X.X] |
| Germany | All | All alkylating drugs similar to bendamustine | Pre- | X.X [X.X-X.X] | X.X [X.X-X.X] |
| Germany | All | All alkylating drugs similar to bendamustine | Post- | X.X [X.X-X.X] | X.X [X.X-X.X] |
| Sweden | All | Bendamustine | Pre- | X.X [X.X-X.X] | X.X [X.X-X.X] |
| Sweden | All | Bendamustine | Post- | X.X [X.X-X.X] | X.X [X.X-X.X] |
| Sweden | All | All alkylating drugs similar to bendamustine | Pre- | X.X [X.X-X.X] | X.X [X.X-X.X] |
| Sweden | All | All alkylating drugs similar to bendamustine | Post- | X.X [X.X-X.X] | X.X [X.X-X.X] |
| England | All | Bendamustine | Pre- | X.X [X.X-X.X] | X.X [X.X-X.X] |
| England | All | Bendamustine | Post- | X.X [X.X-X.X] | X.X [X.X-X.X] |
| England | All | All alkylating drugs similar to bendamustine | Pre- | X.X [X.X-X.X] | X.X [X.X-X.X] |
| England | All | 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. Incidence rates may also be stratified by disease indication (iNHL, CLL, MM) assuming sample size is adequate.

Additional secondary analyses will assess the change in frequency of physician behaviors in the outpatient setting, namely, the use of anti-infective drugs, the use of anti-infective drugs used for prophylaxis of opportunistic infections, and the frequency of laboratory testing for CD-4 positive T-cell levels. 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 and T-cell level tests ordered 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 utilisation studies, including but not limited to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology[7], the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP)[9] as well as the specific [redacted] SOPs. All study programs, log files, and output files will be stored on the [redacted] 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 [redacted] 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 [redacted] 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 anonymised and will not contain any personal identifying data.

Procedures will be consistent with the ISPE GPP[9].

### 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 utilisation, 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 (ie 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.

### 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, Sweden, England).

### 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 13: Exposure and Outcome Codes and Table 14: 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. The secondary outcome of concurrent off-label use of bendamustine with rituximab, obinutuzumab, and idelalisib will also be assessed. In secondary analyses, results will be stratified by disease indication (iNHL, CLL, MM). 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 characterise 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, Sweden, 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 13: 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[6] and are reported in section 9.1.7 STUDY A: Study Size.

### 9.2.8 STUDY B: Data Management

Data Managemnent 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 8 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%.

Such a hypothesis yields the most conservative sample size estimate i.e. the largest sample size. The required sample size would be 385 bendamustine users for a precision of 5% for each of the 16 strata (bendamustine versus alternative treatment, study period pre- versus post-DHPC dissemination, and country). The sample size estimates are presented in Table 8.

**Table 8: 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 [redacted] SOPs, ENCePP[7] 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 9 shows a mock table shell as an example of reporting of results for the pre- and post-DHPC dissemination periods.

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**Table 9: 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 | CLL, MM | Bendamustine | Pre- | XX% [XX-XX%] | XX% [XX-XX%] |
| France | 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 | All | Bendamustine | Pre- | XX% [XX-XX%] | XX% [XX-XX%] |
| Germany | All | Bendamustine | Post- | XX% [XX-XX%] | XX% [XX-XX%] |
| Germany | All | All alkylating drugs similar to bendamustine | Pre- | XX% [XX-XX%] | XX% [XX-XX%] |
| Germany | All | All alkylating drugs similar to bendamustine | Post- | XX% [XX-XX%] | XX% [XX-XX%] |
| Sweden | All | Bendamustine | Pre- | XX% [XX-XX%] | XX% [XX-XX%] |
| Sweden | All | Bendamustine | Post- | XX% [XX-XX%] | XX% [XX-XX%] |

| | | | | | |
|---|---|---|---|---|---|
| Sweden | All | All alkylating drugs similar to bendamustine | Pre- | XX% [XX-XX%] | XX% [XX-XX%] |
| Sweden | All | All alkylating drugs similar to bendamustine | Post- | XX% [XX-XX%] | XX% [XX-XX%] |
| England | All | Bendamustine | Pre- | XX% [XX-XX%] | XX% [XX-XX%] |
| England | All | Bendamustine | Post- | XX% [XX-XX%] | XX% [XX-XX%] |
| England | All | All alkylating drugs similar to bendamustine | Pre- | XX% [XX-XX%] | XX% [XX-XX%] |
| England | All | 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.

In secondary analyses, the main study results will be stratified by 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 characterise 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 ([redacted] 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 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, [redacted] data will be used to conduct a complementary assessment of approved- and off-label drug use for Primary Objective 2. [redacted] proprietary physician survey-based database and data will be used from France, Germany, and UK.

#### 9.3.1.1 STUDY C: [redacted] (France, Germany, UK)

[redacted] 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 [redacted] database is designed to be representative across all specialties involved in the pharmacological treatment and management of cancer. Data are collected in the [redacted] database on a quarterly basis and they are projected to the country-specific estimated cancer treated prevalence.

The variables collected in the [redacted] 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 [redacted]. However, no clinical outcomes are available in the [redacted] database. Table 10 summarizes the data available in the [redacted] database.

**Table 10: Summary of data in [redacted] database**

| [redacted] database | Data Availability | Limitations |
|---|---|---|
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | | |

[redacted]

### 9.3.2 STUDY C: Endpoints

[redacted]

### 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 characterise 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
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.

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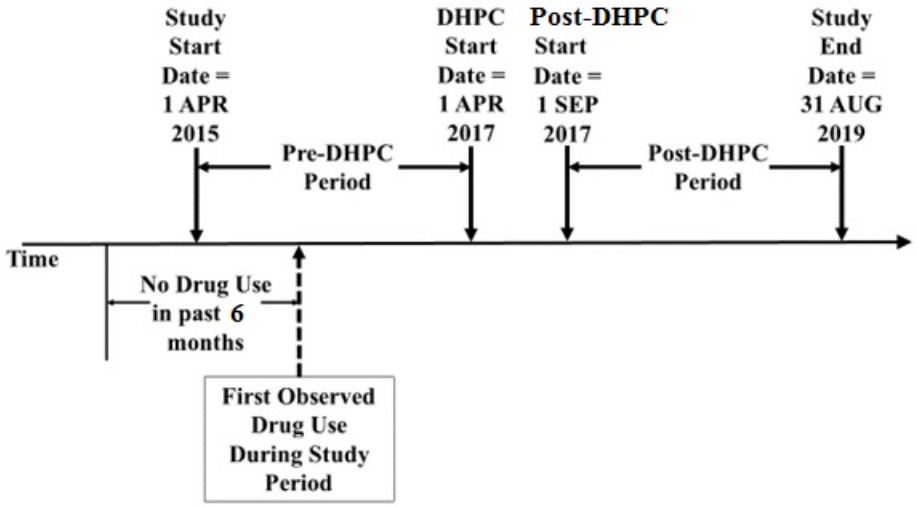


**Figure 7. Example of a new user** (not to scale). The patient has no study drug use in the six months before the first observed use during the study period. The patient is included in the study for the pre-DHPC dissemination period.

### 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 13: 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: [redacted]

### 9.3.6.3 STUDY C: Other Exploratory Variables

[redacted]

### 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[6] and shown for [redacted] in Table 11 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 11: Number of patients available in [redacted] in pre- and post-DHPC dissemination periods**

| [redacted] | 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

[redacted]

### 9.3.9 STUDY C: Statistical Methods

#### 9.3.9.1 STUDY C: Sample Size Justification

[redacted]

#### 9.3.9.2 STUDY C: Statistical Analysis

The overall approach to data analysis (adherence to [redacted] SOPs, ENCePP[7] 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. Table 12 shows a mock table shell as an example of the reporting of results for the pre- and post-DHPC dissemination periods.

**Table 12: 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 | CLL, MM | Bendamustine | Pre- | XX% [XX-XX%] |
| France | 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 | All | Bendamustine | Pre- | XX% [XX-XX%] |
| Germany | All | Bendamustine | Post- | XX% [XX-XX%] |
| Germany | All | All alkylating drugs similar to bendamustine | Pre- | XX% [XX-XX%] |
| Germany | All | All alkylating drugs similar to bendamustine | Post- | XX% [XX-XX%] |
| Sweden | All | Bendamustine | Pre- | XX% [XX-XX%] |
| Sweden | All | Bendamustine | Post- | XX% [XX-XX%] |
| Sweden | All | All alkylating drugs similar to bendamustine | Pre- | XX% [XX-XX%] |
| Sweden | All | All alkylating drugs similar to bendamustine | Post- | XX% [XX-XX%] |
| England | All | Bendamustine | Pre- | XX% [XX-XX%] |
| England | All | Bendamustine | Post- | XX% [XX-XX%] |
| England | All | All alkylating drugs similar to bendamustine | Pre- | XX% [XX-XX%] |
| England | All | 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.

In secondary analyses, the main study results will be stratified by disease indication (iNHL, CLL, MM).

### 9.3.10 STUDY C: Quality Control

Collected data are validated, processed, and thoroughly checked by qualified [redacted] 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 [redacted].

### 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 [redacted] for France, Germany and UK.

**France (SNIIRAM):**

[redacted] will seek approval from the SNIIRAM Independent Scientific Advisory Committee. This will require that [redacted] 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):**

[redacted] will seek approval from Statutory Health Insurance funds Independent Scientific Advisory Committees. Historically, the approval process takes four weeks and may involve revisions of the submitted documents.

**Sweden: (NBHW):**

Approval for use of the data from Swedish national health care registers will be requested by [redacted] from the Regional Ethical Review Boards (EPN) and from the National Board of Health and Welfare and from Statistics Sweden. The study will need one approval for the NBHW, one ethics approval, and one approval from Statistic Sweden for the entire study irrespective of the

number of sites included. All applications have to be submitted in Swedish. Only aggregated data will be provided, in accordance with the Swedish law.

**England (CAS/HES):**

[redacted] will seek approval from the Public Health England Office of Data Release (ODR). This will require completion of an ODR submission form. Historically, the approval process takes 12 weeks and may involve revisions of the submitted documents to address concerns expressed by ODR members.

## 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 Minimisation Measures: Selection of Tools and Effectiveness Indicators[11], ISPE GPP[9], Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA)[12], Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[12], International Ethical Guidelines for Epidemiological Research issued by the Council for International Organisations of Medical Sciences (CIOMS)[14], EMA, ENCePP Guide on Methodological Standards in Pharmacoepidemiology[7] and FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment[15].

## 10.3 Patient Information and Consent

As this study will be conducted through secondary databases of anonymised 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.[17] 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 summarised in the final study report."[16]

## 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 analysed.

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 hospitalisation or leads to prolongation of hospitalisation (hospitalisation 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 jeopardise 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-Authorisation 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[18] guidelines, and communication in appropriate scientific venues, e.g. ISPE conferences, will be considered.

The appropriate STROBE checklist[19] will be followed for study reporting.

# 13 REFERENCES

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ISN 6231-MA-3264
PAS register No: TBC

# 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.

| **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:

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| **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:

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| **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:

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| **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:

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| **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:

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| **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:

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| **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:

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| **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:

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| **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:

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| |

| **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:

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| **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:

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| |

| **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:

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| |

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

Comments:

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|---|
| |

| **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:

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Name of the main author of the protocol: _____

Date:

Signature: _____

# Annex 3 Variable Definitions

## Table 13: Exposure and Outcome Codes

| Variable | Definition and coding |
|---|---|
| Demographics | Year of birth: Age will be analysed as categorical variable<br>Male or female: Gender will be analysed as categorical variable |
| Location | Country |
| *Indication* | |
| • Indolent non-Hodgkin's lymphoma | Follicular lymphoma: ICD-10 C82.0-C82.3, C82.5-C82.9<br>Marginal zone lymphoma ICD-10: C83.0, C88.4<br>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<br>Lamivudine: ATC: J05AF05<br>Adefovir dipivoxil: ATC: J05AF08<br>entecavir hydrate :ATC: J05AF10<br>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<br>K72.90, K72.91, B15.0, B19.0, K70.41, B19.11, B17.11, K72.11, K72.01, K72.11<br>K76.7<br>K72.10 K71.6, K71.2<br>K71<br>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 | ATC: H02AB07 |

| | |
|---|---|
| • fludarabine | ATC: L01BB05 |
| • ofatumumab | ATC: L01XC10 |
| • thalidomide | ATC: L04AX02 |
| • bortezomib | ATC: L01XX32 |
| • lenalidomide | ATC: L04AX04 |
| • ibrutinib | ATC: L01XE27 |
| • Other chemotherapy | ATC: L01 |

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 14: ICD-10 codes for Serious Infections*

| Variable | Definition and coding |
|---|---|
| Meningitis | A02.21,A39.0, A87.2, A51.41, A52.13, A54.81, G04-G05, G00-01-03, A39.81, A52.14, B00.4, A83.0, A84.0, A85.2, A92.3 |
| Cellulitis | A48.0, K94.02, K94.12, I96, M72.6, H00.1, L03.1-L03.3, L03.8, L03.9, K12.2, |
| Endocarditis | A39.51, A32.82, A52.03, M32.11, A54.83, A54.84, I09.89, I01.1, B37.6, I39, I33.9, I40.0,A02.22, A39.51, M05.31, A18.84, A01.02, I09.1 |
| Pneumonia | A01.03, A03.2, 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, A02.22 |
| *Pneumocystis jirovecii* pneumonia | B59 |
| Pyelonephritis/urinary tract infection | N10, N39.0 |
| Septic arthritis | M00-M02, A02.23, B06.82, A 54.42 |
| Osteomyelitis | A02.24, M86, M27.2, H05.029 |
| Bacteremia/septicemia | A40-A41, R78.81, A49.9, B96.89, R65.20, R65.21 |
| Upper respiratory tract infection | H68, H66.0, H70, J00-J06, J09-J18, J20-22, J47.0, J65 |
| Abdominal Abscess | K35.2x, K61, K63.0, K65.1, K67, K68.1, N15.1, N41.2, N43.1, N73.2, N30.90, L02.211 |
| Brain Abscess | G06 |
| Cholecystitis | K83.0, K81.0, K80.0, K80.1, K80.4 |
| Prostate infections | N41 |
| Gastroenteritis | A00-A09, K52, A08.4, A08.8, A09 |
| Infectious conjunctivitis | H10,B30.9,A74.0 |
| Device associated infections | T80.2xx, T82.6, T82.7, T83.5x, T83.6x, T84.5x, T84.6x, T84.7x, T85.7 |
| Local infection of skin and subcutaneous tissue | L00-L08 |
| Gangrene | I96 |

| | |
|---|---|
| Retropharyngeal abscess | J39.0, J39.1 |
| Breast abscess | N61.0, N61.1 |
| Splenic abscess | D73.3 |
| Pyogenic granuloma | L98.0 |
| Post-traumatic wound infection | T79.8, T79.9 |
| Post-operative wound infection | T81.4x |
| Infective myositis | M60.00– M60.09 |
| Necrotising fasciitis | M72.6 |
| Cytomegalovirus | B25.xx |
| Varicella zoster virus | B01.xx, B02.xx |
| Adenovirus | B97.0, B34.0, A08.2, A85.1, A87.1, B30.0, B30.1 |
| Herpes simplex virus | B00.xx |
| Hepatitis B | B16.xx, B17.0, B18.0, B18.1 |
| Hepatitis C | B17.1, B18.2 |
| Other viral hepatitis | B15.xx, B17.2, B17.8, B17.9, B18.8, B18.9, B19.xx, K77 |
| Tuberculosis | A15.xx – A19.xx |
| Toxoplasmosis | B58.xx |
| Non-tuberculous mycobacteria | A31.xx |
| Nocardiosis | A43.xx |
| Actinomycoses | A42.xx |
| Candidiasis | B37.xx |
| Coccidioidomycosis | B38.xx |
| Histoplasmosis | B39.xx |
| Blastomycosis | B40.xx |
| Aspergillosis | B44.xx |
| Cryptococcosis | B45.xx |

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|---|---|
| Other mycoses | B35.xx, B36.xx, B41.xx, B42.xx, B43.xx, B46xx, B47.xx, B48.0 - B48.4, B48.8, B49 |
| Opportunistic mycoses | B48.7 |
| Bacterial infection in conditions classified elsewhere | B96.xx |
| Sepsis | A40.xx, A41.xx, R65, R65.1 |
| Bacterial pneumonia | J13, J14, J15.xx, J16.0, J17.0 |
| Pseudomonas infection | B96.5 |
| Staphylococcal infection | A49.0, B95.6 - B95.8 |
| 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 15: 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 16: 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**<br>1. iNHL as monotherapy in patients who have progressed during or within six months following treatment with Rituximab or a Rituximab-containing regimen<br>2. First-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.<br>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.<br>**as per Arzerra, Imbruvica, MabThera, Gazyvaro labels**<br>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.<br>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.<br>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 patients with stage III-IV follicular lymphoma in combination with bendamustine (chemotherapy).<br>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:<br>- 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.<br>- Bendamustine use with Idelalisib.<br>- **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.<br>- **Excluding Rituximab** use, in combination with bendamustine (chemotherapy), for the treatment of previously untreated patients with stage III-IV follicular lymphoma.<br>2. For CLL patients:<br>- Patients not using bendamustine in monotherapy.<br>- Patients not using bendamustine in first line.<br>- Bendamustine use in patients for whom fluradabine combination chemotherapy is appropriate.<br>- Bendamustine use with Rituximab and/or Obinutuzumab and/or Idelalisib<br>- **Excluding Ofatumumab** use, in combination with bendamustine in previously untreated adult patients ineligible for fludarabine<br>- **Excluding Ibrutinib** use, in combination with bendamustine and rituximab in adult CLL patients who have received at least one prior therapy.<br>- **Excluding Rituximab** use, in combination with bendamustine in adult patients with previously untreated and relapsed/refractory CLL.<br>3. For MM patients:<br>- not in combination with prednisone<br>- patients ≤ 65 years<br>- patients eligible for autologous stem cell transplant<br>- patients who do not have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib.<br>- Use in patients with Durie-salmon stage I or stage II with no progression<br>- Bendamustine use with Rituximab and/or Obinutuzumab and/or Idelalisib<br>4. Bendamustine use for any indications other than iNHL, CLL, or MM. |

| | |
|---|---|
| **<u>for other Alkylating drugs similar to bendamustine (alternative treatments)</u>**<br>1. Alternative treatment for iNHL patients: ***Cyclophosphamide*** *patient population*<br>- Patients using cyclophosphamide (as part of CHOP) used in combination with Rituximab (R-CHOP) and used for iNHL (FL, MCL).<br>2. Alternative treatment for CLL patients: ***Chlorambucil*** *patient population*<br>- Patients using chlorambucil in combination with Obinutuzumab or Ofatumumab; previously untreated patients; ≥18 years old; ineligible for fludarabine<br>3. Alternative treatment for MM patients: ***Melphalan*** *patient population*<br>- Patients using Melphalan in combination with Lenalidomide and Prednisone; previously untreated; ≥18 years old; ineligible for transplant | **<u>for other Alkylating drugs similar to bendamustine (alternative treatments)</u>**<br>1. Alternative treatment for iNHL patients: ***Cyclophosphamide*** *patient population*<br>- Patients not using cyclophosphamide (as part of R-CHOP) or used for any iNHL type other than iNHL (FL, MCL)<br>2. Alternative treatment for CLL patients: ***Chlorambucil*** *patient population*<br>- Patients not using chlorambucil in combination with Obinutuzumab or Ofatumumab; previously treated patients; <18 year old; eligible for fludarabine<br>3. Alternative treatment for MM patients: ***Melphalan*** *patient population*<br>- Patients not using Melphalan in combination with Lenalidomide and Prednisone; previously treated; <18 years old; eligible for transplant |

## Annex 4 Timing of available data per country

### Table 17: 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 SNIIRAM | Q3 2018 | Q3 2019 | Q3 2020 |
| Germany SHI | Q4 2018 | Q4 2019 | Q4 2020 |
| UK CAS /HES | Q2 2019 | Q3 2020 | Q4 2021 |
| Sweden NHWS (registries and EMR) | Q3 2021 | Q3 2021 | Q3 2021 |
| [redacted] | Q3 2017 | Q1 2019 | Q4 2019 |

ISN 6231-MA-3264
PAS register No: TBC

# 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 [redacted]:**

Signature: _____ _____
**Date**

**Printed Name:** _____

**Address:** _____

_____

ISN 6231-MA-3264
PAS register No: TBC

**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**

[redacted]
Pharmacovigilance

Date

[redacted] Pharmacoepidemiology
Pharmacovigilance

Date

[redacted] EU Qualified Person for
Pharmacovigilance

Date

[redacted] Statistics
Medical Affairs

Date

[redacted]
[redacted] Medical Safety
Pharmacovigilance

Date