Global Medical Affairs

GP13/Rixathon®

Non-interventional Study Report

GP13-501

REFLECT: A prospective multicenter 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

Document Status	Final
Date of last version of the study report	13 December 2021
EU PAS register number	Study not registered

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1 Abstract

Title	REFLECT: A prospective multicenter 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 Date: 13 December 2021 (final) Name and affiliation of main author: [redacted], Global Medical Manager Oncology
Keywords	Rixathon®, rituximab, biosimilar, diffuse large B-cell lymphoma, CD20-positive
Rationale and background	Rixathon® is authorized in the European Union as a biosimilar of MabThera®. The purpose of the study was 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 (EMA) 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 of 4 studies: 2 in indolent lymphoma and 2 in rheumatoid arthritis. No patients with DLBCL were involved in these clinical studies.
Research question and objectives	This non-interventional study (NIS) was conducted to obtain effectiveness and safety data for Rixathon® administered in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy in a real-world setting. **Primary objective** The primary objective of the study was 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** The secondary objectives of the study were to assess the overall response rates (ORR) at the end of treatment, defined as patients with either CR or partial response (PR), as well as the progression-free survival (PFS) distribution at 24 months. The general safety and tolerability of Rixathon® in combination with CHOP (R-CHOP) was analyzed. Patient quality of life (QoL) was assessed by patient-reported outcomes (PROs) collected using the validated questionnaire European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire-C30 (QLQ-C30) at Baseline and every 3 months thereafter, for a total duration of 12 months.
Study design	Prospective, multicenter, open-label, non-interventional
Setting	Overall, 184 treatment-naïve CD20-positive adult patients with DLBCL were recruited, of those 169 patients were included for final analysis.

	Before entering the study, eligible patients had to provide written informed consent.
Patients and study size, including dropouts	**Patients** Eligible patients had 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. Selected for therapy with R-CHOP, as per the treating physician's discretion 3. Aged ≥18 years 4. Capability to provide written informed consent Patients fulfilling any of the following criteria were not eligible: 1. Any prior therapy for DLBCL 2. Contraindications according to the SmPC of Rixathon® **Study size** 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 was ± 7.4%. This precision was considered adequate. It was expected that about 180 patients would be available for analysis.
Variables and data sources	**Variables** The following data were to be collected if available in the patients' medical records and without additional intervention out of standard of care: **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 PROs collected using the validated questionnaire EORTC QLQ-C30

	Therapy and 12-month 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 AEs (SAEs) experienced
	• QoL assessed by PROs collected using the validated questionnaire EORTC QLQ-C30 (assessed at Month 3, 6, 9, and 12)
	End of 12-month 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 R-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 were considered related to disease, therapies other than Rixathon®, were not required to be reported during this extended observation period)
	• Details of AEs of special interest (AESIs), including serious AESIs
	• Pregnancy status
	• Reason for study discontinuation
	Data sources
	Data sources were the patient medical records. All data in the study were to be collected routinely in daily medical practice and per standard of care.

Results	The final analysis population (full analysis set) consisted of 169 patients: 24.9% and 4.1% of patients discontinued treatment before the end of 12- and 24-month observation periods, respectively. The most frequent reason for early discontinuation was progressive disease (10.7% during the 12 months and 3.6% during the 24 months observation period). Overall, the median age of patients was 70 years (range: 24-94) and there were slightly

	higher number of females than males (52.1% vs. 47.9%). Majority of patients (80.5%) had ECOG PS of 0 or 1 at baseline, while 4.7% and 1.8% of patients had ECOG PS of 2 or 3. 19.5% and 24.3% of patients had an Ann Arbor disease stage of III or IV. With regard to treatment, 75.1% of patients received R-CHOP every 21 days cycle therapy and 24.9% patients received R-CHOP every 14 days cycle therapy. The primary endpoint for this study, CR rate at the end of treatment was 43.8% and 65.1% was the best response CR rate according to RECIL during the treatment period. Overall response rate was 89.3% and PR rate was 45.6% at the end of treatment and 94.7% (ORR) and 29.6% (PR rate), respectively during the treatment period. K-M estimates of 12-month, 18-month and 24-month PFS rates were 84.9%, 81.0% and 78.5%, respectively. Overall, the incidence of AEs was 84.6%. Of those, suspected AEs that were drug-related were 31.4%, SAEs were 37.3%, suspected SAEs that were drug-related were 6.5%, AEs leading to discontinuation were 7.7%, suspected drug-related AEs leading to discontinuation were 1.8% and AEs requiring dose interruption and/or change were 14.2%. The incidence of on-treatment deaths was 1.8%. The most common AEs by PT (>10% incidence) were fatigue (20.7%), anemia (24.3%), polyneuropathy (17.2%), nausea (12.4%), leukopenia (11.2%) and constipation (10.7%). SAEs suspected to be drug-related by PT were neutropenic sepsis, pneumonia, septic shock, varicella zoster virus infection, haematuria, abdominal pain, erysipelas, tumour lysis syndrome and oedema peripheral. Except pneumonia (3 patients) and erysipelas (2 patients), all other suspected SAEs had single occurrence. In terms of QoL assessed using EORTC QLQ-C30 questionnaire during treatment, scores of emotional functioning and financial difficulties were increased. Scores of global health status (GHS), cognitive functioning, physical functioning, role functioning and social functioning were decreased initially (Month 3) and then increased to baseline levels or higher during follow up. In contrast, scores of appetite loss, constipation, diarrhea, fatigue, dyspnea, insomnia and nausea & vomiting were increased at Month 3/Month 6 and then decreased over the subsequent follow ups except for diarrhea, the mean value at Month 15 was increased to baseline level. Scores of pain were dropped except at Month 15, the mean value was increased to baseline level.
Discussion	In this non-interventional, prospective, multicenter study involving 169 treatment naïve patients with CD20-positive DLBCL were treated with Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as per routine clinical practice. This combination showed CR rate at the end of treatment of 43.8%, PR rate of 45.6% and ORR of 89.3%, respectively. According to the new lymphoma response criteria, RECIL 2017, during the treatment period R-CHOP treatment showed a higher response rate in terms of CR and ORRs: 65.1% of patients had CR, 29.6% had PR and the best ORR was 94.7%. K-M estimate of PFS rate was 84.9% at 12 months, 81.0% at 18 months and 78.5% at 24 months. To conclude, the results showed an acceptable safety profile of R-CHOP and improvement in treatment outcomes on treatment naïve patients with CD20-positive DLBCL.

Marketing Authorization Holder	Sandoz GmbH, Biochemiestrasse 10 6250 Kundl Austria
Name(s) and Affiliation(s) of Principal Investigator(s)	Not applicable

2 List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical therapeutic chemical
CI	Confidence interval
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CR	Complete response
CRO	Contract research organization
DLBCL	Diffuse large B-cell lymphoma
ECOG	Eastern co-operative oncology group
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC	European organisation for research and treatment of cancer
GHS	Global Health Status
ICF	Informed consent form
K-M	Kaplan-Meier
MedDRA	Medical dictionary for regulatory activities
NIS	Non-interventional study
ORR	Overall response rate
PFS	Progression-free survival
PR	Partial response
PRO	Patient-reported outcome
PT	Preferred Term
QLQ-C30	Quality of life questionnaire-C30
QoL	Quality of life
R-CHOP	Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
RECIL	Response evaluation criteria in lymphoma
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SmPC	Summary of product characteristics
WHO	World health organization

3 Investigators

See Annex 1.

4 Other responsible parties

Not applicable.

5 Milestones

Study milestones are presented in Table 5-1.

Table 5-1 Study milestones

Milestone	Planned date	Actual date
Start of data collection	NA	19 October 2017
End of data collection	NA	31 March 2021
Final report of study results	NA	13 December 2021
Date of protocol approval by an Institutional Review Board/Independent Ethics Committee	NA	04 October 2017

6 Rationale and background

Diffuse large B-cell lymphoma (DLBCL) is the most frequent form of non-Hodgkin lymphoma among adults (Tilly et al 2015), with an annual incidence of 7 to 8 cases per 100,000 (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 being 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, comprising of rituximab, 3 chemotherapy agents (cyclophosphamide, doxorubicin, vincristine), and one steroid (prednisone), is a widely used therapy for DLBCL (Tilly et al 2015).

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 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 fragment crystallizable domain of rituximab can exhibit effector functions with the capability of mediating target cell lysis.

Rituximab was approved as the first therapeutic antibody for the treatment of 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).

Rixathon® has been approved by the EMA for use in the same indications as the reference MabThera®, based on the demonstrated biosimilarity. The Rixathon® clinical development program confirmed that Rixathon® and MabThera® match in terms of pharmacological properties, efficacy, and safety. The clinical program comprised 4 clinical studies overall: 2 in indolent lymphoma and 2 in rheumatoid arthritis.

This was the first clinical study of Rixathon® in patients with DLBCL.

The purpose of the study was to assess the effectiveness and safety of Rixathon® in untreated patients with CD20-positive DLBCL under real-world conditions when treated with the R-CHOP regimen.

7 Research question and objectives

7.1 Primary objective

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

7.2 Secondary objectives

Secondary objectives of this study were to assess the overall response rate (ORR) at the end of treatment and the progression-free survival (PFS) rate. Furthermore, the general safety and tolerability of R-CHOP and the patients' quality of life (QoL) were assessed.

The secondary endpoints were as follows:

- ORR, defined as patients with either CR or partial response (PR) to treatment.
- PFS, defined as time from date of first R-CHOP treatment to time from date of first documented progression of disease or death, due to any cause, with up to 24 months of follow-up.
- Incidence of serious adverse events (SAEs), including adverse drug reactions (ADRs).
- QoL assessed by patient-reported outcome (PRO) measures collected using the validated European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire-C30 (QLQ-C30) at baseline and every 3 months thereafter, for a total duration of 12 months.

8 Amendments and updates to the protocol

Amendments and updates to the study protocol are presented in Table 8-1.

Table 8-1 Study protocol amendments and updates

Number	Date	Section of the study protocol	Amendment or update	Reason
Version 2.0	26 September 2018	5 (Research question and objectives); 6.7 (Data analysis); Table 6-1 (Data collection schedule)	Revision of the statistical and safety sections	The statistics section was revised. Plan for an interim analysis in Q4 2018 was included, while the interim analysis planned for Q3 2018 was removed. The process of AE documentation and reporting was clarified.
Version 3.0	14 October 2019	5 (Secondary objectives)	Updated PFS distribution from 12 to 24 months	To extend the follow-up period of the study from 12 to 24 months.
Version 3.0	14 October 2019	6.1 (Study design)	Updated sample size	To reflect the actual recruitment target
Version 3.0	14 October 2019	6.2 (Setting)	Updated PFS distribution from 12 to 24 months	To extend the follow-up period of the study from 12 to 24 months
Version 3.0	14 October 2019	6.3 (Variables)	Addition of an extra observation schedule	To reflect the extended observation period of 24 months
Version 3.0	14 October 2019	6.4 (Data sources)	Updated Table 6-1	To reflect the extended observation period of 24 months
Version 3.0	14 October 2019	6.5 (Study size)	Updated sample size and revised descriptive parameters	To reflect the actual recruitment target
Version 3.0	14 October 2019	6.7 (Data analysis)	Inclusion of an interim analysis for Q4 2019	To include an additional interim analysis to take place in Q4 2019
Version 3.0	14 October 2019	8 (AEs)	Updated AEs of special interest reporting. Collection of related SAEs at the extended observation period of 24 months	To include eCRF requirements. To reflect the extended observation period of 24 months

9 Research methods

9.1 Study design

This was a non-interventional, prospective, multicenter study. A total of 184 treatment-naïve patients with CD20-positive DLBCL were enrolled as per routine clinical practice, of those 169 patients were included for final analysis.

In this study, commercially available Rixathon®, cyclophosphamide, doxorubicin, vincristine, and prednisone, were to be used as prescribed treatment for DLBCL as per the treating physician's best clinical judgement. Therefore, the decision to treat a patient with Rixathon® was independent from the decision to include the patient in the study.

Being an observational study, only data available from routine clinical practice and standard of care, in line with national and international laws and regulations, were to be recorded. The study did not impose any mandatory treatment regimens nor require treating physicians to assess specific tests.

Data were to be transcribed from the patient's medical record and entered into an electronic case report form (eCRF).

9.2 Setting

Prior to entry into this study, eligible patients were required to provide written informed consent.

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

The QoL data were collected at the time of enrollment or before the first dose of R-CHOP and then at the time of patient contact closest to 3, 6, 9, and 12 months.

Written informed consent had to be obtained from all patients prior to any data collection for the study. It was important that the patient personally signed and dated 2 written copies of the informed consent form (ICF) prior to enrollment after having received written and verbal information about the study from the treating physician or designee. One original copy was to be kept by the treating physician and the patient was to receive the second original copy.

Patients who participated in the extended observation period were to be re-consented.

9.3 Patients

Treatment-naïve, CD20-positive, adult patients with DLBCL, who were to be treated with R-CHOP based on the decision of the treating physician were eligible for the study.

9.3.1 Inclusion criteria

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

1. Confirmed diagnosis of CD20-positive DLBCL
2. Considered for therapy with R-CHOP as per the treating physician's discretion and had planned to receive, or had already received at least one dose of Rixathon®
3. Aged ≥ 18 years

4. Capability of providing written informed consent

9.3.2 Exclusion criteria

Patients who met any of the following criteria were not eligible:

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

9.4 Variables

The following data were to be collected according to Table 9-1, but only if routinely assessed during clinical practice and per standard of care and if documented in the patient's medical records:

9.4.1 Baseline

- Patient demographics
- Physical examination findings, 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 PROs collected using the validated questionnaire EORTC QLQ-C30

9.4.2 Therapy and 12-month follow up

- Physical examination findings
- 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 adverse events (AEs) and SAEs experienced
- QoL assessed by PROs collected using the validated questionnaire EORTC QLQ-C30 (completed at Months 3, 6, 9, and 12)

9.4.3 End of 12-month 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 R-CHOP, if applicable
- Reason for study discontinuation

9.4.4 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 were considered related to disease, therapies other than Rixathon®, were not required to be reported during this extended observation period)
- Reason for study discontinuation

9.4.5 Other assessments

- DLBCL subtype analysis
- Hepatitis B virus screening

9.5 Data sources and measurement

Initiation of the participating sites was performed by a designated contract research organization (CRO). A CRO representative reviewed the protocol and eCRF with the physicians and their staff in person or by phone.

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

The CRO followed their internal standard operating procedures for monitoring, which had been reviewed and approved by the Sponsor.

Concomitant or prior medications entered into the database were coded using the World Health Organization (WHO) drug reference list. Medical history/current medical conditions and AEs were coded using medical dictionary for regulatory activities (MedDRA) terminology.

9.5.1 Data collection schedule

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

Table 9-1 shows the recommended data collection schedule designed and developed in alignment with the general and internationally accepted patterns of routine clinical practice and standard of care for patients with DLBCL treated with R-CHOP. Visits 1 to 6/8 (V1 to V6/V8) represent the chemotherapy cycles of R-CHOP (R-CHOP14 or R-CHOP21).

Table 9-1 Data collection schedule

	V0, i.e. Baseline	At each patient contact during observational period, i.e. treatment V1 to V6/8, and every 3 months after treatment	End of 12 months observation	Extended observation (Months 18 and 24)
Informed consent	X			
Inclusion/exclusion criteria	X			
Patient demographics	X			
Physical examination	X	X		
Relevant medical history and comorbidities	X			
Pregnancy status*	X	X	X	X
ECOG performance status/Karnofsky index	X	X	X	
DLBCL characteristics and diagnostic details	X			
Concomitant therapy at Baseline and changes during study	X	X	X	
Rixathon® treatment details	X	X		
CHOP chemotherapy, radiotherapy, supportive therapy details	X	X		
Anti-neoplastic surgery	X	X	X	
Response to treatment with Rixathon® in combination withCHOP chemotherapy		X	X	
AEs and SAEs	X	X (until 30 days after last Rixathon® dose)		
AEs and SAEs considered by the investigator to be related to Rixathon®	X	X	X	
SAEs considered by the investigator to be related to Rixathon®*	X	X	X	X
AESI*	X	X	X	X
QoL assessment (EORTC QLQ-C30)**	X	X (Months 3, 6, 9, 12 only)		
Subsequent therapy, if applicable			X	

	V0, i.e. Baseline	At each patient contact during observational period, i.e. treatment V1 to V6/8, and every 3 months after treatment	End of 12 months observation	Extended observation (Months 18 and 24)
Re-consent				X
Details on patient status (survival, progression or relapse, death)				X
Reason for study discontinuation			X	X

AE = adverse event; AESI = adverse event of special interest, R-CHOP = Rixathon® in combination with 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; QLQ-C30 = quality of life questionnaire-C30; QoL = quality of life; SAE = serious adverse event

*Collected at every patient contact from baseline (V0) until the end of extended observation.

**QoL data were collected at the time of enrollment, before the first dose of R-CHOP, and then at the time of patient contact closest to 3, 6, 9, and 12 months

Note: All data apart from QoL data were acquired according to standard of care.

9.6 Bias

Refer Section 11.2.

9.7 Study size

The study endpoints were descriptive and hence no sample size calculation based on a formal hypothesis test was to be performed. The sample size was calculated based on precision of point estimates of the 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 were ± 7.4%. This precision was considered adequate. It was expected that all 180 patients would be available for analysis.

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

9.8 Data transformation

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

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

9.9 Statistical methods

All data analyses were performed by the Sponsor.

9.9.1 Main summary measures

The statistical methodology is summarized in the following sections and detailed statistical information is provided in version 3.0 of the Statistical Analysis Plan (SAP), dated 01 September 2021 (see Annex 2).

Due to the nature of the study design, no formal statistical testing was applied in this study.

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

Categorical variables were summarized by number of patients and percentages.

The time of enrollment in the study was defined as the point when a patient signed the ICF at V0 (Baseline Visit).

9.9.2 Main statistical methods

9.9.2.1 Analysis sets

The full analysis set (FAS) included all patients who received ≥ 1 dose of R-CHOP. All analyses were based on the FAS.

9.9.2.2 Disposition of patients and protocol deviations

Disposition of patients was presented by frequency tabulations for all patients. Reason for discontinuation were summarized. Percentage for reasons for study discontinuation were based on the number of patients that discontinued the study.

Protocol deviations were also listed by patient.

9.9.2.3 Patient demographics and other baseline characteristics

Data collected at Baseline, including patient demographics and disease characteristics, were listed and summarized descriptively.

Relevant medical history and current medical conditions, results of laboratory screens, and any other relevant information were summarized as appropriate and were listed by patient.

9.9.2.4 Treatments

Summary table for R-CHOP cycles for R-CHOP14 and R-CHOP21 were presented descriptively. There were no patients with R mono treatment; hence, no data were included under this treatment category. Furthermore, R-CHOP treatment data were listed by patient.

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

9.9.2.5 Analysis of the primary endpoint

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

The primary endpoint was the number (%) of patients with CR at the end of R-CHOP treatment (assessed at V6/V8). For patients who discontinued the study early, the last available assessment were considered (last observation carried forward method were applied). Furthermore, the 95% CIs, calculated using the Clopper-Pearson method, were provided.

Additionally, the primary endpoint, CR was also measured using the best response during the study (treatment) period, which was according to International Working Group consensus response evaluation criteria in lymphoma, RECIL (Younes et al 2017).

9.9.2.6 Analysis of secondary endpoints

9.9.2.6.1 Overall response rate

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

9.9.2.6.2 Progression-free survival rate at 24 months

PFS is defined as the time from the start of R-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 were estimated and displayed. The resulting median PFS time, and the rate at 12 and 24 months were provided with 95% CIs.

9.9.2.6.3 Adverse events

All information on AEs, including start and stop dates, duration, and relationship to Rixathon®, were displayed by patient. Summary tables included AEs occurring after a patient had provided informed consent up to until 30 days after the patient received the last dose of Rixathon®, or stopped study participation.

Any AEs and SAEs related to Rixathon® occurring during the 12-month observational period or during the extended 24-month observational period (at patient contacts at 18 and 24 months) were summarized.

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

SAEs (including deaths), ADRs, AEs of special interest (AESIs), and AEs leading to discontinuation were tabulated and listed. A patient with multiple AEs within a primary SOC were only counted once towards the total of the primary SOC.

9.9.2.6.4 Quality of life

QoL was assessed by PROs collected using the EORTC QLQ-C30 and analyzed according to the EORTC scoring manual.

9.9.3 Methods used to examine subgroups and interactions

Not done, as not enough data was available.

9.9.4 Missing values

No imputation for missing values was planned for the effectiveness and safety analyses in this study. The missing values were treated as missing at random.

Missing value handling in the QoL endpoints (EORTC QLQ-C30) followed the standard algorithms according to the EORTC scoring manual, in which missing values were imputed by group average.

9.9.5 Sensitivity analyses

Not applicable.

9.9.6 Interim analyses

Interim analyses were conducted in Q4 2018 and Q4 2019, the latter for analysis of the primary endpoint. Separate SAPs were prepared for each of the interim analyses.

9.9.7 Amendments to the statistical analysis plan

There were 3 amendments to the SAP. Refer version 3.0 of the SAP, dated 01 September 2021 provided in Annex 2 for details.

9.10 Quality control

Data quality and integrity, including accuracy and legibility of collected data and original documents, were controlled by the following measures.

9.10.1 Sponsor data management

The Sponsor ensured 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.

9.10.2 Data recording and document retention

In all scenarios, the treating physician had to 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 also had to keep the original ICF signed by the patient.

The treating physician had to give the Sponsor (or designee) access to all relevant source documents to confirm their consistency with the eCRF entries. Information about the identity of the patients recorded in the source documents was not to be transferred to the eCRF.

All study documentation data were to be archived for at least 15 years after the end of the study or longer if required by national and local legal requirements.

The documents may only be destroyed after a written approval of the Sponsor is granted.

9.10.3 Study site monitoring

Formal study site monitoring was performed by the designated CRO as described in the monitoring plan. The Sponsor was to ensure compliance with the monitoring requirements.

Monitoring activities included reviews of the progress of the study and compliance with the protocol, standard operating procedures, and applicable guidelines.

10 Results

10.1 Participants

A summary of patient disposition is presented in Table 10-1. A total of 169 patients were included in final analysis. Of those 24.9% of patients discontinued treatment before the end of 12 months observation period and 4.1% of patients discontinued treatment before the end of 24 months observation period.

The primary reasons for early discontinuation during the 12 months observation period were progressive disease (10.7%), lost to follow-up (5.3%), AEs and subject withdrawal (1.8% each). There were 7 deaths (4.1%) reported during this period.

The primary reason for early discontinuation during the 24 months observation period was progressive disease (3.6%).

Protocol deviations and reason(s) for exclusion of patients from FAS are listed in Listing 16.2.2.1.

Table 10-1 Patient disposition

Disposition/Reason	All Patients N=169 n (%)
All enrolled patients	**169 (100)**
Completed 12 months observation period	**127 (75.1)**
Premature 12 months discontinuation	**42 (24.9)**
Primary reason for discontinuation treatment (12 months period)	
Adverse Event	3 (1.8)
Death	7 (4.1)
Lost To Follow-Up	9 (5.3)
Other	2 (1.2)
Progressive Disease	18 (10.7)
Withdrawal By Subject	3 (1.8)
Completed 24 months observation period	**100 (59.2)**
Premature 24 months discontinuation	**7 (4.1)**
Primary reason for discontinuation treatment (24 months period)	
Progressive Disease	6 (3.6)
Unknown	1 (0.6)

- N is the number of patients in Full Analysis Set (FAS)
- Percentages are based on N
Source: Table 14.1-1.1

10.2 Descriptive data

10.2.1 Demographics and baseline characteristics

Demographic and baseline characteristics are summarized in Table 10-2. The median age of patients was 70 years (range: 24-94) and 52.1% were women. The ECOG PS at baseline was 0 or 1 among 80.5% of patients (136 of 169 patients); 6.5% (11 of 169) had PS of at least 2, which included 1.8% (3 of 169) with a PS of 3. The majority of patients (115 of 169, 68.1%) had Karnofsky PS $\geq$ 80% at baseline, while 18 of 169 (10.7%) patients had Karnofsky PS $\leq$ 80%. Few patients (4.1%) underwent prior anti-neoplastic surgery.

Patient demographics and baseline characteristics by patient are presented in Listing 16.2.4-1.

Table 10-2 Patient demographics and baseline characteristics (FAS)

Characteristic	All Patients N=169
Age at baseline (years)	

Characteristic	All Patients N=169
N	169
Mean (SD)	67.3 (13.4)
Median	70.0
Q1-Q3	58.0-78.0
Min-Max	24-94
Age group (years) -n (%)	
<60	47 (27.8)
≥ 60	122 (72.2)
Gender -n (%)	
Female	88 (52.1)
Male	81 (47.9)
Height (cm)	
N	169
Mean (SD)	170.64 (9.00)
Median	170.00
Q1-Q3	164.00-178.00
Min-Max	151.0-193.0
Weight (kg)	
N	169
Mean (SD)	76.67 (17.05)
Median	73.00
Q1-Q3	66.00-86.00
Min-Max	48.0-167.0
BMI at baseline (kg/m²)	
N	169
Mean (SD)	26.28 (5.27)
Median	25.00
Q1-Q3	23.10-28.40
Min-Max	17.9-50.8
ECOG performance status at baseline -n (%)	
0	58 (34.3)
1	78 (46.2)
2	8 (4.7)
3	3 (1.8)
Not available	22 (13.0)
Karnofsky performance status at baseline -n (%)	
50	2 (1.2)
60	5 (3.0)
70	11 (6.5)
80	34 (20.1)
90	41 (24.3)
100	40 (23.7)

Characteristic	All Patients N=169
Not available	36 (21.3)
Anti-neoplastic surgery at baseline -n (%)	
No	162 (95.9)
Yes	7 (4.1)
Physical examination findings	
General Appearance -n (%)	
ABNORMAL CS	1 (0.6)
ABNORMAL NCS	3 (1.8)
NORMAL	114 (67.5)
Not available	1 (0.6)
Missing	50 (29.6)
Head and neck -n (%)	
ABNORMAL CS	3 (1.8)
ABNORMAL NCS	2 (1.2)
NORMAL	6 (3.6)
Missing	158 (93.5)
Ears Eyes Nose Throat -n (%)	
ABNORMAL CS	1 (0.6)
NORMAL	7 (4.1)
Missing	161 (95.3)
Cardiovascular system -n (%)	
ABNORMAL CS	2 (1.2)
ABNORMAL NCS	1 (0.6)
NORMAL	17 (10.1)
Missing	149 (88.2)
Pulmonary system -n (%)	
ABNORMAL CS	2 (1.2)
ABNORMAL NCS	1 (0.6)
NORMAL	11 (6.5)
Missing	155 (91.7)
Abdomen -n (%)	
ABNORMAL CS	4 (2.4)
ABNORMAL NCS	2 (1.2)
NORMAL	14 (8.3)
Missing	149 (88.2)
Neurological findings -n (%)	
NORMAL	5 (3.0)
Not available	1 (0.6)
Missing	163 (96.4)
Lymph nodes -n (%)	
ABNORMAL CS	7 (4.1)
ABNORMAL NCS	6 (3.6)

Characteristic	All Patients N=169
NORMAL	5 (3.0)
Not available	2 (1.2)
Missing	149 (88.2)
Skin -n (%)	
ABNORMAL CS	2 (1.2)
NORMAL	7 (4.1)
Missing	160 (94.7)
Musculosceletal system -n (%)	
ABNORMAL NCS	3 (1.8)
NORMAL	4 (2.4)
Not available	2 (1.2)
Missing	160 (94.7)
Pregnancy status at baseline -n (%)	
No	88 (52.1)
Missing	81 (47.9)

Age is calculated from date of screening and date of birth
Weight and height are taken from screening vital signs evaluations
BMI: body mass index and BSA: body surface area are calculated based on raw data measurements
Source: Table 14.1-2.1

10.2.2 DLBCL characteristics

Baseline DLBCL characteristics are summarized in Table 10-3.

Among those with DLBCL subtype details, 54 (32.0%) patients had GCB subtype and 7 (4.1%) patients had ABC subtype. Forty-five out of 169 patients (26.6%) had a stage I disease according to Ann Arbor classification; 41 patients (24.3%) had a stage IV lymphoma, 35 (20.7%), 13 (7.7%) and 33 (19.5%) patients in stages II1, II2 and III, respectively. DLBCL NOS was the most commonly reported category of DLBCL (142 of 169, 84.0%) followed by intravascular large B-cell lymphoma (7 of 169, 4.1%). The most common sites of target lesions were cervical (14.2), axillary (13.0), retroperitoneal (10.7%), intraperitoneal (10.1%), inguinal (7.1%) and intrathoracic (4.7%). Enlarged lymph nodes was the most commonly reported DLBCL symptom (60.9%) while disease-related pain and fatigue occurred in 29.6% and 18.9% of patients, respectively.

Table 10-3 DLBCL characteristics and diagnosis details (FAS)

Characteristic	All Patients N=169 n (%)
DLBCL subtype	
ABC	7 (4.1)
GCB	54 (32.0)
Not done	6 (3.6)
Not available	102 (60.4)

Characteristic	All Patients N=169 n (%)
Staging	
I	45 (26.6)
II1	35 (20.7)
II2	13 (7.7)
III	33 (19.5)
IV	41 (24.3)
Not available	2 (1.2)
Extranodal infiltration	
E	88 (52.1)
S	4 (2.4)
X	12 (7.1)
Unknown	27 (16.0)
Not available	38 (22.5)
IPI score	
0	11 (6.5)
1	38 (22.5)
2	36 (21.3)
3	37 (21.9)
4	17 (10.1)
5	2 (1.2)
Missing	28 (16.6)
Morphology	
B-cell lymphoma unclassifiable intermediate between DLBCL and Burkitt Lymph	2 (1.2)
DLBCL NOS	142 (84.0)
DLBCL centroblastic	1 (0.6)
DLBCL with plasma cell immunophenotype	3 (1.8)
EBV positive DLBCL	3 (1.8)
Intravascular large B-cell lymphoma	7 (4.1)
Primary CNS DLBCL	2 (1.2)
Primary cutaneous DLBCL (leg-type)	2 (1.2)
diffus large B-Cell-Lymphoma Non-GCP-Type	1 (0.6)
diffuse large cell b-cell lymphoma	2 (1.2)
follicular lymphoma	1 (0.6)
Not available	3 (1.8)
Size of target lesion	
extranodal (≤ 10 mm	8 (4.7)
extranodal (> 10 mm)	48 (28.4)
nodal (≤ 15 mm)	15 (8.9)
nodal (> 15 mm)	53 (31.4)
Not available	45 (26.6)

Characteristic	All Patients N=169 n (%)
Site of target lesion	
Axillary	22 (13.0)
Cervical	24 (14.2)
Inguinal	12 (7.1)
Intraperitoneal	17 (10.1)
Intrathoracal	8 (4.7)
Retroperitoneal	18 (10.7)
Other	57 (33.7)
Not available	11 (6.5)
Symptoms	
Enlarged Lymph nodes	
No	60 (35.5)
Yes	103 (60.9)
Unknown	4 (2.4)
Not available	2 (1.2)
Disease related pain	
No	109 (64.5)
Yes	50 (29.6)
Unknown	9 (5.3)
Not available	1 (0.6)
Fatigue	
No	130 (76.9)
Yes	32 (18.9)
Unknown	7 (4.1)

- DLBCL information are assessed at baseline
Source: Table 14.1-3.1

10.2.3 Concomitant medication

Concomitant medications are summarized in Table 10-4. Concomitant medications / non-drug therapies prior to or after the start of study treatment by SOC and PT are listed in Listing 16.2.4-3.

A total of 165 of 169 (97.6%) patients took concomitant medication during the study. The most common concomitant medication class (>50%) were analgesics (74.6%), antihistamines for systemic use (72.2%), antiemetics and antinauseants (68.6%), corticosteroids for systemic use (64.5%), drugs for acid related disorders (64.5%), antibacterials for systemic use (62.1%), cough and cold preparations (57.4%) and immunostimulants (56.2%).

The most common concomitant medication by PT (>25%) were paracetamol (60.4%), mesna (57.4%), sulfamethoxazole (trimethoprim, 42.6%), prednisolone (37.3%), ranitidine hydrochloride (37.3%), aciclovir (30.2%), pegfilgrastim (29.6%), allopurinol (28.4%), pantoprazole (26.0%) and granisetron (26.0%).

Table 10-4 Concomitant medications by ATC class and PT (FAS)

ATC class Preferred term	All Patients N=169 n (%)
Any ATC class	**165 (97.6)**
ANALGESICS	**126 (74.6)**
PARACETAMOL	102 (60.4)
METAMIZOLE SODIUM	20 (11.8)
METAMIZOLE	16 (9.5)
METOPROLOL	7 (4.1)
NALOXONE HYDROCHLORIDE;TILIDINE HYDROCHLORIDE	7 (4.1)
OXYCODONE HYDROCHLORIDE	6 (3.6)
PREGABALIN	6 (3.6)
ACETYLSALICYLIC ACID	2 (1.2)
MORPHINE	2 (1.2)
MORPHINE SULFATE	2 (1.2)
NALOXONE HYDROCHLORIDE;OXYCODONE HYDROCHLORIDE	2 (1.2)
ANALGESICS	1 (0.6)
FENTANYL	1 (0.6)
HYDROMORPHONE	1 (0.6)
HYDROMORPHONE HYDROCHLORIDE	1 (0.6)
TAPENTADOL HYDROCHLORIDE	1 (0.6)
TRAMADOL	1 (0.6)
VENLAFAXINE HYDROCHLORIDE	1 (0.6)
ANTIHISTAMINES FOR SYSTEMIC USE	**122 (72.2)**
DIMETINDENE MALEATE	40 (23.7)
CLEMASTINE FUMARATE	34 (20.1)
CLEMASTINE	25 (14.8)
DIMETINDENE	24 (14.2)
DESLORATADINE	2 (1.2)
DIMENHYDRINATE	2 (1.2)
ANTIHISTAMINES FOR SYSTEMIC USE	1 (0.6)
CETIRIZINE HYDROCHLORIDE	1 (0.6)
FEXOFENADINE HYDROCHLORIDE	1 (0.6)
LEVOCETIRIZINE	1 (0.6)
LEVOCETIRIZINE DIHYDROCHLORIDE	1 (0.6)
ANTIEMETICS AND ANTINAUSEANTS	**116 (68.6)**
GRANISETRON	44 (26.0)
ONDANSETRON	42 (24.9)
PALONOSETRON	27 (16.0)
APREPITANT	16 (9.5)
GRANISETRON HYDROCHLORIDE	9 (5.3)
NETUPITANT;PALONOSETRON HYDROCHLORIDE	6 (3.6)
DIMENHYDRINATE	5 (3.0)
FOSAPREPITANT MEGLUMINE	2 (1.2)
SEROTONIN (5HT3) ANTAGONISTS	2 (1.2)
DRONABINOL	1 (0.6)

ATC class Preferred term	All Patients N=169 n (%)
FOSAPREPITANT	1 (0.6)
PALONOSETRON HYDROCHLORIDE	1 (0.6)
CORTICOSTEROIDS FOR SYSTEMIC USE	**109 (64.5)**
PREDNISOLONE	63 (37.3)
DEXAMETHASONE	42 (24.9)
PREDNISOLONE SODIUM SUCCINATE	14 (8.3)
PREDNISONE	7 (4.1)
METHYLPREDNISOLONE	1 (0.6)
DRUGS FOR ACID RELATED DISORDERS	**109 (64.5)**
RANITIDINE HYDROCHLORIDE	63 (37.3)
PANTOPRAZOLE	44 (26.0)
PANTOPRAZOLE SODIUM SESQUIHYDRATE	29 (17.2)
OMEPRAZOLE	6 (3.6)
ESOMEPRAZOLE	3 (1.8)
CIMETIDINE	2 (1.2)
RANITIDINE	1 (0.6)
ANTIBACTERIALS FOR SYSTEMIC USE	**105 (62.1)**
SULFAMETHOXAZOLE;TRIMETHOPRIM	72 (42.6)
CIPROFLOXACIN	29 (17.2)
PIPERACILLIN SODIUM;TAZOBACTAM SODIUM	10 (5.9)
LEVOFLOXACIN	8 (4.7)
PIPERACILLIN	7 (4.1)
TAZOBACTAM	6 (3.6)
CLARITHROMYCIN	4 (2.4)
MEROPENEM	4 (2.4)
AMOXICILLIN TRIHYDRATE;CLAVULANATE POTASSIUM	3 (1.8)
CEFTRIAXONE SODIUM	3 (1.8)
CEFUROXIME	3 (1.8)
CLINDAMYCIN	3 (1.8)
LINEZOLID	3 (1.8)
VANCOMYCIN	3 (1.8)
AMOXICILLIN	2 (1.2)
AMOXICILLIN;CLAVULANIC ACID	2 (1.2)
AMPICILLIN	2 (1.2)
AZITHROMYCIN	2 (1.2)
CIPROFLOXACIN HYDROCHLORIDE	2 (1.2)
NITROFURANTOIN	2 (1.2)
AMPICILLIN;SULBACTAM	1 (0.6)
CEFAZOLIN	1 (0.6)
CEFPODOXIME	1 (0.6)
CEFTAZIDIME	1 (0.6)
CLAVULANIC ACID	1 (0.6)
DOXYCYCLINE	1 (0.6)
FOSFOMYCIN	1 (0.6)
GENTAMICIN	1 (0.6)

ATC class Preferred term	All Patients N=169 n (%)
GENTAMICIN SULFATE	1 (0.6)
MEROPENEM TRIHYDRATE	1 (0.6)
METRONIDAZOLE	1 (0.6)
MOXIFLOXACIN	1 (0.6)
MOXIFLOXACIN HYDROCHLORIDE	1 (0.6)
PENICILLIN NOS	1 (0.6)
PIPERACILLIN SODIUM;TAZOBACTAM	1 (0.6)
SULTAMICILLIN TOSILATE	1 (0.6)
COUGH AND COLD PREPARATIONS	**97 (57.4)**
MESNA	97 (57.4)
DIHYDROCODEINE THIOCYANATE	1 (0.6)
IMMUNOSTIMULANTS	**95 (56.2)**
PEGFILGRASTIM	50 (29.6)
LIPEGFILGRASTIM	32 (18.9)
FILGRASTIM	18 (10.7)
LENOGRASTIM	4 (2.4)
GRANULOCYTE COLONY STIMULATING FACTOR	2 (1.2)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	**60 (35.5)**
RAMIPRIL	27 (16.0)
CANDESARTAN	8 (4.7)
VALSARTAN	7 (4.1)
AMLODIPINE BESILATE;OLMESARTAN MEDOXOMIL	2 (1.2)
CAPTOPRIL	2 (1.2)
EPROSARTAN	2 (1.2)
LISINOPRIL	2 (1.2)
AMLODIPINE BESILATE;VALSARTAN	1 (0.6)
CANDESARTAN CILEXETIL	1 (0.6)
CAPTOPRIL;HYDROCHLOROTHIAZIDE	1 (0.6)
ENALAPRIL;LERCANIDIPINE	1 (0.6)
HYDROCHLOROTHIAZIDE;IRBESARTAN	1 (0.6)
HYDROCHLOROTHIAZIDE;TELMISARTAN	1 (0.6)
HYDROCHLOROTHIAZIDE;VALSARTAN	1 (0.6)
INDAPAMIDE;PERINDOPRIL	1 (0.6)
IRBESARTAN	1 (0.6)
LOSARTAN	1 (0.6)
QUINAPRIL	1 (0.6)
TELMISARTAN	1 (0.6)
ANTITHROMBOTIC AGENTS	**57 (33.7)**
ACETYLSALICYLIC ACID	22 (13.0)
ENOXAPARIN SODIUM	8 (4.7)
RIVAROXABAN	8 (4.7)
APIXABAN	6 (3.6)
CERTOPARIN SODIUM	5 (3.0)
EDOXABAN TOSILATE	4 (2.4)
PHENPROCOUMON	3 (1.8)

ATC class Preferred term	All Patients N=169 n (%)
TINZAPARIN SODIUM	3 (1.8)
CLOPIDOGREL	2 (1.2)
DALTEPARIN SODIUM	2 (1.2)
FONDAPARINUX SODIUM	2 (1.2)
CLOPIDOGREL BISULFATE	1 (0.6)
EDOXABAN	1 (0.6)
ENOXAPARIN	1 (0.6)
TINZAPARIN	1 (0.6)
BETA BLOCKING AGENTS	**54 (32.0)**
BISOPROLOL	31 (18.3)
METOPROLOL	14 (8.3)
METOPROLOL SUCCINATE	4 (2.4)
NEBIVOLOL	2 (1.2)
ATENOLOL	1 (0.6)
CARVEDILOL	1 (0.6)
METOPROLOL TARTRATE	1 (0.6)
PROPRANOLOL HYDROCHLORIDE	1 (0.6)
ANTIVIRALS FOR SYSTEMIC USE	**53 (31.4)**
ACICLOVIR	51 (30.2)
BICTEGRAVIR SODIUM;EMTRICITABINE;TENOFOVIR ALAFENAMIDE FUMARATE	1 (0.6)
ENTECAVIR	1 (0.6)
LAMIVUDINE	1 (0.6)
TENOFOVIR	1 (0.6)
VALACICLOVIR	1 (0.6)
VALACICLOVIR HYDROCHLORIDE	1 (0.6)
ANTIGOUT PREPARATIONS	**50 (29.6)**
ALLOPURINOL	48 (28.4)
FEBUXOSTAT	2 (1.2)
DIURETICS	45 (26.6)
TORASEMIDE	29 (17.2)
FUROSEMIDE	12 (7.1)
HYDROCHLOROTHIAZIDE	12 (7.1)
SPIRONOLACTONE	2 (1.2)
XIPAMIDE	1 (0.6)
LIPID MODIFYING AGENTS	**36 (21.3)**
ATORVASTATIN	15 (8.9)
SIMVASTATIN	14 (8.3)
ATORVASTATIN CALCIUM;EZETIMIBE	2 (1.2)
PRAVASTATIN	2 (1.2)
ATORVASTATIN;EZETIMIBE	1 (0.6)
COLESTYRAMINE	1 (0.6)
EZETIMIBE	1 (0.6)
FLUVASTATIN	1 (0.6)
VITAMINS	**34 (20.1)**

ATC class Preferred term	All Patients N=169 n (%)
COLECALCIFEROL	29 (17.2)
VITAMIN D NOS	3 (1.8)
ERGOCALCIFEROL;PHYTOMENADIONE;RETINOL PALMITATE; TOCOPHERYL ACETATE	1 (0.6)
MULTIVITAMINS, PLAIN	1 (0.6)
VITAMINS WITH MINERALS	1 (0.6)
THYROID THERAPY	**33 (19.5)**
LEVOTHYROXINE	13 (7.7)
LEVOTHYROXINE SODIUM	13 (7.7)
LEVOTHYROXINE SODIUM;POTASSIUM IODIDE	3 (1.8)
SODIUM PERCHLORATE	2 (1.2)
LEVOTHYROXINE SODIUM;LIOTHYRONINE SODIUM	1 (0.6)
POTASSIUM IODIDE	1 (0.6)
ANTIMYCOTICS FOR SYSTEMIC USE	**32 (18.9)**
FLUCONAZOLE	19 (11.2)
AMPHOTERICIN B	14 (8.3)
CASPOFUNGIN ACETATE	1 (0.6)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	**25 (14.8)**
METOCLOPRAMIDE	24 (14.2)
DEXPANTHENOL	1 (0.6)
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	**24 (14.2)**
SODIUM CHLORIDE	11 (6.5)
RED BLOOD CELLS, CONCENTRATED	4 (2.4)
CALCIUM CHLORIDE DIHYDRATE;MAGNESIUM CHLORIDE HEXAHYDRATE;POTASSIUM CHLORIDE;SODIUM CHLORIDE; SODIUM LACTATE	3 (1.8)
RED BLOOD CELLS	3 (1.8)
GLUCOSE	2 (1.2)
ALANINE;ARGININE;ASPARTIC ACID;CALCIUM CHLORIDE; GLUCOSE MONOHYDRATE;GLUTAMIC ACID;GLYCINE; GLYCINE MAX SEED OIL;HISTIDINE HYDROCHLORIDE; ISOLEUCINE;LEUCINE;LYSINE HYDROCHLORIDE; MAGNESIUM ACETATE TETRAHY	1 (0.6)
ALANINE;ARGININE;CALCIUM CHLORIDE;FISH OIL; GLUCOSE MONOHYDRATE;GLYCINE;GLYCINE MAX SEED OIL;HISTIDINE;ISOLEUCINE;LEUCINE;LYSINE ACETATE; MAGNESIUM SULFATE;MEDIUM-CHAIN TRIGLYCERIDES; METHIONINE;OLEA EUR	1 (0.6)
ALANINE;ARGININE;GLYCINE;HISTIDINE;ISOLEUCINE; LEUCINE;LYSINE ACETATE;METHIONINE;PHENYLALANINE; PROLINE;SERINE;TAURINE;THREONINE;TRYPTOPHAN, L-; TYROSINE;VALINE	1 (0.6)
BLOOD, WHOLE	1 (0.6)
CALCIUM ACETATE;MAGNESIUM ACETATE TETRAHYDRATE; POTASSIUM ACETATE;SODIUM ACETATE TRIHYDRATE;	1 (0.6)

ATC class Preferred term	All Patients N=169 n (%)
SODIUM CHLORIDE	
CALCIUM CHLORIDE DIHYDRATE;MAGNESIUM CHLORIDE HEXAHYDRATE;MALIC ACID;POTASSIUM CHLORIDE;SODIUM ACETATE TRIHYDRATE;SODIUM CHLORIDE	1 (0.6)
ELECTROLYTE SOLUTIONS [UMBRELLA TERM]	1 (0.6)
MEDIUM-CHAIN TRIGLYCERIDES	1 (0.6)
PLATELETS	1 (0.6)
PLATELETS, CONCENTRATED	1 (0.6)
SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	1 (0.6)
DRUGS FOR CONSTIPATION	**24 (14.2)**
MACROGOL 3350;POTASSIUM CHLORIDE;SODIUM BICARBONATE;SODIUM CHLORIDE	14 (8.3)
MACROGOL	6 (3.6)
SODIUM PICOSULFATE	4 (2.4)
BISACODYL	2 (1.2)
LACTULOSE	2 (1.2)
MACROGOL 4000	1 (0.6)
PRUCALOPRIDE SUCCINATE	1 (0.6)
STOMATOLOGICAL PREPARATIONS	**23 (13.6)**
AMPHOTERICIN B	19 (11.2)
OTHER AGENTS FOR LOCAL ORAL TREATMENT	2 (1.2)
CHLORHEXIDINE	1 (0.6)
LIDOCAINE	1 (0.6)
POVIDONE-IODINE	1 (0.6)
DRUGS USED IN DIABETES	**22 (13.0)**
METFORMIN	9 (5.3)
INSULIN GLARGINE	7 (4.1)
INSULIN	6 (3.6)
INSULIN LISPRO	3 (1.8)
INSULIN DETEMIR	2 (1.2)
EMPAGLIFLOZIN	1 (0.6)
GLIBENCLAMIDE	1 (0.6)
GLIMEPIRIDE	1 (0.6)
INSULIN GLULISINE	1 (0.6)
INSULIN HUMAN	1 (0.6)
METFORMIN HYDROCHLORIDE;SITAGLIPTIN PHOSPHATE	1 (0.6)
METFORMIN;SITAGLIPTIN	1 (0.6)
SITAGLIPTIN	1 (0.6)
SITAGLIPTIN PHOSPHATE	1 (0.6)
ANTIANEMIC PREPARATIONS	**17 (10.1)**
FOLIC ACID	10 (5.9)
CYANOCOBALAMIN	3 (1.8)
EPOETIN ZETA	2 (1.2)
VITAMIN B12 NOS	2 (1.2)
EPOETIN THETA	1 (0.6)

ATC class Preferred term	All Patients N=169 n (%)
ERYTHROPOIETIN	1 (0.6)
FERRIC CARBOXYMALTOSE	1 (0.6)
CALCIUM CHANNEL BLOCKERS	**16 (9.5)**
AMLODIPINE	7 (4.1)
LERCANIDIPINE	5 (3.0)
NITRENDIPINE	2 (1.2)
FELODIPINE	1 (0.6)
NIFEDIPINE	1 (0.6)
VERAPAMIL	1 (0.6)
MINERAL SUPPLEMENTS	**16 (9.5)**
POTASSIUM	4 (2.4)
POTASSIUM CITRATE	4 (2.4)
CALCIUM	3 (1.8)
MAGNESIUM	3 (1.8)
POTASSIUM CARBONATE;POTASSIUM CITRATE	2 (1.2)
POTASSIUM CHLORIDE	2 (1.2)
CALCIUM CARBONATE;COLECALCIFEROL	1 (0.6)
CALCIUM;VITAMIN D NOS	1 (0.6)
MAGNESIUM CITRATE;MAGNESIUM GLUTAMATE;MAGNESIUM NICOTINATE	1 (0.6)
PSYCHOLEPTICS	**15 (8.9)**
ZOLPIDEM	7 (4.1)
LORAZEPAM	6 (3.6)
ZOPICLONE	2 (1.2)
LEVOMEPROMAZINE	1 (0.6)
MELPERONE HYDROCHLORIDE	1 (0.6)
ZOLPIDEM TARTRATE	1 (0.6)
ANTINEOPLASTIC AGENTS	**13 (7.7)**
VINCRISTINE SULFATE	9 (5.3)
CYCLOPHOSPHAMIDE	2 (1.2)
RITUXIMAB	2 (1.2)
ETOPOSIDE	1 (0.6)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	**12 (7.1)**
IBUPROFEN	7 (4.1)
DICLOFENAC	2 (1.2)
BENZYDAMINE HYDROCHLORIDE	1 (0.6)
DICLOFENAC SODIUM	1 (0.6)
SULFASALAZINE	1 (0.6)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ ANTIINFECTIVE AGENTS	**9 (5.3)**
LOPERAMIDE HYDROCHLORIDE	8 (4.7)
MESALAZINE	1 (0.6)
ORAL REHYDRATION SALT FORMULATIONS	1 (0.6)
IMMUNOSUPPRESSANTS	**9 (5.3)**
METHOTREXATE	7 (4.1)

ATC class Preferred term	All Patients N=169 n (%)
HYDROXYCHLOROQUINE SULFATE	2 (1.2)
HYDROXYCHLOROQUINE	1 (0.6)
LEFLUNOMIDE	1 (0.6)
METHOTREXATE SODIUM	1 (0.6)
PSYCHOANALEPTICS	**9 (5.3)**
AMITRIPTYLINE HYDROCHLORIDE	2 (1.2)
MIRTAZAPINE	2 (1.2)
OPIPRAMOL	2 (1.2)
AMITRIPTYLINE	1 (0.6)
CITALOPRAM	1 (0.6)
MIANSERIN	1 (0.6)
DRUGS FOR TREATMENT OF BONE DISEASES	**8 (4.7)**
ALENDRONIC ACID	2 (1.2)
DENOSUMAB	2 (1.2)
ZOLEDRONIC ACID MONOHYDRATE	2 (1.2)
BISPHOSPHONATES	1 (0.6)
ZOLEDRONIC ACID	1 (0.6)
ANTIFUNGALS FOR DERMATOLOGICAL USE	**6 (3.6)**
AMPHOTERICIN B	2 (1.2)
CLOTRIMAZOLE	2 (1.2)
METHYLROSANILINIUM CHLORIDE	2 (1.2)
CARDIAC THERAPY	**6 (3.6)**
DIGITOXIN	2 (1.2)
ADRENERGIC AND DOPAMINERGIC AGENTS	1 (0.6)
AMIODARONE	1 (0.6)
IVABRADINE HYDROCHLORIDE	1 (0.6)
PENTAERITHRITYL TETRANITRATE	1 (0.6)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	**6 (3.6)**
SALBUTAMOL	2 (1.2)
ACLIDINIUM BROMIDE	1 (0.6)
BUDESONIDE;FORMOTEROL FUMARATE	1 (0.6)
FENOTEROL HYDROBROMIDE;IPRATROPIUM BROMIDE	1 (0.6)
FLUTICASONE FUROATE;VILANTEROL TRIFENATATE	1 (0.6)
FLUTICASONE PROPIONATE;SALMETEROL XINAFOATE	1 (0.6)
OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS	1 (0.6)
UROLOGICALS	**6 (3.6)**
TAMSULOSIN	2 (1.2)
ASCORBIC ACID;CUCURBITA PEPO;RIBOFLAVIN; VACCINIUM MACROCARPON	1 (0.6)
SOLIFENACIN SUCCINATE	1 (0.6)
TAMSULOSIN HYDROCHLORIDE	1 (0.6)
TROSPIUM	1 (0.6)
ALL OTHER THERAPEUTIC PRODUCTS	**5 (3.0)**
RASBURICASE	3 (1.8)

ATC class Preferred term	All Patients N=169 n (%)
HOMEOPATHIC PREPARATION	1 (0.6)
OXYGEN	1 (0.6)
GENERAL NUTRIENTS	**5 (3.0)**
GENERAL NUTRIENTS	2 (1.2)
OTHER COMBINATIONS OF NUTRIENTS	2 (1.2)
ASCORBIC ACID;BETACAROTENE;BIOTIN;CALCIUM; CARBOHYDRATES NOS;CHLORIDE;CHROMIUM; COLECALCIFEROL;COPPER;FATS NOS;FLUORINE;FOLIC ACID;IODINE;IRON;MAGNESIUM;MANGANESE;MOLYBDENUM; NICOTINIC ACID;PANTOTHENIC A	1 (0.6)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	**5 (3.0)**
VALERIANA OFFICINALIS	2 (1.2)
HYPERICUM PERFORATUM	1 (0.6)
POPULUS SPP. EXTRACT;SERENOA REPENS EXTRACT; URTICA SPP. EXTRACT	1 (0.6)
SALVIA OFFICINALIS LEAF	1 (0.6)
VITIS VINIFERA LEAF	1 (0.6)
THROAT PREPARATIONS	**4 (2.4)**
CHLORHEXIDINE GLUCONATE	2 (1.2)
BENZALKONIUM CHLORIDE;HEXETIDINE	1 (0.6)
CHLORHEXIDINE	1 (0.6)
ANTIHYPERTENSIVES	**3 (1.8)**
CLONIDINE HYDROCHLORIDE	1 (0.6)
DOXAZOSIN	1 (0.6)
SILDENAFIL CITRATE	1 (0.6)
OPHTHALMOLOGICALS	**3 (1.8)**
CLONIDINE HYDROCHLORIDE	1 (0.6)
DEXAMETHASONE	1 (0.6)
TIMOLOL MALEATE;TRAVOPROST	1 (0.6)
ALL OTHER NON-THERAPEUTIC PRODUCTS	**2 (1.2)**
ALL OTHER NON-THERAPEUTIC PRODUCTS	1 (0.6)
WATER FOR INJECTION	1 (0.6)
ANESTHETICS	**2 (1.2)**
FENTANYL	1 (0.6)
LIDOCAINE HYDROCHLORIDE	1 (0.6)
ANTI-PARKINSON DRUGS	**2 (1.2)**
BENSERAZIDE HYDROCHLORIDE;LEVODOPA	1 (0.6)
CARBIDOPA MONOHYDRATE;ENTACAPONE;LEVODOPA	1 (0.6)
LEVODOPA	1 (0.6)
PRAMIPEXOLE DIHYDROCHLORIDE	1 (0.6)
ROTIGOTINE	1 (0.6)
ANTIEPILEPTICS	**2 (1.2)**
LACOSAMIDE	1 (0.6)
PREGABALIN	1 (0.6)
ANTIMYCOBACTERIALS	**2 (1.2)**

ATC class Preferred term	All Patients N=169 n (%)
ISONIAZID	1 (0.6)
RIFAMPICIN	1 (0.6)
CALCIUM HOMEOSTASIS	2 (1.2)
CALCITONIN	2 (1.2)
CONTRAST MEDIA	2 (1.2)
IOMEPROL	1 (0.6)
LYSINE AMIDOTRIZOATE	1 (0.6)
MEGLUMINE AMIDOTRIZOATE;SODIUM AMIDOTRIZOATE	1 (0.6)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	**2 (1.2)**
BUDESONIDE	1 (0.6)
MOMETASONE FUROATE	1 (0.6)
OTHER NERVOUS SYSTEM DRUGS	2 (1.2)
BETAHISTINE	1 (0.6)
DIMENHYDRINATE	1 (0.6)
ANTIHEMORRHAGICS	1 (0.6)
EPINEPHRINE	1 (0.6)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	**1 (0.6)**
DIMETINDENE MALEATE	1 (0.6)
ANTISEPTICS AND DISINFECTANTS	1 (0.6)
CALCIUM CHLORIDE DIHYDRATE;POLIHEXANIDE; POTASSIUM CHLORIDE;SODIUM CHLORIDE	1 (0.6)
POLIHEXANIDE	1 (0.6)
ENDOCRINE THERAPY	1 (0.6)
BICALUTAMIDE	1 (0.6)
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	1 (0.6)
CLOTRIMAZOLE	1 (0.6)
HOMEOPATHIC PREPARATION	1 (0.6)
HOMEOPATHIC PREPARATION	1 (0.6)
MEDICATED DRESSINGS	1 (0.6)
ALGINIC ACID	1 (0.6)
OTHER RESPIRATORY SYSTEM PRODUCTS	1 (0.6)
OTHER RESPIRATORY SYSTEM PRODUCTS	1 (0.6)
PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS	1 (0.6)
DEXPANTHENOL	1 (0.6)
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	1 (0.6)
DESOGESTREL	1 (0.6)
TONICS	1 (0.6)
DIETARY SUPPLEMENT	1 (0.6)
VASOPROTECTIVES	1 (0.6)
DILTIAZEM	1 (0.6)

-ATC classes are presented in descending frequency for all subjects; preferred terms are sorted within ATC class in descending frequency for all subjects.
- A subject with multiple occurrences within an ATC class is counted only once in the total row.
- A medication can appear with more than one ATC class
Source: Table 14.1-5.1

Prior antineoplastic therapy

Details for Prior antineoplastic surgery are summarized in Table 10-5. Prior antineoplastic surgery are listed in Listing 16.2.6-2.

In total 7 (of 169, 4.1%) patients reported prior surgery at baseline. Duration since the last surgery was <1 months in 5 (3.0%) patients and between 1 and <6 months in 2 (1.2%) patients. The common sites of surgery were abdominal (3 patients, 1.8%), cephalic (2 patients, 1.2%) and thoracic (1 patient, 0.6%).

Table 10-5 Prior antineoplastic therapy – Surgery (Full analysis set)

Characteristic	All Patients N=169 n (%)
Prior surgery	
No	162 (95.9)
Yes	7 (4.1)
Time since last surgery	
< 1 month	5 (3.0)
1 - <6 months	2 (1.2)
6 - <12 months	0
≥ 12 months	0
Procedure at last surgery	
No prior surgery	162 (95.9)
Biopsy	0
Other	0
Missing	7 (4.1)
Locations	
Abdominal	3 (1.8)
Cephalic	2 (1.2)
Not available	1 (0.6)
Thoracic	1 (0.6)

Last surgery is based on the date of surgery.
Reference day for time since last surgery is the enrollment date.
Source: Table 14.1-11.1

10.2.4 Medical history

Relevant medical histories/current medical conditions by primary SOC and PT were summarized in Table 10-6. Relevant medical history/current medical conditions by patient are presented in Listing 16.2.4-2.

The majority of patients (122 of 169, 72.2%) had at least one underlying medical condition at baseline. The commonly (>10% occurrence) reported medical conditions at baseline by SOC were vascular disorders (79 patients, 46.7%), metabolism and nutrition disorders (49 patients, 29.0%), blood and lymphatic system disorders (25 patients, 14.8%), endocrine disorders (25 patients, 14.8%), musculoskeletal and connective tissue disorders (20 patients, 11.8%),

gastrointestinal disorders (18 patients, 10.7%) and neoplasms benign, malignant and unspecified (17 patients, 10.1%).

Hypertension (76 patients, 45.0%) was the most commonly reported underlying condition by PT at baseline, while anemia (25 patients, 14.8%), cardiac disorders (25 patients, 14.8%) and hypothyroidism (19 patients, 11.2%) were reported in at least 10% of patients.

Table 10-6 Relevant medical histories/current medical conditions, by primary SOC and PT (FAS)

Primary system organ class Preferred term	All Patients N=169 n (%)
Number of subjects with at least one event	**122 (72.2)**
Vascular disorders	**79 (46.7)**
Hypertension	76 (45.0)
Peripheral arterial occlusive disease	3 (1.8)
Arteriosclerosis	2 (1.2)
Aortic stenosis	1 (0.6)
Arteriosclerosis Moenckeberg-type	1 (0.6)
Jugular vein thrombosis	1 (0.6)
Macroangiopathy	1 (0.6)
Varicose vein	1 (0.6)
Metabolism and nutrition disorders	**49 (29.0)**
Diabetes mellitus	13 (7.7)
Hyperlipidaemia	13 (7.7)
Hypercholesterolaemia	9 (5.3)
Type 2 diabetes mellitus	9 (5.3)
Vitamin D deficiency	6 (3.6)
Hyperuricaemia	3 (1.8)
Obesity	3 (1.8)
Hyperkalaemia	2 (1.2)
Cachexia	1 (0.6)
Decreased appetite	1 (0.6)
Folate deficiency	1 (0.6)
Gout	1 (0.6)
Hypokalaemia	1 (0.6)
Blood and lymphatic system disorders	**25 (14.8)**
Anaemia	25 (14.8)
Cardiac disorders	25 (14.8)
Atrial fibrillation	9 (5.3)
Coronary artery disease	9 (5.3)
Hypertensive heart disease	4 (2.4)
Mitral valve incompetence	4 (2.4)
Aortic valve stenosis	2 (1.2)
Arrhythmia	2 (1.2)
Cardiac failure	2 (1.2)
Atrioventricular block first degree	1 (0.6)
Bradycardia	1 (0.6)

Primary system organ class Preferred term	All Patients N=169 n (%)
Left ventricular failure	1 (0.6)
Myocardial infarction	1 (0.6)
Sinus node dysfunction	1 (0.6)
Endocrine disorders	**25 (14.8)**
Hypothyroidism	19 (11.2)
Goitre	3 (1.8)
Hyperthyroidism	2 (1.2)
Autoimmune thyroiditis	1 (0.6)
Hypothyroidic goitre	1 (0.6)
Musculoskeletal and connective tissue disorders	**20 (11.8)**
Rheumatoid arthritis	6 (3.6)
Osteoporosis	4 (2.4)
Intervertebral disc protrusion	2 (1.2)
Osteoarthritis	2 (1.2)
Spinal stenosis	2 (1.2)
Arthritis	1 (0.6)
Back pain	1 (0.6)
Fibromyalgia	1 (0.6)
Intervertebral disc degeneration	1 (0.6)
Lumbar spinal stenosis	1 (0.6)
Mixed connective tissue disease	1 (0.6)
Polymyalgia rheumatica	1 (0.6)
Rheumatic disorder	1 (0.6)
Gastrointestinal disorders	**18 (10.7)**
Constipation	3 (1.8)
Diverticulum intestinal	3 (1.8)
Chronic gastritis	2 (1.2)
Gastritis	2 (1.2)
Ileus	2 (1.2)
Diverticulum	1 (0.6)
Duodenitis	1 (0.6)
Gastric stenosis	1 (0.6)
Gastric ulcer	1 (0.6)
Gastrointestinal haemorrhage	1 (0.6)
Gastrooesophageal reflux disease	1 (0.6)
Inguinal hernia	1 (0.6)
Proctitis	1 (0.6)
Neoplasms benign, malignant and unspecified (incl	**17 (10.1)**
cysts and polyps)	
Breast cancer	2 (1.2)
Follicular lymphoma	2 (1.2)
Rectal cancer	2 (1.2)
Renal cell carcinoma	2 (1.2)
Cholesteatoma	1 (0.6)
Gastrointestinal neoplasm	1 (0.6)

Primary system organ class Preferred term	All Patients N=169 n (%)
Laryngeal cancer	1 (0.6)
Leiomyoma	1 (0.6)
Metastases to bone	1 (0.6)
Monoclonal gammopathy	1 (0.6)
Non-Hodgkin's lymphoma	1 (0.6)
Ovarian neoplasm	1 (0.6)
Prostate cancer	1 (0.6)
Squamous cell carcinoma	1 (0.6)
Surgical and medical procedures	**16 (9.5)**
Hysterectomy	3 (1.8)
Thyroidectomy	2 (1.2)
Appendicectomy	1 (0.6)
Cancer surgery	1 (0.6)
Cardiac pacemaker insertion	1 (0.6)
Cholecystectomy	1 (0.6)
Coronary angioplasty	1 (0.6)
Hip surgery	1 (0.6)
Hysterosalpingo-oophorectomy	1 (0.6)
Intervertebral disc operation	1 (0.6)
Lymphadenectomy	1 (0.6)
Nephrectomy	1 (0.6)
Prostatectomy	1 (0.6)
Prostatic operation	1 (0.6)
Salpingo-oophorectomy bilateral	1 (0.6)
Small intestinal resection	1 (0.6)
Spinal decompression	1 (0.6)
Spinal laminectomy	1 (0.6)
Tonsillectomy	1 (0.6)
Uterine dilation and curettage	1 (0.6)
Vascular graft	1 (0.6)
Nervous system disorders	**14 (8.3)**
Cerebrovascular accident	3 (1.8)
Hypertonia	3 (1.8)
Polyneuropathy	3 (1.8)
Parkinson's disease	2 (1.2)
Cerebellar ataxia	1 (0.6)
Cervicobrachial syndrome	1 (0.6)
Intracranial aneurysm	1 (0.6)
Nervous system disorder	1 (0.6)
Paresis	1 (0.6)
Parkinsonism	1 (0.6)
General disorders and administration site conditions	**13 (7.7)**
Pain	6 (3.6)
Oedema peripheral	3 (1.8)
Fatigue	2 (1.2)

Primary system organ class Preferred term	All Patients N=169 n (%)
Chronic fatigue syndrome	1 (0.6)
Gait disturbance	1 (0.6)
Hernia	1 (0.6)
Oedema	1 (0.6)
Respiratory, thoracic and mediastinal disorders	**13 (7.7)**
Asthma	5 (3.0)
Cough	2 (1.2)
Pleural effusion	2 (1.2)
Sleep apnoea syndrome	2 (1.2)
Chronic obstructive pulmonary disease	1 (0.6)
Dyspnoea	1 (0.6)
Pulmonary embolism	1 (0.6)
Pulmonary fibrosis	1 (0.6)
Infections and infestations	**8 (4.7)**
Hepatitis B	2 (1.2)
Diverticulitis	1 (0.6)
Herpes zoster	1 (0.6)
Infection	1 (0.6)
Pneumonia	1 (0.6)
Subcutaneous abscess	1 (0.6)
Tuberculosis	1 (0.6)
Urinary tract infection	1 (0.6)
Psychiatric disorders	**8 (4.7)**
Adjustment disorder with depressed mood	3 (1.8)
Insomnia	2 (1.2)
Depression	1 (0.6)
Sleep disorder	1 (0.6)
Tobacco abuse	1 (0.6)
Renal and urinary disorders	**7 (4.1)**
Chronic kidney disease	2 (1.2)
Renal failure	2 (1.2)
Bladder irritation	1 (0.6)
Bladder stenosis	1 (0.6)
Diabetic nephropathy	1 (0.6)
Hydronephrosis	1 (0.6)
Stress urinary incontinence	1 (0.6)
Skin and subcutaneous tissue disorders	**7 (4.1)**
Dermatitis	2 (1.2)
Psoriasis	2 (1.2)
Decubitus ulcer	1 (0.6)
Night sweats	1 (0.6)
Prurigo	1 (0.6)
Investigations	**6 (3.6)**
Red blood cell count decreased	2 (1.2)
Antibody test positive	1 (0.6)

Primary system organ class Preferred term	All Patients N=169 n (%)
Biopsy	1 (0.6)
Blood cholinesterase	1 (0.6)
Blood creatinine increased	1 (0.6)
Blood iron decreased	1 (0.6)
Blood lactate dehydrogenase increased	1 (0.6)
Blood urea increased	1 (0.6)
C-reactive protein increased	1 (0.6)
Gamma-glutamyltransferase increased	1 (0.6)
HIV test positive	1 (0.6)
Heart rate irregular	1 (0.6)
Platelet count increased	1 (0.6)
Serum ferritin increased	1 (0.6)
Reproductive system and breast disorders	**4 (2.4)**
Benign prostatic hyperplasia	4 (2.4)
Hepatobiliary disorders	2 (1.2)
Cholelithiasis	1 (0.6)
Hepatic cirrhosis	1 (0.6)
Immune system disorders	**2 (1.2)**
Immunodeficiency	1 (0.6)
Seasonal allergy	1 (0.6)
Injury, poisoning and procedural complications	**2 (1.2)**
Asbestosis	1 (0.6)
Transfusion reaction	1 (0.6)
Congenital, familial and genetic disorders	**1 (0.6)**
Developmental hip dysplasia	1 (0.6)
Ear and labyrinth disorders	**1 (0.6)**
Vertigo	1 (0.6)
Eye disorders	**1 (0.6)**
Glaucoma	1 (0.6)
Social circumstances	**1 (0.6)**
Immobile	1 (0.6)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system o rgan
class by descending frequency in total column.
- A subject with multiple events within a primary system organ class is counted only once in the total row.
- MedDRA 24.0 has been used for reporting.
Source: Table 14.1-4.1

10.2.5 Physical examination

Physical examination findings post baseline are summarized in Table 10-7.

Very few patients had abnormal clinically significant physical examination findings post baseline. Abnormal clinical significant findings were reported in the following body systems by visit: cardiovascular system, general appearance, neurological findings (1 patient each, 0.6%)

at Month 3; head and neck and musculoskeletal system (1 patient each, 0.6%) at Month 6 and cardiovascular system and lymph nodes 1 patients each (0.6%) at Month 9.

Table 10-7 Physical examination status post- baseline (FAS)

Visit	Body System	Result	All Patients N=169 n (%)
Month 3	ABDOMEN	Normal	6 (3.6)
		Abnormal NCS	1 (0.6)
		Not available	1 (0.6)
Month 3	CARDIOVASCULAR SYSTEM	Normal	10 (5.9)
		Abnormal CS	1 (0.6)
Month 3	GENERAL APPEARANCE	Normal	76 (45.0)
		Abnormal NCS	9 (5.3)
		Abnormal CS	1 (0.6)
		Not available	1 (0.6)
Month 3	HEAD AND NECK	Normal	2 (1.2)
Month 3	LYMPH NODES	Normal	6 (3.6)
Month 3	MUSCULOSCELETAL SYSTEM	Normal	4 (2.4)
		Abnormal NCS	1 (0.6)
Month 3	NEUROLOGICAL FINDINGS	Normal	2 (1.2)
		Abnormal NCS	1 (0.6)
		Abnormal CS	1 (0.6)
Month 3	PULMONARY SYSTEM	Normal	6 (3.6)
		Abnormal NCS	1 (0.6)
Month 3	SKIN	Normal	2 (1.2)
		Abnormal NCS	2 (1.2)
Month 6	ABDOMEN	Normal	4 (2.4)
		Abnormal NCS	1 (0.6)
Month 6	CARDIOVASCULAR SYSTEM	Normal	4 (2.4)
		Abnormal NCS	1 (0.6)
Month 6	GENERAL APPEARANCE	Normal	53 (31.4)
		Abnormal NCS	8 (4.7)
		Not available	2 (1.2)
Month 6	HEAD AND NECK	Abnormal CS	1 (0.6)
Month 6	LYMPH NODES	Normal	4 (2.4)
Month 6	MUSCULOSCELETAL SYSTEM	Normal	2 (1.2)
		Abnormal NCS	1 (0.6)
		Abnormal CS	1 (0.6)
Month 6	PULMONARY SYSTEM	Normal	3 (1.8)
Month 9	ABDOMEN	Normal	9 (5.3)
Month 9	CARDIOVASCULAR SYSTEM	Normal	7 (4.1)
		Abnormal CS	1 (0.6)
Month 9	GENERAL APPEARANCE	Normal	57 (33.7)
		Abnormal NCS	6 (3.6)

Visit	Body System	Result	All Patients N=169 n (%)
Month 9	HEAD AND NECK	Normal	1 (0.6)
Month 9	LYMPH NODES	Normal	8 (4.7)
		Abnormal CS	1 (0.6)
Month 9	MUSCULOSCELETAL SYSTEM	Normal	1 (0.6)
		Abnormal NCS	2 (1.2)
Month 9	NEUROLOGICAL FINDINGS	Normal	1 (0.6)
Month 9	PULMONARY SYSTEM	Normal	5 (3.0)
Month 12	ABDOMEN	Normal	14 (8.3)
Month 12	CARDIOVASCULAR SYSTEM	Normal	6 (3.6)
Month 12	GENERAL APPEARANCE	Normal	64 (37.9)
		Abnormal NCS	7 (4.1)
Month 12	HEAD AND NECK	Normal	2 (1.2)
Month 12	LYMPH NODES	Normal	12 (7.1)
Month 12	MUSCULOSCELETAL SYSTEM	Normal	1 (0.6)
Month 12	NEUROLOGICAL FINDINGS	Abnormal NCS	1 (0.6)
Month 12	PULMONARY SYSTEM	Normal	6 (3.6)
		Not available	2 (1.2)
Month 12	SKIN	Normal	1 (0.6)
Month 15	ABDOMEN	Normal	5 (3.0)
Month 15	CARDIOVASCULAR SYSTEM	Normal	4 (2.4)
Month 15	GENERAL APPEARANCE	Normal	27 (16.0)
		Abnormal NCS	2 (1.2)
Month 15	HEAD AND NECK	Normal	2 (1.2)
Month 15	LYMPH NODES	Normal	4 (2.4)
Month 15	MUSCULOSCELETAL SYSTEM	Normal	1 (0.6)
Month 15	NEUROLOGICAL FINDINGS	Normal	2 (1.2)
Month 15	PULMONARY SYSTEM	Normal	5 (3.0)

10.2.6 ECOG performance status

ECOG PS post baseline are summarized in Table 10-8.

Those with available ECOG status, the percentages of patients with ECOG-PS <2 post baseline were 56.8% (96 of 169) at Month 3, 46.2% (78 of 169) at Month 6 and 9, 42% (71 of 169) at Month 12 and 16% (27 of 169) at Month 15.

Table 10-8 Patient ECOG performance status post- baseline (FAS)

Visit	EGOG performance status	Number of Patients	% available*	All patients % N=169
Month 3	0	30	29.7%	17.8%
	1	66	65.3%	39.1%
	2	4	4%	2.4%
	3	1	1%	0.6%

Visit	EGOG performance status	Number of Patients	% available*	All patients % N=169
	Missing	3		1.8%
	Not available	65		38.5%
Month 6	0	32	38.6%	18.9%
	1	46	55.4%	27.2%
	2	4	4.8%	2.4%
	3	1	1.2%	0.6%
	Missing	31		18.3%
	Not available	55		32.5%
Month 9	0	48	59.3%	28.4%
	1	30	37%	17.8%
	2	3	3.7%	1.8%
	Missing	52		30.8%
	Not available	36		21.3%
Month 12	0	44	57.1%	26%
	1	27	35.1%	16%
	2	5	6.5%	3%
	5	1	1.3%	0.6%
	Missing	63		37.3%
	Not available	29		17.2%
Month 15	0	16	59.3%	9.5%
	1	11	40.7%	6.5%
	Missing	132		78.1%
	Not available	10		5.9%

* : Percentages are calculated based on only available ECOG status counts.

0=Fully active, able to carry on all pre-disease performance without restriction; 1=Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2=Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours; 3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4=Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair; 5=Dead

10.3 Outcome data

All 169 patients who were enrolled into the study received at least one dose of R-CHOP and were included under FAS (Table 10-1). All analyses were based on FAS.

10.4 Main results

10.4.1 Response rate at the end of treatment

Summary of overall response rate at the end of treatment is presented in Table 10-9. Chemotherapy details by treatment-wise (CHOP) are listed in Listing 16.2.6-1.

The proportion of patients with complete response at the end of treatment was 43.8% (95% CI: 36.2 - 51.6) and 45.6% (95% CI: 37.9 - 53.4) had partial response. The overall response rate was 89.3% (95% CI: 83.7 - 93.6).

Table 10-9 Summary of overall response rate (FAS)

Type of response to treatment	All patients N=169
Overall response rate (ORR) –n (%)	151 (89.3)
95% CI for ORR	(83.7, 93.6)
Complete response (CR) –n (%)	74 (43.8)
95% CI for CR	(36.2, 51.6)
Partial response (PR) –n (%)	77 (45.6)
95% CI for PR	(37.9, 53.4)
Not available	1 (0.6)

- ORR = CR + PR.
- 95% CIs are based on the Clopper-Pearson method.
- N is the number of pts in FAS

Source: Table 14.1-6.1

10.4.2 Response rate during the treatment period according to new RECIL criteria 2017

Summary of overall response rate during the treatment period according to RECIL is presented in Table 10-10.

The proportion of patients with complete response as the best response during the treatment period according to the new lymphoma response criteria was 65.1% (95% CI: 57.4 - 72.3) and 29.6% (95% CI: 22.8 - 37.1) had partial response. The overall response rate was 94.7% (95% CI: 90.1 - 97.5).

Table 10-10 Summary of overall best response rate (FAS)

Type of response to treatment	All patients N=169
Overall response rate (ORR) –n (%)	160 (94.7)
95% CI for ORR	(90.1, 97.5)
Complete response (CR) –n (%)	110 (65.1)
95% CI for CR	(57.4, 72.3)
Partial response (PR) –n (%)	50 (29.6)
95% CI for PR	(22.8, 37.1)
Not available	0

- ORR = CR + PR.
- 95% CIs are based on the Clopper-Pearson method.
- N is the number of pts in FAS

Source: Table 14.1-6.11

10.4.3 PFS distribution at 24 months

Kaplan-Meier (KM) estimates of PFS are summarized in Table 10-11. K-M plot of time to event endpoint is shown in Figure 14.1-8.1.

K-M estimates of PFS rates at 12-month, 18-month and 24-month were 84.9% (95% CI: 78.2 - 89.6), 81.0% (95% CI: 73.7 - 86.4) and 78.5% (95% CI: 70.9 - 84.4), respectively.

Table 10-11 Analysis of PFS based on investigator assessment using the Kaplan-Meier method (FAS)

Progression free survival	Months [95% CI]
25th Percentile	26 [17.48,]
Median	[,]
75th Percentile	[,]
Percent of patients not progressed at Kaplan-Meier Estimates	(%) [95% CI]
12 month	84.9 [78.2, 89.6]
18 month	81.0 [73.7, 86.4]
24 month	78.5 [70.9, 84.4]

Median (time to event) and its 95% CI are generated by KM estimation.
Source: Table 14.1-7.1

10.5 Other analyses

Summary information of R-CHOP treatment cycles is presented in Table 14.1-9.1.

A total of 127 patients (75.1%) received R-CHOP every 21 days cycle and 42 (24.9%) patients received R-CHOP every 14 days cycle.

10.6 Adverse events and adverse reactions

Overall summary of AEs are presented in Table 10-12. Adverse events by patient are listed in Listing 16.2.7-1.

There were 8 deaths (4.7%) reported overall, including 3 deaths (1.8%) during the on-treatment period. AEs regardless of study drug relationship were reported in 143 patients (84.6%) including AEs suspected to be drug-related in 53 patients (31.4%). SAEs regardless of study drug relationship were reported in 63 patients (37.3%) including SAEs suspected to be drug-related in 11 patients (6.5%). AEs leading to discontinuation occurred in 13 patients (7.7%) and drug-related AEs leading to discontinuation occurred in 3 patients (1.8%). AEs requiring dose adjustment or interruption were reported in 24 patient (14.2%).

Table 10-12 Overall summary of adverse events (FAS)

Category	All patients N=169 n (%)
All deaths	**8 (4.7)**
On-treatment deaths	3 (1.8)
Adverse events	**143 (84.6)**
Suspected to be study drug-related	53 (31.4)
Serious adverse events	**63 (37.3)**
Suspected to be study drug-related	11 (6.5)
AEs leading to discontinuation	**13 (7.7)**
Suspected to be study drug-related	3 (1.8)
AEs requiring dose interruption and/or change	**24 (14.2)**

Category	All patients N=169 n (%)
- Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category.	
Patients with events in more than 1 category are counted once in each of those categories.	
- On treatment deaths: Deaths up to 30 days after the last dose of the Sandoz drugs of interest taken or last visit whichever is later, are included.	
Source: Table 14.3.1-1	

Analysis of adverse events

Summary of AEs regardless of study drug relationship, by primary SOC and PT are presented in Table 10-13.

The overall incidence of AEs regardless of study drug relationship was 84.6% with most common (>10% incidence) being fatigue (20.7%), anemia (24.3%), polyneuropathy (17.2%), nausea (12.4%), leukopenia (11.2%) and constipation (10.7%).

Table 10-13 Adverse events regardless of study drug relationship by primary SOC and PT (FAS)

Primary system organ class Preferred term	All Patients N=169 n (%)
Number of subjects with at least one AE	**143 (84.6)**
General disorders and administration site conditions	**71 (42.0)**
Fatigue	35 (20.7)
Mucosal inflammation	10 (5.9)
Pyrexia	10 (5.9)
Disease progression	8 (4.7)
Oedema peripheral	8 (4.7)
General physical health deterioration	5 (3.0)
Asthenia	3 (1.8)
Oedema	3 (1.8)
Chest discomfort	2 (1.2)
Chest pain	2 (1.2)
Swelling	2 (1.2)
Adverse drug reaction	1 (0.6)
Catheter site oedema	1 (0.6)
Chills	1 (0.6)
Feeling hot	1 (0.6)
Generalised oedema	1 (0.6)
Influenza like illness	1 (0.6)
Localised oedema	1 (0.6)
Pain	1 (0.6)
Performance status decreased	1 (0.6)

Primary system organ class Preferred term	All Patients N=169 n (%)
Blood and lymphatic system disorders	**65 (38.5)**
Anaemia	41 (24.3)
Leukopenia	19 (11.2)
Neutropenia	13 (7.7)
Thrombocytopenia	9 (5.3)
Pancytopenia	8 (4.7)
Febrile neutropenia	6 (3.6)
Haematotoxicity	1 (0.6)
Leukocytosis	1 (0.6)
Lymphadenopathy	1 (0.6)
Neutrophilia	1 (0.6)
Gastrointestinal disorders	**59 (34.9)**
Nausea	21 (12.4)
Constipation	18 (10.7)
Diarrhoea	12 (7.1)
Vomiting	11 (6.5)
Dyspepsia	4 (2.4)
Abdominal pain	3 (1.8)
Dysphagia	3 (1.8)
Abdominal pain lower	2 (1.2)
Abdominal pain upper	2 (1.2)
Dry mouth	2 (1.2)
Gastritis	2 (1.2)
Ileus	2 (1.2)
Stomatitis	2 (1.2)
Toothache	2 (1.2)
Abdominal hernia	1 (0.6)
Anal fissure	1 (0.6)
Aphthous ulcer	1 (0.6)
Bowel movement irregularity	1 (0.6)
Duodenal ulcer	1 (0.6)
Eructation	1 (0.6)
Gastrointestinal haemorrhage	1 (0.6)
Haemorrhoidal haemorrhage	1 (0.6)
Haemorrhoids	1 (0.6)
Mouth ulceration	1 (0.6)
Oesophagitis	1 (0.6)
Oral pain	1 (0.6)
Small intestinal perforation	1 (0.6)
Subileus	1 (0.6)
Tongue discolouration	1 (0.6)

Primary system organ class Preferred term	All Patients N=169 n (%)
Nervous system disorders	**57 (33.7)**
Polyneuropathy	29 (17.2)
Dizziness	8 (4.7)
Dysgeusia	5 (3.0)
Neuropathy peripheral	5 (3.0)
Peripheral sensory neuropathy	5 (3.0)
Paraesthesia	4 (2.4)
Disturbance in attention	2 (1.2)
Ageusia	1 (0.6)
Ataxia	1 (0.6)
Carotid artery stenosis	1 (0.6)
Hyposmia	1 (0.6)
Lumbosacral radiculopathy	1 (0.6)
Memory impairment	1 (0.6)
Monoplegia	1 (0.6)
Sciatica	1 (0.6)
Sensory disturbance	1 (0.6)
Speech disorder	1 (0.6)
Status epilepticus	1 (0.6)
Syncope	1 (0.6)
Thalamic infarction	1 (0.6)
Transient ischaemic attack	1 (0.6)
Tremor	1 (0.6)
Infections and infestations	**50 (29.6)**
Pneumonia	8 (4.7)
Urinary tract infection	6 (3.6)
Nasopharyngitis	4 (2.4)
Oral candidiasis	4 (2.4)
Infection	3 (1.8)
Influenza	3 (1.8)
Cystitis	2 (1.2)
Device related infection	2 (1.2)
Erysipelas	2 (1.2)
Fungal infection	2 (1.2)
Gastrointestinal infection	2 (1.2)
Oral herpes	2 (1.2)
Pulpitis dental	2 (1.2)
Viral infection	2 (1.2)
Bronchitis	1 (0.6)
Candida infection	1 (0.6)
Diverticulitis	1 (0.6)

Primary system organ class Preferred term	All Patients N=169 n (%)
Febrile infection	1 (0.6)
Gastroenteritis	1 (0.6)
Gingivitis	1 (0.6)
Hepatitis B	1 (0.6)
Herpes zoster	1 (0.6)
Neutropenic sepsis	1 (0.6)
Oesophageal candidiasis	1 (0.6)
Oral fungal infection	1 (0.6)
Otitis media	1 (0.6)
Periodontitis	1 (0.6)
Respiratory tract infection	1 (0.6)
Rhinitis	1 (0.6)
Septic shock	1 (0.6)
Staphylococcal infection	1 (0.6)
Tonsillitis	1 (0.6)
Upper respiratory tract infection	1 (0.6)
Urethritis	1 (0.6)
Urinary tract infection staphylococcal	1 (0.6)
Varicella zoster virus infection	1 (0.6)
Vulvovaginal mycotic infection	1 (0.6)
Respiratory, thoracic and mediastinal disorders	**30 (17.8)**
Dyspnoea	10 (5.9)
Cough	6 (3.6)
Oropharyngeal pain	6 (3.6)
Pleural effusion	4 (2.4)
Epistaxis	2 (1.2)
Pulmonary embolism	2 (1.2)
Acquired diaphragmatic eventration	1 (0.6)
Asthma	1 (0.6)
Dyspnoea exertional	1 (0.6)
Haemoptysis	1 (0.6)
Hiccups	1 (0.6)
Productive cough	1 (0.6)
Pulmonary vascular disorder	1 (0.6)
Respiratory distress	1 (0.6)
Stridor	1 (0.6)
Throat irritation	1 (0.6)
Skin and subcutaneous tissue disorders	**25 (14.8)**
Alopecia	12 (7.1)
Rash	5 (3.0)
Dry skin	2 (1.2)

Primary system organ class Preferred term	All Patients N=169 n (%)
Night sweats	2 (1.2)
Cold sweat	1 (0.6)
Dermatitis	1 (0.6)
Erythema	1 (0.6)
Hyperhidrosis	1 (0.6)
Nail bed inflammation	1 (0.6)
Onychalgia	1 (0.6)
Onychoclasis	1 (0.6)
Onycholysis	1 (0.6)
Pruritus	1 (0.6)
Skin irritation	1 (0.6)
Investigations	**24 (14.2)**
White blood cell count decreased	12 (7.1)
Blood lactate dehydrogenase increased	8 (4.7)
Alanine aminotransferase increased	7 (4.1)
C-reactive protein increased	6 (3.6)
Neutrophil count decreased	6 (3.6)
Red blood cell count decreased	6 (3.6)
Gamma-glutamyltransferase increased	4 (2.4)
Blood creatinine increased	3 (1.8)
Platelet count decreased	3 (1.8)
Protein total decreased	3 (1.8)
Blood alkaline phosphatase increased	2 (1.2)
Blood immunoglobulin G decreased	2 (1.2)
Haemoglobin decreased	2 (1.2)
Neutrophil count increased	2 (1.2)
Aspartate aminotransferase increased	1 (0.6)
Blood calcium increased	1 (0.6)
Blood creatine increased	1 (0.6)
Blood creatinine decreased	1 (0.6)
Blood potassium increased	1 (0.6)
Blood urea	1 (0.6)
Blood uric acid	1 (0.6)
Blood uric acid increased	1 (0.6)
Body temperature increased	1 (0.6)
Fibrin D dimer increased	1 (0.6)
Lymphocyte count decreased	1 (0.6)
Red blood cell sedimentation rate increased	1 (0.6)
Reticulocyte count increased	1 (0.6)
Serum ferritin increased	1 (0.6)
Weight decreased	1 (0.6)

Primary system organ class Preferred term	All Patients N=169 n (%)
White blood cell count increased	1 (0.6)
Musculoskeletal and connective tissue disorders	**24 (14.2)**
Back pain	7 (4.1)
Bone pain	5 (3.0)
Arthralgia	4 (2.4)
Muscular weakness	3 (1.8)
Osteoarthritis	3 (1.8)
Muscle spasms	2 (1.2)
Myalgia	2 (1.2)
Pain in extremity	2 (1.2)
Arthropathy	1 (0.6)
Intervertebral disc protrusion	1 (0.6)
Joint swelling	1 (0.6)
Muscle disorder	1 (0.6)
Sarcopenia	1 (0.6)
Metabolism and nutrition disorders	**20 (11.8)**
Decreased appetite	6 (3.6)
Hypokalaemia	6 (3.6)
Hypercalcaemia	3 (1.8)
Hyperkalaemia	2 (1.2)
Hyperuricaemia	2 (1.2)
Hypocalcaemia	2 (1.2)
Hypouricaemia	2 (1.2)
Cachexia	1 (0.6)
Dehydration	1 (0.6)
Diabetes mellitus	1 (0.6)
Hyperglycaemia	1 (0.6)
Hypernatraemia	1 (0.6)
Hypoglycaemia	1 (0.6)
Tumour lysis syndrome	1 (0.6)
Vitamin D deficiency	1 (0.6)
Injury, poisoning and procedural complications	**17 (10.1)**
Fall	5 (3.0)
Infusion related reaction	3 (1.8)
Spinal fracture	2 (1.2)
Acetabulum fracture	1 (0.6)
Joint dislocation	1 (0.6)
Ligament rupture	1 (0.6)
Multiple injuries	1 (0.6)
Muscle strain	1 (0.6)
Radiation pneumonitis	1 (0.6)

Primary system organ class Preferred term	All Patients N=169 n (%)
Radiation skin injury	1 (0.6)
Radius fracture	1 (0.6)
Rib fracture	1 (0.6)
Scapula fracture	1 (0.6)
Thoracic vertebral fracture	1 (0.6)
Upper limb fracture	1 (0.6)
Vascular disorders	15 (8.9)
Hypertension	3 (1.8)
Lymphoedema	3 (1.8)
Circulatory collapse	2 (1.2)
Axillary vein thrombosis	1 (0.6)
Brachiocephalic vein thrombosis	1 (0.6)
Deep vein thrombosis	1 (0.6)
Hypotension	1 (0.6)
Jugular vein thrombosis	1 (0.6)
Peripheral vascular disorder	1 (0.6)
Thrombophlebitis	1 (0.6)
Thrombosis	1 (0.6)
Renal and urinary disorders	**11 (6.5)**
Haematuria	2 (1.2)
Nocturia	2 (1.2)
Urinary retention	2 (1.2)
Acute kidney injury	1 (0.6)
Bladder obstruction	1 (0.6)
Dysuria	1 (0.6)
Incontinence	1 (0.6)
Renal pain	1 (0.6)
Urinary incontinence	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**10 (5.9)**
Diffuse large B-cell lymphoma	3 (1.8)
Neoplasm progression	3 (1.8)
Bladder cancer	1 (0.6)
Gastric cancer	1 (0.6)
Pancreatic carcinoma	1 (0.6)
Rectal cancer	1 (0.6)
Cardiac disorders	9 (5.3)
Cardiac failure	3 (1.8)
Tachycardia	3 (1.8)
Atrial fibrillation	2 (1.2)
Arrhythmia	1 (0.6)
Cardiac disorder	1 (0.6)

Primary system organ class Preferred term	All Patients N=169 n (%)
Cardiac sarcoidosis	1 (0.6)
Cardiomyopathy	1 (0.6)
Diastolic dysfunction	1 (0.6)
Supraventricular tachycardia	1 (0.6)
Psychiatric disorders	**9 (5.3)**
Depression	2 (1.2)
Insomnia	2 (1.2)
Sleep disorder	2 (1.2)
Anxiety	1 (0.6)
Disorientation	1 (0.6)
Laziness	1 (0.6)
Ear and labyrinth disorders	**6 (3.6)**
Vertigo	5 (3.0)
Tinnitus	1 (0.6)
Immune system disorders	**4 (2.4)**
Hypersensitivity	2 (1.2)
Drug hypersensitivity	1 (0.6)
Seasonal allergy	1 (0.6)
Eye disorders	**3 (1.8)**
Erythema of eyelid	1 (0.6)
Ocular discomfort	1 (0.6)
Visual impairment	1 (0.6)
Reproductive system and breast disorders	**3 (1.8)**
Breast pain	2 (1.2)
Ovarian cyst	1 (0.6)
Surgical and medical procedures	**1 (0.6)**
Diaphragmatic operation	1 (0.6)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of all AEs.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
- MedDRA 24.0 has been used for the reporting of adverse events.

Source: Table 14.3.1-2

10.7 Serious adverse events

SAEs regardless of study drug relationship were reported in 63 patients (37.3%) and SAEs suspected to be drug-related occurred in 11 patients (6.5%) (Table 10-12).

SAEs suspected to be drug-related by PT include neutropenic sepsis, pneumonia, septic shock, varicella zoster virus infection, haematuria, abdominal pain, erysipelas, tumour lysis syndrome

and oedema peripheral. Except pneumonia (3 patients) and erysipelas (2 patients), all other suspected SAEs had single occurrence (Listing 16.2.7-1).

10.8 Quality of life

EORTC QLQ-C30 scores by visits and in sub-scales of global health status (GHS), functional scales and symptom scales are summarized in Table 14.1-10.1. EORTC QLQ-C30 forest plot by domains and by visit is represented in Figure 14.1-11.1.

Global health status and functional scales during treatment

GHS, cognitive functioning, physical functioning, role functioning and social functioning, their mean values were dropped during treatment at Month 3 and then increased to baseline levels or higher over the subsequent follow up time points. In contrast, emotional functioning increased during treatment.

- The mean (SD) score for GHS/QoL at baseline was 54.8 (24.0), 54.7 (20.8) at Month 3, 61.4 (18.9) at Month 6, 64.9 (18.6) at Month 9, 68.8 (21.3) at Month 12 and 66.7 (22.9) at Month 15.
- The mean (SD) score for cognitive functioning at baseline was 82.9 (21.1), 76.7 (25.6) at Month 3, 80.3 (21.8) at Month 6, 78.2 (25.3) at Month 9, 80.9 (22.1) at Month 12 and 82.5 (21.9) at Month 15.
- The mean (SD) score for emotional functioning at baseline was 63.2 (25.2), 67.4 (26.2) at Month 3, 74.0 (23.6) at Month 6, 71.8 (24.6) at Month 9, 75.1 (23.1) at Month 12 and 73.7 (21.2) at Month 15.
- The mean (SD) score for physical functioning at baseline was 73.4 (25.4), 64.3 (24.1) at Month 3, 72.3 (21.8) at Month 6, 76.9 (20.8) at Month 9, 78.7 (22.1) at Month 12 and 77.7 (23.0) at Month 15.
- The mean (SD) score for role functioning at baseline was 62.5 (34.5), 54.3 (31.6) at Month 3, 63.2 (28.6) at Month 6, 66.0 (30.0) at Month 9, 71.3 (31.9) at Month 12 and 67.5 (26.3) at Month 15.
- The mean (SD) score for social functioning at baseline was 68.5 (31.5), 64.4 (30.9) at Month 3, 76.0 (23.2) at Month 6, 75.4 (25.0) at Month 9, 80.1 (24.9) at Month 12 and 73.7 (28.0) at Month 15.

Symptom scales/items during treatment

Appetite loss, constipation, diarrhea, fatigue, dyspnea, insomnia and nausea & vomiting, their mean values remained same or slightly increased at Month 3/Month 6 and then decreased over the subsequent follow up time points until Month 15 except for diarrhea, the mean value at Month 15 was increased to baseline level. Financial difficulties, their mean values increased during the follow up. With regard to pain, their mean values were dropped during treatment until Month 12 and then increased to baseline level at Month 15.

- The mean (SD) score for appetite loss at baseline was 28.7 (35.9), 27.5 (32.8) at Month 3, 15.0 (25.4) at Month 6, 16.8 (26.6) at Month 9, 11.1 (23.6) at Month 12 and 5.3 (12.5) at Month 15.

- The mean (SD) score for constipation at baseline was 20.0 (31.2), 20.6 (31.7) at Month 3, 11.7 (22.1) at Month 6, 10.5 (22.9) at Month 9, 9.8 (19.9) at Month 12 and 7.0 (23.8) at Month 15.
- The mean (SD) score for diarrhoea at baseline was 11.5 (21.7), 13.0 (24.9) at Month 3, 9.2 (19.0) at Month 6, 7.4 (18.9) at Month 9, 7.3 (15.7) at Month 12 and 13.0 (28.3) at Month 15.
- The mean (SD) score for dyspnoea at baseline was 23.4 (31.9), 30.0 (31.4) at Month 3, 24.7 (28.6) at Month 6, 21.8 (26.1) at Month 9, 23.2 (27.6) at Month 12 and 21.1 (19.9) at Month 15.
- The mean (SD) score for fatigue at baseline was 44.4 (28.3), 50.9 (26.5) at Month 3, 39.5 (23.1) at Month 6, 37.9 (25.1) at Month 9, 33.3 (25.8) at Month 12 and 33.3 (24.8) at Month 15.
- The mean (SD) score for financial difficulties at baseline was 11.9 (24.4), 22.2 (29.9) at Month 3, 17.9 (30.8) at Month 6, 19.4 (31.6) at Month 9, 15.6 (28.9) at Month 12 and 31.6 (39.2) at Month 15.
- The mean (SD) score for insomnia at baseline was 41.3 (35.6), 43.1 (33.6) at Month 3, 36.1 (31.3) at Month 6, 31.2 (32.9) at Month 9, 36.6 (33.0) at Month 12 and 31.6 (26.0) at Month 15.
- The mean (SD) score for nausea and vomiting at baseline was 8.6 (18.7), 10.4 (17.8) at Month 3, 5.6 (13.3) at Month 6, 4.7 (13.0) at Month 9, 3.3 (10.3) at Month 12 and 4.4 (12.2) at Month 15.
- The mean (SD) score for pain at baseline was 30.8 (33.3), 27.0 (29.6) at Month 3, 22.1 (27.7) at Month 6, 22.8 (27.9) at Month 9, 22.0 (27.8) at Month 12 and 32.5 (29.1) at Month 15.

11 Discussion

11.1 Key results

The full analysis set population consisted of 169 patients: 24.9% and 4.2% of patients discontinued treatment before the end of 12- and 24-month observation periods, respectively. The most frequent reason for early discontinuation was progressive disease (10.7% during the 12 months and 3.6% during the 24 months observation period). Overall, the median age of patients was 70 years (range: 24-94) and there were slightly higher number of females than males (52.1% vs. 47.9%). Majority of patients (80.5%) had ECOG PS of 0 or 1 at baseline, while 4.7% and 1.8% of patients had ECOG PS of 2 or 3. 19.5% and 24.3% of patients had an Ann Arbor disease stage of III or IV.

With regard to treatment, 75.1% of patients received R-CHOP every 21 days cycle therapy and 24.9% patients received R-CHOP every 14 days cycle therapy.

The primary endpoint for this study, CR rate at the end of treatment was 43.8% and 65.1% was the best response CR rate according to RECIL during the treatment period. Overall response rate was 89.3% and PR rate was 45.6% at the end of treatment and 94.7% (ORR) and 29.6% (PR rate), respectively according to RECIL during the treatment period. K-M estimates of 12-month, 18-month and 24-month PFS rates were 84.9%, 81.0% and 78.5%, respectively.

The incidence of AEs was 84.6%. Of those, suspected AEs that were drug-related were 31.4%, SAEs were 37.3%, suspected SAEs that were drug-related were 6.5%, AEs leading to discontinuation were 7.7%, suspected drug-related AEs leading to discontinuation were 1.8% and AEs requiring dose interruption and/or change were 14.2%. The incidence of on-treatment deaths was 1.8%.

The most common AEs by PT (>10% incidence) were fatigue (20.7%), anemia (24.3%), polyneuropathy (17.2%), nausea (12.4%), leukopenia (11.2%) and constipation (10.7%). SAEs suspected to be drug-related by PT were neutropenic sepsis, pneumonia, septic shock, varicella zoster virus infection, haematuria, abdominal pain, erysipelas, tumour lysis syndrome and oedema peripheral. Except pneumonia (3 patients) and erysipelas (2 patients), all other suspected SAEs had single occurrence.

During treatment, scores of emotional functioning and financial difficulties were increased. Scores of GHS, cognitive functioning, physical functioning, role functioning and social functioning were decreased initially (Month 3) and then increased to baseline levels or higher during follow up. In contrast, scores of appetite loss, constipation, diarrhea, fatigue, dyspnea, insomnia and nausea & vomiting were increased at Month 3/Month 6 and then decreased over the subsequent follow ups except for diarrhea, the mean value at Month 15 was increased to baseline level. Scores of pain were dropped except at Month 15, the mean value was increased to baseline level.

11.2 Limitations

While this is a population-based study, it utilized convenience sampling. Therefore, the selected sample may not accurately reflect the entire patient population, and selection bias cannot be fully excluded. While limited to study sites using Rixathon®, attempts were to be made to enroll a variety of sites with regard to size and academic affiliation (e.g. academic, academic-affiliated, and non-academic sites).

In this population-based, open-label study, only patients treated with Rixathon® were included and there were no comparison group of either untreated patients or patients treated with other rituximab-containing treatment regimens.

Observed relationships between treatment variables and outcome variables could only be interpreted in an observational manner.

11.3 Interpretation

In this non-interventional, prospective, multicenter study involving 169 treatment-naïve patients with CD20-positive DLBCL were treated with Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as per routine clinical practice. This combination showed CR rate at the end of treatment of 43.8%, PR rate of 45.6% and ORR of 89.3%, respectively. According to the new lymphoma response criteria, RECIL 2017, during the treatment period R-CHOP treatment showed a higher response rate in terms of CR and ORRs: 65.1% of patients had CR, 29.6% had PR and the best ORR was 94.7%. K-M estimate of PFS rate was 84.9% at 12 months, 81.0% at 18 months and 78.5% at 24 months.

R-CHOP regimen is the standard of care for patients with newly diagnosed DLBCL, approximately 50 to 60% of patients treated with R-CHOP achieved cure (Wang et al 2020, Liu & Barta 2019). In the first published randomized controlled trial comparing R-CHOP regimen

to standard of care (CHOP) in elderly patients with diffuse large-B-cell lymphoma; rate of CR or unconfirmed CR was significantly higher in the R-CHOP group as compared to standard of care alone (76 percent vs. 63 percent, p=0.005; Coiffier et al 2019). Lugtenburg et al (2017) reported CR/unconfirmed CR at the end of induction among patients receiving Rituximab SC plus CHOP and Rituximab IV plus CHOP as 50.6% and 42.4% respectively and ORR was 82.2% and 78.0% respectively. Mondello & Mian (2019) studied trials investigating new frontline therapies for DLBCL management, reported 2 years PFS from 56% to 77.6% in patients who were using R-CHOP as the first-line therapy. Results of our (REFLECT) study demonstrated ORR of 89.3% and CR of 43.8% at the end of treatment. The PFS at 24-month was 78.5%. The method of CR assessment in our study was closer to unconfirmed CR as this was based on Physician's decision and the study being non-interventional; radiological or ultrasound investigations were made based on physician's decision as per routine medical practice in terms of visit frequency and types of assessments performed and only these data were collected as part of the study.

There were no new safety signals in our study. The safety findings reported in our study are comparable with rates reported in other studies; at least one AE occurred in 94% of patients in R-CHOP group in a recent study from Sehn et al (2020) versus 84.6% in our study and the rate of SAEs was 38.4% versus 37.3%, respectively. Similarly, Delarue et al (2013) reported the rate of AEs and SAEs 76% and 49.2%, respectively in patients treated with R-CHOP.

Thus, REFLECT study confirmed efficacy of Rixathon in naive DLBCL patients without new safety signals.

11.4 Generalizability

By not randomly selecting sites and patients, the generalizability of the findings were limited to the populations under study.

12 Other information

Not applicable.

13 Conclusion

To conclude, the results showed an acceptable safety profile of R-CHOP and improvement in treatment outcomes on treatment-naïve patients with CD20-positive DLBCL with 89.3% of patients responding to treatment at the end of study and 94.7% responding during the treatment period achieved ORR. The PFS rates at the end of 12- and 24-months were 84.9 and 78.5%, respectively.

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Appendices

Annex 1. List of stand-alone documents

1. GP13-501: Site list - List of centers and participating physicians or responsible persons and their affiliations
2. GP13-501: CSR report signature pages - Sponsor signature page and GSC signature page
3. Tables, listings and figures:
    a. GP13-501 final dated 22 October 2021 Post-text tables – Baseline Data
    b. GP13-501 final dated 22 October 2021 Post-text tables – Safety Data
    c. GP13-501 final dated 22 October 2021 Post-text tables – Effectiveness
    d. GP13-501 final dated 22 October 2021 Post-text figures
    e. GP13-501 final dated 22 October 2021 Patient data listings

Annex 2. Additional information

1. Protocol and protocol amendments
2. GP13-501: statistical analysis plan (including interim analysis)
3. List of IECs
4. Representative written information for patients and sample consent forms