Global Medical Affairs

Non-interventional Study Protocol

Study Protocol Number: GP13-501

REFLECT: A prospective multi-center non-interventional study describing the effectiveness and safety of biosimilar rituximab (Rixathon®) administered in combination with CHOP chemotherapy for the treatment of patients with previously untreated CD20-positive diffuse large B-cell lymphoma in current clinical practice

Authors: [Redacted]

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- Austria
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List of abbreviations

ABC  Activated B-cell
ADR  Adverse drug reaction
AE   Adverse event
AESI Adverse events of special interest
ATC  Anatomical Therapeutic Chemical
CHOP Cyclophosphamide, doxorubicin, vincristine, prednisone
CI   Confidence interval
CR   Complete response
CRO  Contract research organization
DLBCL Diffuse large B-cell lymphoma
ECOG Eastern Co-operative Oncology Group
EDC  Electronic data capture
EMA  European Medicines Agency
EORTC European Organisation for Research and Treatment of Cancer
eCRF Electronic case report/record form
ENCePP European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EU   European Union
FAS  Full analysis set
Fc   Fragment crystallizable
GCB  Germinal center B-cell
HBV  Hepatitis B virus
ICF  Informed consent form
ICMJE International Committee of Medical Journal Editors
IEC  Independent ethics committee
IRB  Institutional review board
MedDRA Medicinal Dictionary for Regulatory Activities
NI(S) Non-interventional (study)
ORR  Overall response rates
PFS  Progression-free survival
PR   Partial response
PV   Pharmacovigilance
QoL  Quality of life
R-CHOP Rituximab + CHOP
JFSAE Serious adverse event
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SoC</td>
<td>Standard of care</td>
</tr>
<tr>
<td>SOC</td>
<td>System organ class</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
</tr>
<tr>
<td>STROBE</td>
<td>Strengthening the Reporting of Observational Studies in Epidemiology</td>
</tr>
<tr>
<td>V</td>
<td>Visit</td>
</tr>
</tbody>
</table>
1 Responsible parties

The list of responsible parties is kept in a separate document (see Section 14).

2 Amendments and updates

Amendment 2 (14-Oct-2019)

The purpose of amendment 2 is to extend the follow-up period of the study from 12 months to 24 months and to include an additional interim analysis to take place by Q4 2019.

The progression free survival (PFS) extension to 24 months will provide more meaningful data to DLBCL patients (Sargent et al 2017). A comparative arm is not included as this is not a controlled study and historical data of 12 months PFS is very limited. Therefore, this PFS extension to 24 months will enable a comparison of trial results with historical data.

In addition, minor editorial changes for the sake of clarity, consistency, correction of unintentional omissions and correction of typographical errors have been made throughout the protocol.

Study Status

The GP13-501 study has finished recruitment on 31-Mar-2019, with 184 patients enrolled and is currently in the follow-up/observation period.

Changes to Protocol Amendment

Changes to specific sections are shown in the track-changed version of the protocol amendment using strike through red font for deletions and red underlined for insertions.

The following modifications were implemented in protocol amendment 2:

Research question and objectives (Section 5)
- Secondary Objectives: PFS distribution change from 12 to 24 months.

Study design (Section 6.1)
- Updated sample size to reflect the actual recruitment target.

Setting (Section 6.2)
- Updated PFS distribution from 12 to 24 months.

Variables (Section 6.3)
- Addition of an extra observation schedule to reflect the extended observation period of 24 months.

Data sources (Section 6.4)
- Updated Table 6-1 to reflect the extended observation period of 24 months.

Study size (Section 6.5)
- Updated sample size and revised descriptive parameters.
Data analysis (Section 6.7)

- Inclusion of an interim analysis for Q4 2019.

Management and reporting of adverse events/adverse reactions and technical complaints (Section 8)

- Updated adverse event of special interest reporting to include eCRF requirements.
  Collection of related SAEs at the extended observation period of 24 months is also added to the protocol.

Abstract (Section 3)

- Protocol changes are also reflected in abstract.

Amendment 1 (26-Sep-2018)

The purpose of this amendment was to revise the statistics section of the protocol and to allow for one interim analysis to be conducted in Q4 2018. The interim analysis at Q3 2018 was removed from the protocol. Furthermore, the process of adverse event documentation and reporting was clarified.

In addition, minor editorial changes for the sake of clarity, consistency, correction of unintentional omissions and correction of typographical errors have been made throughout the protocol.

Changes to the protocol

The following sections have been updated:

Section 7: Research question and objectives
Section 8.7: Data analysis
Table 8-1: Data collection schedule
3 Abstract

Title
REFLECT: A prospective multi-center non-interventional study describing the effectiveness and safety of biosimilar rituximab (Rixathon®) administered in combination with CHOP chemotherapy for the treatment of patients with previously untreated CD20-positive diffuse large B-cell lymphoma in current clinical practice.

Version and date
3.0 (14-Oct-2019)

Name and affiliation of main authors

All other authors are affiliated to Hexal AG

Rationale and background
Rixathon® is authorized in the European Union as a biosimilar of MabThera®.

The purpose of this study is to assess the effectiveness and safety of Rixathon® in treatment-naïve patients with CD20-positive diffuse large B-cell lymphoma (DLBCL) under real-world conditions.

Rixathon® has received regulatory approval by the European Medicines Agency for use in the same indications as the reference product, MabThera®, based on the totality of evidence for biosimilarity between Rixathon® and reference rituximab. Rixathon® clinical development program demonstrated Rixathon® to match reference rituximab in terms of pharmacological properties, efficacy, and safety. In total, the clinical program consisted four studies: two in lymphoma and two in rheumatoid arthritis. No patients with DLBCL were involved in these clinical studies.

Research question and objectives
This non-interventional study (NIS) is being conducted to obtain effectiveness and safety data for Rixathon® when administered in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy in a real-world setting.

Primary objective
The primary objective of this study is to evaluate the effectiveness of Rixathon®, measured by complete response (CR) rate at the end of treatment as assessed by the treating physician.

Secondary objectives
Secondary objectives of this study are to assess the overall response rates (ORR) at the end of treatment (defined as the patients with either a CR or partial response [PR]), as well as the progression-free survival (PFS) distribution in these patients at 24 months.

The general safety and tolerability of Rixathon® in combination with CHOP will be analyzed.

Patient quality of life (QoL) will be assessed by patient-reported outcomes collected using the validated questionnaire European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 at baseline and every 3 months thereafter, for a total duration of 12 months.
Study design | Prospective, multi-center, open-label, non-interventional
---|---
Population | Approximately, 180 treatment-naïve, CD20-positive, adult patients with DLBCL
Inclusion/exclusion criteria | Eligible patients have to fulfill all of the following criteria in accordance with the Summary of Product Characteristics (SmPC) of Rixathon®:
1. Confirmed diagnosis of CD20-positive DLBCL
2. Patients must have been selected for therapy with Rixathon® in combination with CHOP (Rixathon®-CHOP), as per the treating physician’s discretion
3. Age ≥18 years
4. Capability to provide written informed consent
Patients fulfilling any of the following criteria are not eligible:
1. Any prior therapy for DLBCL
2. Contraindications according to the SmPC of Rixathon®
Variables | Prior to entry into the study, eligible patients must provide written informed consent.
In this NIS, the following data will be collected, as long as they are available in the patients’ medical records and without intervention of standard of care (SoC):
Baseline
- Patient demographics
- Physical examination results, including height and weight
- Relevant medical history and comorbidities
- Pregnancy status
- Eastern Co-operative Oncology Group (ECOG) performance status/Karnofsky index
- DLBCL characteristics and diagnosis, including biopsy, staging (Ann-Arbor), subtyping, morphology, disease symptoms, immunophenotyping, International Prognostic Index, target lesions
- Details of concomitant medication, including premedication for Rixathon® administration
- Details of Rixathon® treatment
- Details of CHOP chemotherapy, and any radiotherapy and/or supportive therapy received
- Details of any anti-neoplastic surgery received, including date and location and size of target lesion
- QoL assessed by patient-reported outcomes collected using the validated questionnaire EORTC QLQ-C30
Therapy and 12 months follow-up
- Physical examination results
- Pregnancy status
- ECOG performance status/Karnofsky index
- Details of concomitant medication
- Details of Rixathon® treatment
- Details of CHOP chemotherapy, and any other radiotherapy and/or supportive therapy received
- Details of any anti-neoplastic surgery received, including date and location and size of target lesion
- Details of response; CR and PR
- Details of any adverse events (AEs) and serious adverse events (SAEs) experienced
- QoL assessed by patient-reported outcomes collected using the validated questionnaire EORTC QLQ-C30 (assessed at Month 3, 6, 9, and 12)

**End of 12 months observation**
- Pregnancy status
- ECOG performance status/Karnofsky index
- Details of concomitant medication
- Details of any anti-neoplastic surgery received, including date and location and size of target lesion
- Details of response; CR and PR
- Details of any AEs and SAEs experienced
- Data on the first subsequent anti-neoplastic therapy received following Rixathon®-CHOP
- Reason for study discontinuation

**Extended observation (Months 18 and 24)**
- Details on patient status, including:
  - Survival
  - Progression or relapse
  - Death (disease related or not)
- Details of any SAEs considered by the investigator to be related to Rixathon® (AEs/SAEs that are considered related to disease, therapies other than Rixathon®, et al are not required to be reported during this extended observation period)
- Details of AESI, including serious AESI
- Pregnancy status
- Reason for study discontinuation.

<table>
<thead>
<tr>
<th>Data sources</th>
<th>Data sources will be patient medical records. All data in this study will be collected routinely in daily medical practice and per SoC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study size</td>
<td>The sample size was calculated based on precision of point estimate of CR rate. Power evaluation was not applicable. For a sample size of approximately 180 eligible patients, with the assumption of a CR rate of 60% and exact binomial distribution, the 95% confidence interval (CI) limits for the point estimate of CR rate will be ± 7.4%. This precision is considered adequate. It is expected that all about 180 patients will be available for analysis.</td>
</tr>
<tr>
<td>Exposure to medication(s) of</td>
<td>The maximum duration of the observational period per patient will be 24 months.</td>
</tr>
</tbody>
</table>
### Interest and comparator therapy

This study is an open-label, uncontrolled, single-arm, observational, cohort study.

### Outcome(s)/endpoints of interest

The primary endpoint will be the CR rate at the end of treatment. Secondary endpoints are:
- ORR (patients assessed as having either a CR or PR)
- PFS distribution at 24 months
- Incidence of AEs and SAEs, including adverse drug reactions
- QoL assessed by patient-reported outcomes collected using the validated questionnaire EORTC QLQ-C30 at baseline and every 3 months thereafter, for a total duration of 12 months.

### Safety related measurements

AEs (regardless of causality) and the following AEs of special interest will be collected:
- Tumor lysis syndrome; cytokine release syndrome
- Progressive multifocal leukoencephalopathy
- Hepatitis B reactivation
- Serious infections, including those classified as fatal, bacterial, or fungal; new or reactivated viral infections
- Cardiac arrhythmias and angina
- Bowel obstruction and perforation

### Other assessments

- DLBCL subtype analysis (germinal center B-cell [GCB] and activated B-cell [ABC])
- Hepatitis B virus screening

### Data analysis

Due to the nature of the study, no formal statistical testing will be carried out, instead descriptive statistical methods will be applied. The final analysis will take place by the end to the study. One interim analysis was performed in Q4 2018 and a second interim analysis is planned for Q4 2019 for analysis of the primary endpoint.
4 Rationale and background

Rixathon® is authorized in the European Union (EU) as a biosimilar of reference rituximab (MabThera®, Roche Pharmaceuticals).

The purpose of this study is to assess the effectiveness and safety of Rixathon® in untreated patients with CD20-positive diffuse large B-cell lymphoma (DLBCL) under real-world conditions when treated with Rixathon® in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. Rixathon® has been approved by the European Medicines Agency (EMA) for the treatment of patients with DLBCL.

Rituximab is a chimeric murine/human monoclonal immunoglobulin 1 kappa antibody, with murine heavy- and light-chain variable regions (fragment antigen binding domain), and human kappa and gamma-1 constant regions (fragment crystallizable [Fc] domain). It binds to CD20, a non-glycosylated, hydrophobic, transmembrane protein that is present on the cell surface of pre-B-lymphocytes and mature B-lymphocytes, but not on hematopoietic stem cells and terminally differentiated plasma cells or other tissues (Abulayha et al 2014). The Fc domain of rituximab can exhibit effector functions with the capability of mediating target cell lysis. Elicited mechanisms include complement-dependent cytotoxicity, resulting from C1q binding, and antibody-dependent cellular cytotoxicity, mediated by Fcγ receptors on the surface of immune effector cells, such as natural killer cells. Additionally, binding of rituximab to CD20 has been shown to induce tyrosine phosphorylation, inhibition of cell proliferation, and cell death via apoptosis (Demidem et al 1997). Since immature B-cell stem cells in the bone marrow lack the CD20 antigen, they remain unaffected by rituximab, allowing B-cell repopulation to occur within a period of 9–24 months after the initial rituximab-induced depletions (Abulayha et al 2014). It has been reported that human Fcγ receptor polymorphism affects rituximab-induced B-cell depletion (Cartron et al 2002; Weng et al 2003). Rituximab was approved as the first therapeutic antibody for treating B-cell lymphoma and leukemia in 1997 in the United States, where it is marketed as Rituxan® (Genentech Inc. and IDEC Pharmaceutical Corporation, CA, USA), and in 1998 in the EU, where it is marketed as MabThera® (Roche Pharmaceuticals).

DLBCL is the most frequent form of non-Hodgkin lymphoma among adults (Tilly et al 2015), with an annual incidence of 7–8 cases per 100 000 population (Morton et al 2006; Smith et al 2011). DLBCL accounts for 40% of the global lymphoma burden and the incidence increases with age, with the median age of diagnosis approximately 70 years (Swerdlow et al 2008; Smith et al 2011). DLBCL is an aggressive malignancy which can arise in virtually any organ or part of the body (Nowakowski et al 2016). The first sign of DLBCL is usually the observation of rapidly enlarging lymph nodes, which can sometimes be associated with B symptoms: fever, weight loss, and night sweats (Shah et al 2017).

The chemotherapy regimen R-CHOP, comprised of rituximab, three chemotherapy agents (cyclophosphamide, doxorubicin, vincristine), and one steroid (prednisone), is a widely used therapy for DLBCL (Tilly et al 2015).

Rixathon® has been approved by the EMA for use in the same indications as the reference medicine, MabThera®, based on the totality of evidence for biosimilarity between Rixathon® and reference rituximab. The Rixathon® clinical development program confirmed that Rixathon® and reference rituximab match in terms of pharmacological properties, efficacy, and
safety. The clinical program comprised four clinical studies: two in lymphoma and two in rheumatoid arthritis. To date, no patients with DLBCL have been included in a clinical study of Rixathon®.

5 Research question and objectives

The purpose of this study is to describe the effectiveness and safety of Rixathon®, in combination with CHOP (Rixathon®-CHOP), in treatment-naïve patients with CD20-positive DLBCL under real-world conditions.

Primary objective

The primary objective of this study is to evaluate the effectiveness of Rixathon®, measured by complete response (CR) rate at the end of Rixathon®-CHOP treatment, as assessed by the treating physician.

Secondary objectives

Secondary objectives of this study are to assess the overall response rates (ORR) at the end of treatment, defined as patients with either a CR or partial response (PR), as well as the progression-free survival (PFS) rate of these patients at 24 months. Furthermore, the general safety and tolerability of Rixathon®-CHOP and patient quality of life (QoL) will be assessed.

Secondary endpoints are:

- ORR, defined as patients with either a CR or PR to treatment
- PFS distribution at 24 months
- Incidence of (serious) adverse events ([S]AE) including adverse drug reactions (ADRs)
- QoL assessed by patient-reported outcomes collected using the validated questionnaire European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 at baseline and every 3 months thereafter, for a total duration of 12 months.

6 Research methods

6.1 Study design

Design

This is a non-interventional, prospective, multicenter study of approximately 180 treatment-naïve patients with CD20-positive DLBCL that will be treated with Rixathon®-CHOP in routine clinical practice.

In this study, commercially available Rixathon®, as well as cyclophosphamide, doxorubicin, vincristine, and prednisone, will be used as prescribed treatment for DLBCL as per the treating physician’s best clinical judgement. Therefore, the decision to treat the patient with Rixathon® is independent from the decision to include the patient into this study. Being an observational study, only data available from routine clinical practice and standard of care (SoC), in line with national and international laws and regulations, will be recorded. This study does not impose
any mandatory treatment regimens nor require assessment of specific tests by the treating physician.

Data for the study will be transcribed and entered into an electronic Case Report Form (eCRF) from the patient’s medical records.

6.2 Setting

Patients

Treatment-naïve, CD20-positive, adult patients with DLBCL, planned to be treated with Rixathon®-CHOP based on the decision of the treating physician, will be eligible for this study.

Data will be collected at the time of enrollment into the study (Visit V0), at every patient contact during Rixathon®-CHOP therapy, and one timepoint at least 30 days after the last dose of Rixathon®. In total, the patients will be observed for 24 months.

QoL data will be collected at the time of enrollment or before the first dose of Rixathon®-CHOP and then at the time of patient contact closest to 3, 6, 9, and 12 months.

Written informed consent has to be obtained from all patients prior to any data collection under this protocol. It is important that the patient personally signs and dates two written copies of the Informed Consent Form (ICF) prior to enrollment after having received written and verbal information about this study. The treating physician or his designee will inform the patient about the study. One original copy will be kept by the treating physician and the patient will receive the second original copy.

Inclusion criteria

Eligible patients must fulfill all of the following criteria, in accordance with the Summary of Product Characteristics (SmPC) of Rixathon®:

1. Confirmed diagnosis of CD20-positive DLBCL
2. Considered for therapy with Rixathon®-CHOP as per the treating physician’s discretion and have planned to receive, or have already received, at least one dose of Rixathon®
3. Age ≥18 years
4. Capability of providing written informed consent

Exclusion criteria

Patients fulfilling any of the following criteria are not eligible:

1. Any prior therapy for DLBCL
2. Contraindications according to the SmPC of Rixathon®

6.3 Variables

Prior to entry into this study, eligible patients must provide written informed consent. Patients who participate in the extended observation period will be re-consented.
The following data will be collected according to Table 6-1, but only if routinely assessed during clinical practice and per SoC and if documented in the patient’s medical records:

**Baseline**
- Patient demographics
- Physical examination results, including height and weight
- Relevant medical history and comorbidities
- Pregnancy status
- Eastern Co-operative Oncology Group (ECOG) performance status/Karnofsky index
- DLBCL characteristics and diagnosis including biopsy, staging (Ann-Arbor), subtyping, morphology, disease symptoms, immunophenotyping (immunohistochemistry and fluorescence-activated cell sorting), International Prognostic Index, target lesions
- Details of any concomitant therapy, including premedication for Rixathon® administration
- Details of Rixathon® treatment
- Details of CHOP chemotherapy, radiotherapy, and supportive therapy received
- Details of any anti-neoplastic surgery received, including date and location and size of target lesion
- QoL assessed by patient-reported outcomes collected using the validated questionnaire EORTC QLQ-C30

**Therapy and 12 months follow-up**
- Physical examination results
- Pregnancy status
- ECOG performance status/Karnofsky index
- Details of concomitant medication
- Details of Rixathon® treatment
- Details of CHOP chemotherapy, radiotherapy, and supportive therapy received
- Details of any anti-neoplastic surgery received, including date and location and size of target lesion
- Details of response: CR and PR
- Details of any AEs and SAEs experienced
- QoL assessed by patient-reported outcomes collected using the validated questionnaire EORTC QLQ-C30 (completed at months 3, 6, 9, and 12)

**End of 12 months observation**
- Pregnancy status
- ECOG performance status/Karnofsky index
- Details of concomitant medication
- Details of any anti-neoplastic surgery received, including date and location and size of target lesion
• Details of response: CR and PR
• Details of any AEs and SAEs experienced
• Data on the first subsequent anti-neoplastic therapy received following Rixathon®-CHOP, if applicable
• Reason for study discontinuation

Extended observation (Months 18 and 24)
• Details on patient status, including:
  • Survival
  • Progression or relapse
  • Death (disease related or not)
• Details of SAEs considered by the investigator to be related to Rixathon® (AEs/SAEs that are considered related to disease, therapies other than Rixathon®, et al are not required to be reported during this extended observation period)
• Reason for study discontinuation

Other assessments
• DLBCL subtype analysis
• Hepatitis B Virus (HBV) screening

6.4 Data sources
Initiation of the participating sites will be performed by a designated contract research organization (CRO). A CRO representative will review the protocol and eCRF with the physicians and their staff in person or by phone.

Sources for data collection will be patient medical records available at the clinical site. The sites will record the data in an anonymized manner in an eCRF. The eCRFs will be reviewed for any inconsistencies and, when necessary, queries will be raised. Data collected will be verified against the source data to an extent described in the monitoring plan for this study.

The CRO will follow their internal standard operating procedures (SOPs) for monitoring, which have been reviewed and approved by the sponsor.

Concomitant or prior medications entered into the database will be coded using the World Health Organization drug reference list. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Data collection schedule
This is a non-interventional study (NIS) that does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to prescribing information, with visit frequency and assessments performed according to routine medical practice and SoC. Only data corresponding to these visits and assessments will be
collected as part of the study. The treating physician is asked to complete the appropriate eCRF at every patient visit.

Below is the recommended data collection schedule that was designed and developed in alignment with the general and internationally accepted patterns of routine clinical practice and SoC for patients with DLBCL treated with R-CHOP. Visits 1–6/8 (V1–V6/V8) represent the chemotherapy cycles of R-CHOP treatment (R-CHOP14 or R-CHOP21).
Table 6-1  Data collection schedule

<table>
<thead>
<tr>
<th></th>
<th>V0 (baseline)</th>
<th>At each patient contact during observational period (treatment V1–V6/8; and every 3 months after treatment)</th>
<th>End of 12 months observation</th>
<th>Extended observation (Months 18 and 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient demographics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Relevant medical history and comorbidities</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy status*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECOG performance status/Karnofsky index</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>DLBCL characteristics and diagnostic details</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant therapy at baseline and changes during study</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Rixathon® treatment details</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP chemotherapy, radiotherapy, supportive therapy details</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-neoplastic surgery</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Response to treatment with Rixathon® in combination with CHOP chemotherapy</td>
<td>X</td>
<td>x</td>
<td></td>
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</tr>
<tr>
<td>AEs and SAEs</td>
<td>X</td>
<td>X (until 30 days after last Rixathon® dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs and SAEs considered by the investigator to be related to Rixathon®</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>SAEs considered by the investigator to be related to Rixathon®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AESI*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>QoL assessment (EORTC QLQ-C30)**</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Subsequent therapy, if applicable</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
At each patient contact during observational period (treatment V1–V6/8; and every 3 months after treatment)

End of 12 months observation

Extended observation (Months 18 and 24)

<table>
<thead>
<tr>
<th>Details</th>
<th>V0 (baseline)</th>
<th>X</th>
<th>X</th>
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</thead>
<tbody>
<tr>
<td>Re-consent</td>
<td></td>
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</tr>
<tr>
<td>Details on patient status (as described in section 6.3)</td>
<td></td>
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<tr>
<td>Reason for study discontinuation</td>
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*Collected at every patient contact from baseline (V0) until the end of extended observation. **QoL data will be collected at the time of enrollment, before the first dose of Rixathon®-CHOP, and then at the time of patient contact closest to 3, 6, 9, and 12 months. Abbreviations: AE = adverse event; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Co-operative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; QoL = quality of life; SAE = serious adverse event; SoC, standard of care. Note: All data apart from QoL data are acquired according to SoC.
6.5 Study size

The study’s endpoints are descriptive and hence no formal sample size calculation based on a formal hypothesis test can be performed. However, the sample size was calculated based on precision of point estimate of CR rate. Power evaluation was not applicable.

For a sample size of approximately 180 eligible patients, with the assumption of CR rate of 60% and exact binomial distribution, the 95% confidence interval (CI) limits for the point estimate of CR rate will be ± 7.4%. This precision is considered adequate. It is expected that all about 180 patients will be available for analysis.

Patients who drop out for any reason (e.g. lost to follow-up, withdrawal, death) will not be replaced.

6.6 Data management

A fully validated electronic data capture (EDC) system will be used. All entries/adjustments into the EDC system need to be performed by the site. Automated checks to identify discrepancies during data capture will be programmed into the system. In addition, medical and data review will be performed as outlined in the data management plan. The treating physician will electronically sign off the eCRF pages, confirming that the entered data is complete and accurate.

After database lock, the treating physician will receive a CD-ROM with the complete eCRF data collected at the site during the study, for archiving at the site.

6.7 Data analysis

All data analyses will be performed by the sponsor.

Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, median, and maximum. For selected parameters, 25th and 75th percentiles will also be presented.

Categorical variables will be summarized by number of patients and percentages.

In addition to the statistical methods outlined below, further details and any additional exploratory analyses that may be performed will be described in the statistical analysis plan (SAP).

The time of enrollment into the study is defined as the point when a patient signs the ICF at V0 (baseline visit).

Analysis sets

The full analysis set (FAS) includes all patients who received at least one dose of Rixathon®.CHOP. All analyses will be based on the FAS.
Subject demographics and other baseline characteristics

Data collected at baseline, including patient demographics and disease characteristics, will be listed and summarized descriptively.

Relevant medical histories and current medical conditions, such as DLBCL details at baseline, will be summarized.

Treatments

All Rixathon®-CHOP treatment data will be listed.

Concomitant medications and relevant non-drug therapies received prior to and after the start of the study treatment, including rescue medication therapy, will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

Analysis of the primary endpoint(s)

The primary objective of this study is to evaluate the effectiveness of Rixathon®-CHOP, measured by CR rate at the end of treatment as assessed by the treating physician.

The primary endpoint is the number (%) of patients with CR at the end of Rixathon®-CHOP treatment (assessed at V6/V8). For patients who discontinue the study early, the last available assessment will be considered (last observation carried forward method will be applied). Furthermore, the 95% CI, calculated using the Clopper-Pearson method, will be provided.

Analysis of the secondary endpoints

Overall response rate:

The number (%) of patients with either CR or PR at the end of Rixathon®-CHOP treatment (assessed at V6/V8) will be provided, together with the 95% CI.

Progression-free survival rate at 24 months:

PFS is defined as the time from the start of Rixathon®-CHOP treatment to the first documented progression of disease, or relapse or death due to any cause within the 24-months observational period. The Kaplan-Meier estimate of the PFS survival function will be estimated and displayed. The resulting median PFS time, as well the rate at 12 and 24 months will be provided with 95% confidence intervals.

General safety and tolerability:

The incidence of AEs, SAEs, and ADRs will be tabulated and listings will be provided. Please refer to “Safety endpoint(s)” section below for more details.

Quality of life:

QoL will be assessed by patient reported outcomes collected using the EORTC QLQ-C30 and outcomes will be analyzed according to the EORTC scoring manual. An exploratory analysis will be carried out to handle missing data, if applicable.
Safety endpoint(s)

Adverse events

All information on AEs, including start and stop date, duration and relatedness to Rixathon®, will be displayed by patient. Summary tables for AEs will only include AEs occurring after a patient has provided informed consent up until 30 days after the patient has received the last dose of Rixathon®, or has stopped study participation. Any AEs and SAEs related to Rixathon® occurring during the 12-month observational period will be summarized. Any AEs and SAEs related to Rixathon® occurring during the extended 24-months observational period (at patient contacts at 18 and 24 months) will be summarized.

AEs will be summarized by system organ class (SOC) and/or preferred term, severity, type of AE, and relation to Rixathon®.

SAEs, ADRs, adverse event of special interest (AESI), and AEs leading to discontinuation will be tabulated. All deaths will be summarized. All AEs, SAEs, and ADRs will be listed. A patient with multiple AEs within a primary SOC will only be counted once towards the total of the primary SOC.

Other assessments

All data collected, e.g. weight, height, ECOG performance status/Karnofsky index, HBV screening, pregnancy information, and differential blood counts, will be listed and may be summarized, if appropriate.

Supportive analyses

Separate analyses may be performed for patient subgroups, defined by the key molecular subtypes of DLBCL (germinal center B-cell [GCB] and activated B-cell [ABC]), if sufficient data are available.

Interim analyses

One interim analysis was performed in Q4 2018. A separate SAP will be written for the interim analysis. An additional interim analysis will be conducted in Q4 2019 for analysis of the primary endpoint. A SAP for interim analysis 2 will be finalized prior to the analysis, which will describe in detail the statistical analysis methods used.

6.8 Quality control

Data quality and integrity, including accuracy and legibility of collected data and original documents, will be controlled by the following measures:

Sponsor data management

The sponsor will ensure database quality by reviewing the data entered into the eCRFs by investigational staff for completeness and accuracy, and in accordance with the data management plan.
Data recording and document retention

In all scenarios, the treating physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. The treating physician must also keep the original ICF signed by the patient (a signed copy is given to the patient). The physician must give the sponsor (or designee) access to all relevant source documents to confirm their consistency with the eCRF entries. Any information about the identity of the patients recorded in source documents will not be transferred to the eCRF.

All documentation and data collected for the study will be archived for at least 15 years after the study has been terminated, or longer if required by national and local legal requirements. The documents may only be destroyed after a written approval of the sponsor has been granted.

Site monitoring

Formal site monitoring will be performed by the designated CRO, as described in the monitoring plan for this study. The sponsor will ensure compliance with the monitoring requirements.

Monitoring activity will include reviews of the progress of the study and compliance with the protocol, SOPs, and applicable guidelines.

6.9 Limitations of the research methods

While this is a population-based study, it utilizes convenience sampling. Therefore, the selected sample may not reflect the entire patient population accurately, and selection bias cannot be fully excluded. While limited to centers using Rixathon®, attempts will be made to enroll a variety of centers with regard to center size and academic affiliation (e.g. academic as well as academic-affiliated and non-academic centers). In this population-based, open-label study, only patients treated with Rixathon® will be included and there will be no comparison group of either untreated patients or patients treated with other rituximab-containing treatment regimens. Observed relationships between treatment variables and outcome variables can only be interpreted in an observational manner. By not randomly selecting centers and patients, the generalizability of the findings will be limited to the populations under study.

6.10 Other aspects

Not applicable.

7 Protection of human subjects

Protection of personal data

Documentation in the eCRF may only start after the patient has signed an ICF. Every patient will be assigned a unique patient number and all collected study information will be coded with this number. Patient numbers will not be reused. The identification log allows linking of the
patient number to her/his name. This document will only be kept at the site for monitoring and audit/inspection purposes and must not be disclosed.

Patients’ personal information will be accessible only to the following authorized people or agencies who are obligated to maintain confidentiality by the nature of their work, or are bound by confidentiality agreements: treating physician and her/his staff, as well as entitled representatives of the treating physician; sponsor and authorized CRO representatives; national and foreign health authority inspectors; and the institutional review board (IRB)/independent ethics committee (IEC) responsible for evaluation of this study at this hospital/doctor’s practice, as applicable by local regulations. If required and where applicable, the treating physician may contact a patient’s personal physician to collect additional medical information and relevant medical history.

**Risks and benefits**

There are no additional medical risks or benefits resulting from participation in the study, since the treatment will follow SoC. Information on potential side effects is available to the patients in the package insert and will be explained in detail as usual by the treating physician at the start of therapy. Patients will be informed in a timely manner if information becomes available that could influence their decision to participate in the study.

Collected medical information may be of possible future benefit to patients suffering from DLBCL, though most probably there is no personal benefit for the study participant resulting from this data.

For analysis orarchiving, coded patient medical data could be transferred to countries that may not offer the same level of privacy protection as the country in which this study is being conducted. However, the sponsor will keep any information received to the same standard of confidentiality, as far as permitted by applicable local law. The sponsor has also entered into agreements with third parties working for the sponsor to secure adequate protection of patients’ data.

**Regulatory and ethical compliance**

Compliance with the sponsor and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki), and that the study data are credible and responsibly reported.

This study was designed, and shall be implemented and reported, in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), applicable Good Clinical Practice guidelines, and with the ethical principles laid down in the Declaration of Helsinki (World Medical Association 1996).

Prior to start of data collection at a particular site, the study will be submitted to the relevant competent authorities and IRBs/IECs as required by local regulations.
Eligible patients may only be enrolled in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents.

Each patient has the right to withdraw from the study at any time for any reason and withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

**Responsibilities of the treating physician**

Prior to study start, the treating physician, or other involved site personnel, are required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents, to follow all of the instructions and procedures found in this protocol, and to give access to all relevant data and records to sponsor monitors, auditors, sponsor clinical quality assurance representatives, designated representatives of sponsor, IRBs/IECs/research ethics boards, and regulatory authorities, as required. If an inspection of the clinical site is requested by a regulatory authority, the treating physician, or other involved site personnel, must inform the sponsor immediately that this request has been made.

**8 Management and reporting of adverse events/adverse reactions and technical complaints**

From 1st Rixathon® treatment to 30 days after last Rixathon® treatment: All AEs – including SAEs, safety endpoints (where relevant) and AESI occurring up until 30 days after last Rixathon® dose – must be collected and recorded in the eCRF, irrespective of causal association. The SAEs also have to be immediately reported to the Sandoz safety database.

From 30 days after last Rixathon® treatment to 12 months of the study: Only AEs, including SAEs considered by the investigator to be related with exposure to the Sandoz study drug of interest (Rixathon®) must be collected and recorded in the eCRF and also immediately reported to the Sandoz Safety database. All AESI must be collected and recorded in the eCRF, irrespective of causal association.

From 12 months to 24 months of the study (extended observation period): Only SAEs considered by the investigator to be related with exposure to the Sandoz study drug of interest (Rixathon®) must be collected and recorded in the eCRF and also immediately reported to the Sandoz Safety database. All AESI must be collected and recorded in the eCRF, irrespective of causal association.

All adverse reactions identified for non-Sandoz products should be reported to the local health authority in accordance with national regulatory requirements for individual case safety reporting or the marketing authorization holder by the investigator, as these will not be recorded in the Sandoz safety database.

The overall summary of adverse events and pregnancy reporting is shown in Table 8-1.
Table 8-1  Adverse events and pregnancy reporting

<table>
<thead>
<tr>
<th></th>
<th>1st treatment to 30 days after last Rixathon® dose</th>
<th>30 days after last Rixathon® dose to 12 months</th>
<th>12 months to 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>All AEs</td>
<td>Only related AEs</td>
<td>Not reported anymore</td>
</tr>
<tr>
<td>SAEs</td>
<td>All SAEs</td>
<td>Only related SAEs</td>
<td>Only related SAEs</td>
</tr>
<tr>
<td>AESI*</td>
<td>All AESI</td>
<td>All AESI</td>
<td>All AESI</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>All pregnancies to be reported</td>
<td>All pregnancies to be reported</td>
<td>All pregnancies to be reported</td>
</tr>
</tbody>
</table>

*All AESI that are classified as serious are also to be reported, regardless of the relationship to Rixathon

Adverse event reporting

An adverse event is any untoward medical occurrence in a patient that does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Sandoz drug of interest, whether or not it is related to the Sandoz drug of interest.

In this study, the Sandoz drug of interest is Rixathon® given at any time during the study. Medical conditions/diseases present before starting Rixathon® are only considered AEs if they worsen after starting Rixathon®. The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

AEs recorded in the eCRF must include the following information:
1. The severity grade (mild, moderate, severe)
2. The relationship to Rixathon® (suspected/not suspected)
3. The duration (start and end dates or if continuing at final examination)
4. Whether it constitutes an SAE

In addition, all reports of the following special scenarios are also considered an AE irrespective of if a clinical event has occurred:
- Drug use during lactation or pregnancy
- Lack of efficacy
- Overdose
- Intentional drug abuse and misuse
- Medication errors including drug maladministration
- Dispensing or prescribing errors
Reports of lack of efficacy without an associated clinical event must be recorded on the AE eCRF, even if lack of efficacy parameters are being collected and recorded elsewhere within the study database.

Reports of overdose, drug abuse and misuse, drug maladministration, and dispensing errors/medication errors, without an associated clinical event, must be recorded on the AE eCRF, irrespective of whether or not the information is also being captured on the drug administration record form.

Note: Occupational or accidental exposure, for example of study personnel or family members of the patient, should be reported to the local health authority in accordance with national regulatory requirements for individual case safety reporting or to the local pharmacovigilance (PV) department as a spontaneous report.

Any treatment of any AE should be recorded on the corresponding AE eCRF page.

Once an AE is detected, it should be followed until resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship (suspected/not suspected) to Rixathon®, the interventions required to treat it, and the outcome.

Information about common AEs already known to be associated with Rixathon® use can be found in the prescribing information. This should be discussed with the patient prior to study start and during the study as needed.

Non-serious AEs associated or not with Rixathon® must be recorded in the safety database according to the study period as described below:

- From 1st Rixathon® treatment to 30 days after last Rixathon® treatment: All AEs occurring up until 30 days after last Rixathon® dose – must be collected and recorded in the eCRF, irrespective of causal association.
- From 30 days after last Rixathon® treatment to 12 months of the study: Only AEs, considered by the investigator to be related with exposure to the Sandoz study drug of interest (Rixathon®) must be collected and recorded in the eCRF.
- From 12 months to 24 months of the study (extended observation period): AEs are not to be collected and recorded in the eCRF anymore.

Information on all non-serious AEs entered into the eCRF by the investigator is then transferred from the study database to Novartis Chief Medical Office and Patient Safety by data management on a periodic basis, but not less frequently than once per month.

**Serious adverse event reporting**

An SAE is defined as an event which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
• Requires inpatient hospitalization, or prolongation of existing hospitalization, unless hospitalization is for:
  o Routine treatment or monitoring of the studied indication
  o Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of Rixathon® treatment
  o Social reasons and respite care in the absence of any deterioration in the patient’s general condition
• Is medically significant, defined as an event that jeopardizes the life of the patient or may require medical or surgical intervention to prevent one of the outcomes listed above, for example, may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission

Note: Transmission of infectious disease via medication is considered to be a serious adverse reaction and should be reported and assessed as medically significant in the absence of other seriousness criteria.

To ensure patient safety, all available information on an SAE(s) and any associated AE(s), if applicable and regardless of causality assessment, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation must be reported to Sandoz immediately (i.e. within 24 hours of learning of its occurrence).

All available information for the SAE and any associated AE(s) must be entered immediately into the EDC system.

Note: Should the EDC system become non-operational, the site must complete the appropriate paper SAE Form. The completed form is then faxed to the sponsor within 24 hours of the treating physician or site awareness; however, the reported information must be entered into the EDC system once it becomes operational.

The telephone number, telefax number, and email of the contact persons in the local PV department specific to the site, are listed in the treating physician or other involved site personnel folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the Case Report Form documentation at the study site.

Additional/follow-up information for any applicable event is to be reported in the eCRF as soon as it becomes available. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

Any SAEs experienced after this 30-day period should only be reported to Sandoz if considered by the investigator to be related with exposure to Rixathon® and must be recorded in the eCRF and also immediately reported to the Sandoz Safety database. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This information must be reported within 24 hours of the treating physician or other involved site personnel receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.
If the SAE is not previously documented in the prescribing information, a local patient safety
associate may urgently require further information from the treating physician or other involved
site personnel for health authority reporting.

**Pregnancies**

To ensure patient safety, any occurrence of a pregnancy in a patient receiving Rixathon® must
be reported to Sandoz within 24 hours of learning of its occurrence. The pregnancy should be
followed-up via fax or email to determine outcome, including spontaneous or voluntary
termination, details of the birth, and the presence or absence of any birth defects, congenital
abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Pharmacovigilance Pregnancy Form and reported by the
treating physician, or another involved site personnel, to the local PV department. In case of
any congenital abnormality, birth defect, or maternal and newborn complications, the possible
relationship to Rixathon® should be reported.

Additionally, any SAE experienced during pregnancy must be reported into the EDC system.

**Adverse events of special interest for Rixathon®**

In addition, for Rixathon®, any AESI must recorded in the AE report form in the eCRF
throughout the whole duration of the study. All AESI that are classified as serious are also
to be reported, regardless of the relationship to Rixathon. Targeted questionnaires have been
prepared for these AESIs and will be sent to the treating physicians to obtain more detailed
information, as necessary:

For Rixathon®, the following AESI require additional follow-up and should be recorded in
the AE report form in the eCRF:
- Tumor lysis syndrome; cytokine release syndrome
- Progressive multifocal leukoencephalopathy
- HBV reactivation
- Serious infections, including those classified as fatal, bacterial, or fungal; new or reactivated
  viral infections
- Cardiac arrhythmias and angina
- Bowel obstruction and perforation

**Technical complaints**

A technical complaint is any dissatisfaction with the quality of a sponsor medicinal product.
Technical complaints about an optical, organoleptic, qualitative, quantitative, mechanical, or
functional defect of a pharmaceutical product or medical device may include:
- Any fault of the quality and/or effectiveness of a product
- Any fault of the containers and outer packages, including surface imperfection, broken or
  leaking container, missing contents, and device malfunction
- Any fault of the labeling, including missing or illegible labels
• Any falsification of the medical product or device, including suspected product mix-up, tampering, or counterfeiting

Information about all technical complaints, including the batch number, is collected and recorded on the technical complaint report form. The treating physician, or other involved site personnel, must assess whether the technical complaint is related to any AE (i.e. mixed complaint), complete the technical complaint form and send the completed, signed form by fax within 24 hours to the local PV department. A sample of the affected material must be retained for return to the sponsor, if required.

The telephone number, telefax number, and e-mail address of the contact persons in the local PV department specific to the site, are listed in the treating physician, or other involved site personnel, folder provided to each site. The original copy of the technical complaint form and the fax confirmation sheet (if applicable) must be kept with the Case Report Form documentation at the study site.

Follow-up information is sent to the same person to whom the initial technical complaint form was sent, using a new technical complaint form stating that this is a follow-up to the previously reported technical complaint and giving the date of the initial report.

9 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this study may be either submitted for publication and/or posted in a publicly accessible database of results. During conduct of the study, data from the planned interim analysis could be presented at scientific meetings or in any scientific journal. Publications will comply with internal sponsor standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.
10 References


11 Annexes

11.1 Annex 1 – List of stand-alone documents

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</tr>
<tr>
<td></td>
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