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CLINICAL REVIEW(S)

CLINICAL REVIEW

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Division / Office	Division of Hematology Products
Reviewer Name(s)	Alexandria Schwarsin, MD
Review Completion Date	May 23, 2017
Established Name	rituximab and hyaluronidase
(Proposed) Trade Name	Rituxan Hycela
Therapeutic Class	CD20-cytolytic antibody
Applicant	Genentech, Inc
Formulation(s)	• 1400 mg rituximab and 23,400 USP units hyaluronidase per 11.7 mL (120 mg/2000 USP units per mL) solution in a single-dose vial • 1600 mg rituximab and 26,800 USP units hyaluronidase per 13.4 mL (120 mg/2000 USP units per mL) solution in a single dose vial
Dosing Regimen	• FL/DLBCL: RITUXAN HYCELA 1400 mg rituximab and 23,400 U hyaluronidase by subcutaneous injection after a dose of intravenous rituximab • CLL: RITUXAN HYCELA 1600 mg rituximab and 26,800 U hyaluronidase by subcutaneous injection after a dose of intravenous rituximab
Indication(s)	Refer to section 1.1
Intended Population(s)	Patients ≥18 years of age

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List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARR	administration-related reaction
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BSA	body surface area
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisolone
CI	confidence interval
CNS	central nervous system
CR	complete response
CRi	complete response with incomplete bone marrow recovery
CrCl	creatinine clearance
CRR	complete response rate
CRu	complete response unconfirmed
CSR	clinical study report
CT	computed tomography
CTSQ	Cancer Treatment Satisfaction Questionnaire
C _{trough}	trough or minimum serum concentration
CVP	cyclophosphamide, vincristine, prednisolone
DFS	disease free survival
dL	deciliter
DLBCL	diffuse large B-cell lymphoma
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Clinical Oncology Group
EFS	event free survival
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
G	grams
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
HIV	human immunodeficiency virus
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
IPI	International Prognostic Index
IRRs	infusion related reactions
ITT	intent-to-treat
IV	intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukemia

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IWG	International Working Group
L	liter
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
m	meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute- Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PR	partial response
PK	pharmacokinetics
PR	partial response
PRO	Patient reported outcome
RASQ	Rituximab Administration Satisfaction Questionnaire
R-CHOP	rituximab plus cyclophosphamide, vincristine, prednisolone
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SC	subcutaneous
SMQ	Standardized MedDRA Query
SOC	system organ class
SD	stable disease
ULN	upper limit of normal
WHO	World Health Organization

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommendation is traditional approval of rituximab and hyaluronidase for the proposed indications. Rituximab and hyaluronidase is indicated for the treatment of patients with

- Relapsed or refractory, FL (follicular lymphoma) as a single agent.
- Previously untreated FL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab and hyaluronidase for subcutaneous injection in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), FL as a single agent after first-line CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy.
- Rituximab and hyaluronidase is indicated for the treatment of patients with previously untreated DLBCL (diffuse large B-cell lymphoma) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or other anthracycline-based chemotherapy.
- Rituximab and hyaluronidase is indicated in combination with FC (fludarabine and cyclophosphamide) for the treatment of patients with previously untreated and previously treated CLL (chronic lymphocytic leukemia).

1.2 Risk Benefit Assessment

Rituximab and hyaluronidase is a biological product which contains two active ingredients. Rituximab is a CD20-directed cytolytic antibody and hyaluronidase human injection is an endoglycosidase. Rituximab and hyaluronidase offers patients with FL, DLBCL, and CLL a different route of administration for Rituxan[®]. Rituximab and hyaluronidase is not a replacement for Rituxan[®], as patients receive rituximab intravenously prior to receiving rituximab and hyaluronidase. If the patient is able to receive the full dose of a rituximab product administered intravenously for the first cycle subsequent cycles may then be given subcutaneously with rituximab and hyaluronidase. The benefit risk assessment of rituximab and hyaluronidase supports traditional approval for the oncologic indications of Rituxan[®].

FL, DLBCL, and CLL are different diseases with different approaches to treatment. FL is an indolent subtype of NHL(non-Hodgkin lymphoma) with a variable clinical course. Treatment options for FL range from observation to chemoimmunotherapy. DLBCL is an aggressive subtype of NHL, which is also heterogeneous. Initial treatment is dependent on the amount of disease but typically involves treatment with systemic

chemotherapy in combination with rituximab. CLL is a B cell chronic lymphoproliferative disease with an extremely variable clinical course. Again, treatment options range from observation to systemic chemotherapy combined with rituximab. While the diseases are different, they have in common treatment options may include chemotherapy combined with Rituxan®.

Rituximab and hyaluronidase offers appropriate patients a SC (subcutaneous) route of administration. Aside from the different route of administration, several other aspects are different in comparing rituximab and hyaluronidase to Rituxan®. These changes include combination with hyaluronidase and a flat dose of rituximab and hyaluronidase (rituximab IV dose is determined based on a patient's body surface area). SC administration takes place over several minutes compared to a minimum of 90 minutes IV (intravenous) administration of Rituxan®. The benefit of rituximab and hyaluronidase was established using a pharmacokinetic bridging development. The PK (pharmacokinetic) bridge supported by descriptive clinical trials.

In these clinical trials the efficacy of rituximab and hyaluronidase was shown to be comparable to a non-U.S. approved rituximab. In patients with FL the ORR at the end of induction treatment was shown to be comparable with 84.9% (95% CI 79.2, 89.5) on non-U.S. approved rituximab IV compared to 84.4% (95% CI 78.7, 89.1) on rituximab and hyaluronidase arm. In follicular lymphoma, the secondary time to event endpoints of PFS and OS were also comparable with stratified HRs of 0.97 (95% CI 0.65, 1.44) and 0.82 (95% CI 0.41, 1.63) respectively. In patients with DLBCL, patients achieving a CR/CRu was also comparable, with 42.1% (95% CI 35.1, 49.0) on the non-U.S. approved rituximab arm and 47.0% (42.0, 52.0) on the rituximab and hyaluronidase arm achieving CR/CRu. The stratified HRs for PFS and OS were also comparable at 1.23 (95% CI 0.86, 1.76) and 1.06 (95% CI 0.68, 1.65) respectively. In CLL, a comparable response rate was seen with 80.7% (95% CI 70.9, 88.3) on the rituximab IV responding and 85.2% (95% CI 76.1, 91.9) on the rituximab SC arm.

The safety of rituximab and hyaluronidase was comparable with that of a non-U.S. approved rituximab. For the trial done in patients with untreated FL, common TEAEs (treatment emergent adverse events) (>10% of patients), that were more common (≥5% difference) on the rituximab and hyaluronidase arm were nausea, pneumonia, injection site erythema and cough. For the trial done in patients with untreated DLBCL, for nonfatal TEAE none of the TEAE that occurred in >5% of patients on the rituximab and hyaluronidase arm had a difference >5% between the arms. For the trial done in patients with untreated CLL, nonfatal TEAE that occurred in >10% of patients with a >5% increase on the rituximab SC arm were neutropenia, pyrexia, injection site erythema, injection site pain and erythema. In general the safety profile of rituximab and hyaluronidase was comparable to a non-U.S. approved rituximab given IV with a few differences. One, due to the different routes of administration, rituximab and hyaluronidase was associated injection site reactions including injection site erythema and injection site pain, in the majority of cases these were grade 1 and 2, and ranged in

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incidence across the trials from 1.9% to 25.9%. There was a trend of increased neutropenia grades 3 and 4 and increased SAEs (serious adverse events) in the SOC (system organ class) of infections and infestations in the rituximab and hyaluronidase arm.

Table 1 Benefit Risk Summary and Assessment

Benefit-Risk Summary and Assessment		
Rituxan Hycela was developed to give patients with FL, DLBCL, and CLL a different route of administration compared to a non-U.S. approved rituximab. Rituximab and hyaluronidase offers patients a SC route of administration over several minutes compared to at least 90 minutes for rituximab given IV. The development of rituximab and hyaluronidase was a PK based bridging program designed to achieve a C_{trough} with rituximab and hyaluronidase at least as high as rituximab IV. This was accompanied by descriptive clinical trials in FL, DLBCL and CLL. The efficacy of rituximab and hyaluronidase was comparable to rituximab IV on these descriptive clinical trials. The safety was comparable. Some of the more common TEAEs (>10% of patients) were increased ($\geq 5\%$) on the rituximab SC arm. For FL this included, nausea, pneumonia, injection site erythema and cough. For patients with DLBCL, none of the TEAE had this $\geq 5\%$ increase. For patients with CLL, this included neutropenia, pyrexia, injection site erythema, injection site pain and erythema. The other significant differences in terms of safety include an increased risk of neutropenia across the trials associated with an increase in infections and serious infections. This is concerning for the patient as rituximab and hyaluronidase offers patients a faster route of administration, but this may be associated with a potential increased risk of hospitalization for infections. Another notable difference in terms of safety is related to the SC route of administration. This was injection site reactions including injection site erythema and injection site pain in the majority of cases these were grade 1 and 2, and ranged in incidence across the trials from 1.9% to 25.9%.		
Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	FL and CLL are indolent diseases with variable clinical courses but are not considered curable. The typical course can include several treatments with the potential for the disease to become unresponsive to treatment. DLBCL is an aggressive non-Hodgkin's lymphoma with a 5-year relative survival of 62% [1].	FL, CLL and DLBCL are life threatening diseases.
Current Treatment Options	Current treatment options for FL and CLL range from observation to chemotherapy combined immunotherapy. Current treatment options for DLBCL include chemotherapy and immunotherapy.	Treatment options for FL, CLL and DLBCL vary depending on the disease and stage of disease the patient has. Rituximab can be combined with chemotherapy for treatment of FL, CLL and DLBCL.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	The benefit of rituximab and hyaluronidase given SC has been demonstrated in clinical trials in FL, DLBCL and CLL to be comparable to that of a non-U.S. approved rituximab given IV.	The efficacy of rituximab and hyaluronidase is comparable to a non-U.S. approved rituximab.
Risk	The risk of rituximab and hyaluronidase is comparable to that of a non-U.S. approved rituximab IV with a few notable differences. In each of the disease, FL, DLBCL, and CLL the risk of some adverse events may be increased slightly. Rituximab and hyaluronidase was associated with injection site reactions. Across three trials there was an increased risk of neutropenia and infections both serious and non-serious.	The risks of rituximab and hyaluronidase are comparable to that of a non-U.S. approved rituximab with an increased risk of some adverse events including infections. The Prescribing Information will describe the rates of adverse events in FL, CLL and DLBCL.
Risk Management	The risk of reactions is minimized by previous administration of a dose of rituximab IV. Serious and life-threatening toxicities can be managed with appropriate supportive treatment.	The Prescribing Information will clearly state rituximab and hyaluronidase is to be given subcutaneously and all patients must receive a full dose of IV rituximab prior to starting rituximab and hyaluronidase.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for postmarket risk evaluation and mitigation strategy for Rituxan Hycela.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for postmarket requirements and commitments based on this review. Routine pharmacovigilance will be conducted by the Applicant.

2 Introduction and Regulatory Background

Rituximab (Rituxan®) is a CD20-directed cytolytic antibody indicated for the treatment of patients with the following oncologic indications:

FL

- Relapsed or refractory, low-grade or FL, CD20-positive, B-cell NHL as a single agent
- Previously untreated FL, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy

DLBCL

- Previously untreated DLBCL, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens

CLL

- In combination with FC for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

In addition to the above oncologic indications rituximab has indications in the treatment of patients with rheumatoid arthritis and granulomatosis with polyangiitis and microscopic polyangiitis.

Rituximab and hyaluronidase, hereafter referred to as rituximab SC, is a combination of rituximab and hyaluronidase which offers patients a different route of administration compared to a non-U.S. approved IV rituximab hereafter referred to as rituximab IV.

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The Applicant seeks approval for the oncologic indications of IV rituximab based on a PK bridging program to rituximab IV in patients with DLBCL, FL and CLL.

2.1 Product Information

The established name is rituximab and hyaluronidase. The proposed trade name is Rituxan Hycela.

The Applicant's proposed indications are identical to the oncologic indications for IV rituximab listed in section 2. Two different doses of rituximab and hyaluronidase were developed: a 1400 mg SC dose to represent the 375 mg (milligrams)/m(meter)² IV rituximab dose and a 1600 mg SC dose to represent the 500 mg/m² IV rituximab dose.

2.2 Tables of Currently Available Treatments for Proposed Indications

The alternative to rituximab and hyaluronidase is the approved Rituxan[®]. There are two other CD20-directed cytolytic antibodies approved, obinutuzumab and ofatumumab.

Ofatumumab is a CD20-directed cytolytic monoclonal antibody that was initially approved in 2009. The current indications for ofatumumab are for the treatment of CLL:

- in combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.
- in combination with FC for the treatment of patients with relapsed CLL
- for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL.
- for the treatment of patients with CLL refractory to fludarabine and alemtuzumab.

Obinutuzumab is a CD20-directed cytolytic antibody and is indicated:

- in combination with chlorambucil, for the treatment of patients with previously untreated CLL.
- in combination with bendamustine followed by obinutuzumab monotherapy, for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen.

2.3 Availability of Proposed Active Ingredient in the United States

The drug contains two active moieties, rituximab and hyaluronidase, which are marketed in the US as stand-alone products.

2.4 Important Safety Issues With Consideration to Related Drugs

Rituximab has a boxed warning for fatal infusion reactions, severe mucocutaneous reactions, hepatitis B virus reactivation and progressive multifocal leukoencephalopathy.

In addition to the boxed warning it has warnings and precautions for tumor-lysis syndrome, infections, cardiac arrhythmias and angina, bowel obstruction and perforation, live virus vaccines and cytopenias. In addition to the boxed warning and warnings and precautions, rituximab has a limitation of use and is not recommended for use in patients with severe, active infections. Hyaluronidase human injection has warnings and precautions for spread of localized infections, ocular damage and enzyme inactivation with intravenous administration.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The applicant began development of rituximab SC with a focus other than the U.S. and feedback from the Agency was not obtained during development. Rituximab solution for SC injection was first approved on March 21, 2014 in EU as MabThera 1400 mg solution for SC injection for the treatment of NHL. MabThera 1600 mg solution for SC injection for the treatment of patients with CLL was approved in the EU on May 25, 2016.

The applicant also had several formal meetings with the Agency. A type B pre-IND meeting held September 2, 2015, a type C pre-IND meeting to discuss the CMC development strategy on October 2, 2015 and another type B pre-IND meeting on February 23, 2016. The type B pre-IND meetings are summarized below.

Type B pre-IND meeting held September 2, 2015

During this meeting, the first interaction between the Applicant and the Division of Hematology Products, the Applicant presented to the Division of Hematology Products the clinical development program for rituximab SC. The clinical development was a PK based bridging to the rituximab IV dose and dosing intervals. The applicant developed the PK based bridge on the assumption that rituximab exerts its anti B-cell activity upon binding to its target. The Applicant argued that the minimum concentration of rituximab prior to the next administration, C_{trough} , reflects the degree of target saturation on B cells. Thus, the Applicant argued, C_{trough} levels at least as high as those following IV injection were expected to result in at least the same degree of clinical activity.

During this meeting, the Division of Hematology Products expressed several concerns with the development program. While PK bridging may be possible to establish a new dosage form, concerns were discussed that PK bridging alone would be insufficiency to support a submission of the SC rituximab product for the following reasons:

1. Multiple changes were made in the comparison of the SC formulation to the IV formulation and concerns were discussed regarding the impact of these changes on rituximab safety, efficacy and pharmacokinetics should be evaluated. The changes made included:
 - a. A change from body surface area-based dosing to a flat dose
 - b. A change from the IV to SC route of administration

- c. Changes to the dose level; the administered dose level for rituximab SC is higher than the rituximab IV dose.
2. The SC formulation of the proposed product includes rituximab and hyaluronidase. The contribution of rHuPH20 (hyaluronidase) to the overall safety and efficacy of the new fixed combination product should be determined.
3. Since the Applicant was claiming that rHuPH20 was an absorption-enhancing agent, a PK trial comparing the PK of SC rituximab in the presence and absence of rHuPH20 should be conducted.
4. Once the above items were addressed, the Applicant should identify a therapeutic threshold concentration and one or more PK parameters that can predict safety and efficacy of rituximab in order to conduct a comparative PK assessment.

In addition to the concerns regarding the PK bridge, the Agency also had concerns regarding the clinical trials. In general, the concerns included the heterogeneity of patient populations and dosing regimens, the use of response rate as the primary endpoint which is different from the primary endpoint of PFS (progression free survival) used in the rituximab IV registrational trials, and the use of investigator assessments to determine ORR (overall response rate).

- In SparkThera, the patient population was heterogenous as well as the dosing regimen. Induction therapy was either rituximab IV as monotherapy or in combination with chemotherapy and the maintenance regimen used was either every 2 months or every 3 months.
- The SABRINA trial was heterogenous as well with two different chemotherapy regimens, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or CVP (cyclophosphamide, vincristine, prednisolone).
- In SABRINA and SAWYER the efficacy endpoint of response rate was different from the endpoint of PFS used in rituximab IV registrational trials.

In conclusion of this meeting, the Agency recommended the Applicant in the future include a proposal how they plan to demonstrate substantial evidence of efficacy and safety to support an approval. The Agency also informed the sponsor a future submission should include clinical trials and high level results. It was recommended to include a discussion of the Legacy data to support the application. The Agency was interested in how the Applicant intended to address establishing long term efficacy for the rituximab SC formulation. The Agency also stated the safety database should include patients in clinical trials and in the post marketing setting.

Type B pre-BLA meeting held February 23, 2016

This meeting was requested by the Applicant to discuss the additional PK and clinical data to address concerns raised by the Agency regarding the proposed BLA for rituximab SC.

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During the meeting, the Agency agreed with the proposal to include PFS data for trial BO22334 SABRINA and trial MO28107 MabEase. The Kaplan Meier curves overlapped, however the concern expressed was that the confidence intervals were wide. The applicant was asked pre-specify in the application the analysis method used and type I error rate control for PFS. The Applicant was asked to include power calculations for PFS with respect to different lengths of follow-up.

For the Summary of Clinical Efficacy, the Agency agreed to the proposal of an integrated approach without pooling of data. For the Summary of Clinical Safety the Agency requested an integrated safety evaluation with pooling of data across all trials. The Agency recommended separate pooling for monotherapy and combination therapy. The pooling should specifically address adverse reactions associated with infusion and subcutaneous injection reactions including grade, time to occurrence and resolution for CLL and NHL.

Other concerns expressed by the Agency include:

- Multiple versions of study reports were not acceptable. The Agency recommended only the final or most current complete study report and datasets for each trial.
- Financial disclosure information should be submitted for all trials.
- The Applicant was informed a 120 day safety update was required.
- The Applicant was informed as the trials were conducted outside the U.S., justification was required regarding the relevance of the results to the U.S. population.
- The Agency requested the identification of the rituximab IV products used in each country for SparkThera, SABRINA, SAWYER, MabEase and PrefMab. This information should be submitted as a tabular summary.

2.6 Other Relevant Background Information

The 1400 mg dose of rituximab solution for SC injection was approved in the EU on March 21, 2014 for the treatment of NHL and following this was approved in 42 countries worldwide. The 1600 mg dose of rituximab solution for SC injection was approved in the EU on May 25, 2016 and in South Korea on June 24, 2016.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission quality and integrity was of sufficient quality to allow for adequate review.

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3.2 Compliance with Good Clinical Practices

The five studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

A Division of Scientific Investigation audit was obtained. Two clinical sites, the contact research organization, and the Applicant were inspected. A classification of Voluntary Action Indicated was determined for Monica Tani, M.D. in Rome, Italy. Per the Clinical Inspection Summary Report, by Anthony Orencia, M.D. this site appeared to be in compliance with Good Clinical Practice.

The site, Rome Italy, associated with investigator Monica Tani, M.D. failed to conduct the investigation in accordance with the investigational plan as AEs (adverse events) were not reported according to the protocol-required time intervals. The report states adverse events of special interest or administration-related reactions for three patients (five episodes for one patient, and one episode each for the other two patients) were not signed by the sub-investigator and were reported just prior to the inspection. As a result, there are no AEs reported in the data listing corresponding to these episodes. Per the report, this was due to the fact that the AEs were documented in the nursing records and not noted by the physician. Despite this, the trial data derived from the clinical sites was considered reliable in support of the requested application per the Clinical Inspection Summary Review by Anthony Orencia, M.D.

3.3 Financial Disclosures

Refer to the Clinical Investigator Financial Disclosure Review in the appendix. While financial interests were disclosed for a few investigators and some investigators did report financial interests, there is integrity in the data. This is due to the fact that a small percentage of investigators had disclosable financial interests, and multiple investigators were used in all of the clinical trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761064 for Rituxan HYCELA, manufactured by Genentech pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of Rituxan HYCELA is well controlled and leads to a product that is pure and potent. We recommend that Rituxan HYCELA be approved for human use under the conditions specified in the package insert.

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4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Per pharmacology toxicology review, despite exposure differences in animal models there were no major differences in pharmacodynamic effects of tumor growth inhibition or B-cell depletion in mice or monkeys in mantle cell lymphoma mice and monkey xenograft models. Several pharmacology studies demonstrated the transient local effects of rHuPH20 in animals within the range proposed for humans.

Evidence was provided that support the addition of rHuPH20 to rituximab to improve the absorption rate. In animal toxicology studies decreases in neutrophils, cardiac arrhythmias, and liver toxicity were observed that were not observed in nonclinical studies to support rituximab IV. Also present was injection site findings that could be related to SC administration.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Rituximab is a monoclonal antibody that targets the CD20 antigen on the surface of pre-B and mature B-lymphocytes. This binding mediates B-cell lysis. Hyaluronidase depolymerizes the substrate hyaluronan at the injection site. This modifies the permeability of the connective tissue and thus hyaluronidase acts as a dispersion agent.

4.4.2 Pharmacodynamics

See clinical pharmacology review.

4.4.3 Pharmacokinetics

See clinical pharmacology review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The five key trials in this application are displayed in Table 2. Also included in the application are two trials evaluating rHuPH20. These trials were phase 1 trials evaluating the safety of rHuPH20 as a single agent in healthy volunteers. Study R04-0851 evaluated sensitivity to a single intradermal injection and study HALO-104-104 assessed safety, tolerability, and PK/PD (pharmacodynamics) of intravenously administered rHuPH20.

Table 2 Table of Clinical Trials

Trial	Design	Objectives
BO22334 SABRINA	Phase III randomized, two-stage, rituximab SC1400 mg vs rituximab IV in previously untreated NHL induction followed by maintenance	Stage 1: non-inferior rituximab C _{trough} SC vs IV Stage 2: primary efficacy ORR at end of induction
MO28107 MabEase	Phase IIIb randomized of rituximab SC 1400 mg vs rituximab IV in untreated CD20+ DLBCL	Primary: CRR at end of treatment Secondary: EFS, DFS, PFS, OS, patient satisfaction questionnaire, safety, immunogenicity
MO28457 PrefMab	Phase IIIb randomized crossover trial evaluating patient preference for rituximab IV vs rituximab SC in patients with NHL	Primary: PRO Secondary: safety, immunogenicity, efficacy (CRR at end of treatment, EFS, DFS, PFS, OS)
BO25341 SAWYER	Phase Ib, two-part, randomized trial in untreated CD20+ CLL Part 1: dose-finding single SC injection Part 2: dose-confirmation 1600 mg SC Q4 weeks	Primary: non-inferior rituximab C _{trough} SC vs IV Secondary: Safety, B cells, immunogenicity; questionnaires; efficacy (ORR at end of treatment, minimal residue disease, PFS, EFS, OS)
BP22333 SparkThera	Phase Ib two-stage randomized adaptive trial in newly diagnosed or relapsed CD20+ FL Stage 1: dose finding single SC injection Stage 2: dose confirmation 1400 mg SC Q 2months/Q 3 months	Primary: non-inferior rituximab C _{trough} SC vs IV Secondary: safety, B cells, immunogenicity

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[EFS=event free survival, DFS=disease free survival, OS=overall survival, PRO=patient reported outcomes]

5.2 Review Strategy

The trials listed above served as the primary basis for the review. Safety and efficacy data including data analysis datasets, and clinical study reports was reviewed. In order to reproduce key efficacy and safety analysis and for additional exploratory analysis JMP, JReview and MAED tools were used. Analyses done were done by the clinical review unless otherwise stated.

5.3 Discussion of Individual Studies/Clinical Trials

Protocol BO22334 SABRINA

Title:

A Two-stage Phase III, International, Multi-Center, Randomized, Controlled, Open-label Study to Investigate the Pharmacokinetics, Efficacy and Safety of Rituximab SC in Combination With CHOP or CVP Versus Rituximab IV in Combination With CHOP or CVP in Patients With Previously Untreated FL Followed by Maintenance Treatment With Either Rituximab SC or Rituximab IV

Reviewer Comments: For this trial, rituximab SC was MabThera SC and rituximab IV was MabThera IV.

Objectives:

Stage 1:

The primary objective is to estimate the ratio of trough concentrations at cycle 7, 21 days of SC administration to that obtained IV ($C_{\text{trough SC}}/C_{\text{trough IV}}$).

The secondary objectives include:

- To compare observed serum concentrations area under the plasma concentration-time curve (AUC), rituximab IV vs SC during induction treatment given every 3 weeks
- To explore additional PK parameter during induction including predicted PK parameter for induction regimens given every 4 weeks
- To compare ORR including CR (complete response), CRu (complete response unconfirmed) and PR (partial response) of rituximab SC and IV given in combination with CHOP or CVP as induction treatment at the end of induction

Stage 2:

The primary objective is to estimate the ORR including CR, CRu and PR (partial response) in each treatment arm at the end/completion of induction treatment

Secondary objectives stage 1 and stage 2:

- To compare peripheral blood B-cell depletion and repletion after rituximab SC and IV treatment
- To compare CRR including CR and CRu, of rituximab SC and IV given in combination with CHOP or CVP at the end or completion of induction
- To compare ORR including CR, CRu, PR and CRR including CR, CRu of rituximab SC and IV at end/completion of maintenance treatment
- To compare PFS, EFS and OS of rituximab SC and IV
- To compare observed rituximab serum C_{trough} levels during induction
- To compare observed C_{trough} during maintenance treatment
- To compare safety profile of SC and IV including:
 - AEs including laboratory values
 - Incidence of incidence and severity of infusion/injection-related reactions
 - Physical examination including weight, performance status and vital signs
 - Medical history, prior treatments for cancer, concomitant medications
 - Immunogenicity
- To gather physician/nurse opinions on resource savings with SC compared to IV
- To assess physician/nurse opinions on convenience with SC compared to IV

Design:

This is a two-stage, phase 3, international, multicenter, randomized, controlled, open-label trial of rituximab, SC and IV, both in combination with CHOP or CVP in patients with previously untreated FL followed by maintenance treatment (SC or IV rituximab).

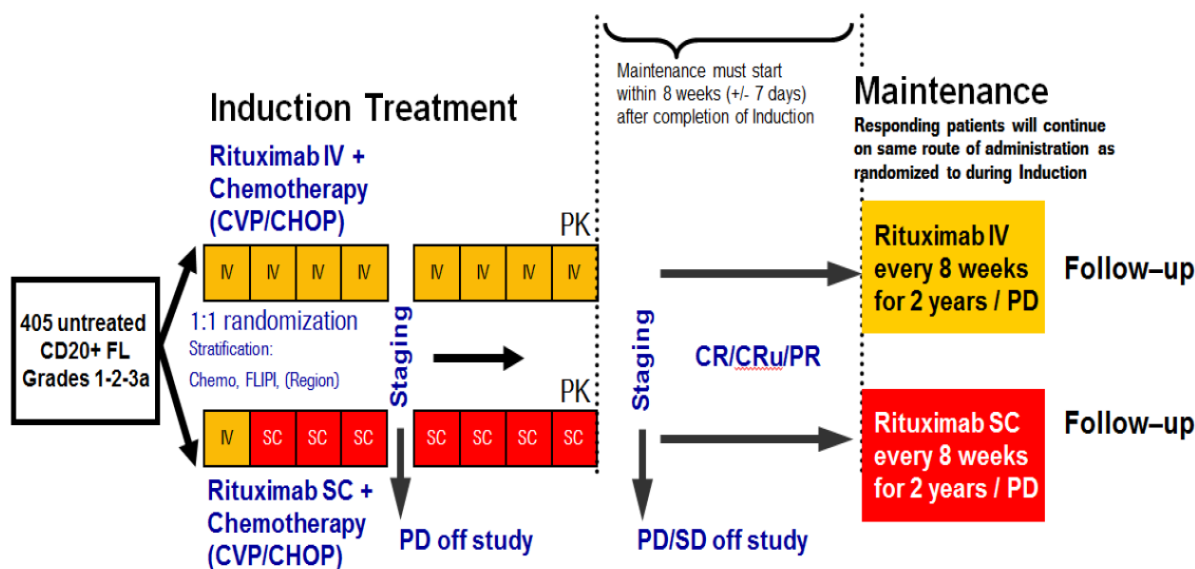
Stage 1 was to establish the rituximab SC dose that results in comparable rituximab serum C_{trough} level compared to rituximab IV when given as part of induction treatment every 3 weeks. One PK futility interim analysis was planned after 35 patients in each treatment arm complete cycle 7 of induction treatment. This futility analysis was for dose confirmation or further dose adjustment. The main criterion to adjust the rituximab SC dose was based on a specific lower boundary of the 90% CI (confidence interval) for the estimated ratio $C_{trough\ SC}/C_{trough\ IV}$. After the rituximab SC dose was established, stage 2 enrolled. The trial design was the same for stage 1 and stage 2, except for increased PK sampling in stage 1. Patients are randomized into two groups. The rituximab SC group, which is given the first cycle rituximab IV, then 7 cycles of rituximab SC combined with 8 cycles of CHOP or CVP chemotherapy every 3 weeks. Rituximab IV was 375 mg/m². The rituximab SC dose was 1400 mg. Patients achieving at least PR were given maintenance rituximab SC. The rituximab IV group was given 8 cycles of rituximab IV in combination with 8 cycles of CHOP or CVP chemotherapy every 3 weeks. Rituximab IV was 375 mg/m². Patients achieving at least a PR were to enter rituximab IV maintenance therapy once every 8 weeks for 24 months.

Randomization was 1:1. The combination chemotherapy in both groups, CHOP or CVP, was selected at the discretion of the investigator. Randomization was stratified by selected chemotherapy, CHOP, CVP, FLIPI (Follicular Lymphoma International

Prognostic Index), low-risk, intermediate-risk, high-risk, and region, Europe and North America, South and Central America, Asia.

Patients treated with CHOP who achieved CR, CRu, PR or SD (stable disease) at the interim assessment, at the discretion of the Investigator, were to receive either an additional 4 cycles rituximab (SC or IV depending on assigned arm) + CHOP or 2 cycles of rituximab (SC or IV) + CHOP and 2 cycles of rituximab monotherapy (SC or IV). Patients who received CVP chemotherapy were to receive 8 cycles. For rituximab SC, the first rituximab SC is given on day 0 (both rituximab SC-CHOP and rituximab SC-CVP) of cycle 2 and for cycles 3-8 rituximab SC was given on day 1. Following induction therapy, responding patients (CR, CRu, and PR) were given maintenance single agent rituximab at a dose of either 375 mg/m² for rituximab IV or 1400 mg for rituximab SC depending on treatment arm, every 8 weeks for up to 2 years or until disease progression.

Figure 1 Trial Design BO22334 SABRINA



[taken from CSR page 39]

Dose:

Rituximab SC-CHOP

- Cycle 1: rituximab IV 375 mg/m² as slow IV infusion on day 0, 1, or 2
- Cycle 2: rituximab SC 1400 mg on day 0
- Cycle 3-8 rituximab SC 1400 mg on day 1
- Cyclophosphamide 750 mg/m² IV on day 1
- Doxorubicin 50 mg/m² IV on day 1
- Vincristine 1.4 mg/m² (maximum 2 mg) IV on day 1

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- Prednisone (or prednisolone) 100 mg/day IV or oral for 5 consecutive days starting on the day of rituximab administration prior to rituximab
- Cycles repeated on day 22, CHOP for a maximum of 6-8 cycles. Rituximab for a total of 8 cycles independent from the total number of chemotherapy cycles.

Rituximab SC-CVP

- Cycle 1: rituximab IV 375 mg/m² as slow IV infusion on day 0, 1 or 2
 - Cycle 2: rituximab SC 1400 mg on day 0
 - Cycles 3-8: rituximab SC 1400 mg on day 1
 - Cyclophosphamide 750 mg/m² IV on day 1
 - Vincristine 1.4 mg/m² (maximum 2 mg) IV day 1
 - Prednisone (or prednisolone) 40 mg/m²/day IV or oral for 5 consecutive days starting on the day of rituximab administration prior to the rituximab
- Cycles will be repeated on day 22 for a maximum of 8 cycles. Rituximab should be given for a total of 8 cycles, independent from the total number of chemotherapy cycles.

All patients were to receive oral premedication 30 to 60 minutes prior to each administration of rituximab, SC or IV

- 1000 mg of paracetamol (acetaminophen)
- 50 to 100 mg of diphenhydramine hydrochloride or alternative antihistamine

Maintenance Treatment

Patients who achieve CR, CRu or PR after completion of 8 cycles of induction will receive rituximab maintenance. Patients on the rituximab IV arm, will continue with rituximab IV maintenance at 375 mg/m² every 8 weeks (±7 days) for up to 2 years. Responding patients (CR, CRu, and PR) on the rituximab SC arm were to continue with rituximab SC maintenance at 1400 mg every 8 weeks (±7 days) for up to 2 years.

Endpoints:

Primary Endpoint

Stage 1

- Estimated ratio of observed rituximab C_{trough SC}/C_{trough IV} cycle 7 of induction treatment given every 3 weeks

Stage 2

- Estimated ORR (CR, CRu, and PR) in each treatment arm at the end of induction

Secondary Endpoints

Stage 1

- Observed rituximab serum concentration AUC during induction treatment given every 3 weeks
- Additional explorative rituximab serum PK parameter during induction treatment, including, but not limited to, predicted PK parameter for induction regimens given every 4 weeks

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- ORR at the end/completion of induction treatment

Stage 1 and Stage 2

- Peripheral blood B-cell depletion and repletion after rituximab SC and rituximab IV
- CRR at the end of induction treatment
- ORR and CRR at the end of maintenance treatment
- Time to event efficacy endpoints including PFS, EFS and OS
- Observed rituximab serum C_{trough} levels at each induction treatment cycle
- Observed rituximab serum C_{trough} levels at each maintenance treatment cycle and rituximab levels 12 weeks, 24 weeks, and 36 weeks after the last rituximab administration
- Safety assessments including AEs, rituximab IRR (infusion related reactions), laboratory assessments, physical examinations and vital signs
- Immunogenicity: anti-rituximab antibodies and anti-hyaluronidase antibodies were to be assessed at each visit immediately pre-dose rituximab as well as every 12 weeks (± 7 days) after the last rituximab administration until 96 weeks after the last rituximab administration
- Physician/nurse opinion on resource savings and satisfaction with rituximab SC compared with rituximab IV

Inclusion Criteria (summarized)

- Informed consent and ability to comply with visit schedule and assessments
- Age ≥ 18 years
- Histologically confirmed CD20-positive, follicular non-Hodgkin's lymphoma grade 1, 2, or 3a according to the WHO (World Health Organization) classification system.
- No prior treatment
- At least one of the following signs and symptoms requiring treatment
 - Bulky disease defined as a nodal or extranodal (except spleen) mass ≥ 7 cm in its greatest diameter
 - B-symptoms
 - Elevated serum LDH (lactate dehydrogenase) or $\beta 2$ -microglobulin
 - Involvement of at least 3 nodal sites (each with a diameter greater than 3 cm)
 - Symptomatic spleen enlargement
 - Compressive syndrome
 - Pleura/peritoneal effusion
- ECOG (Eastern Clinical Oncology Group) performance status of 0-2
- Life expectancy of 6 months or more
- Bi-dimensionally measureable disease
- Adequate hematological function (unless related to lymphoma infiltration)
 - Hemoglobin ≥ 8.0 g (grams)/dL (deciliter)
 - ANC (absolute neutrophil count) $\geq 1.5 \times 10^9/L$ (liter)

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- Platelet count $\geq 100 \times 10^9/L$

Exclusion Criteria (summarized)

- Grade 3b FL
- Transformation to high-grade lymphoma secondary to FL
- Types of NHL other than FL according to the WHO classification
- Presence or history of CNS (central nervous system) disease (CNS lymphoma or lymphomatous meningitis)
- Corticoid therapy during the last 4 weeks, unless the dose was below 20 mg (milligrams)/day prednisone equivalent
- Any of the following abnormal laboratory values:
 - Serum creatinine >2 mg/dL
 - Total bilirubin >1.5 times the ULN (upper limit of normal) (except Gilbert's disease)
 - AST (aspartate aminotransferase) or ALT (alanine aminotransferase) >2.5 times the ULN (or >5 times the upper limit of normal in the presence of liver involvement)
- Active hepatitis B virus or hepatitis C virus or history of hepatitis B virus infection
- Known HIV (human immunodeficiency virus) infection
- History of organ transplantation including HSCT (hematopoietic stem cell transplantation)
- Known active bacterial, viral, fungal, or mycobacterial or recent major episodes
- Uncontrolled concomitant diseases

Assessment of Response:

Radiographic response was assessed according the IWG (International Working Group) criteria. During induction, clinical and radiological evaluation of tumor response was performed after 4 cycles of induction treatment and after the end or completion of induction treatment. Bone marrow was to be repeated after induction in patients with CR per other criteria.

During maintenance, clinical evaluation was done at every visit every 8 weeks. If there were no signs of disease progression after clinical evaluation, patients were to receive routine CT (computed tomography) scans every 24 weeks (cycles 12, 15, and 18 and final assessment after cycle 20).

At the end of maintenance, patients were followed every 12 weeks with clinical evaluation of tumor. If there was evidence of disease progression on clinical evaluation, a CT scan was to be performed within 4 weeks. If no evidence of disease progression on clinical evaluation, routine CT scans were to be done every 24 weeks. After disease progression, patients were to be followed for survival every 12 weeks.

Dose Modifications:

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Patients who experienced a delay over 21 days in the next cycle were to be removed from receiving study treatment. The dose was not to be modified for rituximab IV or rituximab SC. If the chemotherapy was delayed, rituximab should have been delayed as well.

Modification of the induction treatment secondary to hematologic toxicity was to be based on institutional practice (although guidelines were in protocol regarding dose reduction of cyclophosphamide for hematologic toxicity). Routine G-CSF (granulocyte colony stimulating factor) was not required, but if severe or life-threatening granulocytopenia (grade 3 or 4) was present, SC G-CSF was recommended.

For clinically relevant non-hematological adverse events of grade 2 or higher, the next cycle was to be delayed in 1 week increments for up to a maximum of 14 days until the event resolves to grade ≤ 1 . The protocol specifically addressed hemorrhagic cystitis and cyclophosphamide, hepatotoxicity and doxorubicin, cardiotoxicity and doxorubicin and neurotoxicity and vincristine.

Patients randomized to the rituximab SC arm, who were not able to receive the full dose of rituximab at cycle 1, as a result of an IRR, should have received the second rituximab administration intravenously. If the patient did not experience grade 3 or 4 IRR they should have then received the 3rd rituximab administration subcutaneously. Patients with grade 3 or 4 IRR after the second rituximab infusion should have been withdrawn from receiving study treatment.

During maintenance therapy, no dose modifications should have been done for rituximab IV or SC. Maintenance treatment could have been delayed up to 8 weeks, however, delays beyond 8 weeks should have been removed from receiving study treatment.

Schedule of Assessments

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Figure 2 Schedule of Assessment trial BO22334 SABRINA

	Screening	within 1 Week prior to randomization Days -7 to 0 ^a	Induction Treatment ³										Pre-planned Radiotherapy ⁷ Cycle 8, Day 1	Maintenance (Cycles 9-20) Day 1 ^c each cycle	Final Assessment Maintenance (Cycle 20) Day 57 (± 7 days)	Unscheduled Visits	Early Withdrawal	Follow Up (FLU Visits 1-8)	Survival
			Cycle 1 Day 1	Cycle 2		Cycle 3 Day 1	Cycle 4		Cycle 5, 6, 7 Day 1	Cycle 8									
				Day 0 ^a	Day 1		Interim Assessment 19 (± 2)	Day 1		Final Assessment 19 (± 2) ^{ab} Day 1	Day 1								
Written Informed Consent	X																		
Inclusion/Exclusion Criteria	X																		
Demographics	X																		
Height	X																		
Weight	X		X ^b	X ^{bj}	X ^{bk}	X ^b	X ^b	X	X ^b	X ^b	X	X ^{ac}	X ^{b,c}	X	X	X	X ^d		
BSA	X																		
Nicotine History	X																		
Medical History ¹	X																		
Physical Examination ²	X		X ^b	X ^{bj}	X ^{bk}	X ^b	X ^b	X	X ^b	X ^b	X	X ^{ac}	X ^{b,c}	X	X	X	X ^d		
Vital Signs ³	X		X ^{bw}	X ^{bj}	X ^d	X ^d	X ^d	X	X ^d	X ^d	X	X ^{ac}	X ^{c,d}	X	X	X	X ^d		
ECOG Performance Status		X ^{ib}						X			X		X ^{b,c}	X	X	X	X ^d		
Ann-Arbor Staging	X																		
B-symptoms	X							X			X		X ^{b,c}	X	X	X	X ^d		
FLIPI score	X																		
12-lead ECG ⁴	X							X ^f			X				X				
LVEF ⁵	X							X ^f			X				X				
Serology for HCV and HBV (HBsAg, anti-HBs, anti-HBc)	X																		
Serum Pregnancy Test (if applicable) ⁶		X																	
Hematology ⁷		X	X ^b	X ^{bj}	X ^{bk}	X ^b	X ^b	X	X ^b	X ^b	X	X ^{ac}	X ^{b,c}	X	X	X	X ^d		

Survival	Follow Up	Early Withdrawal	Unscheduled Visits	Final Assessment Maintenance (Cycle 20)	Maintenance (Cycles 9-20)	Pre-planned Radiotherapy	Induction Treatment ³												
							Cycle 8	Cycle 5, 6, 7	Cycle 4		Cycle 3	Cycle 2		Cycle 1					
									Interim Assessment 19 (± 2)	Day 1		Day 1	Day 0 ^a		Day 1				
	(FLU Visits 1-8)			Day 57 (± 7 days)	Day 1 ^c each cycle	3-4 weeks after Cycle 8, Day 1	Final Assessment 19 (± 2) ^{ab}	Day 1	X	X ^b	X ^b	X ^b	X ^b	Day 1	Day 0 ^a	Day 1	Days -7 to 0 ^a	Days -28 to -1	
Serum Chemistry ⁸	X ^d	X	X	X	X ^{bc}	X ^{ac}	X	X ^b	X	X ^b	X ^b	X ^b	X ^b	X ^{bk}	X ^{bj}	X ^b	X		
β-2 microglobulin	X ^e	X		X	X ^b		X		X									X	
Quantitative immunoglobulins IgG, IgA, IgM	X ^e	X		X	X ^b		X											X	
INR and aPTT	X ^d	X	X	X	X ^b		X	X ^b	X	X	X	X	X				X		
Urinalysis ⁹	X ^d	X	X	X	X ^{bc}		X	X ^b	X	X ^b	X ^b	X ^b	X ^b	X ^{bk}	X ^{bj}	X ^b	X		
Tumor Biopsy for Confirmation of FL																		X ^f	
Bone Marrow Aspirate and Biopsy	X ^f						X ^g											X ^f	
Clinical Tumor Assessment ¹⁰	X ^d	X		X	X ^{bc}		X	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^{bk}	X ^{bj}	X ^b	X		
CT Scans ¹¹	X ^f	X	X		X ^b		X		X				X					X	
Optional FDG-PET scan ¹⁹							X ^{ac}											X	
CSF examination and brain CT/MRI if clinically indicated																		X	

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Survival	Follow Up	Early Withdrawal	Unscheduled Visits	Final Assessment Maintenance (Cycle 20)	Maintenance (Cycles 9-20)	Pre-planned Radiotherapy ¹⁷	Induction Treatment ⁷																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					
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1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1

Screening	within 1 Week prior to randomization	Induction Treatment ⁷										Pre-planned Radiotherapy ¹⁷	Maintenance (Cycles 9-20)	Final Assessment Maintenance (Cycle 20)	Unscheduled Visits	Early withdrawal	Follow Up	Survival
		Cycle 1	Cycle 2		Cycle 3	Cycle 4		Cycle 5, 6, 7	Cycle 8		Final Assessment 19 (± 2) ¹⁸							
	Days -28 to -1	Day 1	Day 0 ^a	Day 1	Day 1	Day 1	Interim Assessment 19 (± 2)	Day 1	Day 1	Final Assessment 19 (± 2) ¹⁸	Day 1	3-4 weeks after Cycle 8, Day 1	Day 1 ^a each cycle	Day 57 (± 7 days)			(PL-Visits 1-8)	
Concomitant Medication ¹⁶	X	X					X					X	X	X	X	X	X	
Documentation of Pre-planned Consolidation Radiotherapy to be given (Screening) / Record Pre-planned Consolidation Radiotherapy given (after completion of Induction Treatment) ¹⁷	X											X						
New Anti-Lymphoma Treatment (Survival) ¹⁸																		X
Adverse Events ^{15, 15.1}							X					X	X	X	X	X	X	X
Survival Status Assessment																		X ^a

1. Including previous and concurrent relevant diseases, history of HBV and HIV infection.
2. Including cardiopulmonary examination and palpation of the abdomen for assessment of hepatosplenomegaly. Any clinically significant changes from baseline are recorded as AEs.

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3. Including single measurements of blood pressure and pulse rate.
4. Subsequent ECGs as clinically indicated.
5. 2D-ECHO or MUGA scan. Subsequent assessments as clinically indicated.
6. Quantitative serum β -HCG test is indicated in pre-menopausal women who are not surgically sterile and women < 2 years after the onset of menopause (within 7 days prior to starting therapy) or within 14 days with a confirmatory urine pregnancy test within 7 days prior to study treatment start. Throughout the study conduct pregnancy tests need to be repeated in case of a suspected pregnancy.
7. Standard Hematology = hemoglobin, hematocrit, RBC, WBC with differential leukocyte counts, platelet count.
8. "Serum Chemistry = sodium, potassium, calcium, phosphate, AST (SGOT), ALT (SGPT), total serum bilirubin, serum creatinine, alkaline phosphatase, total protein, urea (BUN), serum albumin, glucose, LDH and CRP."
9. Including pH, glucose, protein, ketones, and blood. If urine protein by dipstick is $\geq 2+$, quantitative protein in 24-hour urine needs to be measured prior to the next administration of study treatment.
10. Including examination of palpable lymph nodes, clinical examination of spleen and liver. If progressive disease has been diagnosed clinically, the PD has to be confirmed by a CT scan examination within 4 weeks.
11. CT scans (or MRI if CT is medically contraindicated) of abdomen, chest, pelvis and, if clinically indicated, neck. If progressive disease has been diagnosed clinically, the PD has to be confirmed by a CT scan examination within 4 weeks. Response assessment will be done according to the International Working Group response criteria for non-Hodgkin lymphomas (Cheson 1999).
12. Peripheral blood sample for flow cytometry testing including, but not limited to, CD19+, CD3+, CD4+, CD8+, CD16+, and CD56+ to determine lymphocyte subsets.
13. Roche Clinical Repository (RCR) non-DNA specimen(s) will be taken from subjects consenting to RCR sampling. Desired samples include a 5-6 mL serum sample, 5-6 mL plasma sample, 2 x 2.5 mL PAXgene vacutainers (RNA samples) and tissue samples (5-10 formalin-fixed paraffin-embedded slides) and/or cryoconserved tissue samples obtained within 4 months prior to screening.
14. RCR DNA specimen (6 mL EDTA blood) will be taken from subjects consenting to RCR sampling.
15. Adverse events (AEs) occurring after the initiation of trial treatment will be recorded until 28 days after completion of study treatment. Serious adverse events (SAEs) considered to be unrelated to study treatment will be recorded for 1 year post treatment. SAEs considered to be possibly related to study treatment will be recorded indefinitely. All unresolved study-related AEs and SAEs should be followed up to their resolution or stabilization. Second malignancies will be recorded indefinitely or until new anti-lymphoma treatment.
- 15.1. Following drug administration, any patient experiencing a severe or serious adverse event which is considered immunogenic and possibly related to rituximab administration, serum samples for rituximab PK, anti-rituximab, (and following Cycle 2 for patients randomized in the subcutaneous arm anti-rHuPH20) are to be collected within 7 days of the event becoming known to the Investigator.
16. Concomitant medications (non-investigational products) includes any prescription and over-the-counter medications, herbal therapy, prior cancer treatments and pre-study medications taken between 28 days prior to study screening through study termination.
17. Any radiotherapy must be pre-planned before randomization and documented on the eCRF at Screening. Radiotherapy should be given starting 3-4 weeks after the last induction treatment cycle.
18. Pre-planned radiotherapy given is not regarded as "new Lymphoma Treatment".
19. FDG-PET scans can be done according to the institutional practice. Results as well as deviations from the response assessment according to the Cheson 1999 response criteria needs to be recorded on the eCRF.
- a) Assessments can be performed on Day 0 pre-dose rather than Day -1 but must be performed prior to treatment.
- b) Within 72 hours prior to the administration of study treatment.
- c) Every 8 weeks (+/- 7 days) for 96 weeks or until documented disease progression.
- d) Every 12 weeks (+/- 2 weeks) for 96 weeks or until documented disease progression.
- e) Every 24 weeks (+/- 2 weeks) until documented disease progression.
- f) Tumor biopsy should have been performed within 6 months *prior to screening* with material available for central pathology review. Material for central pathology review should consist of 1 slide with HE staining and 5 unstained slides.
- g) Bone marrow aspirate and biopsy to be performed only for confirmation of a CR/CRu for patients with bone marrow involvement at screening. Bone marrow should be assessed within 14 days after the first tumor assessment that documents CR/CRu.
- h) Cycles 11, 14 and 17 on Day 1 (+/- 7 days).
- i) PK sample needs to be taken within 2 hours before rituximab administration.
- j) Only patients randomized to the rituximab SC arm.
- k) Only patients randomized to the rituximab IV arm.
- l) Cycle 9, Day 1 is 8 weeks ($\pm$ 7 days) after Day 1 of the last cycle of induction treatment. Maintenance treatment cycles will be repeated every 8 weeks ($\pm$ 7 days) for 96 weeks (i.e. in total 12 cycles of maintenance) or until disease progression.
- m) Please refer to the PK schedule of assessment for Stage 1.
- n) Within 72 hours prior to rituximab administration and every 12 weeks after last rituximab administration until 96 weeks after last rituximab administration.
- o) Survival follow-up information will be collected via telephone calls and/or clinic visits every 12 weeks (+/- 2 weeks) until death, loss to follow-up, or study termination.
- p) Please note that Day 21 of Cycle 1 and Day 0 of Cycle 2 are the same calendar day.
- q) Before study treatment.

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- r) Only patient treated with CHOP as chemotherapy backbone.
- s) FU-visits 2, 4, 6, 8 (+/- 2 weeks).
- t) Only in patients otherwise assessed as CR with bone marrow involvement at baseline and PR at last assessment need to receive a bone marrow biopsy in order to confirm the CR.
- u) Rituximab at Cycle 1 will always be given intravenously. Rituximab at Cycle 1 can be given on Day 0, Day 1 or Day 2, depending on the institutional practice.
- v) PK samples need to be taken within 2 hours pre-dose.
- w) If rituximab and chemotherapy are given on different days, vital signs need to be done on both days prior to the study drug administration.
- x) Only if progressive disease has been diagnosed clinically. In such case PD has to be confirmed by a CT scan examination within 4 weeks.
- y) Induction treatment cycles will be repeated on Day 22 for up to 8 cycles.
- z) Unless bone marrow aspirate and biopsy were done within 6 months prior to randomization. *Note: if a bone marrow biopsy was performed >6 months prior to the first dose of study medication and was positive, it does not need to be repeated unless it is institutional practice to do so. If the bone marrow biopsy was performed >6 months and was negative then it should be repeated before the first dose of study medication.*
- aa) CT scans of neck (if clinically indicated), chest, abdomen, and pelvis to document nodal disease to be performed at Day 57 (+/- 14 days)
- bb) ECOG Performance Status must be 0-2 to meet study criteria.
- cc) Only if an optional baseline PET scan was done and was positive. PET scans should be done 6-8 weeks after completion of induction treatment (defined as Cycle 8, Day 1).
- dd) For patients receiving pre-planned irradiation, final response assessment will be performed after completion of radiotherapy.
- ee) According to the institutional practice.
- ff) Physicians and nurses involved in the study will be asked about their experience with rituximab SC and IV formulations at three time-points: at the end of induction (i.e. after Cycle 8), during maintenance (i.e. after Cycle 15), and after the end of the maintenance (i.e. after Cycle 20).

[taken from CSR pages 2841-2847]

Protocol Amendments

The protocol was amended twice, in protocol version B and version C. The amendments involved clarifications and minor changes which did not alter the integrity of the trial.

Protocol Amendment C

The protocol was amended to include the possibility of performing safety evaluations including AEs (adverse events), laboratory parameters, immunogenicity and B-cell depletion and repletion for health authority or regulation concerns. It was also added to the protocol that if a bone marrow biopsy was positive > 6 months, there would be no need to repeat it. If the bone marrow biopsy was > 6 months and negative, then it should be repeated.

Protocol BO22334 SAP (Statistical Analysis Plan)

The SAP stated randomization was done using the Pocock Simon dynamic randomization algorithm stratified by induction chemotherapy, FLIPI and region. A PK futility interim analysis was planned after 35 patients in each treatment arm completed cycle 7. This was done in case a dose adjustment was needed.

The sample size in the SAP was 530 patients. For stage 1, it was approximately 125 patients to be enrolled, with another potential 125 patients if dose adjustment was needed.

For stage 1 a sample size of 50 patients per arm was determined to be enough to provide the estimated value of the ratio $C_{\text{trough SC}}/C_{\text{trough IV}}$ above 0.84 with 95% confidence assuming 0.56 coefficient of variation and the mean $C_{\text{trough SC}}$ was to be 5%

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above C_{trough} IV. Assuming 20% would not have valid PK data, a total of 125 patients were to be enrolled.

For stage 2 a sample size of 280 was planned. If the observed ORR in the rituximab SC arm ranged from 0.80 to 0.95, the precision for estimating ORR in the rituximab SC in stage 2 was further defined.

The intent to treat population, defined as all patients randomized according to assignment at randomization, was to be used for all efficacy endpoints.

The safety population was defined as all patients who received at least one dose either IV or SC analyzed as treated.

Protocol MO28107 MabEase

Title: A Comparative, Randomized, Parallel-Group, Multi-center, Phase IIIB Study to Investigate the Efficacy of SC Rituximab versus IV Rituximab Both in Combination with CHOP In Previously Untreated Patients with CD20-Positive DLBCL.

Reviewer Comments: In this trial rituximab IV was MabThera IV and rituximab SC was MabThera SC.

Objectives:

The primary efficacy objective was to estimate the efficacy of rituximab administered subcutaneously or intravenously in combination with CHOP measured by CRR (CR + CRu) one month after the end of rituximab based treatment.

The secondary efficacy objectives were EFS, PFS, and OS from randomization and DFS from CR/CRu.

The safety objectives included the safety of rituximab SC with a focus on SAEs (serious adverse events), grade ≥ 3 AEs, grade ≥ 3 application associated reactions and IRRs.

The PRO (Patient Reported Outcomes) objectives were to compare patient satisfaction measured by the CTSQ (Cancer Treatment Satisfaction Questionnaire) and RASQ (Rituximab Administration Satisfaction Questionnaire).

The pharmacoeconomic objectives were to evaluate the method of administration of rituximab SC and IV in terms of:

- Rituximab administration time
- Chair time for a single treatment cycle of rituximab and CHOP
- Hospital time, defined as the time a patient is in the hospital for the course of one cycle of rituximab and CHOP

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Design:

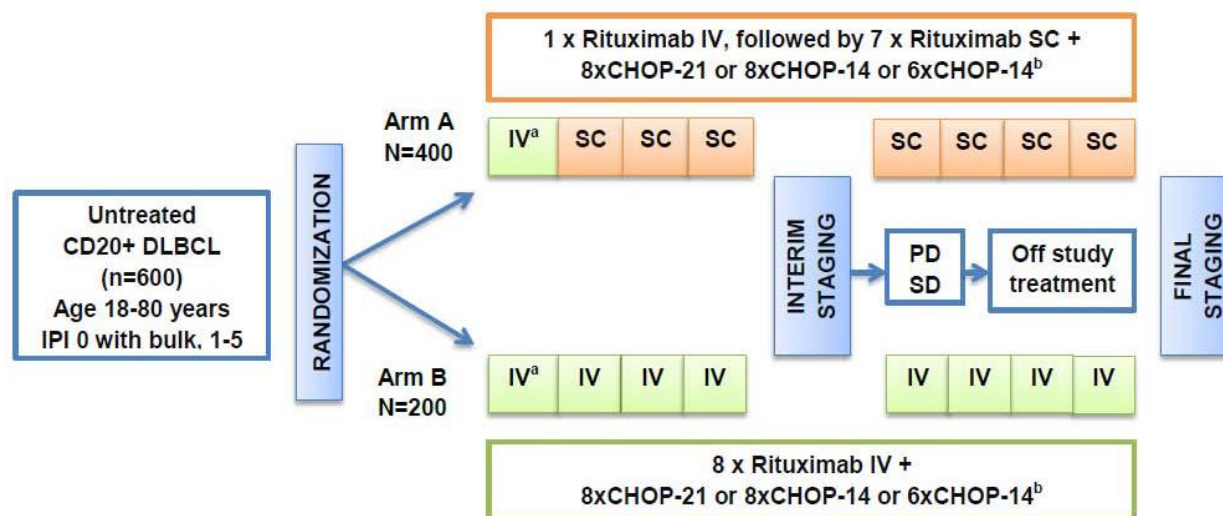
This is a phase 3b, prospective, multinational, open label randomized study in approximately 600 patients with previously untreated CD20-positive DLBCL. Patients were randomized to rituximab SC or rituximab IV in a 2:1 ratio. Patients were stratified according to age (<60 years, ≥60 years), IPI (International Prognostic Index) risk category (low, low-intermediate, high-intermediate, high) and chemotherapy regimen (CHOP every 21 days or CHOP every 14 days).

Study treatment consisted of 8 cycles administered with either 8 cycles of rituximab, SC or IV, combined with 8 cycles of CHOP-21, 8 cycles of CHOP-14 or 6 cycles of CHOP-14. Patients receiving 6 cycles of CHOP-14 will receive 2 additional cycles consisting of rituximab only, for a total of 8 cycles of rituximab. Patients allocated to rituximab SC will receive rituximab IV for the first cycle and, in the absence of IRRs, rituximab SC for the remaining 7 treatment cycles.

Endpoints:

The primary endpoint is CR/CRu, based on investigator assessment according to the IWG response criteria at the end of induction treatment (visit 10).

Figure 3 Trial Design MO28107 MabEase



[From CSR page 1767]

Dose:

Patients randomized to the rituximab SC arm were to receive rituximab 375 mg/m² IV for cycle 1 followed by 1400 mg SC for cycles 2-8. Patients randomized to the rituximab IV arm received rituximab IV 375 mg/m² on day 1 of each 14 or 21 day cycle. For CHOP the doses were cyclophosphamide 750 mg/m² IV day 1, doxorubicin 50 mg/m² IV day 1, vincristine 1.4 mg/m² (absolute 2 mg maximum) IV day 1, and prednisone/prednisolone

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100 mg PO days 1-5. For CHOP-14 and CHOP-21 the cycle length was 14 days and 21 days respectively.

On the rituximab SC arm, patients who were not able to the full dose of rituximab IV due to IRRs, were to receive the second dose of rituximab IV as well. If the second dose was not associated with a grade 3 or 4 IRR, the patient was to receive the third rituximab dose SC. Patients with grade 3 or 4 IRR after the second rituximab infusion were to be withdrawn from the trial.

For patients who achieve a CR/CRu at interim staging (after cycle 4), CHOP-21 may have been reduced to two additional cycles of CHOP-21 with rituximab followed by two additional cycles of rituximab only.

Endpoints:

The primary endpoint is CR/CRu based on Investigator's assessment according to the IWG response criteria at the end of induction.

Secondary efficacy endpoints include EFS, DFS, PFS and OS.

Inclusion Criteria (summarized)

- Informed consent
- Age ≥ 18 and ≤ 80 years
- Histologically confirmed, previously untreated CD20-positive DLBCL according to the WHO classification system.
- Patients with an IPI score of 1-5 or IPI score of 0 with bulky disease, defined as one lesion ≥ 7.5 cm
- At least one bi-dimensionally measureable lesion defined as ≥ 1.5 cm in its largest dimension on CT scan
- Adequate hematologic function (unless related to involvement of bone marrow by DLBCL) defined as:
 - Hemoglobin ≥ 9 g/dL (no transfusions within 2 weeks prior to start of study drug)
 - ANC $\geq 1.5 \times 10^9/L$
 - Platelet count $\geq 75 \times 10^9/L$
- ECOG performance status ≤ 2
- Agreement to use adequate contraception during the treatment period and for 12 months after the last dose.

Exclusion criteria (summarized)

- Primary CNS lymphoma, blastic variant of mantle cell lymphoma, or histologic evidence of transformation of Burkett lymphoma, primary mediastinal DLBCL, primary effusion lymphoma, primary cutaneous DLBCL, or primary DLBCL of the testis

- Transformed lymphoma or FL IIIB
- Prior therapy for DLBCL, except nodal biopsy or local irradiation
- History of other malignancy except:
 - Curatively treated basal or squamous cell carcinoma or melanoma of the skin or carcinoma in situ of the cervix are eligible
 - A malignancy treated but not with curative intent was to be excluded, unless the malignancy has been in remission without treatment for ≥ 5 years prior to enrollment.
- Inadequate renal function, creatinine > 1.5 times ULN, unless CrCl (creatinine clearance) normal or calculated CrCl < 30 mL/min
- Inadequate hepatic function, defined as:
 - ALT or AST $> 2.5 \times$ ULN
 - Alkaline phosphatase $> 2.5 \times$ ULN
 - Total bilirubin $\geq 1.5 \times$ ULN (unless Gilbert disease than total bilirubin $\leq 3 \times$ ULN)
- Know HIV or HIV seropositive status
- Active or severe bacterial, viral, mycobacterial, parasitic or other infection or any major episode of infection requiring IV antibiotics or hospitalization within 4 weeks prior to the start of study drug administration
- Active hepatitis B virus, or active hepatitis C virus infection
- Other serious medical conditions that would impair participation
- Recent major surgery (within 4 weeks) other than diagnostic purposes
- History of severe allergy to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Contraindication to CHOP, including prior anthracyclines
- Prior treatment with cytotoxic drugs or rituximab or prior use of an anti-CD20 antibody
- Treatment with a monoclonal antibody within 3 months prior to study drug administration
- Ongoing corticosteroid treatment > 20 mg/day of prednisone or equivalent
- Chemotherapy or investigational therapy within 4 weeks prior to study drug

Assessment of Response

Response will be determined using the original IWG criteria for response assessment of lymphoma. The primary efficacy endpoint is CR/CRu approximately one month after the end of rituximab based treatment. Tumor assessments will be based on CT scans of the neck, chest, abdomen and/or pelvis. CT with contrast was recommended. MRI (magnetic resonance imaging) and a non-contrast CT scan may be used if contrast is contraindicated. Response assessments will be completed according to IWG response criteria for NHL after the first 4 cycles (interim staging) and after 30 ± 3 days after start of the last cycle.

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Follow-up after induction therapy was to occur every 3 months for the first two years and then every 6 months until end of trial.

Dose Modification

In this trial, patients randomized to the rituximab SC arm and were not able to receive the full dose of rituximab IV infusion in cycle 1 were to receive the second rituximab dose IV. Patients with a grade 3 or 4 infusion reaction after the second rituximab IV dose were to be withdrawn from the trial.

The dose of rituximab SC was not modified. Guidelines were in for protocol for management of specific adverse events. These are displayed in

Figure 4 Guidelines for managing certain AEs related to rituximab-CHOP for trial MO28107 MabEase

Event	Action to Be Taken
Haematologic toxicity: Grade 4	• Hold all study treatment for a maximum of 3 weeks. • Give supportive treatment. • If improvement to grade ≤ 2 does not occur within 3 weeks, discontinue all study treatment. • First episode: If improvement to grade ≤ 2, decrease cyclophosphamide dose to 500 mg/m² and doxorubicin dose to 35 mg/m² for subsequent cycles. • Second episode: If improvement to grade ≤ 2, decrease cyclophosphamide dose to 375 mg/m² and doxorubicin dose to 25 mg/m² for subsequent cycles. • Third episode: Discontinue CHOP. If improvement to grade ≤ 2, continue rituximab at full dose. • Fourth episode: Discontinue all study treatment.
Haematologic toxicity: Grade 3	• Hold all study treatment for a maximum of 3 weeks. • Give supportive treatment. • If improvement to grade ≤ 2 does not occur within 3 weeks, discontinue all study treatment. • If improvement to grade ≤ 2, continue CHOP at current dose and continue rituximab at full dose.
Haematologic toxicity: Grade 1 or 2	• No action required.
Neurotoxicity: Grade 4	• Discontinue CHOP. • Hold rituximab for a maximum of 3 weeks. • If improvement to grade ≤ 1 does not occur within 3 weeks, discontinue all study treatment.

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Event	Action to Be Taken
	If improvement to grade ≤ 1, continue rituximab at full dose.
Neurotoxicity: Grade 2 or 3	- Hold all study treatment for a maximum of 2 weeks. - If improvement to grade ≤ 1 does not occur within 2 weeks, discontinue all study treatment. - If improvement to grade ≤ 1, reduce vincristine dose by 50% for subsequent cycles, continue cyclophosphamide, doxorubicin, and prednisone at current dose, and continue rituximab at full dose.
Neurotoxicity: Grade 1	No action required.
Other non-haematologic toxicities: Grade 3 or 4	- Hold all study treatment for a maximum of 3 weeks. - If improvement to grade ≤ 1 or baseline does not occur within 3 weeks, discontinue all study treatment. - First episode: If improvement to grade ≤ 1 or baseline, decrease cyclophosphamide dose to 500 mg/m² and doxorubicin dose to 35 mg/m² for subsequent cycles. - Second episode: If improvement to grade ≤ 1 or baseline, decrease cyclophosphamide dose to 375 mg/m² and doxorubicin dose to 25 mg/m² for subsequent cycles. - Third episode: Discontinue CHOP. If improvement to grade ≤ 1 or baseline, continue rituximab at full dose. - Fourth episode: Discontinue all study treatment.
Other non-haematologic toxicities: Grade 2	- Hold all study treatment for a maximum of 3 weeks. - If improvement to grade ≤ 1 or baseline does not occur within 3 weeks, discontinue all study treatment. - If improvement to grade ≤ 1 or baseline, continue CHOP at current dose and continue rituximab at full dose.
Other non-haematologic toxicities: Grade 1	No action required.

[Taken from CSR page 2039-2040]

Schedule of Assessments

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Figure 5 Schedule of Assessments for Trial MO28107 MabEase

Study Period	Screening/ Baseline	Induction Treatment Rituximab IV/SC + CHOP				Observation	End of Study / Early Termination
Visit	Screening/ Baseline Visit	V1-V4	V5 Interim Staging	V6-V9	V10 Final Staging	V11-V23	
Timing / Assessments	D -28 to D 1	D1 Every 14-21 days 4 cycles	after 4 cycles [a]	D1 Every 14-21 days 4 cycles	End of study treatment [b]	Every 3 months [91 ± 7 days] for first 2 years, then every 6 months [182 ± 7 days] until end of study	Within 4 weeks of last visit [c]
Written informed consent [d]	X						
Demographic data	X						
Medical history	X						
DLBCL diagnosis and Ann Arbor staging [e]	X						
Documentation of HIV and other infections, testing for Hepatitis [f]	X	As clinically indicated [f]					
Tumour evaluation [g]	X		X		X	X (according to local practice)	X
Physical examination, infection assessment, vital signs [h]	X	X		X	X	X	X
Height, weight and BSA [i]	X	X (Arm B only)		X (Arm B only)			
12-lead ECG	X						
IPI score [j]	X						
ECOG performance status [k]	X		X		X	X	X
Serum pregnancy test [l]	X	If clinically indicated					
Laboratory: Haematology, Biochemistry, Coagulation tests [m]	X	X	X	X	X	X	X
Review of Inclusion / Exclusion criteria Randomization by IVRSIWRS [n]	X						
Rituximab + CHOP administration [o]		X		X			
Adverse event recording [p]	X	X	X	X	X	X	X
Concomitant treatments & therapies [q]	X	X	X	X	X	X	X
Patient satisfaction with therapy questionnaire [r]		V3		V8			

- Interim staging assessment performed within 14–28 days after Day 1 of the 4th cycle of rituximab-based induction treatment, and should be performed before Cycle 6.
- Final staging assessment performed 30±3 days after Day 1 of the last cycle of rituximab-based study treatment, and should be performed before visit 10.
- Randomized patients who do not complete the induction treatment per protocol will undergo End of Study / Early Termination assessment within 4 weeks after their last dose of induction treatment and will be followed until the end of the whole study according to local practice for resolution of SAEs related to rituximab therapy (as applicable), disease progression, survival, and documentation of any new anti-lymphoma treatment. For these patients, survival status may be determined by telephone follow-up.
- Signed informed consent must be obtained prior to any screening/baseline assessments or other study-related changes to the patient's management. Tests that are performed as standard of care prior to obtaining informed consent may be used for screening and baseline assessments, provided that they have been performed within the allowable timeframe as described in the Schedule of Assessments.
- Diagnosis of diffuse large B-cell lymphoma before treatment must have included histological diagnosis and initial CD20 expression confirmation.
- Patients with HIV, Hepatitis C, active Hepatitis B or signs or symptoms of other active and/or severe infection must not be included in the study. See Section 4.5.1.8. Patients with occult or prior HBV infection (defined as positive total HBcAb and negative or positive HBsAg with undetectable HBV DNA) may be included, but these patients must be followed closely, with testing for HBV DNA levels approximately every 4 weeks during induction treatment and for 1 year after completing study treatment. Patients with positive for HBsAg that are negative for HBV DNA by PCR test and negative PCR must be treated with lamivudine (or other standard antiviral therapy) beginning prior to the initiation of study treatment and continuing for 6 months after completing study treatment). Patients positive for HCV antibody are eligible only if PCR testing is negative for HCV RNA is negative. During treatment with rituximab, additional serology should be performed according to clinical judgment. Local guidelines for patient consent to viral testing must be adhered to.
- Tumour assessment at baseline, after four cycles of treatment (interim staging) and at end of treatment will be based on CT scans of the neck, chest, abdomen and/or pelvis, as applicable. CT scan with contrast is the recommended technique. Combined PET-CT scans may be used instead of a CT scan, if performed with contrast and collected with sufficient resolution. MRIs with a non-contrast CT scan may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). In the observation period patients should have tumour assessments according to local practice. The CT scan, PET-CT scan or MRI used for eligibility assessment may be up to 35 days old at the start of study drug administration. The end-of-treatment response assessment including radiology/imaging report must be obtained 30±3 days after Day 1 of the last treatment cycle. Patients with SD or PD at the interim staging will come off study treatment. Screening/baseline bone marrow examinations should include biopsy and aspirate for morphology (flow studies are optional) for staging purposes unless it has been performed within 4 months prior to the start of study drug administration. Subsequent bone marrow assessments are required at final staging to confirm any suspected CR in patients with bone marrow involvement at baseline. If a confirmatory bone marrow assessment is not obtained, these patients should be considered as only having a PR. See Section 4.5.1.3 for additional details.
- As part of physical exams, SC injection sites will be checked at every treatment visit. As part of tumour assessments, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Patients should be assessed for presence of active infections throughout the treatment periods. Vital signs assessment includes resting heart rate, body temperature and blood pressure.
- Weight will be measured at each treatment visit for patients in Arm B, so that BSA can be re-calculated if necessary.
- IPI score (according to Shipp et al. 1993) determined at baseline (prior to Cycle 1). Where possible, the baseline IPI score should be calculated from the patient notes. Missing IPI scores will not preclude enrolment/randomization.
- ECOG performance status needs to be ≤ 2 for inclusion of the patient into the study.
- Women of childbearing potential (defined as pre-menopausal women or women who are < 2 years after the onset of menopause and not surgically sterile) must undergo serum pregnancy test within 7 days prior to the start of study drug administration or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to the start of study drug administration. If pregnancy is suspected during the study treatment period, a pregnancy test must be conducted.
- Haematology parameters will include haemoglobin, RBC, WBC, differential leukocyte count and platelet count. Biochemistry parameters at screening will include sodium, potassium, ALT/SGPT, AST/SGOT, total bilirubin, serum creatinine, alkaline phosphatase, albumin, BUN (or plasma urea if BUN not performed locally), C-reactive protein and LDH. Biochemistry parameters at any further timepoint during the study will include sodium, potassium, ALT/SGPT, AST/SGOT, total bilirubin, and serum creatinine. Coagulation tests will include: INR, PT, and aPTT. Safety laboratory assessments should be performed no more than 3 days prior to the administration of study treatment, and the results must be available on treatment days, prior to the rituximab administrations.
- Randomization can occur only after all screening assessments have been completed and the patient's eligibility is confirmed. Randomization should occur as close as possible (no later than within 3 days prior) to the first rituximab administration.
- The first rituximab dose will be administered by IV infusion on Day 1 of Cycle 1, at a dose of 375 mg/m² BSA (rounded to the nearest 10 mg), regardless of whether the patient was randomized to Arm A (rituximab SC) or Arm B (rituximab IV). The initial dose of rituximab can also be administered one day before Day 1 of CHOP chemotherapy (depending on institutional practice). For patients at high risk of TLS, the initial rituximab dose can be administered depending on institutional practice; one day before Day 1 of CHOP chemotherapy, over Days 2 and 3 after receiving CHOP chemotherapy, or anytime between Day 2 and Day

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7. Patients randomized to Arm A, who were able to receive the full first dose of rituximab IV, will receive rituximab SC at a fixed dose of 1400 mg in Cycles 2 to 8, while patients randomized to Arm B will continue receiving rituximab IV for a total of 8 cycles. Patients receiving six cycles of CHOP-14 or CHOP-21 as chemotherapy will receive two additional cycles consisting of rituximab only (according to the previous chemotherapy schedule), for a total of 8 cycles of rituximab.
- p. All clinical and laboratory AEs reported during the study will be documented and graded using the NCI CTC-AE criteria, version 4.0. AEs of special interest include acute infusion-related toxicity. Serious adverse events (SAE) will be reported according to the ICH E2 Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting. After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported (e.g. SAEs related to invasive procedures such as biopsies). After study closure, investigators should report any deaths, SAEs or adverse events of special interest that are believed to be related to prior treatment with study drug or study procedures.
 - q. Recording of concomitant treatments & therapies will include any new anti-lymphoma treatment initiated after the baseline visit.
 - r. Patient reported outcomes: treatment satisfaction for rituximab SC or rituximab IV administration will be assessed using the Cancer Treatment Satisfaction Questionnaire (CTSQ) and the Rituximab Administration Satisfaction Questionnaire (RASQ) at Visit 3/Cycle 3 and Visit 8/Cycle 7. At these visits, CTSQ will be completed prior to rituximab administration, whereas RASQ will be completed immediately after rituximab administration and before chemotherapy administration.

[Taken from CSR pages 2069-2071]

Protocol Amendments

There were three versions of the protocol. Version one was dated March 27, 2012, version two was dated May 2, 2012, and the third version was dated March 20, 2013.

Statistical Analysis Plan

Patients were randomly allocated to rituximab SC or rituximab IV in a 2:1 ratio. Randomization occurred using a centralized interactive voice/web response system. Patients were stratified according to age (<60 years/ ≥60 years), IPI risk category (low, low-intermediate, high-intermediate, high), and chemotherapy regimen (CHOP-21, CHOP-14), which were to be selected by the Investigator prior to randomization. Treatment was 8 cycles of rituximab in combination with CHOP-21, 8 cycles of CHOP-14 or 6 cycles of CHOP-14. Patients receiving only 6 cycles were to receive an additional 2 cycles of rituximab only.

Response assessments were to be completed according to IWG response criteria after the first 4 cycles and 30±3 days after day 1 of the last cycle of rituximab based study treatment. Follow-up after induction was every 3 months for the first two years and then every 6 months until the end of study.

This trial was designed as a descriptive trial to evaluate for major differences in efficacy between the treatment arms measured by CR/CRu rates. A sample size of 600 randomized patients was planned, randomized 2:1 (rituximab SC:rituximab IV). There was no formal statistical hypothesis for the treatment comparisons. The calculated sample size was based on the primary endpoint (CR/CRu rate at the end of induction) and no power calculations were performed for EFS, DFS, PFS or OS.

The analyses planned for this trial included analyses for IDMC periodic review, interim analysis of response rates (CR/CRu), patient reported outcomes data and safety data after the first 120 patients have completed induction treatment, primary analysis (analysis after all patients have reached the primary endpoint), and final analysis at the end of follow up.

The SAP defined several populations. The all subjects enrolled population was defined as all subjects who provided informed consent for the trial. The all subjects randomized population was defined as all subjects who were randomized to study medication. The ITT (intent to treat) population was defined as all randomized patients who completed

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baseline and at least one on-treatment efficacy assessment. Within the ITT population patients were to be allocated to treatment groups according to their randomization schedule. The safety population was to include all patients who received at least one dose of study drug and was to be allocated to treatment groups according to the treatment they received.

The only statistical testing was to be comparison of the primary efficacy endpoint of complete response rate (CR/CRu). This analysis was to be performed using a two-stage O'Brien-Fleming procedure. The critical values of the z-test at the first stage (interim analysis of the first 120 patients to complete induction treatment) was to be ± 4.382 , corresponding to a p-value of approximately 0.00001. The critical values used in the final primary efficacy analysis was to be ± 1.960 .

Subgroups was to be performed for the primary efficacy analysis including age (<60, ≥ 60 years) IPI risk category (low, low-intermediate, high intermediate, high) chemotherapy regimen (CHOP-21, CHOP-14). The primary analysis of the primary efficacy variable was to be repeated for each subgroup.

EFS was defined as the time from randomization to first occurrence of progression of disease, or initiation of a non-protocol specified anti-lymphoma therapy, or death, whichever is first. DFS was to be determined in patients achieving CR/CRu and was defined as the time from the date of initial CR/CRu until the date of progression or death from any cause. PFS was defined as the time from randomization to the first occurrence of progression of disease or death from any cause. OS was defined as the time from randomization until death from any cause.

Each of the secondary efficacy endpoints (EFS, DFS, PFS and OS) was to be presented graphically using Kaplan-Meier curves. The median and the corresponding 95% confidence intervals were to be reported for each treatment group.

BO25341 (SAWYER)

Title: An adaptive, comparative, randomized, parallel-group, multi-center, Phase Ib study of SC rituximab versus intravenous rituximab both in combination with chemotherapy FC (fludarabine and cyclophosphamide), in patients with previously untreated CLL

Reviewer Comments: Rituximab IV was MabThera IV.

Objectives:

This trial consisted of two parts. The primary objective for part 1 was to confirm a selected SC rituximab dose that results in a C_{trough} level that is comparable to IV rituximab. For part 2 the primary objective was to establish the non-inferiority in the observed C_{trough} between the confirmed rituximab SC dose and rituximab IV dose.

The secondary objectives for part 1 was to describe the rate of injection related reactions associated with SC administration and to describe patient and nurse preference regarding administration method, SC or IV. Secondary objective for part 2 included safety parameters in patients receiving rituximab SC compared to patients receiving rituximab IV, site experience regarding physician and nurse opinions on time savings and convenience, and exploratory assessment of minimal residual disease comparing patients receiving rituximab SC to patients receiving rituximab IV.

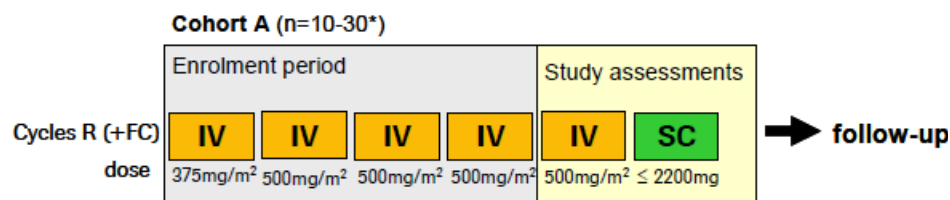
Secondary objectives for part 1 and 2 were, assess PK parameters (including AUC), the comparison of immunogenicity of rituximab SC to rituximab IV, examination of peripheral blood B-cell levels and B cell depletion and repletion, and exploratory assessment of efficacy. The exploratory assessment of efficacy included response rate (CR +CRi + PR), PFS, EFS and overall OS.

Design:

Part 1

Part 1 was a pilot dose confirmation, initially in 10 untreated patients with CLL, with possible expansion up to 60 patients. Patients enrolled prior to cycle 5 of FC. Patients in part 1 were to receive a single SC rituximab dose in cycle 6. PK parameters were assessed in cycle 5, for IV rituximab, and in cycle 6 for SC rituximab. Patients in part 1, or cohort A, were to receive IV rituximab (375 mg/m^2) + FC in cycle 1, rituximab IV 500 mg/m^2 + FC in cycles 2-5 followed by rituximab SC 1870 mg + FC in cycle 6. Once rituximab PK data was available from 10 patients in part 1, this was used with safety and tolerability data to determine the SC rituximab dose for part 2.

Figure 6 Trial Schema for part 1 trial BO25341 SAWYER



[taken from CSR page 2149]

Part 2

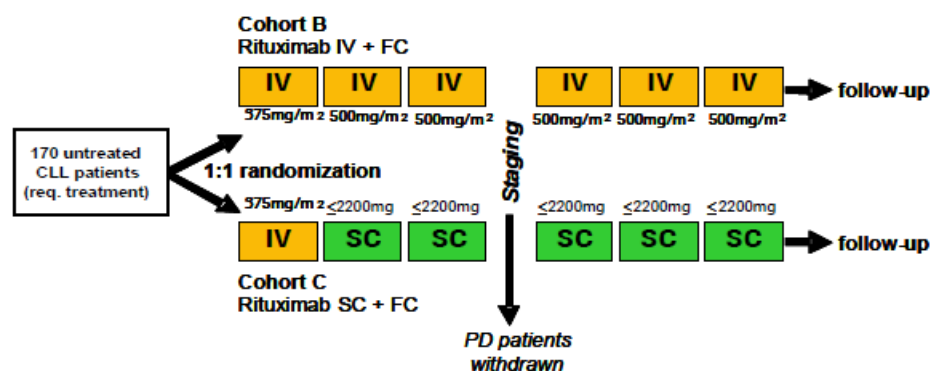
Part 2 was designed to determine C_{trough} non-inferiority, consisting of cohort B and cohort C. In part 2, about 170 patients with untreated CLL were to be randomized 1:1 to rituximab IV (cohort B) or rituximab SC (cohort C). All patients were to receive rituximab IV in the first cycle. Cohort B, rituximab IV, received rituximab 375 mg/m^2 IV + FC followed by rituximab 500 mg/m^2 IV + FC for up to 5 more cycles. Cohort C patients

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received 375 mg/m² IV + FC for the first cycle followed by rituximab 1600 mg SC + FC for up to 5 more cycles.

The dosing regimen for fludarabine was 25 mg/m² IV days 1-3, or 24 mg/m² orally on days 1-5, or 30-40 mg/m² orally on days 1-3. Cyclophosphamide was given 250 mg/m² IV days 1-3, or 150 mg/m² orally on days 1-5 or 200-250 mg/m² orally on days 1-3.

Figure 7 Trial schema for part 2 trial BO25341 SAWYER



[taken from CSR page 2150]

Inclusion Criteria (summarized)

- CD20+ B-cell CLL according to iwCLL (International Workshop on Chronic Lymphocytic Leukemia) criteria
- CLL requiring treatment according to iwCLL criteria
- ECOG performance status of 0-1
- Negative pregnancy test for appropriate females.
- Age ≥18 years
- Life expectancy > 6 months
- Able to give informed consent and adhere to trial protocols

Exclusion criteria (summarized)

- Transformation to an aggressive B cell malignancy
- History of another malignancy with some exceptions.
- Cumulative Illness Rating Score score >6
- Women who are pregnant or breastfeeding
- Hepatitis B virus seropositivity unless due to vaccination
- HIV infection
- Clinically significant autoimmune cytopenia determined by the treating physician
- Inadequate liver function defined as alkaline phosphatase and transaminases > 2 x ULN or total bilirubin > 2 x ULN. Patients out of range with the presence of CLL involvement of the liver may be eligible if investigator or Roche Clinical Scientist agree

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- Inadequate renal function defined as $\text{CrCl} < 70 \text{ ml/min}$ calculated using Cockcroft and Gault formula
- A concurrent disease regarding use of glucocorticoids for > 1 month unless the dose was below 20 mg/day of prednisone or equivalent
- Known hypersensitivity with anaphylactic reaction to humanized monoclonal antibodies or any of the study drugs
- Cerebral dysfunction which would make it impossible to perform immuno-chemotherapy
- Active infection, bacterial, viral or fungal, requiring systemic therapy
- A medical or psychological condition that would preclude participation
- Treatment with another investigational agent or participation in another clinical trial within 30 days
- Uncontrolled concurrent diseases including cardiovascular disease, or pulmonary disease
- Any previous treatment for CLL, with the exception of rituximab IV 375 mg/m^2 in cycle 1 followed by 500 mg/m^2 in cycles 2-4 in combination with FC as first line treatment for patients enrolled in part 1 only.
- For patients in part 1 only, a previous rituximab infusion related reaction of grade 3 or 4 was an exclusion criteria.

Primary Variable

Part 1

- To confirm the selected SC rituximab dose results in a comparable C_{trough} to rituximab IV

Part 2

- To establish non-inferiority in observed C_{trough} levels at cycle 6 between the confirmed rituximab SC dose and the rituximab IV dose.

Secondary variables

Part 1

- To describe the rate of incidence of injection related reactions during the SC rituximab cycle
- To describe patient and nurse preference regarding SC or IV administration

Part 2

- To evaluate safety among patients who receive SC rituximab compared to patients who receive only rituximab IV
- To assess site experience regarding
 - Physician/nurse opinions on time savings
 - Physician/nurse opinions on convenience
- Exploratory assessment of minimal residual disease in patients who receive rituximab SC compared to rituximab IV

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For both part 1 and part 2

- Assessment of additional PK parameters including AUC
- Comparison of immunogenicity
- Comparison of peripheral blood B-cell levels and B-cell depletion and repletion
- Exploratory assessment of efficacy
 - Response rate [CR, CRi (complete response with incomplete bone marrow recovery), PR]
 - PFS
 - EFS
 - OS

Schedule of Assessments

Figure 8 Schedule of assessment part 1 trial BO25341 SAWYER

	Screening ^a	Treatment Period [#]								
Cycle		1-4 [*]			5			6		
Day	-28 to -1	1	2-3	4-5	1	2-3	4-5	1	2-3	4-5
Informed Consent ^s	X									
Demographics	X									
Medical History ^a	X									
Medication History ^b	X									
CIRS Score	X									
Physical Examination ^c , including lymph nodes, liver and spleen	X	<i>as per standard practice</i>			X			X		
Vital Signs ^d	X	<i>as per standard practice</i>			X			X		
12-lead ECG ^e	X	<i>as per standard practice</i>			<i>if clinically indicated</i>					
ECOG Performance Status	X	<i>as per standard practice</i>			X			X		
B-symptoms	X	<i>as per standard practice</i>			X			X		
Coombs test (direct and indirect)	X									
Coagulation (aPTT, PT and INR)	X									
Pregnancy Test, if required ^f	X									
Serology ^g	X									
Hematology	X ^h	<i>as per standard practice</i>			X ⁱ			X ⁱ		
Biochemistry	X ^h	<i>as per standard practice</i>			X ⁱ			X ⁱ		
Urine dipstick	X									
Rituximab Administration		X ^k			X			X		
FC Administration (if IV)		X	X		X	X		X	X	
FC Administration (if p.o.) ^j		X	X	X	X	X	X	X	X	X
Patient/Nurse Preference Questions ^m										X ⁿ
Adverse Events ^{o, p}										
Concomitant Medications ^q										

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Each cycle is 28 ($\pm$ 1) days in length, i.e. Day 1 of cycle 6=Day 29 of cycle 5, if no treatment delays occur. However, due to the mandatory rituximab PK sample at cycle 5 Day 29, the time window for cycle 6 is $\pm$ 1 day only.

α Screening to be performed prior to cycle where patient is enrolled, this may be prior to any cycle up to treatment cycle 5

* Cycles 1-4 may take place prior to enrolment or within study.

$\S$ Informed consent to be obtained prior to any study-specific procedures being performed, close to the time of enrolment but not strictly limited to -28 to -1 day

Notes:

- a) Including baseline Binet stage i.e. documented prior to commencing therapy with first line R-FC.
- b) If applicable, record also accurate details (dates, doses etc) of first 4 cycles of R-FC.
- c) Including weight. Height at screening only. Physical exam, including examination of lymph nodes, liver and spleen should be performed at each cycle pre-dose on day of dosing or up to 3 days prior according to standard site practice.
- d) Pre-dose measurements. Includes single measurements of blood pressure and pulse rate (oral body temperature at screening only). All measurements to be taken after the patient has rested in a semi-supine position for at least 5 minutes.
- e) ECG to be taken after the subject has rested in a semi-supine position for at least 5 minutes.
- f) To be performed in women of child-bearing potential. A serum pregnancy test must be performed within 7 days prior to study treatment. Alternatively, this test could be done within 14 days prior to study treatment if, additionally, a urine pregnancy test is performed no more than 7 days prior to study treatment. If the urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.
- g) HBV, see Section 5.9.1 for details.
- h) To be performed no more than 7 days prior to first dose. If screening visit performed earlier, these assessments must be repeated.
- i) Pre-dose sample. Can be done on day of dosing or up to 3 days prior according to site practice. Hematology includes hemoglobin, hematocrit, platelet count, white blood cell (WBC) count and WBC differential.
- j) Pre-dose sample. Can be done on day of dosing or up to 3 days prior according to site practice. Blood chemistry includes LDH, sodium, potassium, calcium, total protein, albumin, ALP, ALT, AST, GGT, total bilirubin, blood glucose, BUN, uric acid, serum creatinine and calculated creatinine clearance.
- k) The first dose of rituximab may be split over 2 days according to site practice.
- l) Oral FC administration may be over 3 or 5 days, dependent on regimen.
- m) Preference questions to be answered by participating patients and treating nurses, see Section 5.12.
- n) To be completed any time after last study drug administration in Cycle 6.
- o) See Section 7.2 for AE reporting requirements.
- p) Following drug administration at cycle 5 and cycle 6, any patient who experiences a severe or serious adverse event which is at least possibly related to rituximab administration, serum samples of rituximab PK, anti-rituximab, and following cycle 6 also anti-rHuPH20, are to be collected within 7 days of the event becoming known to the investigator.
- q) Including details of any new anti-leukemia treatment. Note that an alternative anti-leukemia treatment will lead to patient discontinuation. After initiation of a new anti-leukemia treatment, patients will be followed up for survival only for up to 4 years after their last dose of study medication.
- r) If a patient is enrolled prior to cycle 5, i.e. during cycles 1-4, only concomitant medications relevant to any adverse events are required to be reported in the eCRF.

[taken from CSR pages 2158-2160]

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Figure 9 Schedule of Assessments part 2 for trial BO25341 SAWYER

Cycle Day	Screenin g -28 to -1	Treatment Period ^a																					
		1				2				3				4				5				6	
		0	1	2-3	4-5	1	2-3	4-5	1	2-3	4-5	1	2-3	4-5	1	2-3	4-5	1	2-3	4-5	1	2-3	4-5
Informed Consent ^e	X																						
Demographics	X																						
Medical and Medication History	X																						
CIRS score and Binet Stage	X																						
Physical Examination ^a , including lymph nodes, liver and spleen	X	X				X			X			X			X			X			X		
Vital Signs ^b	X	X				X			X			X			X			X			X		
12-lead ECG ^c	X	If clinically indicated																					
ECOG Performance Status	X	X				X			X			X			X			X			X		
B-symptoms	X	X				X			X			X			X			X			X		
Coombs test (direct & indirect)	X																						
Coagulation (aPTT, PT and INR)	X																						
Pregnancy Test, if required ^d	X																						
Serology ^e	X																						
Lymphocyte Immunophenotyping	X	X																					
Bone marrow biopsy and aspirate ^g	X																						
CT scans ^h	X											X ^h											
Tumor measurement ⁱ	X											X											
Hematology ^j	X ^j	X				X			X			X			X			X			X		
Biochemistry ^k	X ^j	X				X			X			X			X			X			X		
Urine dipstick	X																						

Cycle Day	Screenin g -28 to -1	Treatment Period ^a																					
		1				2				3				4				5				6	
		0	1	2-3	4-5	1	2-3	4-5	1	2-3	4-5	1	2-3	4-5	1	2-3	4-5	1	2-3	4-5	1	2-3	4-5
Serum parameters – CD23, β2 microglobulin & thymidine kinase		X ^m																					
Minimal Residual Disease		X ⁿ																					
Rituximab Administration		X ^o				X ^o			X ^o			X ^o			X ^o			X ^o			X ^o		
FC Administration (if IV)			X	X		X	X		X	X		X	X		X	X		X	X		X	X	
FC Administration (if p.o.) ^p			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
5 x optional RCR samples (plasma, serum, RNA, DNA & exploratory biomarkers)		X ^q																					
Immunoglobulins (IgA, IgG, IgM)		X ^r																					
Samples for FISH cytogenetics and molecular characterization		X ^s																					
Physician/Nurse Opinion Questions ^t					X ^u																		X ^v
Adverse Events ^{w, x}		←																					→
Concomitant Medications ^y		←																					→

^aEach cycle is 28 (± 1) days in length, i.e. Day 1 of cycle 2=Day 29 of cycle 1, if no treatment delay occurs. However, due to the mandatory rituximab PK sample at cycle 5 Day 29, the time window for cycle 6 is +1 day only.

^eInformed consent to be obtained prior to any study-specific procedures being performed, close to the time of enrolment but not strictly limited to -28 to -1 day.

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Notes:

- a) Including weight. Height at screening only. Physical exam, including examination of lymph nodes, liver and spleen should be performed at each cycle pre-dose on day of dosing or up to 3 days prior according to standard site practice.
- b) Pre-dose measurements. Includes single measurements of blood pressure and pulse rate (oral body temperature at screening only). All measurements to be taken after the patient has rested in a semi-supine position for at least 5 minutes.
- c) ECG to be taken after the subject has rested in a semi-supine position for at least 5 minutes.
- d) To be performed in women of child-bearing potential. A serum pregnancy test must be performed within 7 days prior to study treatment. Alternatively, the serum test could be done within 14 days prior to study treatment if, additionally, a urine pregnancy test is performed no more than 7 days prior to study treatment. If the urine test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.
- e) HBV, see Section 5.9.1 for details.
- f) At Screening, Immunophenotyping to be done locally for diagnostic purposes. A blood sample will also be taken at baseline (post-randomization and prior to any study drug being administered) for confirmatory analysis at a central lab.
- g) Bone marrow biopsy and aspirate are not mandatory but are recommended at Screening, in particular for patients with Cytopenia.
- h) CT scans to be performed at Screening and at Interim staging (after 3 cycles of treatment and prior to dosing in cycle 4) if previously abnormal. Also at any other time-point when PD is assessed based on Physical Examination.
- i) Measurable lymphadenopathy, hepatomegaly and splenomegaly will be reported in the eCRF based on physical exam and CT scans. Baseline measurements must be taken a maximum of 28 days prior to randomization. Interim staging to be performed after 3 cycles of treatment.
- j) Post-screening, samples to be taken pre-dose. Can be done on day of dosing or up to 3 days prior according to site practice. Hematology includes hemoglobin, hematocrit, platelet count, white blood cell (WBC) count and WBC differential.
- k) Post-screening, samples to be taken pre-dose. Can be done on day of dosing or up to 3 days prior according to site practice. Blood chemistry includes LDH, sodium, potassium, calcium, total protein, albumin, ALP, ALT, AST, GGT, total bilirubin, blood glucose, BUN, uric acid, serum creatinine and calculated creatinine clearance.
- l) To be performed no more than 7 days prior to first dose. If screening visit performed earlier, these assessments must be repeated.
- m) Sampling to be performed after randomization and prior to any study drug being administered, see Section 5.10.2 for details.
- n) All patients will receive their first rituximab as IV administration on day 0. See Section 6.2 for details on premedication.
- o) In Cycles 2-6 rituximab IV or SC will be given on day 1 prior to chemotherapy (FC).
- p) FC oral administration may be over 3 or 5 days, dependent on regimen.
- q) Optional samples for RCR to be taken prior to any study drug being administered, see Section 5.11. Blood will be taken as follows from consenting patients: 6 ml for exploratory biomarker assessment, 6 ml for plasma, 6 ml for serum, 2 x 2.5 mL for RNA and a further 6 ml for DNA.
- r) Sampling to be performed after randomization and prior to any study drug being administered, see Section 5.9.1 for details.
- s) Sampling to be performed after randomization and prior to any study drug being administered, see Section 5.10.1 for details.
- t) Site Evaluation questions are to be completed by treating Physician/Nurse and NOT patients, see 5.13 for details.
- u) To be completed any time after completion of rituximab administration in cycle 1.
- v) To be completed any time after completion of rituximab administration in cycle 6.
- w) See Section 7.2 for AE reporting requirements.
- x) In any patient who experiences a severe or serious adverse event which is at least possibly related to rituximab administration, serum samples of rituximab PK, anti-rituximab, and for cohort C following cycle 2 anti-rHuPH20, are to be collected within 7 days of the event becoming known to the investigator.
- y) Including details of any new anti-leukemia treatment. Note that an alternative anti-leukemia treatment will lead to patient discontinuation. After initiation of a new anti-leukemia treatment, patients will be followed up for survival only for up to 4 years after their last dose of study medication.
- z) Sampling to be performed after randomization and prior to any study drug being administered, see Section 5.10.6 for details

[taken from CSR pages 2161-2164]

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Figure 10 Schedule of Assessments treatment free follow up trial BO25341 SAWYER

	Follow-up Visits from last study drug administration until PD							Withdrawal / Termination Visit^c
Day/Month	+28 days^a	+56 days^a	+3 month^b end of treatment response assessment	+6 months^a	+9 months^a	+12 months^a and then every 3 months^a until 3 years from last treatment	Every 6 months^d until 4 years from last treatment	
Physical Examination ^a , including lymph nodes, liver and spleen	X	X	X	X	X	X	X	X
Vital Signs ^b	X	X	X	X	X	X	X	X
12-lead ECG	X	if clinically indicated						
ECOG - Performance Status	X	X	X	X	X	X	X	X
B-symptoms	X	X	X	X	X	X	X	X
CT Scan ^e			X ^d					X ^e
Bone marrow biopsy and aspirate			X ^f					
Hematology ^g and Biochemistry ^h	X	X	X	X	X	X	X	X
Rituximab PK and anti-rituximab antibody sampling	X ⁱ	X ^j	X	X	X	X ^k		X
rHuPH20 PK and anti-rHuPH20 antibody sampling (Cohorts A&C)	X ⁱ	X ^j	X	X	X			X
B-cell PD sampling	X ^l	X ^l	X	X	X	X ^k		X
Immunoglobulins (IgA, IgG, IgM) ^m	X	X	X	X	X			
Minimal Residual Disease (part 2 patients only)	X		X ^f	X		X ^e		
Adverse Events ^{n,o}	X							X
SAEs ^p and grade 3&4 Infections	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X					X
Disease progression if not already occurred								
New anti-leukemia treatment ^q and Survival								

α: Visit to be performed on specified day $\pm$ 3 days. **Note** Cycle 6 day 29 rituximab PK sample needs to be taken exactly on the 29th day of cycle 6

β:Visit should be performed no earlier than 2 and no later than 3 months after the end of treatment. However, if a patient is assessed as being in CR or CRI, a bone marrow examination should be performed no earlier than 3 months after the end of treatment. MRD sample is to be taken no earlier than 3 months after the end of treatment

λ: Visit to be performed ± 1 month of specified date

φ: Visit to be performed $\pm$ 2 months of specified date

Σ: If patient is withdrawn during Treatment period, this visit should be performed within 4 weeks of last dose of study medication. A Termination visit is not needed if patient completes the 4 years of follow-up.

Notes:

- a) Weight. Physical exam at each follow-up visit will include examination of lymph nodes, liver and spleen to monitor for disease progression
- b) Includes single measurements of blood pressure and pulse rate. All measurements to be taken after the patient has rested in a semi-supine position for at least 5 minutes.
- c) CT scans of involved nodes are also to be performed at any visit if PD is determined by physical examination alone
- d) In responding (PR, CRi and CR) patients only.
- e) If needed to confirm an assessment of PD.
- f) To confirm response of CR or CRi. Should be performed no earlier than 3 months after the last dose of study treatment.
- g) Hematology includes hemoglobin, hematocrit, platelet count, white blood cell (WBC) count and WBC differential.
- h) Blood chemistry includes LDH, sodium, potassium, calcium, total protein, albumin, ALP, ALT, AST, GGT, total bilirubin, blood glucose, BUN, uric acid, serum creatinine and calculated creatinine clearance.
- i) Also detailed as day 29 sample in [Table 10](#) and [Table 11](#).
- j) Also detailed as day 57 sample in [Table 10](#) and [Table 11](#).
- k) Sampling required until +24 month follow-up visit.
- l) Taken for patients enrolled in [part 2](#) ONLY.
- m) To be assessed locally, see [Section 5.9.1](#) for details.
- n) See [Section 7.2](#) for AE reporting requirements.
- o) In any patient who experiences a severe or serious adverse event which is at least possibly related to rituximab administration, a serum sample of rituximab PK, anti-rituximab, and for cohorts A and C anti-rHuPH20, is to be collected within 7 days of the event becoming known to the investigator.
- p) Related SAEs and secondary malignancies to be reported indefinitely, see [Section 7.2](#).
- q) An alternative anti-leukemia treatment will lead to patient discontinuation. After initiation of a new anti-leukemia treatment, patients will be followed up for survival only for up to 4 years after their last dose of study medication.
- r) MRD sample at end of treatment response visit to be taken no earlier than 3 months after the last dose of study treatment.
- s) At 12 month visit only

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[taken from CSR pages 2169-2170]

Dose modifications and delays

Rituximab and FC may be delayed for 4 weeks for recovery from hematologic toxicities or infections. If it is necessary to delay the treatment by more than 4 weeks FC must be discontinued but the patient may continue receiving rituximab only at investigator discretion.

Exception to dosing schedule for cohort C

For patients randomized to cohort C who experience a grade 3 or 4 IRR, may receive the second cycle of rituximab IV as well based on investigator discretion. If a patient also experiences a grade 3 or 4 IRR after their second IV rituximab administration they were to be withdrawn from study treatment.

Dose modifications for hematologic toxicity are displayed in Figure 11.

Figure 11 Dose Modifications for Hematologic Toxicity in Trial BO25341 SAWYER

	Fludarabine / Cyclophosphamide	Rituximab (IV or SC)
Grade 3 or 4 hematologic toxicity	Delay dosing for a maximum of 4 weeks First episode: If improvement to $\leq$ Grade 2, decrease FC doses to 75% of initial planned dose for subsequent cycles Second episode: If improvement to $\leq$ Grade 2, decrease FC dose to 50% of Initial planned dose for subsequent cycles Third episode: Discontinue FC	Delay dose for a maximum of 4 weeks. If improvement to $\leq$ Grade 2, administer full dose If FC is discontinued rituximab (IV or SC) may continue at investigator discretion.

[taken from sponsor submission BO25341 CSR page 2189]

Protocol Amendments

This protocol was amended three times, amendment B, C, and D.

In amendment B, it was found that a number of sites were administering FC orally. This amendment allowed for an additional 30 patients to be enrolled in part 1 and for part 2 FC administrations was added as a stratification factor. Sites were asked to choose a route of administration on a per center basis to be used throughout part 2. The acceptable oral regimens for FC were added to the protocol. In amendment B, the protocol was changed to allow patients to enroll at any point during treatment prior to cycle 5 for patients in part 1. The protocol was amended such that patients who have a grade 3 or 4 IRR after both their first and second cycles of rituximab will be withdrawn from study treatment. If a patient experiences a grade 3 or 4 IRR but is able to receive the full dose at cycle 1, the investigator may choose to administer rituximab SC at cycle 2.

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In amendment C, the protocol was amended to reflect a new size of rituximab SC vials. The 10 mL size vial was replaced by 15 mL size vials. Also, minimal residual disease was added as a secondary endpoint for part 2.

In amendment D, the protocol was amended to allow the possibility of a safety snapshot during the trial to address potential health authority or regulatory questions.

Additional changes were made in amendment B, C and D which did not affect the overall integrity of the trial.

SAP

Part 1

Initially 10 patients with untreated CLL were to be enrolled in Part 1. Following analysis from the first 10 patients, approximately 20 additional patients could have been enrolled into cohort A, or part 1. Dependent on analysis, and due to possible variability in rituximab PK parameters due to either oral or IV FC, another 30 patients could have been enrolled to include a total of 60 patients in cohort A.

Part 2

Approximately 170 previously untreated CLL patients were randomized 1:1 to cohort B (rituximab IV) or cohort C (rituximab SC).

Determination of Sample Size for Part 2

Assuming a coefficient of variation of 63%, a non-inferiority margin of 0.8 for the ratio of C_{trough} was used. In each treatment arm, 68 patients were needed to achieve 80% power with a one sided alpha of 0.05 and when assuming the true PK of rituximab SC is 5% above rituximab IV. The sample size included a 20% dropout rate for not achieving valid PK data for a total of 170 patients needed.

Analysis Timing

Part 1 was evaluated in an open label fashion on an ongoing basis. For part 2, a futility analysis was planned after PK data from 60 patients was available. The main analysis performed was C_{trough} at cycle 5 and overall response at 3 months of follow-up.

Populations

The ITT population was defined as all patients randomized into the trial regardless of whether trial medication was received, and treatment was assigned as randomized. The per-protocol population was defined as all patients in the ITT population who were treated for more than 5 cycles and without major eligibility deviations that occurs up to 3 months after treatment phase. Patients treated in a different group as randomized were

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to be excluded. The safety population was defined as all patients who received at least one dose of rituximab, IV or SC, analyzed as treated.

Pharmacokinetic analysis

For part 2 the primary objective was to establish non-inferiority in observed C_{trough} between the rituximab SC dose and the rituximab IV dose. The null hypothesis tested in the primary analysis of the primary variable, observed C_{trough} cycle 5.

$H_0: C_{trough\ SC}/C_{trough\ IV} \leq 0.8$ compared to $H_1: C_{trough\ SC}/C_{trough\ IV} > 0.8$

Secondary objectives for efficacy for part 2 included response rate, PFS, EFS and OS. The response was defined as the assessment that occurred at 3 months of follow-up post last trial treatment.

BP22333 SparkThera

Reviewer Comments: Refer to the Clinical Pharmacology Review for the results of this trial and for further discussion regarding stage 1. The individual results of this trial are not discussed in this review but is included in a pooled safety analysis.

Title: A Two-Stage Phase Ib Study To Investigate the Pharmacokinetics, Safety, and Tolerability of Rituximab Subcutaneous Formulation in Patients with FL as Part of Maintenance Treatment

Design

Stage 1 was designed select a dose with a C_{trough} that was non-inferior to the 375 mg/m² dose of rituximab IV in the maintenance setting. Stage 2 was designed to determine the noninferiority of the C_{trough} of the selected 1400 mg rituximab SC dose compared to rituximab 375 mg/m² as monotherapy in the maintenance setting given on an every 2 or every 3 month schedule.

In stage 2 patients were randomized 1:1 to treatment with either rituximab IV or rituximab SC. Patients were randomized by the maintenance regimen used, Q 2 months or Q 3 months. The primary objective for stage 2 was to compare C_{trough} of rituximab IV and rituximab SC. Secondary objectives for stage 2 included peripheral blood B cell depletion and repletion, comparison of the safety profile, and comparison of AUC levels. Rituximab, either IV or SC, was given as monotherapy maintenance on day 1 of each cycle with cycles every 2 or 3 months, for a maximum of 8-12 cycles (24 months). For stage 2 the rituximab IV dose was 375 mg/m² and the rituximab SC dose was 1400 mg flat dose. Patients were to be followed for a minimum of 9 months following the last dose of maintenance treatment.

The patient population was patients who were diagnosed with CD20 positive FL grade 1, 2, or 3a and requiring treatment. Patients before trial enrollment were treated with induction therapy containing rituximab IV and achieved a CR or PR and given at

least one dose of rituximab IV maintenance treatment. The minimum number of induction therapy cycles, given prior to enrollment on the trial, was 4 cycles of rituximab with any number of chemotherapy cycles. Patients began rituximab maintenance within 12 weeks of induction. Patient with evidence of transformation or other types of NHL were excluded. Patients with a history of presence or history of central nervous system disease, such as CNS lymphoma lymphomatous meningitis were also excluded.

The primary endpoint for stage 2 was C_{trough} levels after the first dose of IV after randomization compared to the first SC administration. Secondary endpoints included $AUC_{0-\tau}$, C_{max} , t_{max} , $t_{1/2}$ of rituximab, B-cell levels, B-cell depletion and repletion and safety. For safety endpoints adverse events were collected during the trial and laboratory tests including hematology, chemistry, urinalysis, calculated creatinine clearance, and human antichimeric antibody levels, and physical examination.

6 Review of Efficacy

Efficacy Summary

Trial BO22334 SABRINA (Follicular Lymphoma)

For this trial, a total of 410 patients were randomized, 205 to each arm to constitute the ITT population. The mean age of the patient population for this trial was 56.5 (range 28-86). The majority of the patients were white at 79%. A total of 63.9% received CHOP chemotherapy and 36.1% received CVP chemotherapy as the backbone. A total of 28.8% on the rituximab IV arm and 32.7% on the rituximab SC arm withdrew from treatment early. The most common reason was disease progression, which was 12.2% on rituximab IV compared to 13.7% on rituximab SC. The primary endpoint for stage 2 of ORR at end of induction was 84.9% (95% CI 79.2, 89.5) on rituximab IV compared to 84.4% (95% CI 78.7, 89.1) on rituximab SC. The secondary endpoint of CR/CRu at the end of induction was 32.2% on the rituximab IV arm compared to 32.2% on the rituximab SC arm. The ORR at the end of maintenance was 78.1% on the rituximab IV arm compared to 77.9% on the rituximab SC arm. The secondary endpoint of CR/CRu at the end of maintenance was 56.2% on the rituximab IV arm compared to 50.6% on the rituximab SC arm. The secondary time to event endpoints of PFS, EFS and OS were compared with stratified HR of 0.97 (95% CI 0.65, 1.44), 1.03 (95% CI 0.71, 1.5) and 0.82 (0.41, 1.63) respectively. Overall the efficacy of rituximab IV and rituximab SC was comparable in the trial BO22334 SABRINA.

Trial MO28107 MabEase (Diffuse Large B Cell Lymphoma)

For this trial, done in patients with previously untreated DLBCL, a total of 381 patients were randomized to rituximab SC and 195 to rituximab IV. The average age for the trial population was 60.6 with a minimum age of 18 and a maximum of 80. The majority of

patients were white at 83.3%. A total of 10.1% received CHOP-14 chemotherapy and 90.0% received CHOP-21 chemotherapy. A total of 81.6% overall completed treatment, 8.5% overall did not complete treatment secondary to an adverse event and 2.4% secondary to progressive disease. This was balanced between the two arms. The primary endpoint was CR/CRu which was 42.1% (95% CI 35.1, 49.0) on the rituximab IV arm and 47.0% (42.0, 52.0) on the rituximab SC arm. The stratified HR for the secondary endpoints of PFS, EFS, DFS and OS were 1.23 (95% CI 0.86, 1.76), 1.14 (95% CI 0.84, 1.56), 1.56 (95% CI 0.80, 3.01) and 1.06 (95% CI 0.68, 1.65) respectively. Overall, the efficacy results of trial MO28107 MabEase were comparable.

Trial BO25341 SAWYER (Chronic Lymphocytic Leukemia)

For this trial a total of 176 patients were randomized in part 2, 88 patients to each arm. The mean age of the population was 58.8 with a range of 25-78. Approximately 68% received the chemotherapy, FC intravenously and 30% orally. The majority of patients in each treatment group in part 2 completed the treatment period, 81.8% on the rituximab IV arm and 83% on the rituximab SC arm. The response rate was comparable between the two arms, with 80.7% (95% CI 70.9, 88.3) on the rituximab IV responding and 85.2% (95% CI 76.1, 91.9) on the rituximab SC arm. The risk ratio, SC/IV was 1.06 (95% CI 0.92, 1.21). The efficacy results on trial BO25341 are comparable.

Overall

The efficacy of rituximab SC was compared to rituximab IV in trial BO22334 SABRINA in patients with FL, trial MO28107 MabEase in patients with DLBCL, and BO25341 SAWYER in patients with CLL. The statistical evaluation in these trials is descriptive. None of the trials had pre-specified hypotheses testing for efficacy nor were the trials powered for clinical efficacy endpoints.

6.1 Indication

The proposed indications are identical to that of Rituxan[®]. The proposed indications are:

Rituximab and hyaluronidase for subcutaneous injection is a combination of rituximab and recombinant human hyaluronidase and is indicated for the treatment of patients with:

FL

- Relapsed or refractory, FL as a single agent.
- Previously untreated FL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan Hycela for subcutaneous injection in combination with chemotherapy, as single-agent maintenance therapy.

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- Non-progressing (including SD), FL as a single agent after first-line cyclophosphamide, vincristine, and prednisone chemotherapy.

DLBCL

- Rituxan Hycela (rituximab and hyaluronidase) for subcutaneous injection is indicated for the treatment of patients with previously untreated DLBCL in combination with CHOP or other anthracycline based chemotherapy regimens.

CLL

- Rituxan Hycela (rituximab and hyaluronidase) for subcutaneous injection is indicated, in combination with FC, for the treatment of patients with previously untreated and previously treated CLL.

6.1.1 Methods

The analysis focused on the two phase 3 trials, trial BO22334 SABRINA conducted in patients with FL, and trial MO28107 MabEase, conducted in patients with DLBCL, both of which compared the 1400 mg dose of rituximab SC to rituximab 375 mg/m² IV. The review also focused on the trial BO25341 SAWYER trial, conducted in patients with CLL, comparing the 1600 mg dose of rituximab SC to rituximab 375 mg/m² IV for the first cycle followed by rituximab 500 mg/m² IV

Reviewer Comments: Given the different patient populations in each of the clinical trials, a pooling of data for clinical efficacy was not done.

Reviewer Comments: For trial MO28107 or MabEase, the ITT population was defined as all randomized patients who completed baseline and at least one on-treatment efficacy assessment. The all randomized population was defined as all patients who were randomized to study medication. For the efficacy analysis, the all subjects randomized population was used.

6.1.2 Demographics

Trial BO22334 SABRINA

For trial BO22334, the mean age of the patient population was 56.5 with the youngest patient 28 and the oldest patient 86. The age demographics for trial BO22334 are displayed in Table 3. Other demographic information for the patient population of trial BO22334 is displayed in Table 4. Overall, the majority of patients were female at 53.4%, with the rituximab SC arm having a female predominance of 58.5%. The majority of the patients were white at 79%. A total of 63.9% received CHOP as the chemotherapy component.

Table 3 Age Demographics Trial BO22334

	Rituximab IV N=205	Rituximab SQ N=205	Total N=410
Age			
Mean	56.9	56.1	56.5
Median	57	56	57
Minimum	28	28	28
Maximum	86	85	86

Table 4 Demographics Trial BO22334

	Rituximab IV N=205 n %		Rituximab SQ N=205 n %		Total N=410 n %	
Gender						
Male	106	51.7	85	41.5	191	46.6
Female	99	48.3	120	58.5	219	53.4
Race						
American Indian/Alaska Native	1	0.5	3	1.5	4	1.0
Asian	11	5.4	10	4.9	21	5.1
Black	1	0.5	0	0.0	1	0.2
Other race	14	6.9	13	6.3	27	6.6
White	160	78.0	164	75.1	324	79.0
Chemotherapy combination						
CHOP	130	63.4	132	64.4	262	63.9
CVP	75	36.6	73	35.6	148	36.1

Disease characteristics for the patient population for trial BO22334 are displayed in Table 5. Regarding disease characteristics for trial BO22334, approximately half of the patients 53.9% had stage IV disease at entry into the trial. The majority of patients had grade 2 follicular lymphoma at 49.3%, grade 1 was 27.3%, grade 3 was 4.4% and grade 3A was 18.8%.

Table 5 Baseline Disease Characteristics BO22334

	Rituximab IV N=205 n %		Rituximab SQ N=205 n %		Total N=410 n %	
Ann Arbor Stage at Diagnosis						
I	8	3.9	9	4.4	17	4.1
II	30	14.6	21	10.2	51	12.4
III	62	30.2	71	34.6	133	32.4
IV	91	39.5	94	45.9	185	45.1

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	Rituximab IV N=205		Rituximab SQ N=205		Total N=410	
	n	%	n	%	n	%
unknown	14	6.8	10	4.9	24	5.9
Ann Arbor Stage at Entry						
I	8	3.9	6	2.9	14	3.4
II	25	12.2	21	10.2	46	11.2
III	63	30.7	65	31.7	128	31.2
IV	108	52.7	113	55.1	221	53.9
unknown	1	0.5	0	0.0	1	0.2
Follicular lymphoma grade						
1	45	22.0	67	32.7	112	27.3
2	109	53.2	93	45.4	202	49.3
3	9	4.4	9	4.4	18	4.4
3A	42	20.5	35	17.1	77	18.8
FLIPI risk category						
High risk (≥ 3)	95	46.3	90	43.9	185	45.1
Intermediate risk (=2)	66	32.2	73	35.6	139	33.9
Low risk (0-1)	44	21.5	42	20.5	86	21.0
ECOG at screening						
0	128	62.4	125	61.0	253	61.7
1	70	34.1	69	33.7	139	33.9
2	7	3.4	11	5.4	18	4.4
Time from diagnosis (months)						
Mean	5.2		5.7		5.4	
Median	1.6		1.5		1.6	
Minimum	0.1		0.1		0.1	
Maximum	279.9		99.8		279.9	
Antibody CD20 at baseline						
(cell blank)	16	7.8	15	7.3	31	7.6
Dimly Positive	1	0.5	0	0.0	1	0.2
Expressed	6	2.9	6	2.9	12	3.0
Negative	2	1.0	1	0.5	3	0.7
Not Done	20	9.8	16	7.8	36	8.8
Positive	160	78.0	166	81.0	326	79.5
Unknown	0	0.0	1	0.5	1	0.2
Follicular Lymphoma Confirmation						
(cell blank)	16	7.8	15	7.3	31	7.6
Confirmed	167	81.5	171	83.4	338	82.4
Not confirmed	2	1.0	3	1.5	5	1.2
Not done	19	9.3	16	7.8	35	8.5
Tissue Exhaustion; no tumor cells present	1	0.5	0	0.0	1	0.2

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Reviewer Comments: For trial BO22334 or SABRINA, selected chemotherapy, FLIPI and region were stratification factors. The stratification factors of FLIPI and selected chemotherapy were balanced between the two groups. There was an imbalance in the grade of follicular lymphoma between the two groups, this was most pronounced with grade 1.

As demonstrated in the table under antibody CD20 at baseline, 3 patients were negative for CD20 at baseline. This is based on the central lab review, however, these 3 patients had positive CD20 based on investigator assessment. CD20 positivity was part of the inclusion criteria.

Trial MO28107 MabEase

Patients were randomized 2:1 to rituximab SC and rituximab IV. A total of 381 patients were randomized to rituximab SC and 195 to rituximab IV. The demographics for age are displayed in Table 6 and other demographic information in Table 7. The average age of the trial population for MO28107 was 60.6 with a minimum age of 18 and a maximum age of 80. As displayed in Table 7, the majority of the patients were white at 83.3% and there was a male predominance overall at 53.6%. For the population overall 31.1% were in the low risk IPI category, 29.7% in the low-intermediate, 34.5% in the high-intermediate, and 14.8% in the high risk IPI category. The countries for the ITT population are displayed in Table 8.

Table 6 Age Demographics of ITT population for trial MO28107

	Rituximab SC N=381	Rituximab IV N=195	Total N=576
Mean	60.4	61.0	60.6
Median	64	64	64
Minimum	18	24	18
Maximum	80	80	80

Table 7 Demographics of ITT population for MO28107

	Rituximab IV N=195		Rituximab SQ N=381		Total N=576	
	n	%	n	%	n	%
Race						
White	166	85.1	314	82.4	480	83.3
Asian	11	5.6	23	6.0	34	5.9
Black or African American	0	0.0	1	0.3	1	0.2
N/A per local regulation	13	6.7	26	6.8	39	6.8
Other	5	2.6	17	4.5	22	3.8
Gender						

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	Rituximab IV N=195		Rituximab SQ N=381		Total N=576	
	n	%	n	%	n	%
Female	95	48.7	172	45.1	267	46.4
Male	100	51.3	209	54.9	309	53.6
IPI risk category						
Low	61	31.3	118	31.0	179	31.1
Low-intermediate	57	29.2	114	29.9	171	29.7
High-intermediate	47	24.1	94	24.7	141	24.5
High	30	15.4	55	14.4	85	14.8
Chemotherapy Regimen						
CHOP-14	22	11.3	36	9.4	58	10.1
CHOP-21	173	88.7	345	90.6	518	90.0
BSA Category						
Low ($\leq 1.7 \text{ m}^2$)	56	28.7	115	30.2	171	29.7
Medium ($>1.7 \text{ m}^2$ and $\leq 1.9 \text{ m}^2$)	65	33.3	123	32.3	188	32.6
High ($>1.9 \text{ m}^2$)	74	37.9	143	37.5	217	37.7

Reviewer Comments: For demographics listed above in Table 7, the two treatment groups were balanced. Age, IPI risk category and chemotherapy regimen were stratification factors, and were balanced.

Table 8 Countries of ITT Population for MO28107

	Rituximab IV N=195		Rituximab SQ N=381		Total N=576	
	n	%	n	%	n	%
Argentina	0	0	4	1.1	4	0.7
Belgium	3	1.5	14	3.7	17	3.0
Brazil	0	0	7	1.8	7	1.2
Bulgaria	3	1.5	7	1.8	10	1.7
Canada	15	7.7	15	3.9	30	5.2
Colombia	1	0.5	12	3.2	13	2.3
Finland	5	2.6	16	4.2	21	3.7
France	11	5.6	19	5.0	30	5.2
Greece	9	4.6	21	5.5	30	5.2
Ireland	5	2.6	6	1.6	11	1.9
Israel	9	4.6	21	5.5	30	5.2
Italy	30	15.4	45	11.8	75	13.0
Netherlands	13	6.7	30	7.9	43	7.5
Peru	2	1.0	4	1.1	6	1.0
Poland	4	2.1	9	2.4	13	2.3
Portugal	4	2.1	8	2.1	12	2.1

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Russia	12	6.2	25	6.6	37	6.4
Serbia	2	1.0	5	1.3	7	1.2
South Africa	1	0.5	2	0.5	3	0.5
Spain	14	7.2	26	6.8	40	6.9
Thailand	6	3.1	15	3.9	21	3.7
Turkey	195	15.9	44	11.5	75	13.0
Ukraine	7	3.6	13	3.4	20	3.5
United Kingdom	7	3.6	12	3.2	19	3.3
Venezuela	1	0.5	1	0.3	2	0.4

Reviewer Comments: All clinical trials in this submission were done outside the U.S.

BO25341 SAWYER part 2

For trial BO25341 SAWYER part 2 only, a total of 88 patients were randomized to rituximab SC and rituximab IV. The age demographics are displayed in Table 9. The mean age of the patient population for part 2 overall was 58.8 with a range of 25 to 60. Other demographics and disease demographics and displayed in Table 10. As displayed, there was a male predominance overall at 65.3%. The majority of the patient population was white at 93.8%. The more common Binet stage was B at 62.5%. Approximately 2/3 or 67.3% actually received the chemotherapy treatment intravenously.

Table 9 Age Demographics for part 2 of SAWYER

	Rituximab IV N=88	Rituximab SC N=88	Total N=176
Mean	58.8	58.9	58.8
Median	60	59	60
Minimum	28	25	25
Maximum	78	74	78

Table 10 Demographics and Disease Characteristics for part 2 SAWYER

	Rituximab IV N=88		Rituximab SQ N=88		Total N=176	
	n	%	n	%	n	%
Gender						
Male	53	60.2	62	70.5	115	65.3
Female	35	39.8	26	29.5	61	34.7
Race						
White	81	92.0	84	95.5	165	93.8
American Indian/Alaska Native	2	2.3	0	0.0	2	1.1

	Rituximab IV N=88		Rituximab SQ N=88		Total N=176	
	n	%	n	%	n	%
Other	3	3.4	2	2.3	5	2.8
Blank	2	2.3	2	2.3	4	2.8
Binet Stage						
A	13	14.8	11	12.5	24	13.6
B	55	62.5	55	62.5	110	62.5
C	20	22.7	22	25.0	42	23.9
Actual chemotherapy route						
IV	59	67.0	60	68.2	119	67.6
Oral	28	31.8	26	29.5	54	30.7
Both	0	0.0	1	1.1	1	0.6
Time from first CLL diagnosis						
Mean (months)	38.4		33.9		36.1	
Median (months)	19.7		18.3		18.5	
Min (months)	0.3		0.03		0.03	
Max (months)	388.5		149.1		388.5	
ECOG performance status						
0 (at screening)	54	61.4	55	62.5	109	61.9
1 (at screening)	34	38.6	33	37.5	67	38.1

Reviewer Comments: The stratification factors for this trial were chemotherapy route, (oral versus IV), and Binet stage. The table above under actual chemotherapy route reflects the chemotherapy route the patient received, not what was used for stratification.

6.1.3 Subject Disposition

Trial BO22334 SABRINA

A total of 410 patients were randomized, 205 to each arm, rituximab SC and rituximab IV to constitute the ITT population. A total of 59 patients (28.8%) on the rituximab IV arm and 67 patients (32.7%) on the rituximab SC arm withdrew from treatment early. The reason for early treatment discontinuation is displayed in Table 11. The most common reason for treatment discontinuation was disease progression. Withdrawal secondary to adverse event, death and disease progression was slightly higher on the rituximab SC arm as displayed in the table.

Table 11 Reason for Early Treatment Discontinuation for trial BO22334

	Rituximab IV N=205		Rituximab SC N=205	
	n	%	n	%
Adverse event	10	4.9	14	6.8
Death	3	1.5	6	2.9
Disease progression	25	12.2	28	13.7
Lack of efficacy	6	2.9	3	1.5
Lost to follow-up	3	1.5	1	0.5
Physician decision	6	2.9	8	3.9
Protocol violation	1	0.5	4	2.0
Withdrawal by patient	5	2.4	3	1.5

Trial MO28107 MabEase

For this trial, a total of 662 patients were screened, 86 patients failed the screening process, and 576 were enrolled. Of the 576 patients who were enrolled, 4 patients did not receive at least one dose of rituximab. For the four patients who did not receive treatment the reason was withdrawal of consent (2 patients), death and lack of compliance (1 patient each). Of the 576 patients enrolled, 557 received a second cycle. A total of 470 completed treatment. For the remaining patients the reason for the lack of completion of treatment is displayed in Table 12.

Table 12 Disposition of ITT population for MO28107

	Rituximab IV N=195		Rituximab SQ N=381		Total N=576	
	n	%	n	%	n	%
Received cycle 2	188	96.4	369	96.9	557	96.7
Completed treatment	159	81.5	311	81.6	470	81.6
Stable Disease	1	0.5	2	0.5	3	0.5
Adverse event	16	8.2	33	8.7	49	8.5
Progressive disease	5	2.6	9	2.4	14	2.4
Protocol violation	4	2.1	6	1.6	10	1.7
Investigator decision	2	1.0	6	1.6	8	1.4
Withdrawal of consent	3	1.5	5	1.3	8	1.4
Lack of compliance	2	1.0	3	0.8	5	0.9
Intercurrent illness	0	0.0	2	0.5	2	0.3
Lost to follow-up	1	0.5	1	0.3	2	0.3
Treatment failure	1	0.5	0	0.0	1	0.2
Not stated	1	0.5	3	0.8	4	0.7

BO25341 SAWYER

A total of 176 patients were randomized in part 2. Two patients withdrew prior to receiving study treatment. An additional 2 patients randomized to rituximab SC, received only the first cycle of treatment (rituximab IV 375 mg/m²) and were withdrawn due to a protocol violation. The majority of patients in each treatment group in part 2, completed the treatment period, 81.8% (72 patients) on the rituximab IV arm and 83% (73 patients) on the rituximab SC arm. A total of 15 patients on the rituximab IV withdrew from the treatment period, the reasons were adverse event (7 patients), physician decision (2 patients), protocol violation (5 patients) and death (1 patient). A total of 14 patients on the rituximab SC arm withdrew from treatment period, the reasons were adverse event (9 patients), withdrawal by patient (2 patients) and protocol violation (3 patients).

6.1.4 Analysis of Primary Endpoint(s)

BO22334 SABRINA

The primary endpoint for stage 2 for trial BO22334 was the estimated ORR in each treatment arm at the end/completion of induction treatment. Given the identical trial design (except for PK sampling) for stage 1 and 2, the pooled analysis is displayed in Table 13. The result of ORR was comparable between the two arms.

Table 13 ORR for ITT population for trial BO22334

Study	Endpoints	IV; 95% CI	SC; 95% CI	Diff: SC-IV, 95% CI	Risk Ratio: SC/IV, 95% CI
BO22334/SABRINA	ORR at end of Induction	84.9% [79.2, 89.5]	84.4% [78.7, 89.1]	-0.5% [-7.7, 6.8]	0.99 [0.92, 1.08]

[Taken from ODAC Briefing Document page 31, analysis by Statistical Reviewer]

MO28107 MabEase

The primary efficacy endpoint was complete response rate (CR/CRu). The results of the completed response rate for the randomized population are displayed in Table 14. As shown, the CR rate at the end of induction was higher in the rituximab SC arm.

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Table 14 Primary Efficacy Endpoint for all randomized patients for MO28107

Study	Endpoints	IV; 95% CI	SC; 95% CI	Diff: SC-IV, 95% CI	Risk Ratio: SC/IV, 95% CI
MO28107/MabEase	CR at end of Induction	42.1% [35.1,49]	47% [42,52]	4.9% [-3.6,13.5]	1.12 [0.92, 1.36]

[Table from ODAC Briefing Document page 40, analysis by Statistical Reviewer]

Trial BO25341 SAWYER part 2

The primary endpoint for trial BO25341 SAWYER part 2 was to establish the non-inferiority of observed C_{trough} level at cycle 6 between the rituximab SC dose and the rituximab IV dose. Refer to the Clinical Pharmacology Review for this analysis.

6.1.5 Analysis of Secondary Endpoints(s)

BO22334 SABRINA

Secondary endpoints for stage 1 and stage 2 included CRR at the end/completion of induction treatment, ORR and CRR at the end/completion of maintenance treatment and time to event secondary efficacy endpoints including PFS, EFS and OS. The secondary endpoints of CRR at completion of induction, ORR at completion of maintenance, and CR at completion of maintenance are displayed in Table 15.

As displayed in Table 15 there is no difference between the two arms for CR/CRu at the end of induction and a 0.2% difference for ORR at the end of maintenance. For the CR/CRu at the end of maintenance, rituximab SC achieved a 5.6% less response for CR/CRu than rituximab IV.

Table 15 Secondary Endpoints (ITT population) for trial BO22334

Endpoints	IV	SC	Diff: SC-IV, 95% CI	Risk Ratio: SC/IV, 95% CI
CR/CRu at end of induction	32.2% (66/205)*	32.2% (66/205)*	0.0% [-9.3, 9.3]	1.00 [0.76, 1.32]
ORR at end of maintenance	78.1% (139/178)*	77.9% (134/172)*	-0.2% [-9.2, 8.8]	1.00 [0.89, 1.12]
CR/CRu at end of maintenance	56.2% (100/178)*	50.6% (87/172)*	-5.6% [-16.4, 5.2]	0.90 [0.74, 1.10]

*the number of patients achieving the response / the total number in the evaluation.

[Table taken from Statistical Review and ODAC Briefing Document]

Reviewer Comments: As displayed in Table 15 there was a 5.6% less CR/CRu at the end of maintenance for rituximab SC. The trial was not powered to detect differences in these endpoints and the statistical evaluation is descriptive.

Secondary time to event endpoints for trial BO22334 are displayed in Table 16. Progression free survival was defined as the time from randomization to disease progression/relapse or death due to any cause.

Table 16 Secondary time to event endpoints for trial BO22334 SABRINA

	# of Patients with event (%); IV	# of Patients with event (%); SC	HR Stratified [95% CI]*	2-Year Rate, IV	2-Year Rate, SC
PFS	57 (27.8%)	50 (24.4%)	0.97 [0.65, 1.44]	82.1%	82.1%
EFS	61 (29.8%)	57 (27.8%)	1.03 [0.71, 1.50]	79.5%	78.5%
OS	20 (9.8%)	16 (7.8%)	0.82 [0.41, 1.63]	95.4%	94.4%

[Table from Statistical Review and ODAC Briefing Document]

*The HR, done by the statistical reviewer, was obtained through a Cox-regression model, stratified by chemotherapy backbone, FLIPI and region.

Reviewer Comments: The percent of patients with progression or death is lower in the rituximab SC arm. The 2 year rates for PFS and OS appear similar, however, this comparison is descriptive.

The Kaplan Meier curves for PFS and OS are displayed in Figure 12 and Figure 13 respectively.

Figure 12 Kaplan Meier for PFS for ITT population for trial BO22334

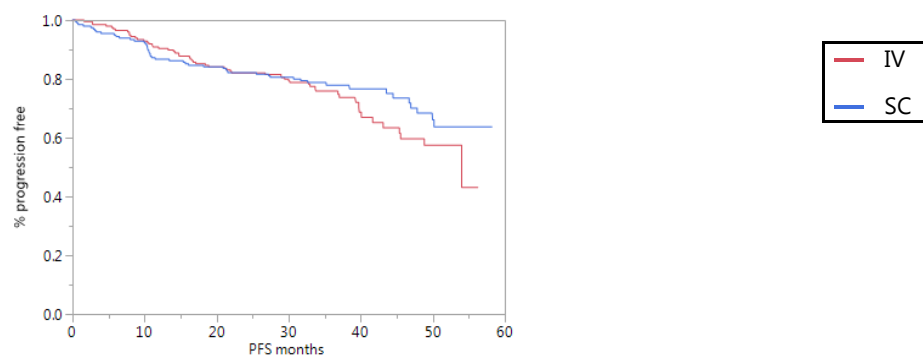
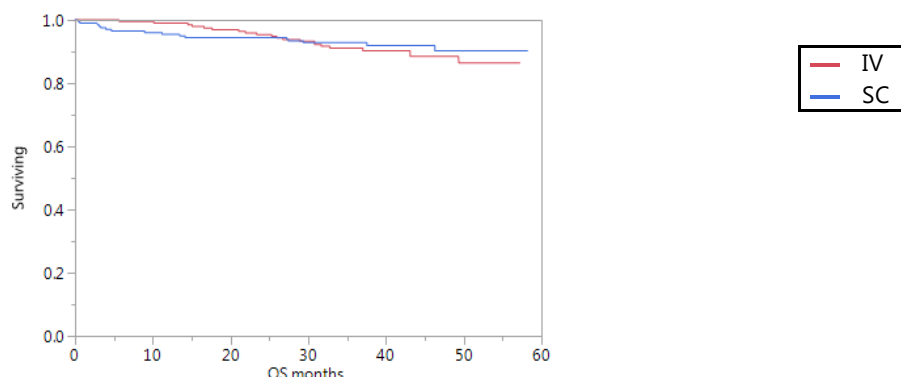


Figure 13 Kaplan Meier for overall survival for ITT population for trial BO22334



Reviewer Comments: In looking at all efficacy results for trial BO22334 SABRINA, the efficacy of rituximab SC and rituximab IV are comparable based on a descriptive analysis.

MO28107 MabEase

The secondary time to event endpoints are displayed in Table 17. As displayed, the percent of patients with an event in each of the time to event endpoints displayed in Table 17 are higher in the rituximab SC arm. The 2-year rate for each of the endpoints is higher in the rituximab IV arm, with the greatest differences in 2-year PFS, EFS and DFS. There is a small difference of only 1.1% in 2 year OS. The Kaplan Meier curve for PFS is displayed in Figure 14.

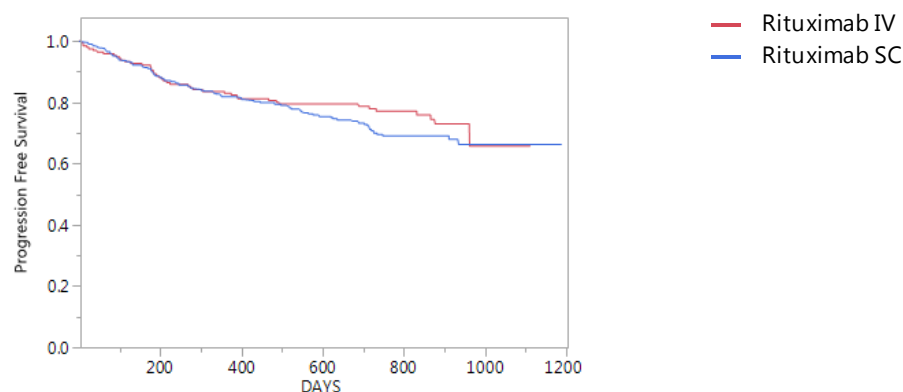
Table 17 Secondary endpoints trial MO28107 MabEase

	# of Patients with event (%); IV	# of Patients with event (%); SC	HR Stratified [95% CI]*	2-Year Rate, IV	2-Year Rate, SC
PFS	44 (22.6%)	104 (27.3%)	1.23 [0.86, 1.76]	77.9%	69.9%
EFS	59 (30.3%)	129 (33.9%)	1.14 [0.84, 1.56]	70.5%	64.0%
DFS	12 (10.4%)	38 (16%)	1.56 [0.80, 3.01]	88.8%	80.5%
OS	29 (14.9%)	63 (16.5%)	1.06 [0.68, 1.65]	84.4%	83.3%

[Taken from ODAC document and analysis done by statistical reviewer]

*HR done by statistical reviewer using Cox-regression model stratified by stratification factors age ((< 60 years, ≥ 60 years), IPI risk category (low, low-intermediate, high-intermediate, high) and chemotherapy regimen (CHOP-21 or CHOP-14)

Figure 14 Kaplan Meier for progression free survival for all randomized patients for MO28107



BO25341 SAWYER

The response rate for trial BO25341 SAWYER in patients with CLL is displayed in Table 18. As shown in the table, the response rate is higher in the rituximab SC arm.

Table 18 Response rate for trial BO25341 SAWYER

Endpoints	IV (95% CI)	SC (95% CI)	Diff: SC-IV (95% CI)	Risk Ratio: SC/IV (95% CI)
Response Rate	80.7% [70.9, 88.3]	85.2% [76.1, 91.9]	4.6% [-7.2, 16.3]	1.06 [0.92, 1.21]

6.1.6 Other Endpoints

MO28107 MabEase

Trial MO28107 MabEase done in patients with DLBCL used the CTSQ and RASQ to obtain patient satisfaction with rituximab SC compared to rituximab IV measured by the CTSQ and the RASQ.

Reviewer Comments: Refer to the Patient preference and Patient Reported Outcomes Review and Clinical Outcome Assessment Consult Review regarding the Agency concerns with these instruments.

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6.1.7 Subpopulations

Refer to Statistical Review for analysis of subpopulations.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose of 1400 mg in patients with FL and DLBCL was evaluated and the dose of 1600 mg was evaluated in patients with CLL. For evaluation of other doses studied, refer to the Clinical Pharmacology Review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

For persistence of efficacy refer to second 6.1.5 analysis of the secondary endpoints including PFS and OS.

6.1.10 Additional Efficacy Issues/Analyses

Refer to Statistical Review for additional efficacy analyses.

7 Review of Safety

Safety Summary

Trial BO22334 SABRINA (Follicular Lymphoma)

Treatment in this trial consisted of up to 8 cycles of induction treatment followed by 12 cycles of maintenance treatment. The mean number of cycles overall was 16.8, this was balanced between the two arms. A total of 1.4% on the rituximab IV arm died within 30 days of last dose compared to 2.0% on the rituximab SC arm. The common nonfatal SAEs on the rituximab SC arm were pneumonia and febrile neutropenia. There was not a nonfatal SAE with a difference in overall incidence greater than 2% between the two arms. More patients on the rituximab SC arm discontinued treatment secondary to an adverse event (7.1% on rituximab SC compared to 4.8% on rituximab IV) and disease progression (14.2% on rituximab SC compared to 11.9% on rituximab IV). For nonfatal TEAE that occurred in 10% or greater on either arm, 5 had a difference in overall incidence $\geq 5\%$. Of these, nausea, pneumonia, injection site erythema and cough were more common on the rituximab SC arm and urinary tract infection was more common on the rituximab IV arm. In evaluating TEAE with a difference in incidence $>4\%$, the majority are more common on the rituximab SC arm.

Trial MO28107 MabEase (Diffuse Large B Cell Lymphoma)

Treatment in this trial consisted of 8 cycles of rituximab with a maximum of 8 cycles of CHOP chemotherapy. The mean number of cycles was 7.4 for rituximab and 6.7 for rituximab SC. This was balanced between the two arms. For deaths within 30 days, 3.9% on the rituximab IV arm died compared to 3.5% on the rituximab SC arm. For the SAE of febrile neutropenia there was a 2% higher incidence on the rituximab SC arm (13.0% on rituximab SC compared to 10.8% on rituximab IV). The two most common reasons for withdrawal from study treatment was adverse event and progressive disease both of which were more common on the rituximab IV arm. For nonfatal TEAE that occurred in 5% of patients on the rituximab SC arm, none had a difference >5% between the two arms. The TEAE of grade 3 and 4 neutropenia was approximately 5% higher on the rituximab SC arm.

Trial BO25341 SAWYER part 2 (Chronic Lymphocytic Leukemia)

Treatment in this trial consisted of 6 cycles of rituximab combined with CVP. The mean number of cycles was 5.4 on rituximab IV and 5.6 on rituximab SC. There were no deaths within 30 days of last dose in part 2 of this trial. The SAE of febrile neutropenia was increased 6.1% on the rituximab SC arm (10.6% on rituximab SC compared to 4.5% on rituximab IV). More patients on the rituximab SC arm withdrew from treatment secondary to an adverse event (10.6% on rituximab SC compared to 7.9% on rituximab IV). Nonfatal TEAE that occurred in >10% on either arm with a difference in all grades greater than 5% were neutropenia, pyrexia, injection site erythema, injection site pain, and erythema which were greater on the rituximab SC arm and asthenia and anemia which were greater on the rituximab IV arm.

Overall

Across all three trials, grade 3 and 4 neutropenia and the TEAEs and SAEs in the SOC of infections and infestations were increased. Grade 3 or 4 neutropenia was increased 6.9% on trial BO22334 SABRINA, 2.1% on trial MO28107 MabEase, and 5.3% on trial BO25341 SAWYER. TEAE in the SOC of infections and infestations was increased 4.1% in trial BO22334 SABRINA, 6.7% in trial MO28107 MabEase, and 7.0% in trial BO25341 SAWYER. Nonfatal SAEs in the SOC infections and infestations was increased across the trials as well, 5.2% in BO22334 SABRINA, 6.1% in MO28107 MabEase, and 1.7% in BO25341 SAWYER.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

For trial BO22334 SABRINA, the safety analysis population was defined as all patients who received at least one dose of rituximab, either IV or SC. Patients were analyzed according to treatment received. AEs that occurred during or within 24 hours of the

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administration and assessed by the investigator to be related to rituximab IV or rituximab SC were considered to be ARR (administration related reactions).

For trial MO28107 the safety population was all patients who received at least one dose of study drug. None of the 381 patients randomized to the SC group only received the first IV infusion and were analyzed as part of the IV group for safety analysis. ARR for this trial was again defined as an AE that occurred within 24 hours after administration and was considered related to rituximab.

For trial BO25341, the safety population was all patients who received at least one dose of study medication; patients in the safety population were analyzed as treated. In this trial, an ARR was defined as any AEs which occurred during or within 24 hours of infusion/injection and was considered by the investigator to be related to rituximab.

7.1.2 Categorization of Adverse Events

For trial BO22334 SABRINA adverse events were classified by MedDRA version 18.1. The severity of AEs was graded using NCI-CTCAE version 4.0.

For trial MO28107 MabEase adverse events were classified by MedDRA version 17.1. The severity of AEs was graded using NCI CTCAE version 4.0.

For trial BO25341 SAWYER adverse events were classified by MedDRA version 17.0. The severity of AEs were graded using NCI CTCAE version 4.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

A pooling of data across trials using the 1400 mg dose, BO22334 SABRINA, MO28107 MabEase and BP22333 SparkThera part 2, was done. TEAE where the difference in incidence of all grades is greater than 3% are displayed in Table 19. The TEAE with the greatest difference with a higher incidence in the rituximab SC patient population are displayed at the top of the table. The only TEAE more common in the rituximab IV arm in the table is urinary tract infection.

Table 19 TEAE from trials BO22334, MO28107 and BP22333 part 2

	Rituximab IV N=490				Rituximab SC N=643			
	All grades		Grade 3, 4 and 5		All grades		Grade 3, 4 & 5	
	n	%	n	%	n	%	n	%
Injection site erythema	0	0.0	0	0.0	42	6.5	0	0.0

	Rituximab IV N=490				Rituximab SC N=643			
	All grades		Grade 3, 4 and 5		All grades		Grade 3, 4 & 5	
	n	%	n	%	n	%	n	%
Injection site pain	0	0.0	0	0.0	28	4.4	1	0.2
Neutropenia	118	24.1	85	17.3	182	28.3	148	23
Pneumonia	20	4.1	11	2.2	50	7.8	26	4.0
Anemia	70	14.3	8	1.6	115	17.9	28	4.4
Alopecia	70	14.3	1	0.2	115	17.9	1	0.2
Diarrhea	56	11.4	5	1.0	95	14.8	9	1.4
Myalgia	13	2.7	0	0.0	38	5.9	0	0.0
Febrile neutropenia	37	7.6	37	7.6	69	10.7	68	10.6
Urinary tract infection	46	9.4	3	0.6	28	4.4	4	0.6

7.2 Adequacy of Safety Assessments

For trial BO22334 SABRINA, safety assessments consisted of scheduled laboratory studies and physical examination, and adverse event collection. A physical examination, serum hematology laboratory studies and serum chemistry laboratory studies were done at least once per cycle for both induction and maintenance. A serum chemistry included sodium, potassium, calcium, phosphate, AST, ALT, total serum bilirubin, serum creatinine, alkaline phosphatase, total protein, urea, serum albumin, glucose, LDH and C-reactive protein. ECG (electrocardiogram) and LVEF (left ventricular ejection fraction) obtained with a 2D-ECHO (echocardiogram) or MUGA scan was to be obtained at screening and at the final assessment of induction (after 8 cycles of induction therapy). For patients receiving CHOP, ECG and LVEF was done as well at the interim assessment after completion of 4 cycles for patients receiving CHOP chemotherapy backbone.

For trial MO28107 MabEase safety assessments consisted of scheduled laboratory studies, physical examinations, and adverse event collection. Physical examination including infection assessment and vital signs were done at screening, day 1 of every cycle, the visit at the end of study treatment, and every 3 months for the first two years of observation followed by every 6 months until end of the trial. Laboratory studies including hematology, chemistry and coagulation studies were done at screening, day 1 of every cycle, interim staging and final staging visits, and observation visits (every 3 months for the first two years, then every 6 months until end of the trial). Adverse events were assessed at each visit. A 12 lead ECG was done at screening only.

For part 2 in trial BO25341 SAWYER safety assessments consisted of scheduled laboratory studies, physical examinations and adverse event collection. Physicals examinations and vital signs were done at screening, at the start of each cycle, followed

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by approximately monthly for the first 3 months after treatment, then every 3 months until 3 years from treatment, then every 6 months until 4 years from last treatment. Hematology and biochemistry laboratory studies were done on the same schedule as the physical examination. A 12 lead ECG was done at screening and 28 days after completion of treatment.

Reviewer Comments: The safety assessments in the three trials were adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

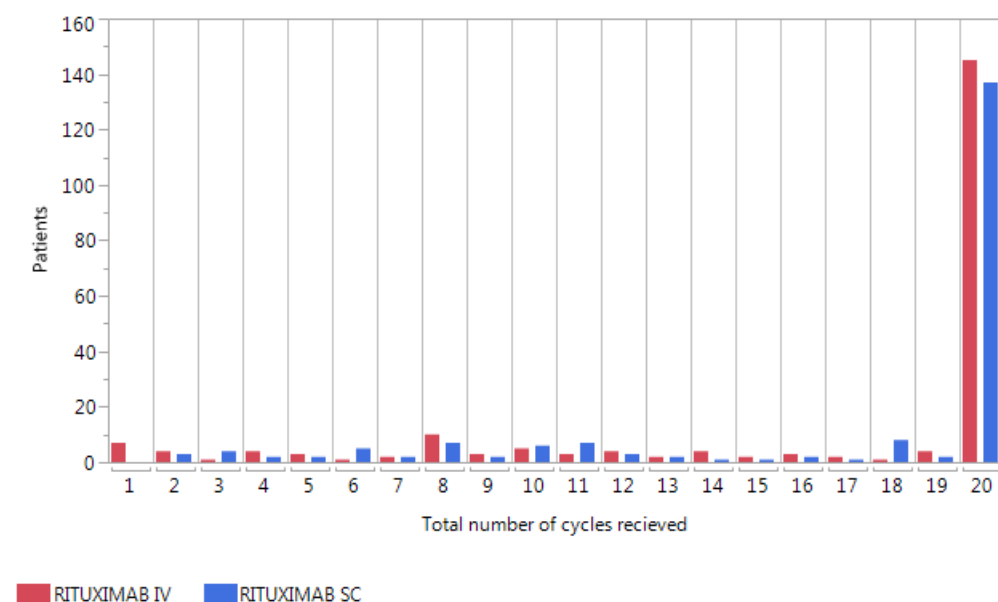
Trial BO22334 SABRINA

Patients in trial BO22334 SABRINA were to receive up to 8 cycles of induction therapy given every 3 weeks with responding patients receiving up to 12 cycles of maintenance treatment given 8 weeks. Thus, the total number of cycles a patient could receive according to the protocol was 20. The mean, median, minimum and maximum number of cycles received for the safety population is displayed in Table 20. The total number of cycles received is displayed in Figure 15. As shown, the majority of the patients completed 20 cycles of treatment.

Table 20 Number of cycles Received BO22334

	Rituximab IV N=210	Rituximab SQ N=197	Total N=410
Mean	16.6	17.0	16.8
Median	20	20	20
Minimum	1	2	1
Maximum	20	20	20

Figure 15 Total Number of Cycles Received BO22334



Trial MO28107 MabEase

The summary of exposure for rituximab for the safety population is displayed in Table 21 and the exposure for CHOP is displayed in Table 22.

Table 21 Total number of rituximab cycles received for safety population trial MO28107

	Rituximab IV	Rituximab SC
Mean	7.0	7.4
Median	8	8
Minimum, Maximum	1, 8	2, 8

Table 22 Total number of CHOP cycles received for safety population trial MO28107

	Rituximab IV	Rituximab SC
Mean	6.3	6.7
Median	6	6
Minimum, Maximum	1, 8	2, 8

Trial BO25341 SAWYER

The mean, median, minimum and maximum number of cycles received for the safety population of trial BO25341 SAWYER part 2 is displayed in Table 23. The total number of cycles completed is displayed in Figure 16, as displayed the majority of patients

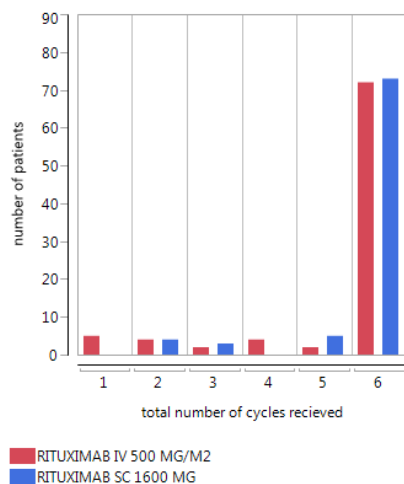
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completed all 6 cycles, 80.9% (72/89) on rituximab IV and 85.9% (73/85) on the rituximab SC arm.

Table 23 Number of cycles for safety population part 2 trial BO25341

	Rituximab IV N=89	Rituximab SC N=85
Mean	5.4	5.6
Median	6	6
Minimum, Maximum	1, 6	2, 6

Figure 16 Total number of cycles part 2 safety population CLL trial



7.2.2 Explorations for Dose Response

Explorations for dose and duration were not done. Two doses are being considered for approval, the 1400 mg dose for patients with FL and DLBCL and the 1600 mg dose for patients with CLL. As discussed in section 7.2.1 the majority of patients in each of the trials discussed received the same number of doses.

7.2.3 Special Animal and/or In Vitro Testing

Rituximab SC is a combination of rituximab and hyaluronidase. Hyaluronidase human injection was initially approved in 2005. Rituxan® was initially approved in 1997. Rituximab SC is a combination of rituximab and hyaluronidase human injection. Animal studies were done to determine the contribution of hyaluronidase human injection. For discussion, refer to the clinical pharmacology review and pharmacology toxicology review.

7.2.4 Routine Clinical Testing

Rituximab has warnings and precautions for tumor lysis syndrome, infections cardiac arrhythmias and angina, bowel obstruction and perforation, live virus vaccines and cytopenias. For the three trials discussed, BO22334 SABRINA, MO28107 MabEase and BO25341 SAWYER laboratory studies including hematology and chemistry, and clinical assessments were done at adequate intervals. While rituximab has a warning and precaution for cardiac arrhythmias and angina the cardiac monitoring across the three trials was not the same. The SABRINA trial had LVEF and ECGs done at screening and repeated at the final assessment which was after 8 cycles. For patients enrolled on the SABRINA trial who were receiving CHOP chemotherapy ECG and LVEF were repeated as well at the interim assessment. The cardiac monitoring for MabEase and SAWYER was less frequent. For these trials, ECGs were done at screening only and there was not routine monitoring of LVEF.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Ofatumumab, an approved CD20-directed cytolytic monoclonal antibody has a boxed warning for hepatitis B virus reactivation and progressive multifocal leukoencephalopathy. Ofatumumab has warnings and precautions for infusion reactions, tumor lysis syndrome and cytopenias. Obinutuzumab has a boxed warning again for hepatitis B virus reactivation and progressive multileukoencephalopathy. Obinutuzumab has warnings and precautions for infusion reactions, tumor lysis syndrome, neutropenia, thrombocytopenia and immunization.

Hepatitis B reactivation

The CD20 directed antibodies, rituximab, ofatumumab and obinutuzumab, have boxed warnings for hepatitis B reactivation. The clinical trials, BO22334 SABRINA, MO28107 MabEase, and BO25341 SAWYER, had various exclusion criteria to exclude patients with hepatitis B virus. BO22334 SABRINA and MO28107 MabEase excluded patients with active hepatitis B and BO25341 SAWYER excluded patients with hepatitis B seropositivity unless due to vaccination. In addition to exclusion criteria, the protocols recommended treatment for appropriate patients.

Given the exclusion of patients with hepatitis B, there were few TEAE related to hepatitis B. On trial BO22334 SABRINA, there was a case of hepatitis B surface antibody positive on the rituximab SC arm. In addition to this there was a TEAE of hepatitis viral on the rituximab SC arm, although this may not be due to hepatitis B. On the rituximab IV arm, there was a case of hepatitis on trial BO22334 SABRINA and a

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case of hepatitis viral on the rituximab IV arm of trial MO28107 MabEase. Again, this is not specific for hepatitis B. On trial BO25341 SAWYER, patient (b) (6) on the rituximab IV arm had grade 3 hepatitis B reactivation.

Reviewer Comments: No new information can be derived from these trials. As hepatitis B reactivation is a known risk of rituximab IV, rituximab SC should have the same boxed warning.

Reviewer Comments: Information from these trials should not alter the boxed warning for progressive multifocal leukoencephalopathy.

7.3 Major Safety Results

7.3.1 Deaths

Trial BO22334 SABRINA

For trial BO22334 a total of 36 (8.8%) patients died. On the rituximab IV arm, 22/210 patients died, on the rituximab SC arm, 14/197 patients died based on the safety population. The majority of these deaths were 30 days after last dose. For deaths within 30 days of last dose, based on the safety population, 3 patients (1.4%) on the rituximab IV arm died and 4 patients (2.0%) on the rituximab SC arm died. The narratives for the deaths within 30 days of last dose are in section 9.4.

Trial MO28107 MabEase

For deaths in the safety population a total of 33 of 203 (16.3%) patients died on the rituximab IV arm and 58 of 369 (15.7%) patients on the rituximab SC arm. For deaths within 30 days, a total of 8 of 203 (3.9%) of the rituximab IV arm died within 30 days and a total of 13 of 369 (3.5%) died on the rituximab SC arm within 30 days. Narratives for deaths within 30 days are in section 9.4.

Trial BO25341 SAWYER

In part 2 of trial BO25341 a total of 4 patients died (4/89) on the rituximab IV arm and 5 (5/85) died on the rituximab SC arm. All of these deaths were 30 days after last dose of trial drug. On this rituximab IV arm, 2 of the 4 deaths were due to disease progression and the other 2 were due to adverse events of diarrhea in one patient and listeriosis in another patient. On the rituximab SC arm 3 deaths were due to disease progression and the other 2 deaths were due to adverse events of progressive multifocal leukoencephalopathy in one patient and herpes zoster in another patient.

7.3.2 Nonfatal Serious Adverse Events

Trial BO22334 SABRINA

For trial BO22334 nonfatal serious adverse events were similar between the two arms. A total of 66 patients (31.4%) of the rituximab IV arm had a nonfatal SAE and 69 patients (35.0%) on the rituximab SC arm had a nonfatal SAE. There was not a nonfatal SAE with difference in overall incidence greater than 2%. The common nonfatal SAEs on the rituximab SC arm (>5% incidence) were pneumonia and febrile neutropenia. Nonfatal serious AE that occurred in more than 3 patients on the rituximab SC arm are displayed in Table 24.

Table 24 Nonfatal SAE for trial BO22334 SABRINA

	Rituximab IV N=210		Rituximab SC N=197	
	N	%	N	%
Pneumonia	7	3.3	10	5.1
Febrile neutropenia	10	4.8	10	5.1
Neutropenia	4	1.9	6	3.1
Pyrexia	5	2.4	6	3.1
Sepsis	0	0.0	3	1.5

Trial MO28107 MabEase

For trial MO28107 a total of 69 patients (34%) had a nonfatal serious adverse event on the rituximab IV arm and a total of 146 patients (39.6%) had a nonfatal serious adverse event on the rituximab SC arm. The nonfatal SAE which occurred in more than 5 patients overall is displayed in Table 25. Adjudication occurred with this analysis and neutrophil count decreased was changed to neutropenia. As shown in the table, there is a 2% higher incidence of febrile neutropenia in the rituximab SC arm.

Table 25 Nonfatal SAEs for trial MO28107 MabEase

	Rituximab IV N=203		Rituximab SC N=369	
	N	%	N	%
Febrile Neutropenia	22	10.8	48	13.0
Neutropenia	13	6.4	26	7.0
Pneumonia	6	3.0	17	4.6
Pyrexia	2	1.0	8	2.2
White blood cell count decreased	1	0.5	4	1.1
Abdominal Pain	2	1.0	3	0.8

Atrial Fibrillation	3	1.5	2	0.5
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Trial BO25341 SAWYER part 2

For stage 2 of trial CLL a total of 29 patients (32.6%) on the rituximab IV arm and 25 patients (29.4%) on the rituximab SC arm had at least one nonfatal serious adverse event. Nonfatal serious adverse events which occurred in 2 or more patients overall are displayed in Table 26. The incidence of febrile neutropenia and pyrexia were higher in the rituximab SC while neutropenia and anemia were higher in the rituximab IV arm.

Table 26 Nonfatal SAEs in part 2 of BO25341 SAWYER

	Rituximab IV N=89		Rituximab SC N=85	
	N	%	N	%
Febrile Neutropenia	4	4.5	9	10.6
Neutropenia	9	10.1	1	1.2
Pyrexia	1	1.1	3	3.5
Anemia	3	3.4	0	0.0
Upper respiratory tract infection	2	2.3	1	1.2
Bronchopneumonia	1	1.1	1	1.2
Hemolytic anemia	1	1.1	1	1.2
Leukopenia	1	1.1	1	1.2
Lower respiratory tract infection	2	2.3	0	0
Pneumonia	1	1.1	1	1.2

7.3.3 Dropouts and/or Discontinuations

Trial BO22334 SABRINA

For trial BO22334 a total of 3 patients in the ITT population, discontinued prior to any treatment and are not included in the safety population. Based on the safety population a total of 64 patients (30.5%) on the rituximab IV arm and 59 patients on (29.9%) the rituximab SC arm discontinued during the treatment period. The reasons for discontinuations for the safety population are displayed in Table 27. As shown in the table, the most common reason was disease progression, followed by adverse event.

Table 27 Discontinuations during the treatment period for trial BO22334

	Rituximab IV N=210		Rituximab SC N=197	
	N	%	N	%
Adverse event	10	4.8	14	7.1

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	Rituximab IV N=210 N %		Rituximab SC N=197 N %	
Death	5	2.4	4	2.0
Disease progression	25	11.9	28	14.2
Lack of efficacy	6	2.9	3	1.5
Lost to follow up	3	1.4	1	0.5
Physician decision	5	2.4	7	3.6
Protocol Violation	3	1.4	1	0.5
Withdrawal by subject	7	3.3	1	0.5

Trial MO28107 MabEase

Based on the safety population, 82.2% of patients completed study treatment. The reasons patients did not complete study treatment is displayed in Table 28. Of those patients who did not complete study treatment, adverse event was the most common reason, which was followed by progressive disease.

Table 28 Reason for withdrawal from study treatment in trial MO28107 MabEase

	Rituximab IV N=203 N %		Rituximab SC N=369 N %	
Completed	159	78.3	311	84.3
Adverse event	21	10.3	28	7.6
Progressive disease	6	3.0	8	2.2
Protocol violation	5	2.5	5	1.4
Investigator decision	2	1.0	6	1.6
Withdrawal of consent by patient	5	2.5	3	0.8
Lack of compliance	2	1.0	3	0.8
Stable disease	1	0.5	2	0.5
Intercurrent illness	0	0.0	2	0.5
Lost to follow up	1	0.5	1	0.3
Treatment failure	1	0.5	0	0.0

Trial BO25341 SAWYER

Based on the safety population a total of 17 patients (19.1%) on the rituximab IV arm compared to 12 patients (14.1%) on the rituximab SC arm did not complete rituximab treatment. The reason for withdrawal from rituximab treatment is displayed in Table 29.

Table 29 Reason for withdrawal from rituximab treatment for trial BO25341 SAWYER

	Rituximab IV N=89		Rituximab SC N=85	
	N	%	N	%
Adverse event	7	7.9	9	10.6
Death	1	1.1	0	0.0
Physician decision	2	2.2	0	0.0
Protocol Violation	7	7.9	1	1.1
Withdrawal by patient	0	0.0	2	2.4

7.3.4 Significant Adverse Events

Trial BO22334 SABRINA

TEAE, where the difference in incidence between the two arms is greater than 4%, are displayed in Table 30 for trial BO22334. The majority of the adverse events listed for more common on the rituximab SC arm except leukopenia and urinary tract infection which were more common on the rituximab IV arm.

Table 30 Nonfatal TEAE for trial BO22334

	Rituximab IV N=205				Rituximab SC N=197			
	All grades		Grade 3 & 4		All grades		Grade 3 & 4	
	n	%	n	%	n	%	n	%
Blood and Lymphatic System Disorders								
Neutropenia	57	27.1	44	21.5	63	32.0	52	26.4
Leukopenia	23	11.2	5	2.4	12	6.1	8	4.1
Gastrointestinal Disorders								
Nausea	46	21.9	0	0.0	62	31.5	0	0.0
General Disorders and Administration Site Conditions								
Injection site erythema	0	0.0	0	0.0	26	13.2	0	0.0
Injection site pain	0	0.0	0	0.0	16	8.1	0	0.0
Asthenia	27	12.9	0	0.0	34	17.3	2	1.0
Infections and Infestations								
Pneumonia	9	4.3	6	2.9	21	10.7	9	4.6
Upper respiratory tract infection	21	10.0	0	0.0	29	14.7	1	0.5
Urinary tract infection	28	13.3	1	0.5	15	7.6	2	1.0
Musculoskeletal and Connective Tissue Disorders								
Muscle spasms	6	2.9	0	0.0	16	8.1	0	0.0
Pain in extremity	11	5.2	0	0.0	19	9.6	0	0.0
Nervous System Disorders								

	Rituximab IV N=205				Rituximab SC N=197			
	All grades		Grade 3 & 4		All grades		Grade 3 & 4	
	n	%	n	%	n	%	n	%
Headache	18	8.6	0	0.0	26	13.2	0	0.0
Respiratory, Thoracic and Mediastinal Disorders								
Cough	28	13.3	1	0.5	45	22.8	0	0.0
Nasal congestion	0	0.0	0	0.0	8	4.1	0	0.0

Trial MO28107 MabEase

Nonfatal TEAE which occurred in $\geq 5\%$ of patients on the rituximab SQ arm are displayed in Table 31. This is limited to the maximum grade for each TEAE per patient. None of the TEAE listed had a difference of greater than 5% between the two arms for all grades. Regarding the difference between TEAE grade 3 and 4 only, grade 3 and 4 neutropenia was approximately 6% higher of the rituximab SC arm. Aside from grades 3 and 4 neutropenia, there does not appear to be a clinically significant difference in adverse events at the preferred term level.

Table 31 Nonfatal TEAE for trial MO28107 (MabEase)

	Rituximab IV N=203				Rituximab SC N=369			
	All grades		Grade 3 & 4		All grades		Grade 3 & 4	
	n	%	n	%	n	%	n	%
Blood and Lymphatic System Disorders								
Neutropenia	59	29.1	39	19.2	113	30.6	93	25.2
Anemia	42	20.7	8	3.9	85	23.0	19	5.2
Febrile neutropenia	23	11.3	23	11.3	53	14.4	53	14.4
Leukopenia	15	7.4	6	3.0	27	7.3	11	3.0
Lymphopenia	12	5.9	6	3.0	19	5.2	4	1.1
Gastrointestinal Disorders								
Nausea	48	23.6	1	0.5	80	21.7	2	0.5
Constipation	35	17.2	1	0.5	56	15.2	2	0.5
Diarrhea	21	10.3	3	1.5	52	14.1	5	1.4
Vomiting	17	8.4	1	0.5	42	11.4	3	0.8
Abdominal pain	14	6.9	1	0.5	25	6.8	2	0.5
Stomatitis	11	5.4	0	0.0	23	6.2	3	0.8
Dyspepsia	15	7.4	0	0.0	19	5.2	0	0.0
General Disorders and Administrative Site Conditions								
Fatigue	30	14.8	3	1.5	70	19.0	2	0.5
Pyrexia	26	12.8	0	0.0	47	12.7	1	0.3

	Rituximab IV N=203				Rituximab SC N=369			
	All grades		Grade 3 & 4		All grades		Grade 3 & 4	
	n	%	n	%	n	%	n	%
Asthenia	24	11.8	2	1.0	41	11.1	2	0.5
Mucosal inflammation	16	7.9	3	1.5	30	8.1	3	0.8
Peripheral edema	9	4.4	0	0.0	28	7.6	1	0.3
Infections and Infestations								
Pneumonia	7	3.5	4	2.0	21	5.7	12	3.3
Investigations								
Neutropenia count decreased	29	14.3	23	11.3	51	13.8	40	10.8
Weight decreased	8	3.9	1	0.5	29	7.9	1	0.3
WBC count decreased	15	7.4	10	4.9	24	6.5	15	4.1
Lymphocyte count decreased	7	3.5	4	2.0	19	5.2	7	1.9
Metabolism and Nutrition Disorders								
Decreased appetite	18	8.9	2	1.0	28	7.6	1	0.3
Nervous System Disorders								
Peripheral neuropathy	24	11.8	0	0	44	11.9	3	0.81
Paraesthesia	13	6.4	0	0	32	8.67	1	0.27
Headache	15	7.39	0	0	21	5.69	0	0
Psychiatric Disorders								
Insomnia	13	6.4	1	0.5	24	6.5	1	0.3
Respiratory, Thoracic and Mediastinal Disorders								
Cough	19	9.4	0	0.0	42	11.4	1	0.3
Dyspnea	9	4.4	2	1.0	22	6.0	0	0.0
Skin and Subcutaneous Tissue Disorders								
Alopecia	48	23.6	0	0.0	87	23.6	0	0.0

Trial BO25341 SAWYER

Nonfatal TEAE for part 2 of CLL trial which occurred in $\geq 5\%$ on either arm are displayed in Table 32. Regarding nonfatal TEAE for part 2 of trial CLL, the AEs where the difference in the incidence is $\geq 5\%$ and greater on the rituximab SC arm are injection site erythema, injection site pain, erythema, arthralgia, pyrexia, and neutropenia. AEs where the difference in incidence is $\geq 5\%$ and are greater on the rituximab IV arm are urinary tract infection, insomnia, hypotension, hypertension, asthenia, and anemia. The TEAE with the largest differences are injection site erythema and injection site pain, which can be expected due to the different routes of administration.

Table 32 Nonfatal TEAE part 2 of CLL trial

	Rituximab IV N=89				Rituximab SC N=85			
	All grades n %		Grade 3 & 4 n %		All grades n %		Grade 3 & 4 n %	
Blood and lymphatic system disorders								
Neutropenia	52	58.4	46	51.7	55	64.7	48	56.5
Thrombocytopenia	23	25.8	8	9.0	20	23.5	5	5.9
Anemia	21	23.6	8	9.0	11	12.9	4	4.7
Leukopenia	14	15.7	11	12.4	16	18.8	12	14.1
Febrile neutropenia	7	7.9	7	7.9	9	10.6	7	8.2
Gastrointestinal Disorders								
Nausea	31	34.8	0	0.0	32	37.6	1	1.2
Vomiting	20	22.5	1	1.1	18	21.2	2	2.4
Diarrhea	10	11.2	3	3.4	10	11.8	0	0.0
Constipation	7	7.9	0	0.0	7	8.2	0	0.0
Abdominal Pain	5	5.6	0	0.0	8	9.4	0	0.0
General Disorders and Administration Site Conditions								
Pyrexia	22	24.7	1	1.1	27	31.8	4	4.7
Asthenia	15	16.9	2	2.3	7	8.24	1	1.2
Chills	9	10.1	1	1.1	11	12.9	0	0.0
Fatigue	9	10.1	0	0.0	9	10.6	0	0.0
Injection site erythema	0	0.0	0	0.0	22	25.9	2	2.4
Injection site pain	0	0.0	0	0.0	14	16.5	1	1.2
Infections and Infestations								
Upper respiratory tract infection	11	12.4	1	1.1	11	12.9	0	0.0
Urinary tract infection	7	7.9	1	1.1	2	2.4	0	0.0
Bronchitis	5	5.6	0	0.0	6	7.1	0	0.0
Pneumonia	5	5.6	2	2.3	2	2.4	2	2.4
Respiratory tract infection	4	4.5	1	1.1	7	8.2	1	1.2
Musculoskeletal and connective tissue disorders								
Pain in extremity	2	2.3	0	0.0	6	7.1	1	1.2
Bone pain	2	2.3	0	0.0	5	5.9	0	0.0
Arthralgia	1	1.1	0	0.0	8	9.4	0	0.0
Nervous system disorders								
Headache	8	9.0	0	0.0	6	7.1	0	0.0
Psychiatric disorders								
Insomnia	6	6.7	0	0.0	1	1.2	0	0.0
Respiratory, thoracic and mediastinal disorders								
Cough	10	11.2	0	0.0	11	12.9	0	0.0
Dyspnea	7	7.9	1	1.1	3	3.5	0	0.0
Oropharyngeal pain	3	3.4	0	0.0	5	5.9	0	0.0

	Rituximab IV N=89				Rituximab SC N=85			
	All grades		Grade 3 & 4		All grades		Grade 3 & 4	
	n	%	n	%	n	%	n	%
Skin and subcutaneous tissue disorders								
Rash	9	10.1	1	1.1	10	11.8	0	0.0
Erythema	6	6.7	0	0.0	13	15.3	0	0.0
Pruritus	4	4.5	0	0.0	7	8.2	0	0.0
Vascular disorders								
Hypotension	6	6.7	1	1.1	1	1.2	0	0.0
Hypertension	5	5.6	1	1.1	0	0.0	0	0.0

7.3.5 Submission Specific Primary Safety Concerns

For further evaluation of submission specific safety concerns, an analysis of SMQs (standardized MedDRA queries) was conducted to examine certain adverse events. The following is a pooled analysis of the trials involving the rituximab 1400 mg SC dose. This includes trials BO22334 SABRINA in patients with FL, MO28107 MabEase in patients with DLBCL, and BP22333 SparkThera maintenance treatment of FL. SMQs are groupings of MedDRA preferred terms of adverse events that relate to a defined medical condition. SMQs may be broad or narrow. Administration related reactions are addressed, in addition to the warnings and precautions of rituximab IV.

Administration Related Reactions

With the subcutaneous administration route different administration related reactions are a specific safety concern. Administration related reactions were defined as AEs occurring within 24 hours of administration and considered by the investigator as related to study drug. A pooled analysis of administration related reactions including trials BO22334 SABRINA, MO28107 MabEase and part 2 of BP22334 SparkThera limited to the worse grade for each patient with each patient only counted once is displayed in Table 33. Administration related reactions where the incidence is greater than 2% in the rituximab SC arm are displayed.

Table 33 Pooled Analysis of Administration Related Reactions

	Rituximab IV N=490				Rituximab SC N=643			
	All grades		Grade 3 & 4		All grades		Grade 3 & 4	
	n	%	n	%	n	%	n	%
Injection site (pooled)	0	0.0	0	0.0	57	8.9	3	0.5
Injection site erythema	0	0.0	0	0.0	35	5.4	0	0.0
Erythema	9	1.84	0	0.0	19	3.0	0	0.0
Chills	19	3.9	0	0.0	16	2.5	0	0.0

	Rituximab IV N=490				Rituximab SC N=643			
	All grades		Grade 3 & 4		All grades		Grade 3 & 4	
	n	%	n	%	n	%	n	%
Injection site pain	0	0.0	0	0.0	15	2.3	1	0.2
Rash	7	1.43	0	0.0	15	2.3	0	0.0
Pruritis	15	3.06	1	0.2	14	2.2	0	0.0

Injection site pooled includes injection site, erythema, bruising, discolouration, erythema, hematoma, hypertrophy, induration, inflammation, edema, pain, paraesthesia, pruritus, rash, swelling and warmth

As displayed in Table 33, injection site erythema, injection site pain and injection site pooled did not occur in the rituximab IV arm given the different routes of administration. The rate of these reactions in the rituximab SC arm ranges from approximately 2% to 8%. To be considered an administration related reaction; the adverse event had to be considered related to the trial medication by the investigator. The TEAEs of injection site erythema and injection site pain on the rituximab SC arm, without attribution, are displayed in Table 34. As seen in the table, the rates vary across the trials. The reason for the variation across the trials is unclear. Trial BO25341 SAWYER used the rituximab 1600 mg SC dose, while the other two trials evaluated the rituximab 1400 mg SC dose. This alone, however, does not explain the variation between the BO22334 SABRINA and MO28107 MabEase trials.

Table 34 Rate of injection site erythema and pain across trials on rituximab SC arm

	BO22334 SABRINA	MO28107 MabEase	BO25341 SAWYER
Injection site erythema	13.2%	2.7%	25.9%
Injection site pain	8.1%	1.9%	16.5%

Tumor Lysis syndrome

There was a patient on the rituximab SC arm in the BO22334 SABRINA trial with an SAE of tumor lysis syndrome. Using an algorithmic SMQ analysis another patient on the rituximab IV arm on the MO28107 MabEase developed hyperkalemia and increased creatinine, however, these two adverse events were separated by over two months, leading to a conclusion that they were caused one inciting event of tumor lysis syndrome less likely. Using a pooled 1400 mg dose dataset and a broad SMQ for tumor lysis, 4.0% of the rituximab SQ population compared to 2.7% of the rituximab IV population had AE that met the criteria for the broad SMQ tumor lysis syndrome. However, broad SMQ analysis included the AE terms acute kidney injury, blood creatinine increased, blood potassium increased, blood urea increased, cytokine release syndrome, hyperkalameia, hyperuricaemia, hypocalcaemia, metabolic acidosis,

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multi-organ failure, oliguria, renal failure, renal impairment and tumor lysis syndrome. These AEs could be due to other causes.

On the SAWYER trial which used the 1600 mg there were a total of two AE of tumor lysis syndrome. These events did not occur with rituximab SC.

Infections

On the BO22334 SABRINA trial there were 6 fatal infections, 5 (2.4%) patients on the rituximab IV arm (infection, pneumonia, pulmonary tuberculosis, sepsis, urinary tract infection) and 1 (0.5%) patient on the rituximab SC arm (Creutzfeldt-Jakob Disease).

On the MO28107 MabEase trial there were 15 patients with fatal infections, 4 (2.0%) patients on the rituximab IV arm and 11 (3.0%) patients on the rituximab SC arm. On the rituximab IV arm this included (pneumonia 1 patient and septic shock 3 patients). On the rituximab SC arm this included lung infection in 2 patients, peritonitis 1 patient, pneumonia 4 patients, respiratory tract infection 1 patient, sepsis 1 patient, and septic shock 2 patients.

On the BO25341 SAWYER trial there were a total of two patients with AEs in the SOC of infections and infestations which lead to death. This included 1 (1.1%) patient on the rituximab IV arm from listeriosis and 1 (1.2%) patient on the rituximab SC arm from progressive multifocal leukoencephalopathy.

In Table 35 and Table 36 are the nonfatal TEAE and SAEs in the SOC of infections and infestations respectively. As shown in the tables, both nonfatal TEAE and SAEs in the SOC infections and infestations are increased overall across the trials.

Table 35 Nonfatal TEAE in SOC Infections and Infestations

	Rituximab IV				Rituximab SC			
	All grades		Grade 3 & 4		All grades		Grade 3 & 4	
	n	%	n	%	n	%	n	%
BO22334 SABRINA	132/210	62.9	26/210	12.4	132/197	67.0	28/197	14.2
MO28107 MabEase	69/203	34.0	12/203	5.9	150/369	40.7	48/369	13.0
BO25341 SAWYER	43/89	48.3	8/89	9.0	47/85	55.3	10/85	11.8

Table 36 Nonfatal SAE in SOC Infections and Investments

	Rituximab IV		Rituximab SC	
	N	%	n	%

	Rituximab IV		Rituximab SC	
	N	%	n	%
BO22334 SABRINA	21/ 210	10.0	30/ 197	15.2
MO28107 MabEase	14/ 203	6.9	48/ 369	13.0
BO25341 SAWYER	9/ 89	10.1	10/ 85	11.8

Cardiac arrhythmias and angina

A broad level 1 SMQ of cardiac arrhythmias did not demonstrate a significant safety signal, this is displayed in Table 37. Cardiac arrhythmias terms (including bradyarrhythmias and tachyarrhythmias) a level 2 SMQ under cardiac arrhythmias is displayed as well. The risk difference of this SMQ was approximately 1%. The specific AE terms encompassed by these SMQs are displayed in Table 38.

Table 37 SMQ analysis for cardiac arrhythmias pooled 1400 mg dose

	Rituximab SC (N=643)			Rituximab IV (N=490)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Cardiac arrhythmias	68	50	7.78	46	36	7.35	0.43
Cardiac arrhythmias terms (including bradyarrhythmias and tachyarrhythmias)	26	24	3.73	17	13	2.65	1.08

Table 38 Specific AEs for cardiac related SMQs

Cardiac arrhythmias		Cardiac arrhythmias terms (including bradyarrhythmias and tachyarrhythmias)
Syncope (24)	Extrasystoles (2)	Atrial fibrillation (18)
Tachycardia (20)	Atrial Tachycardia (1)	Atrial flutter (6)
Palpitations (19)	Atrioventricular block (1)	Sinus tachycardia (6)
Atrial fibrillation (18)	Bradycardia (1)	Supraventricular tachycardia (3)
Atrial flutter (6)	Cardiac flutter (1)	Arrhythmia (2)
Sinus tachycardia (6)	Heart rate increased (1)	Extrasystoles (2)
Cardiac arrest (5)	Sinus bradycardia (1)	Atrial tachycardia (1)
Supraventricular	Sinus node dysfunction (1)	Atrioventricular block (1)

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tachycardia (3)		
Arrhythmia (2)	Sudden death (1)	Cardiac flutter (1)
Wolff-Parkinson-White syndrome (1)		Sinus bradycardia (1)
		Sinus node dysfunction (1)
		Wolff-Parkinson-White syndrome (1)

Bowel obstruction and perforation

Using a SMQ analysis the warning and precaution of bowel obstruction and perforation was evaluated. The broad SMQs are displayed in Table 39 and the more specific SMQs in Table 40. Table 39 displays the SMQ of gastrointestinal perforation, ulceration, haemorrhage or obstruction. Using this broad SMQ there is a potential safety signal. When the more specific SMQs are evaluated the signal is mainly limited to non-specific findings and procedures and gastrointestinal hemorrhage. The AEs that are under each of the SMQs in Table 40 are displayed in Table 41. The majority of AEs under the non-specific findings and procedures were abdominal discomfort and epigastric discomfort. The more common AE in the gastrointestinal haemorrhage SMQ are haematochezia, haemorrhoidal haemorrhage and rectal hemorrhage.

Table 39 Level 1 SMQ with pooled 1400 mg dose

	Rituximab SC (N=643)			Rituximab IV (N=490)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Gastrointestinal perforation, ulceration, haemorrhage or obstruction	46	42	6.53	26	23	4.69	1.84

Table 40 Level 2 SMQ analysis under gastrointestinal perforation, ulcer, haemorrhage, obstruction with pooled 1400 mg dose

	Rituximab SC (N=643)			Rituximab IV (N=490)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Non-specific findings and procedures	15	15	2.33	7	6	1.22	1.11
Gastrointestinal haemorrhage	20	17	2.64	9	8	1.63	1.01
Gastrointestinal obstruction	5	4	0.62	1	1	0.2	0.42

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Gastrointestinal perforation	5	5	0.78	5	5	1.02	-0.24
Gastrointestinal ulceration	1	1	0.16	4	3	0.61	-0.46

Table 41 TEAE for SMQs

Non-specific findings and procedures	Gastrointestinal haemorrhage	Gastrointestinal obstruction	Gastrointestinal perforation	Gastrointestinal ulceration
Abdominal discomfort (9)	Anal hemorrhage (2)	Gastric stenosis (1)	Anal abscess (2)	Colitis ulcerative (1)
Enterocolitis (3)	Gastric haemorrhage (1)	Ileus (1)	Anal fistula (3)	Duodenal ulcer (2)
Epigastric discomfort (6)	Gastrointestinal haemorrhage (1)	Ileus paralytic (1)	Enterovesical fistula (1)	Erosive duodenitis (1)
Gastrointestinal hypomotility (1)	Haematemesis (1)	Intestinal obstruction (1)	Gastric perforation (1)	Gastric erosive (1)
Mucosal Ulceration (2)	Haematochezia (5)	Obstruction gastric (1)	Large intestinal perforation (1)	
Esophageal discomfort (1)	Haemorrhoidal haemorrhage (7)	Volvulus (1)	Peritonitis (1)	
	Lower gastrointestinal haemorrhage (1)		Small intestinal perforation (1)	
	Melaena (4)			
	Rectal haemorrhage (5)			
	Upper gastrointestinal Haemorrhage (2)			

Cytopenias

Rituximab IV has a warning and precaution for cytopenias. The percentage of patients who developed Grade 3 and 4 neutropenia, anemia and thrombocytopenia are

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displayed in Table 42, Table 43, and Table 44 respectively. This is based on the worst grade per patient per laboratory study. As seen in the 3 tables, grades 3 or 4 neutropenia is consistently higher on the rituximab SC arm across the trials.

Table 42 Percentile of patients with grade 3 or 4 neutropenia

	Rituximab IV	Rituximab SC
BO22334 SABRINA	30.7%	37.6%
MO28107 MabEase	4.9%	7.0%
BO25341 SAWYER	37.1%	42.4%

Table 43 Percentile of patients with grade 3 or 4 anemia

	Rituximab IV	Rituximab SC
BO22334 SABRINA	1%	4.6%
MO28107 MabEase	5.9%	6.0%
BO25341 SAWYER	7.9%	1.2%

Table 44 Percentile of patients with grade 3 or 4 thrombocytopenia

	Rituximab IV	Rituximab SC
BO22334 SABRINA	1.9%	3.0%
MO28107 MabEase	9.4%	8.1%
BO25341 SAWYER	14.6%	7.1%

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

See section 7.3.4.

7.4.2 Laboratory Findings

Laboratory values were analyzed for limited to worst grade per patient for each laboratory study.

Trial BO22334 SABRINA

As demonstrated in Table 45, hemoglobin, white blood cell count, neutrophil count, lymphocyte count, platelet count, ALT, AST, alkaline phosphatase, low albumin, and hyponatremia were increased in all grades and grades 3 and 4. The majority of these

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increases are small with unclear clinical significance, however, there is approximately a 7% increase in grades 3-4 leukocyte count and grades 3-4 absolute neutrophil count.

Table 45 BO22334 SABRINA lab findings

	Rituximab IV N=210				Rituximab SC N=197			
	All grades n %		Grade 3 & 4 n %		All grades n %		Grade 3 & 4 n %	
Hemoglobin	115	54.8	2	1.0	115	58.4	9	4.6
White blood cell (hypo)	149	71.0	23	11.0	146	74.1	36	18.3
Absolute neutrophils	136	64.8	63	30.0	134	68.0	74	37.6
Lymphocytes (hypo)	138	65.7	45	21.4	136	69.0	47	23.9
Platelets	35	16.7	4	1.9	38	19.3	6	3.0
ALT	66	31.4	0	0.0	70	35.5	3	1.5
AST	67	31.9	0	0.0	73	37.1	3	1.5
Bilirubin	31	14.8	1	0.5	20	10.2	2	1.0
Alkaline phosphatase	43	20.5	0	0.0	47	23.9	2	1.0
Creatinine	35	16.7	2	1.0	31	15.7	4	2.0
Albumin (hypo)	33	15.7	0	0.0	38	19.3	2	1.0
Potassium (hypo)	34	16.2	1	0.5	39	19.8	5	2.5
Potassium (hyper)	39	18.6	6	2.9	41	20.8	3	1.5
Sodium (hypo)	37	17.6	2	1.0	37	18.8	6	3.0
Sodium (hyper)	36	17.1	1	0.5	28	14.2	0	0.0
Calcium (hypo)	60	28.6	9	4.3	46	23.4	8	4.1
Calcium (hyper)	30	14.3	1	0.5	29	14.8	0	0.0
Phosphate (hypo)	60	28.6	5	2.4	51	25.9	7	3.6
Fasting glucose (hypo)	30	14.3	0	0.0	27	13.7	1	0.5
Fasting glucose (hyper)	111	52.9	9	4.3	101	51.3	11	5.6

Trial MO28107 MabEase

The laboratory values for the worst grade per patient, per laboratory study, are displayed in Table 46. The difference between two arms for grades 3-4 were not greater than 3% for the laboratory values listed. The largest difference for all grades, was 13% for anemia. Absolute neutrophils, creatinine and hypokalemia were increased in all grades approximately 5%.

Table 46 MO28107 MabEase Laboratory findings

	Rituximab IV N=203				Rituximab SC N=369			
	All grades n %		Grade 3 & 4 n %		All grades n %		Grade 3 & 4 n %	

	Rituximab IV N=203				Rituximab SC N=369			
	All grades		Grade 3 & 4		All grades		Grade 3 & 4	
	n	%	n	%	n	%	n	%
Hemoglobin	97	47.8	12	5.9	225	61.0	22	6.0
Leukocytes	125	61.6	37	18.2	237	64.2	76	20.6
Absolute neutrophils	27	13.3	10	4.9	68	18.4	26	7.0
Platelets	60	29.6	19	9.4	115	31.2	30	8.1
ALT	50	24.6	1	0.5	102	27.6	8	2.2
AST	50	24.6	4	2.0	99	26.8	4	1.1
Bilirubin	19	9.4	1	0.5	34	9.2	8	2.2
Creatinine	126	62.1	0	0.0	249	67.5	2	0.5
Potassium (hyper)	46	22.7	1	0.5	68	18.4	2	0.5
Potassium (hypo)	18	8.9	2	1.0	51	13.8	7	1.9
Sodium (hyper)	23	11.3	0	0.0	53	14.4	0	0.0
Sodium (hypo)	28	13.8	4	2.0	65	17.6	9	0.3

Reviewer Comments: In the MabEase trial alkaline phosphatase and albumin were measured at screening only and not repeated during the trial per protocol.

BO25341 SAWYER

Pertinent laboratory values for the CLL trial, limited to worst grade per patient, are displayed in Table 47. Laboratory values with a greater than 5% difference was neutrophil count all grades and grades 3-4, ALT all grades, and creatinine all grades which were increased on the rituximab SC arm and hemoglobin grades 3-4, and platelets grades 3-4, and bilirubin all grades, which were increased on the rituximab IV arm.

Table 47 BO25341 SAWYER part 2 lab finding

	Rituximab IV N=89				Rituximab SC N=85			
	All grades		Grade 3 & 4		All grades		Grade 3 & 4	
	n	%	n	%	n	%	n	%
Hemoglobin	41	46.1	7	7.9	35	41.2	1	1.2
Absolute neutrophils	45	50.6	33	37.1	51	60.0	36	42.4
Platelets	48	53.9	13	14.6	43	50.6	6	7.1
ALT	26	29.2	2	2.2	31	36.5	0	0.0
AST	21	23.6	2	2.2	24	28.2	1	1.2
Bilirubin	30	33.7	2	2.2	22	25.9	2	2.4
Alkaline phosphatase	12	13.5	0	0.0	11	12.9	0	0.0
Creatinine	7	7.9	1	1.1	14	16.5	0	0.0

7.4.3 Vital Signs

Refer to analysis of adverse events for clinically significant abnormalities in vital signs.

7.4.4 Electrocardiograms (ECGs)

Repeat ECGs were obtained at cycle 4 and cycle 8 on trial BO22334 SABRINA. The percentage of patients with normal ECGs is displayed in Table 48. As shown in the table, the percentage of patients with normal ECGs was lower on the rituximab IV arm for this trial.

Table 48* ECG results from BO22334 SABRINA

	BO22334 Sabrina	
	Rituximab IV	Rituximab SC
Screening	79%	79%
Cycle 4	51%	58%
Cycle 8	63%	68%

*data from sponsor CSR

7.4.5 Special Safety Studies/Clinical Trials

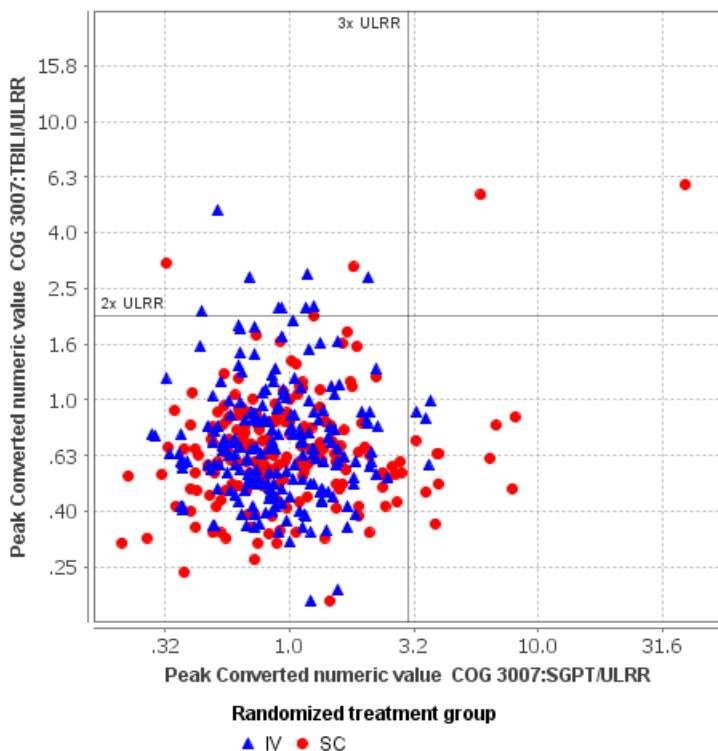
Hy's Law

BO22334 SABRINA

Figure 17 displays the Hy's Law plot for trial BO22334 SABRINA. For this trial, two patients on the rituximab SC arm met the criteria for Hy's Law.

- Patient (b) (6) on the rituximab SC arm had elevated ALT, total bilirubin and alkaline phosphatase at week 62. At this time the patient was diagnosed with jaundice. These laboratory abnormalities were normal at approximately week 68. Concomitant medications at this time include omeprazole, chlorpheniramine, paracetamol, arnica, salbutamol, cetirizine, prochlorperazine, morphine, furosemide, senna and buprenorphine. The patient did not receive further rituximab SC following this.
- Patient (b) (6) had an elevated ALT, AST and total bilirubin at week 158 with a normal alkaline phosphatase at this time. The last dose of rituximab SC was around week 122 and the patient did not receive further treatment with rituximab SC following this. The laboratory abnormalities in ALT, AST, and total bilirubin were normal upon repeat at approximately week 169. Concomitant medications at this time include bromazepam, loratadine and paracetamol.

Figure 17 Hy's Law graph for trial BO22334 of ALT vs total bilirubin with alkaline phosphatase filter



MO28107 MabEase

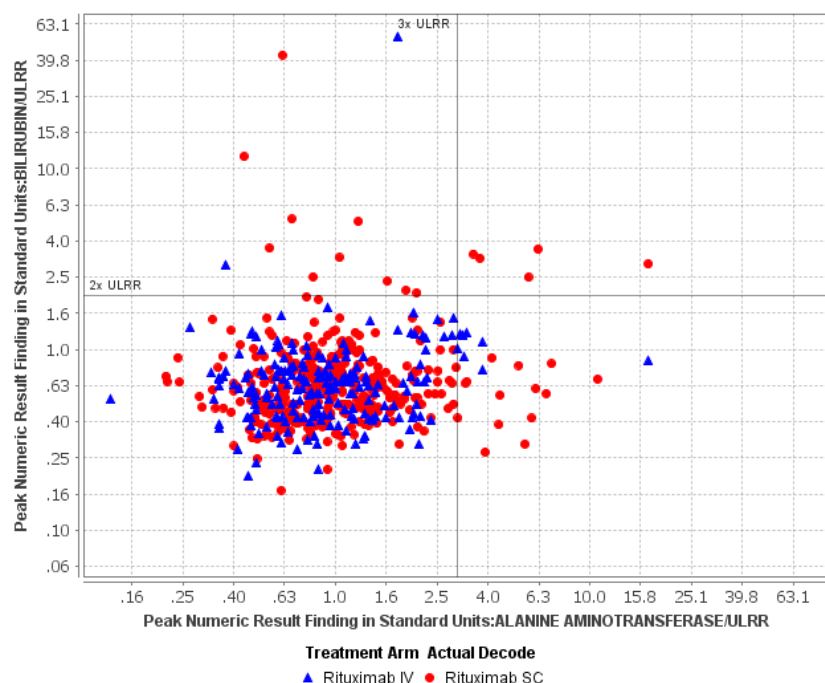
Displayed in Figure 18 is the Hy's Law plot of ALT and bilirubin for trial MO28107 MabEase in patients with DLBCL. As shown in the figure, 5 patients on the rituximab SC arm met criteria for Hy's Law. These five patients are discussed below.

- Patient (b) (6) had ALT, AST and bilirubin elevated at baseline which then normalized with treatment. This is not consistent with Hy's law.
- Patient (b) (6) had ALT and AST elevation around week 3 and at the same time received the first dose of rituximab SC. The ALT and AST subsequently improved while the bilirubin increased. The patient completed 6 cycles of CHOP and 8 cycles of rituximab.
- Patient (b) (6) was a 60-year-old male who had elevated ALT, AST and bilirubin at approximately week 18. Previous ALT, AST and bilirubin measurement was normal at approximately week 16. At the time of the increased ALT, AST and bilirubin the patient died from pneumonia. The pneumonia was diagnosed on study day 125 with a chest xray revealing increased infiltrations. The patient was treated with oxygen, immunoglobulin, ceftriaxone sodium,

noradrenaline acid tartrate and clarithromycin for the pneumonia. The patient died due to pneumonia on the same day. There is an alternative explanation for this patient.

- Patient (b) (6) is a 47-year-old female who had an elevated bilirubin at the start of treatment which then normalized. While the ALT and AST were normal at the start and increased during the treatment period. This is not consistent with Hy's Law.
- Patient (b) (6) is a 72-year-old man who had ALT, AST and bilirubin increase during treatment which were normal at the start of treatment. His increased ALT and AST started at week 3. His ALT was repeated at week 4 and 5 and was improving although ALT, AST and bilirubin were all increased at week 6 and prior to his time he was diagnosed with diarrhea. At approximately week 8 his was diagnosed with bile duct obstruction giving an alternative cause to his abnormal liver function, thus not meeting Hy's Law criteria.

Figure 18 Hy's Law plot (ALT and bilirubin) for trial MO28107 MabEase



Trial BO25341 SAWYER

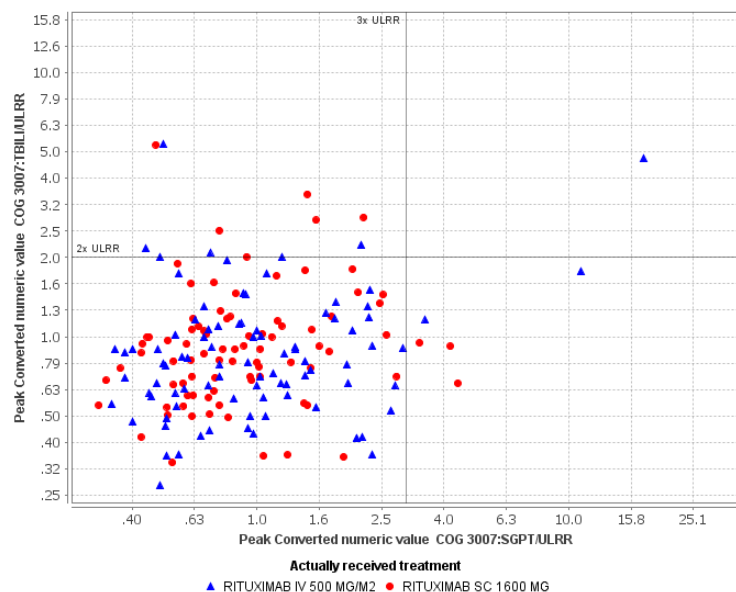
The graph for Hy's law is displayed in Figure 19. This plot displays ALT and bilirubin using an filter for alkaline phosphatase. The was one patient who met the criteria for Hy's Law on the rituximab IV arm.

- Patient (b) (6) on the rituximab IV arm had elevated ALT, AST, total bilirubin and alkaline phosphatase between weeks 6-7, his dose prior to this was week 4. At this time the patient was diagnosed with neutropenia and hepatitis toxic grade 4.

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He was treated with meglumine sodium succinate, Ringer's irrigation, dexamethasone, lecithin as well as furosemide. His laboratory values improved, his next dose was given at week 10 and the patient went on to complete the six doses of rituximab IV.

Figure 19 Hy's Law plot ALT and bilirubin for BO25341 SAWYER



Reviewer Comments: Across the three trials several patients met the laboratory criteria for Hy's Law. On trial MO28107 MabEase, the majority of patients that met the laboratory criteria were not consistent with Hy's Law. For the two patients on trial BO22334 SABRINA there were concomitant medications and the liver function tests improved on follow-up.

7.4.6 Immunogenicity

Refer to clinical pharmacology and chemistry review.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Refer to Clinical Pharmacology Review.

7.5.2 Time Dependency for Adverse Events

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Regarding time dependency for adverse events, the length of the adverse events was evaluated. A total of 242 TEAE on the rituximab IV arm and 257 TEAE on the rituximab SC arm did not have an end date. In evaluating all SAE with an end date, the mean duration of SAE was longer on the rituximab SC arm although the median was higher on the rituximab IV arm. This is displayed Table 49.

Table 49 Duration of SAEs for trial BO22334 SABRINA

	Rituximab IV N=210	Rituximab SQ N=197
Total number of SAE with end date	126	122
Mean duration, days	28.9	47.3
Median duration, days	8	6.5
Minimum duration, days	0	0
Maximum duration, days	380	1069

Trial MO28107 MabEase

A total of 261 TEAE on the rituximab IV arm and 532 TEAE on the rituximab SC arm did not have an end date. For duration of SAEs, the mean, median, minimum and maximum days are displayed in Table 50 for all SAEs. For Trial MO28107 MabEase there is a trend for SAEs to last for a longer time with the mean and median increased in the rituximab SC arm.

Table 50 Duration of SAEs for trial MO28107 MabEase

	Rituximab IV N=	Rituximab SQ N=
Total number of SAE with end date	125	268
Mean duration, days	10.1	16.8
Median duration, days	5	7
Minimum duration, days	0	0
Maximum duration, days	180	408

7.5.3 Drug-Demographic Interactions

Reviewer Comments: Drug demographic interactions for gender and age are displayed. As the majority of patients were white in the trials, drug demographic interactions for race is not shown.

BO22334 SABRINA

Overall TEAEs, TEAE $\geq$ grade 3 and SAEs by gender and age are presented in Table 51. Females were more likely to have a TEAE $\geq$ grade 3 or an SAE. This trend was present in rituximab IV as well as rituximab SC. Patients >65 years of age were also more likely to have a TEAE $\geq$ grade 3 or SAE.

Table 51 TEAE, TEAE $\geq$ grade 3, and SAEs by gender and age

	Rituximab IV N=210 n/total %		Rituximab SC N=197 n/total %		Total N=407 %
AEs by gender					
Male	101/109	93	78/80	98	95
Female	98/101	97	111/117	95	96
AEs by age					
<65	142/150	95	143/148	97	96
>65	57/60	95	46/49	94	94
Grade ≥ 3 AEs by gender					
Male	53/109	49	38/80	48	48
Female	63/101	62	73/117	62	62
Grade ≥ 3 AEs by age					
<65	81/150	54	81/148	55	54
>65	35/60	58	30/49	61	60
SAEs by gender					
Male	30/109	28	22/80	28	28
Female	42/101	42	51/117	44	43
SAEs by age					
<65	43/150	29	48/148	32	31
>65	29/60	48	25/49	51	50

[Data from sponsor submission CSR BO22334 pages 138-140]

MO28107 MabEase

TEAE $\geq$ grade 3 and SAEs by age and gender are displayed in Table 52. As seen in the table, females were more likely than males to have a TEAE $\geq$ grade 3 in the rituximab SC arm. Older patients, ≥ 65 years of age, were more likely to have a SAE, this trend was present on both the rituximab IV and rituximab SC arms.

Table 52 TEAE grade 3 and SAEs by age and gender

	Rituximab IV n/total %		Rituximab SC n/total %	
TEAEs $\geq$ grade 3 by gender				
Male	59/103	57.3	123/204	60.3

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	Rituximab IV		Rituximab SC	
	n/total	%	n/total	%
Female	56/100	56.0	109/165	66.1
TEAEs ≥grade 3 by age				
<65	34/79	43.0	79/142	55.6
≥65	81/124	65.3	153/227	67.4
SAEs by gender				
Male	44/103	42.7	84/204	41.2
Female	32/100	32.0	71/165	43.0
SAEs by age				
<65	22/79	27.8	40/142	28.2
≥65	54/124	43.5	115/227	50.7

[Data from sponsor submission CSR MO28107 pages 90, 92]

Reviewer Comments: In the DLBCL trial, patients ≥65 years of age had an approximately 7% increase in SAEs.

7.5.4 Drug-Disease Interactions

Patients with DLBCL and FL received the same dose of rituximab SC. A higher dose of rituximab SC was developed for patients with CLL.

7.5.5 Drug-Drug Interactions

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Trial SABRINA

On this trial, a total of 14 patient were diagnosed with another malignancy, 10 on the rituximab IV arm and 4 on the rituximab SC arm. On the rituximab IV arm this included basal cell carcinoma (3 patients), colon cancer, lung cancer, myelodysplastic syndrome, rectal cancer, skin neoplasm excision, squamous cell carcinoma of the lung and squamous cell carcinoma of the skin. On the rituximab SC arm this included adenocarcinoma of the colon, basal cell carcinoma, renal cell carcinoma and squamous cell carcinoma of the skin each in 1 patient.

Trial MabEase

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For this trial, a total of one patient on the rituximab IV arm and 9 patients on the rituximab SC arm were diagnosed with another malignancy. On the rituximab IV arm it was transitional cell carcinoma. On the rituximab SC arm it was lung adenocarcinoma, non-small cell lung cancer (2 patients), renal cell carcinoma (2 patients), skin neoplasm excision, squamous cell carcinoma, thyroid neoplasm, and transitional cell carcinoma.

Trial SAWYER part 2

For this trial, there was myelodysplastic syndrome and squamous cell carcinoma, 1 patient each, on the rituximab IV arm and basal cell carcinoma (1 patient) on the rituximab SC arm.

7.6.2 Human Reproduction and Pregnancy Data

Refer to pharmacology toxicology review.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of rituximab SC has not been established in pediatrics patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant notes in trial BO22334 SABRINA 3 patients were administered the rituximab SC dose intravenously in error.

- Patient (b) (6), a 58-year-old woman received 50mL of rituximab IV (500mg/50mL) and 19 mL of rituximab SC (2290 mg) for a total of 2780 mg rituximab at the second cycle of maintenance treatment. The intended dose was 690 mg. Per narrative, the patient felt well with no obvious complications following this. The patient continued on the protocol and completed the maintenance phase.
- Patient (b) (6), a 56-year-old woman received 50 mL of rituximab IV (500 mg/50 mL) and 16 mL of rituximab SC (1920 mg) intravenously in error at the last cycle of maintenance. The intended dose was 660 mg but the patient received 2420 mg of rituximab. Per narrative, the patient was closely monitored following this medication error and no untoward events were observed.
- Patient (b) (6), a 74-year-old man received 668 mg rituximab from an IV vial and a 1400 mg rituximab SC dose from a SC vial for a total dose of 1068 mg of rituximab intravenously administered during a maintenance cycle. It was unclear from dispensing records which maintenance cycle, cycle 9, 10 or 11. Per the patient narrative, the patient was closely monitored and no untoward events were observed.

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In the BO25341 SAWYER trial one patient received a total of 2200 mg in error and no untoward events occurred. The patient was scheduled to receive a dose of 1600 mg. The patient was monitored and no untoward events were observed.

7.7 Additional Submissions / Safety Issues

Given the development of a fixed dose of rituximab SC compared to the body surface area based dosing for rituximab IV the concern for an increased risk of TEAEs with the low BSA patient was a concern given the potential for higher drug exposures in this population. AEs overall, SAEs overall, and AEs overall and SAEs overall in the SOC Infections and Infestations across the three trials are displayed in Figure 15. Across the trials the BSA subgroups were defined differently. In BO22334 SABRINA and BO25341 SAWYER the BSA subgroups were based on the 33rd and 66th percentiles. In trial MO28107 MabEase a low BSA was $\leq 1.70\text{m}^2$, medium $1.70 < \text{BSA} \leq 1.90\text{m}^2$, and high $\text{BSA} > 1.90\text{m}^2$.

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Figure 20 AEs, SAEs, and AEs and SAEs in SOC Infections and Infestations by BSA

		BO22334/ SABRINA		MO28107/ MabEase		BO25341/ SAWYER, Part 2	
		IV (%) N=210	SC (%) N=197	IV (%) N=203	SC (%) N=369	IV (%) N=89	SC (%) N=85
AEs overall							
low BSA		56/59 (95%)	77/81 (95%)	56/59 (94.9%)	107/112 (95.5%)	31/35 (89%)	24/24 (100%)
medium BSA		73/78 (94%)	53/56 (95%)	60/68 (88.2%)	112/119 (94.1%)	28/29 (97%)	30/31 (97%)
high BSA		70/73 (96%)	59/60 (98%)	70/76 (92.1%)	128/138 (92.8%)	22/25 (88%)	28/30 (93%)
SAEs overall							
low BSA		22/59 (37%)	36/81 (44%)	19/59 (32.2%)	53/112 (47.3%)	14/35 (40%)	7/24 (29%)
medium BSA		29/78 (37%)	19/56 (34%)	30/68 (44.1%)	59/119 (49.6%)	7/29 (24%)	10/31 (32%)
high BSA		21/73 (29%)	18/60 (30%)	27/76 (35.5%)	43/138 (31.2%)	8/25 (32%)	8/30 (27%)
SOC Infections and Infestations – AEs							
low BSA		40/59 (68%)	50/81 (62%)	23/59 (39.0%)	50/112 (44.6%)	15/35 (43%)	14/24 (58%)
medium BSA		50/78 (64%)	39/56 (70%)	27/68 (39.7%)	56/119 (47.1%)	15/29 (52%)	16/31 (52%)
high BSA		44/73 (60%)	43/60 (72%)	22/76 (28.9%)	51/138 (37.0%)	14/25 (56%)	18/30 (60%)
SOC Infections and Infestations – SAEs							
low BSA		8/59 (14%)	13/81 (16%)	6/59 (10.2%)	16/112 (14.3%)	5/35 (14%)	1/24 (4%)
medium BSA		10/78 (13%)	10/56 (18%)	6/68 (8.8%)	22/119 (18.5%)	3/29 (10%)	5/31 (16%)
high BSA		7/73 (10%)	8/60 (13%)	6/76 (7.9%)	19/138 (13.8%)	2/25 (8%)	5/30 (17%)

[Taken from sponsor submission, response to Information Request April 19, 2017]

Reviewer Comments: As seen in the figure in the BO22334 SABRINA trial patients with a low BSA had increased SAEs overall on the rituximab SC arm.

8 Postmarket Experience

Rituximab 1400 mg dose for subcutaneous injection was approved in the European Union on March 21, 2014 and following this was approved in an additional 41 countries. Rituximab 1600 mg solution used for patients with CLL was first approved in the European Union on May 25, 2016.

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The Applicant provided a summary of the events and cases in the company safety database comparing rituximab IV and rituximab SC. The Applicant notes the data should be interpreted with caution given the difference in the number of patients exposed and differences in the number of cases reported. In general, the Applicant notes the postmarketing profile was consistent with findings during development.

General disorders and administration site reactions and AEs related to local cutaneous reactions were increased in rituximab SC. Also, noted is an increase in the SOCs of blood and lymphatic disorders and infections and infestations. Also noted was a higher proportion of AEs in male patients receiving rituximab SC and higher proportion of AEs in elderly patients (≥65).

Figure 21 Postmarketing Data Events and Cases by SOC

	Rituximab IV		Rituximab SC	
	Events	Cases	Events	Cases
Infections and infestations	9241 (12.33%)	7633 (20.98%)	305 (17.69%)	253 (25.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2310 (3.08%)	2057 (5.65%)	65 (3.77%)	63 (6.23%)
Blood and lymphatic system disorders	8412 (11.22%)	6212 (17.08%)	244 (14.15%)	184 (18.18%)
Immune system disorders	1469 (1.96%)	1432 (3.94%)	14 (0.81%)	14 (1.38%)
Endocrine disorders	61 (0.08%)	59 (0.16%)	1 (0.06%)	1 (0.10%)
Metabolism and nutrition disorders	1527 (2.04%)	1314 (3.61%)	26 (1.51%)	24 (2.37%)
Psychiatric disorders	995 (1.33%)	817 (2.25%)	11 (0.64%)	8 (0.79%)
Nervous system disorders	4386 (5.85%)	3470 (9.54%)	66 (3.83%)	61 (6.03%)
Eye disorders	538 (0.72%)	434 (1.19%)	11 (0.64%)	9 (0.89%)
Ear and labyrinth disorders	245 (0.33%)	226 (0.62%)	6 (0.35%)	6 (0.59%)
Cardiac disorders	2333 (3.11%)	1989 (5.47%)	55 (3.19%)	47 (4.64%)
Vascular disorders	2148 (2.87%)	1980 (5.44%)	32 (1.86%)	32 (3.16%)
Respiratory, thoracic and mediastinal disorders	5939 (7.92%)	4717 (12.97%)	83 (4.81%)	76 (7.51%)
Gastrointestinal disorders	6896 (9.20%)	4828 (13.27%)	133 (7.71%)	105 (10.38%)
Hepatobiliary disorders	831 (1.11%)	752 (2.07%)	15 (0.87%)	14 (1.38%)
Skin and subcutaneous tissue disorders	4039 (5.39%)	3171 (8.72%)	127 (7.37%)	111 (10.97%)
Musculoskeletal and connective tissue disorders	2735 (3.65%)	2166 (5.95%)	32 (1.86%)	28 (2.77%)

	Rituximab IV		Rituximab SC	
	Events	Cases	Events	Cases
Renal and urinary disorders	780 (1.04%)	712 (1.96%)	16 (0.93%)	14 (1.38%)
Pregnancy, puerperium and perinatal conditions	119 (0.16%)	112 (0.31%)	2 (0.12%)	2 (0.20%)
Reproductive system and breast disorders	150 (0.20%)	144 (0.40%)	4 (0.23%)	4 (0.40%)
Congenital, familial and genetic disorders	18 (0.02%)	18 (0.05%)	2 (0.12%)	2 (0.20%)
General disorders and administration site conditions	12885 (17.19%)	9897 (27.21%)	367 (21.29%)	274 (27.08%)
Investigations	4180 (5.58%)	3007 (8.27%)	36 (2.09%)	31 (3.06%)
Injury, poisoning and procedural complications	2525 (3.37%)	2396 (6.59%)	66 (3.83%)	61 (6.03%)
Surgical and medical procedures	108 (0.14%)	100 (0.27%)	2 (0.12%)	2 (0.20%)
Social circumstances	40 (0.05%)	40 (0.11%)	2 (0.12%)	2 (0.20%)
Product issues	46 (0.06%)	46 (0.13%)	1 (0.06%)	1 (0.10%)
Total	74956 (100.00%)	36376 (100.00%)	1724 (100.00%)	1012 (100.00%)

[Taken from sponsor submission Summary of Clinical Safety pages 131-132]

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Figure 22 Postmarketing Data Events and Cases by Gender, Seriousness and Age Groups

	Rituximab IV		Rituximab SC	
	Events	Cases	Events	Cases
Gender				
Female	32329 (43.13%)	15896 (43.70%)	908 (52.67%)	534 (52.77%)
Male	33443 (44.62%)	17050 (46.87%)	801 (46.46%)	464 (45.85%)
Unknown	9184 (12.25%)	3430 (9.43%)	15 (0.87%)	14 (1.38%)
Seriousness				
Serious	40796 (54.43%)	24773 (68.10%)	1265 (73.38%)	812 (80.24%)
Non-serious	34160 (45.57%)	15861 (43.60%)	459 (26.62%)	264 (26.09%)
Age				
< 18 years	344 (0.46%)	180 (0.49%)	1 (0.06%)	1 (0.10%)
18– <65 years	32556 (43.43%)	16519 (45.41%)	615 (35.67%)	376 (37.15%)
≥65 years	27096 (36.15%)	13663 (37.56%)	1020 (59.16%)	580 (57.31%)
Unknown	14960 (19.96%)	6014 (16.53%)	88 (5.10%)	55 (5.43%)
Total	74956 (100.00%)	36376 (100.00%)	1724 (100.00%)	1012 (100.00%)

[Taken from sponsor submission Summary of Clinical Safety page 137]

9 Appendices

9.1 Literature Review/References

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.

9.2 Labeling Recommendations

The Prescribing Information for rituximab SC would keep a similar boxed warning compared to rituximab IV. The boxed warning of fatal infusion reactions can be deleted as this is related to intravenous infusion and does not apply to rituximab SC. The warnings and precautions would remain with same with the warning and precaution for infections specifically addressing the potential for increased infections associated with rituximab SC.

Aside from the boxed warning and warnings and precautions the Prescribing Information should describe the efficacy and safety in a descriptive manner for the SABRINA, MabEase and SAWYER trials.

9.3 Advisory Committee Meeting

This application was taken to the Oncologic Drugs Advisory Committee on Wednesday March 29, 2017. During the committee meeting it was discussed that in certain cases effectiveness of new product may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. This is ordinarily secondary to the fact that other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form. It was also stated that it may be possible to conclude that a new dose, regimen or disease form is effective on the basis of PK data without an additional clinical efficacy trial.

Some concerns associated with the application were discussed during the meeting. This included the use of a PK bridging approach that targeted a trough concentration for the rituximab SC product that would be at least as high as that achieved with rituximab IV. Another concern expressed by the FDA, is the clinical trials did not have pre-specified hypotheses to test for efficacy in any of the studies.

Following presentations from the Applicant and the Agency, a few of the concerns were raised by committee members. This include the low BSA patient and if there is a threshold BSA level below which flat dosing is not a good idea. Also raised by the committee members was if the lower BSA patient has highly variable serum concentrations for a given dose why not use weight adjusted dosing for rituximab SC. Another concern was the concentration of rituximab and late onset neutropenia. Particular patients the committee members expressed concern about include thin patients with low BSAs receiving fixed doses and are they at greater risk for grade 3 and above AEs or SAEs, and the older patients who are 80 years of age and above.

The question proposed to the committee was, is the benefit-risk favorable for rituximab SC for the proposed indications in follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia. The result of the voting was 11 yes and zero for no with no one abstaining.

9.4 Narratives for Deaths Within 30 Days.

Rituximab IV safety population trial BO22334 SABRINA

Patient (b) (6)

This patient was a 63-year-old female with Stage III follicular lymphoma diagnosed on (b) (6) randomized on (b) (6) in Brazil. At entry, she had follicular lymphoma stage III, grade 2, with a high risk FLIPI score. Her past medical history included hypertension and surgery on the esophagus. Concurrent medical conditions included vertigo, urine infection and abdominal distension. She was randomized to the rituximab SC arm and received her first cycle of rituximab IV along with CHOP chemotherapy. On study day 11 she developed acute respiratory failure, was hospitalized, and treated with metamizole, metoclopramide, tramadol, paracetamol, codeine, sodium chloride, ampicillin, furosemide, oxygen, sulbactam, adrenaline, dopamine and ipratropium. She died on study day 12 due to acute respiratory failure. No autopsy was performed. She was randomized to the rituximab SC arm but did not receive a dose of rituximab SC and is therefore part of the rituximab IV safety population.

Patient (b) (6)

Patient (b) (6) was a 61-year-old male diagnosed with stage III follicular lymphoma on (b) (6) and randomized on (b) (6) in Mexico. At the start of the trial he had stage III disease, grade 1, and a low risk FLIPI score (0-1 adverse factor). Concurrent medical issues included undernourishment and cutaneous rash. No other medical history was reported. He was randomized to rituximab SC and received his first cycle of rituximab IV with CHOP chemotherapy.

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On study day 17 he had a myocardial infarction along with grade 4 cachexia, grade 4 pneumonia, and grade 3 oral candidiasis. He was treated with moxifloxacin for pneumonia. There is no other significant information provided regarding his hospitalization. He died on study day 19 due to myocardial infarction. No autopsy was performed. He was randomized to rituximab SC and did not receive a rituximab dose SC.

Patient (b) (6)

Patient (b) (6) was a 75-year-old man diagnosed with stage IV FL on (b) (6). He was randomized on (b) (6) in Denmark to rituximab IV. At the start of the trial he has stage IV, grade 2 disease and a high risk FLIPI score (3 or more adverse factors). He had a past medical history of concussion (1954), kidney stones (1979), "new hip" (2010) and ocular migraine. Prior procedures included ureteric stent insertion (2012). Concomitant medications included zopiclone and sodium picosulfate. He received rituximab IV and CHOP chemotherapy.

His treatment course was complicated by grade 3 acute coronary syndrome, fainting with hospitalization of suspicion of clot in the heart, grade 1 pyrexia due to gum boil, hospitalization due to pyrexia, reflux and dysphagia, and a second episode of acute coronary syndrome. Following this he underwent an unspecified procedure for acute coronary syndrome. A heart operation was planned for 3 months after the completion of chemotherapy. Following the unspecified procedure he developed dyspnea while walking and fainted. On study day 156 he was hospitalized due to laboratory examination revealing high rate of infection. On the same day he received cycle 8 of rituximab infusion and completed induction. On day 158 he was diagnosed with infection. On day 167 he was transferred to the ICU with suspicion of sepsis and deterioration in health. On day 168 he developed multiorgan failure and sepsis. On day 169 he developed grade 3 fungal infection. On day 171 he developed grade 4 hepatic coma and died on the same day. The hepatic coma was felt to be related to multiorgan failure caused by acute coronary syndrome and possible sepsis.

Trial BO22334 SABRINA rituximab SC safety population

Patient (b) (6)

Patient (b) (6) was a 79-year-old woman with stage III FL diagnosed on (b) (6). She was randomized on (b) (6) in Italy to rituximab SC arm. At the start of the trial she had stage III, grade 1, and a high risk FLIPI score (3 or more adverse factors). No medical history was reported other than previous cholecystectomy. Concurrent medical conditions included hypertension. She received CVP as the chemotherapy component of her treatment. On study day 86 she developed febrile neutropenia, subsequent sepsis and died on this day. She received cycle 3 on study day 72.

Patient (b) (6)

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Patient (b) (6) was a 59-year-old woman diagnosed with stage IV FL on (b) (6) and randomized (b) (6) in Brazil to rituximab SC. At the start she had stage IV, grade 1 disease with a high risk FLIPI score (3 or more adverse factors). No medical or surgical history was noted. She received concurrent CVP chemotherapy. Concurrent medical conditions included hypertension, diabetes and ascites. She received her first dose of rituximab IV and during the infusion the patient developed grade 3 chest pain and hypoxia. Her second cycle, first dose of rituximab SC, was prematurely stopped (received a total of 1041.02 mg) due to grade 2 chest discomfort, dyspnea, hypoxia and wheezing. She received hydrocortisone, diphenhydramine, paracetamol and oxygen and the events resolved the same day. Her treatment course was complicated by two episodes of grade 3 neutropenia. On study day 97 she developed grade 3 febrile neutropenia, which worsened. She subsequently developed abdominal infection and septic shock. On day 101 she died due to febrile neutropenia. Her last dose of study medication was day 90, cycle 5.

Patient (b) (6)
Patient (b) (6) was a 64-year-old woman diagnosed with stage III FL on (b) (6) and randomized on (b) (6) in South Africa. At the start she had stage III, grade 1 disease with a high risk FLIPI score (3 or more adverse factors). No medical history or surgical history was reported. Concurrent medical conditions included hypertension and hypothyroidism. She was randomized to rituximab SC and her chemotherapy backbone regimen was CHOP. During her chemotherapy course she had grade 3 febrile neutropenia. On study day 92 she had generalized weakness and grade 4 neutropenia and she declined hospitalization. On day 94 she was hospitalized with a myocardial infarction, on admission her Glasgow coma scale was low. Resuscitation was attempted, but she died and no autopsy was performed. Her last dose of study drug was cycle 5 on study day 86.

Patient (b) (6)
Patients (b) (6) is a 60-year-old woman with stage IV FL diagnosed on (b) (6) (b) (6). She was randomized to rituximab SC arm on (b) (6) with grade 2, stage IV disease and a high risk FLIPI score (3 or more adverse factors) in Turkey. Concurrent medical conditions include congestive heart failure, and diabetes. She received CVP as her chemotherapy backbone. At screening an ECHO demonstrated an ejection fraction of 35% with left ventricular systolic dysfunction and local wall motion abnormality. Also at screening her ECG was abnormal, although considered clinically insignificant, no further details provided. On study day 87 an ECG was abnormal, not clinically significant (although no details provided) and an LVEF was 20%. On study day 118 she had worsening of her congestive heart failure, she died the following day. Her last dose was study day 111, which was cycle 6.

Narratives for deaths within 30 days trial MO28107 MabEase on the rituximab IV arm

Patient (b) (6)

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Patient (b) (6) was a 75-year-old woman diagnosed with DLBCL on (b) (6). Her PMH included transient ischemic attack and concurrent medical conditions included epigastric pain. Concurrent medications included atorvastatin, omeprazole, acetyl salicylic acid, lorazepam, paracetamol, lamivudine, methylprednisolone, paracetamol, lorazepam, and dexchlorpheniramine. On entry to the trial she had stage II disease with low intermediate IPI score, her ECOG PS was 1. Her first cycle was complicated by grade 2 neutropenia on study day 8, grade 2 nausea on study day 9, and digestive hemorrhage due to intestinal perforation on study day 10. On study day 10 the patient was hospitalized with septic shock and died the same day.

Patient (b) (6) was a 61-year-old woman with a PMH of gastrointestinal hemorrhage. Her concurrent medical conditions were post menopause, chronic renal failure, hypertension, diabetes, hernia disk, and cardiac arrhythmia. Concomitant medications were metoprolol and insulin aspart. At entry she had stage IV disease with high intermediate risk IPI score. On study day 7 the patient developed grade 3 syncope followed by cardiac arrest and was hospitalized. The patient died on study day 10.

Patient (b) (6) was a 78-year-old man. Concurrent conditions included chronic obstructive pulmonary disease and mitral valve incompetence. Concurrent medications included warfarin, diltiazem, paracetamol, pheniramine, granisetron, and dexamethasone. At entry he had stage IV disease with high risk IPI score. ECOG performance status was 2. The patient received a single cycle of rituximab IV and CHOP and on study day 4 developed febrile neutropenia and was hospitalized. He died on the same day.

Patient (b) (6) was a 73-year-old woman with concurrent conditions of menopause, coronary artery disease, and hypertension. Concurrent medications were trimetazidine, isosorbide mononitrate, aspirin, carvedilol, atorvastatin, ramipril, nystatin, chlorhexidine gluconate, allopurinol, and granisetron. On entry she had stage III disease with low intermediate IPI risk score. ECOG performance status was 1. She received rituximab IV and CHOP one cycle. On study day 11 she had grade 3 neutropenia and leukopenia. She was started on filgrastim. On day 19 she died suddenly due to an unspecified reason.

Patient (b) (6) was an 80-year-old man with concurrent conditions of hypertension, aortic aneurysm, and anemia. Concomitant medications included carvedilol, hydrochlorothiazide/quinapril hydrochloride, aspirin, lansoprazole, benzydamine/chlorhexidine, granisetron, paracetamol, pheniramine, dexamethasone, and allopurinol. On entry he has stage II disease with low risk IPI score. ECOG performance status was 1. On study day 73 he was hospitalized with grade 4 neutropenia. On study day 85 he

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had his last dose of rituximab. He received a total of 5 cycles of rituximab IV and CHOP. On study day 87 tumor assessment showed complete response. On study day 98 he developed a myocardial infarction. On study day 100 he died due to myocardial infarction.

Patient (b) (6)

Patient (b) (6) was a 69-year-old woman. Concurrent conditions included essential tremor, myocardial ischemia, atherosclerosis, and heart failure IIA. Concomitant medications included paracetamol, clemastine, and allopurinol. On entry she had stage IVE disease with high intermediate risk IPI. ECOG performance status was 1. On study day 3 she developed dyspnea and grade 2 pleuritis and a therapeutic thoracentesis was performed. On study day 5 another therapeutic thoracentesis was performed and hospitalization was prolonged. From study day 6 to study day 90 multiple therapeutic thoracentesis were done. On study day 80 tumor assessment showed partial response. Her last dose was cycle 5 of rituximab IV and CHOP on study day 86. On study day 111 she developed signs of respiratory failure, her condition worsened and she refused hospitalization. She died the same day due to respiratory failure.

Patient (b) (6)

Patient (b) (6) was a 77-year-old man with a PMH of dermatitis allergic. Concurrent conditions included cataract of both eyes, hypermetropia of both eyes, retinal vascular disorder, osteoarthritis, Grade 2 vascular encephalopathy, Grade 2 essential hypertension, atherosclerosis coronary artery, cardiac failure, coronary artery disease, failure of both atrioventricular valves Grade 3, cholelithiasis, chronic atrophic gastritis (Grade 2-3), focal erythematous gastropathy and pyloric sphincter insufficiency. Concurrent medications included torasemide, spironolactone, acetylsalicylic acid, clopidogrel, sodium chloride, corvitan, famotidine, magnesium hydroxide, ondansetron, trimetazidine, phospholipid, esomeprazole, torasemide, calcium chloride dehydrate/ magnesium chloride, hexahydrate/ malic acid/ potassium chloride/ sodium acetate trihydrate/ sodium chloride, mesna, diphenhydramine, paracetamol and meldonium and sodium chloride.

On entry he had stage IIE disease with high intermediate risk IPI score. ECOG performance status was 2. On study day 23 the patient had his last dose of rituximab IV and CHOP. On study day 32 he had grade 3 fatigue and loss of appetite. On day 33 he had grade 2 neutropenia and grade 2 leukopenia. On day 34 (b) (6) he had epistaxis twice. The patient was reported to have previously received enoxaparin (b) (6) (b) (6) warfarin (b) (6) and clopidogrel (b) (6). On study day 35 he had profuse nasal bleeding and outpatient symptomatic therapy was given. A posterior nasal tamponade was performed, however, he died due to epistaxis.

Patient (b) (6)

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Patient (b) (6) was a 79-year-old man with a past medical history of tubulovillous adenoma of anal canal, and thrombophlebitis superficial. His surgical history included coronary artery bypass, central venous catheterization, and tubulovillous adenoma of anal canal exeresis. His concurrent conditions included hypertension, myocardial ischemia, diabetes mellitus, diverticulum intestinal, and Grade 1 aortic valve incompetence. Concomitant medications included simvastatin, furosemide and gliclazide, aspirin DL-lysine, Ramipril, acebutalol, sitagliptin phosphate, lercanidipine, nicorandil, paracetamol, ondansetron, and dexchlorpheniramine.

On entry he had stage IV disease with high risk IPI score. ECOG performance status was 1. Following his first cycle the patient had grade 3 febrile bone marrow aplasia (day 12) and grade 4 pulmonary embolism (day 15). On day 50 he was discharged from the hospital. His second and last cycle of rituximab and CHOP was given day 41. On day 60 he died from cardiac arrest.

Narratives for rituximab SC arm for deaths within 30 days trial MO28107 MabEase

Patient (b) (6)
Patient (b) (6) was a 72-year-old man. His past medical history included hypertension, dyspnea, and leg edema. At entry he had stage IIIS disease with high risk IPI score. ECOG performance status was 1. CHOP was administered on day 1. During his first cycle, day 8 he had grade 4 neutropenia and grade 3 hemorrhoids. Day 10 he had grade 2 anemia. One day 15 he received his first cycle of rituximab IV and next cycle of CHOP was administered day 26. On day 26 he received his first cycle of rituximab SC. On day 47 he received his last dose of rituximab. As of that day he received a total of 3 cycles of rituximab and CHOP. One day 52 he developed hemorrhoidal hemorrhage and was hospitalized. In response to the event his treatment was interrupted. He received transfusion on study Day 55 and study Day 56. On study day 56 he was transferred to another hospital. In response to the event of hemorrhoidal hemorrhage, study treatment with rituximab and CHOP was temporarily interrupted. Study treatment was permanently discontinued due to disease progression with the last dose of rituximab administered on Study Day 47. The patient had received 3 cycles each of rituximab and CHOP. On study Day 68 the patient died due to disease progression.

Patient (b) (6)
Patient (b) (6) was a 63-year-old man. Concurrent conditions included drug hypersensitivity (allergy to metamizole), asthma anxiety, chronic gastritis and esophagitis, and grade 2 asthenia. His concomitant medications included allopurinol and esomeprazole. On entry he had stage IIIS+E lymphoma with high intermediate risk IPI score. ECOG performance status was 1. On study day 9 he visited the emergency room with fever, and was hospitalized with a diagnosis of grade 4 pancytopenia on day 10. On day 16 this resolved. On day 36 he had his last dose of rituximab and CHOP for a total of 3 cycles. On day 44 he visited an emergency room with fever and grade 2

abdominal pain. He was hospitalized with grade 4 febrile neutropenia. A blood culture was positive for *Clostridium septicum* and was diagnosed with grade 2 bacteremia. On day 46 he was diagnosed with peritonitis. On day 47 he received plasma for generalized peritonitis. On day 52 he received one unit of platelets along with plateletpheresis. He also underwent exploratory laparostomy with cavity washes. On study Day 65 the patient died due to the event of generalized peritonitis.

Patient (b) (6)

Patient (b) (6) was an 80-year-old man. His past medical history included bubonocoele. His concurrent conditions included cardiac failure chronic, chronic obstructive pulmonary disease and thyroid disorder. His concomitant medications included furosemide, carvedilol, acetylsalicylic acid and glyceryl trinitrate, thiamazole, methylprednisolone, dimetidine, apomorphine, paracetamol and ondansetron.

On entry he had stage II lymphoma with low intermediate risk IPI. ECOG performance status was 2. On day 22 he received a total of 2 cycles of rituximab and CHOP. On day 31 he had grade 3 neutropenia. On day 33 he was hospitalized with lung infection. Due to lung infection treatment was permanently discontinued. He was treated with piperacillin, teicoplanin, filgrastim, tazobactam, and paracetamol. The patient was further treated with moxifloxacin, oseltamivir, ipratropium, salbutamol, budesonide and colistin. On study day 44, a chest X-ray revealed diffused infiltrates and pleural effusion. The following day, a chest CT showed multilobular infiltrates and pleural effusion. On day 46 he had dyspnea, hypotension, contusion, and oliguria. On day 47 ECG results were "slashed" and he was treated with atropine and epinephrine. He died the same day.

Patient (b) (6)

Patient (b) (6) was a 73-year-old man. His concurrent conditions included hypertension, diabetes mellitus, and esophagitis. His concomitant medications included verapamil, nadroparin, iron sucrose, fluconazole, trazodone, and allopurinol. On entry he had stage IV lymphoma with high risk IPI score. ECOG performance status was 2. He had pneumonia and septic shock after a single cycle of rituximab IV and CHOP. On day 2 he had grade 3 nosocomial pneumonia leading to a prolonged hospitalization. On day 24 he had grade 3 septic shock. He was treated with meropenem and vancomycin and was also kept on mechanical ventilation. On study day 25, a tracheal secretion was positive for *Staphylococcus aureus*. The same day, he was diagnosed with non-serious grade 2 soft tissue infection on right arm.

On day 62 he had his third cycle of rituximab and CHOP. On study day 71, a nasofibrolaryngoscopy showed abnormal results. On study Day 72, he developed second episode of serious Grade 3 septic shock associated with a prolonged hospitalization. On day 89 the second episode of septic shock was resolved. His 4 cycle of rituximab and CHOP was given on study day 93. On day 93 he abundant secretions with occluded tracheal cannula. On day 102 he had severe leucopenia. The

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same day he had a blood culture show gram negative bacilli. He died on day 105 secondary to the third episode of septic shock.

Patient (b) (6) was a 63-year-old woman. Her concurrent conditions included hypertension. Her concomitant medications included metoprolol, losartan, nadroparin, amlodipine, and omeprazole. On entry she had stage IV disease with high risk IPI score. ECOG performance status was 1. She had third cycle of rituximab and CHOP on study day 42. On day 51 she had grade 3 febrile neutropenia. On study Day 54, she presented to emergency room with three day history of respiratory and gastrointestinal symptoms (not specified) and was hospitalized. She was diagnosed with grade 2 pancytopenia. On study day 57 she had grade 2 pneumonia. On day 64 febrile neutropenia, monoliasis esophageal and pneumonia resolved.

On day 64 she had her 4th cycle of rituximab and CHOP the following day. On day 69 she had three day history of diffuse abdominal pain, hypotexia, fatigue, weakness, fever and cough and was hospitalized. She also had grade 2 neutropenia. On day 73 she had a positive blood culture for Klebsiella pneumonia and was diagnosed with grade 3 septic shock. Pancytopenia and neutropenia resolved on days 75 and 77 respectively. On day 83 tumor assessment showed partial response. On day 87 she was discharged on day 113 septic shock was considered resolved.

Her last rituximab was given day 121 for a total of 6 cycles of rituximab and CHOP. On day 129 she had acute diarrhea. She received intravenous hydration at home and refused referral to the emergency room. On day 131 she died due to acute diarrhea.

Patient (b) (6) was a 60-year-old man. No past medical history or concurrent conditions were reported. Concurrent medications included pheniramine, granisetron, dexamethasone and paracetamol. On entry he had stage IV lymphoma with low intermediate IPI score. ECOG performance status was 1. On day 112 he had his last dose of rituximab. He had a total of 5 cycles of rituximab and CHOP. On day 121 he was hospitalized with grade 3 febrile neutropenia. On day 125 he was diagnosed with pneumonia and grade 3 thrombocytopenia. He died due to pneumonia on day 125.

Patient (b) (6) was a 78-year-old woman. Concurrent conditions were cerebrovascular disorder, and atrial fibrillation. Concomitant medications were gabapentin, furosemide, guaifenesin/pseudoephedrine, digoxin, warfarin, ramipril, lansoprazole, paracetamol, dexamethasone, pheniramine, allopurinol, and granisetron. On entry she had stage III disease with low risk IPI score. ECOG performance status was 2. Her 4th cycle and last cycle of rituximab and CHOP was given day 64. On day 81 she was diagnosed with a lung infection. On day 89 her condition worsened and she

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developed hypotension and respiratory distress. On the same day she had cardiac arrest and died.

Patient (b) (6) was a 62-year-old woman. Past medical history included tachycardia. Concurrent conditions included osteoarthritis and abdominal pain. Concomitant medications were sulfamethoxazole/trimethoprim, allopurinol, pantoprazole, morphine, paracetamol, clemastine, granisetron, polyethylene glycol, and metoclopramide. On entry she has stage IVE lymphoma with high intermediate risk IPI score. ECOG performance status was 1. On day 15 she started rituximab SC, which was her last dose. She had 2 cycles of rituximab and CHOP. On day 20 she had stomatitis and pharyngitis. She was diagnosed with grade 4 febrile neutropenia and elevated hepatic enzymes. On day 21 an ultrasound showed stenosis hepatitis. One day 22 herpes test was positive from an oral ulcer for herpes simplex virus type 1. The patient was diagnosed with a serious event of grade 4 herpes simplex hepatitis. On day 22 she developed multi organ failure. On the same day her condition deteriorated and she died.

Patient (b) (6) was a 75-year-old woman. Her past medical history included bilateral breast cancer. Surgical history included pacemaker insertion. Concurrent conditions included lymphedema right arm, atrial fibrillation, cardiac decompensation, hypertension, pain, constipation, obesity, edema of peripheral legs, fatigue, renal failure, and hyperkalemia. Concomitant medications included Lisinopril, amitriptyline, spironolactone, acenocoumarol, polyethylene glycol, oxycodone, paracetamol, allopurinol, sodium polystyrene sulfonate, prednisone and oxycodone. On entry she had stage III disease and high risk IPI score. ECOG performance status was 2. Following her 3rd cycle she had grade 4 leukopenia and grade 4 febrile neutropenia. On day 50 she received her last dose of rituximab for a total of 4 cycles of rituximab and CHOP. On day 61 she had grade 3 febrile neutropenia. On day 62 her neutrophil count 0.5 x 10⁹/L and she also had grade 1 stomatitis. On day 65 the second episode of febrile neutropenia resolved. The same day she developed cardiac failure which prolonged her hospitalization. On day 70 she had a blood transfusion. On day 71 she had a positive urine culture. On day 73 she had grade 2 dyspnea. On day 75 she died due to cardiac failure.

Patient (b) (6) was a 64-year-old man. His concurrent condition was mass at submental area. Concomitant medications included ondansetron, hydrocortisone, paracetamol, chlorpheniramine, lamivudine, acyclovir, and omeprazole. At screening he had stage IV lymphoma with a high intermediate risk IPI score. ECOG performance status was 0. On day 76 tumor assessment showed partial response. His 5th and last dose of rituximab was given on day 86. He had 5 doses of rituximab and CHOP. On day 95 he was hospitalized with septic shock. He died from septic shock of day 96.

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Patient (b) (6)

Patient (b) (6) was a 79-year-old woman. Concurrent conditions included chronic cholecystitis, atherosclerotic cardiosclerosis, hypertension, hepatic steatosis, and renal cyst. Concomitant medications included allopurinol, omeprazole, and clemastine. At entry she had stage II lymphoma with high risk IPI score. ECOG performance status was 1. On day 64 she had her 4 cycle of rituximab, she had a total of 4 cycles of CHOP. On day 68 tumor assessment showed complete response. On day 77 she developed acute cardiac failure and died the same day.

Patient (b) (6)

Patient (b) (6) was a 64-year-old woman. Her concurrent condition was duodenal ulcers. No concomitant medications were reported. At entry she had stage IV lymphoma with high risk IPI score. ECOG performance status was 0. On study day 14 she had grade 4 neutropenia. On day 85 tumor assessment showed partial response. On day 134 she had her seventh and last dose of rituximab and CHOP. On day 152 the patient died due to an unknown cause.

Patient (b) (6)

Patient (b) (6) was a 75-year-old woman. Her past medical history included VIth nerve paralysis and vaginal prolapse. Concurrent conditions included hypothyroidism, cholelithiasis, type 2 diabetes mellitus, and osteoporosis. Concomitant medications included levothyroxine, insulin, paracetamol, zoledronate, calcium carbonate/cholecalciferol, and metoclopramide. At entry she had stage IV disease with high intermediate IPI score. She received her third cycle of rituximab CHOP on day 43. On day 49 she had grade 1 malaise, grade 2 productive cough, and grade 2 chest infection. On day 50 a nasogastric tube was placed for nutritional support. On day 54 she developed grade 3 hypoxia. Pneumothorax was noted and neutropenic sepsis was suspected. She was diagnosed with respiratory failure. On day 55 she was placed on mechanical ventilation. On day 58 she underwent a chest drain for pneumothorax. On day 60 she underwent tracheostomy. On day 62 she was diagnosed with grade 2 pneumonia. She died on day 64 due to type 1 respiratory failure.

9.5 Clinical Investigator Financial Disclosure Review

Application Number: BLA 761064

Submission Date(s): August 26, 2016

Applicant: Genentech, Inc

Product: rituximab and hyaluronidase

Reviewer: Alexandria Schwarsin, MD

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Date of Review: May 3, 2017

Covered Clinical Study (Name and/or Number): Study BO22334/SABRINA, Study MO28107/MabEase, Study BO25341/SAWYER, Study MO28457/PrefMab and Study BP22333/Spark Thera.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 3065		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 458		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request information from applicant)

On March 26, 2009 F. Hoffmann-La-Roche Ltd acquired Genentech, Inc. and investigators and sub-investigators were asked to sign an updated financial disclosure form for financial interests in Genentech and Roche. In the U.S. Biogen is considered a co-development partner, thus investigators and sub-investigators that were still open in 2016 were asked to sign an updated financial disclosure form. For the updated

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Financial Disclosure form with Biogen, for the ongoing studies, 82% of investigators responded.

Disclosable financial interests were recorded by 3 out of 762 (0.004%) investigators in Study BO22334/SABRINA and 1 out of 378 (0.003%) investigators in Study BO25341/SAWYER. A small percentage of investigators have disclosures and the majority of investigators, disclosed financial interests.

There is integrity in the data given the small percentage of investigators with disclosable financial interests, and multiple investigators were used in all of the clinical trials.

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/s/

ALEXANDRIA N SCHWARSIN
05/23/2017

ROMEO A DE CLARO
05/23/2017

PATIENT PREFERENCE AND PATIENT REPORTED OUTCOMES REVIEW

BLA NUMBER	761064
ESTABLISHED NAME/TRADE NAME	Rituximab/hyaluronidase
APPLICANT	Genentech, Inc.
INDICATION	Treatment of follicular lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia
BLA SUBMISSION DATE	October 11, 2016
PDUFA GOAL DATE	June 26, 2017
REVIEW COMPLETION DATE	April 24, 2017
REVIEW DIVISION	Division of Hematology Products (DHP)
MEDICAL REVIEWER	Vishal Bhatnagar, MD
CROSS-DISCIPLINE TEAM LEADER	R. Angelo De Claro, MD

1. Introduction

Rituxan (rituximab) is an intravenously (IV) administered CD20-directed cytolytic monoclonal antibody approved under BLA 103705 for the treatment of adult patients with Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), Rheumatoid Arthritis, and Granulomatosis with Polyangiitis/Microscopic Polyangiitis. The applicant (Genentech, Inc.) submitted a biologic license application (BLA) to support approval of a co-formulation of rituximab and hyaluronidase to be administered subcutaneously (SC) for the same oncologic indications as the IV formulation.

The combination of rituximab and hyaluronidase, hereafter referred to as rituximab SC, offers patients a different route of administration compared to intravenous rituximab, hereafter referred to as rituximab IV. The applicant submitted the results from a dedicated preference study as a part of their BLA submission for rituximab SC. The purpose of this review is to describe and analyze the results and to provide a recommendation as to whether the results are relevant for patients and practitioners.

2. Description of Preference Study

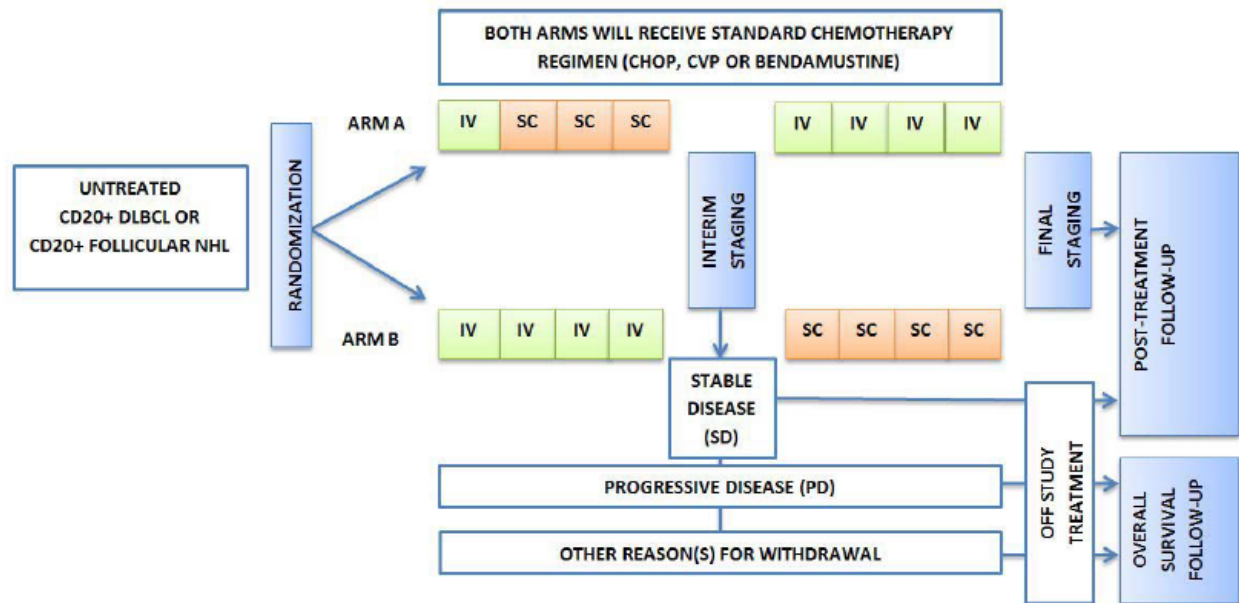
Study Title: *MO28457 – PrefMab: A Randomized, Open-Label, Multi-Center Study to Evaluate Patient Preference with Subcutaneous Administration of Rituximab versus Intravenous Rituximab in Previously Untreated Patients with CD20+ Diffuse Large B-Cell Lymphoma or CD20+ Follicular Non-Hodgkin's Lymphoma Grades 1, 2, or 3a*

Study Design

PrefMab was a prospective, multi-center, multinational, open-label, randomized study in 743 adult patients with previously untreated CD20+ diffuse large B-cell lymphoma (DLBCL) or CD20+ follicular NHL Grade 1, 2, or 3a. Patients with follicular NHL Grade 3b were excluded because these patients usually require more aggressive treatment than permitted in the trial. Prior to starting therapy, all eligible patients were randomized in a 1:1 ratio to Treatment Arm A or Arm B (see Figure 1 below) using a centralized interactive voice/web response system. Patients were stratified according to age (<60 years and ≥60 years), International Prognostic Index (IPI) or Follicular Lymphoma International Prognostic Index (FLIPI) risk category (low, low-intermediate, high-intermediate, and high), and chemotherapy regimen (cyclophosphamide, hydroxydaunorubicin (doxorubicin, Adriamycin), Oncovin (vincristine),

prednisone/prednisolone [CHOP]; cyclophosphamide, vincristine, prednisone/prednisolone [CVP]; or bendamustine), which was selected by the investigator before randomization.

Figure 1 PrefMab Design



Source: PrefMab protocol v3, figure 1, page 47

Study Objectives

Primary Objective:

To evaluate the proportion of patients indicating an overall preference via a Patient Preference Questionnaire (PPQ) for either the SC or IV route of rituximab administration.

Secondary Objectives:

To evaluate and compare the methods of rituximab administration (SC versus IV) in terms of:

- Rituximab administration time, defined as the time from start to end of either the rituximab SC injection or the rituximab IV infusion
- Patient-assessed satisfaction and convenience using the Cancer Therapy Satisfaction Questionnaire (CTSQ) and Rituximab Administration Satisfaction Questionnaire (RASQ)
- Immunogenicity (anti-rituximab and anti-human recombinant hyaluronidase [rHuPH20] antibodies) and the associated rituximab concentration level at each anti-rituximab sampling time point

To evaluate efficacy of rituximab SC in terms of:

- Complete response (CR) rate, including complete response unconfirmed (CRu), 28 ($\pm$ 3) days after Day 1 of the last dose of induction treatment
- Event-free survival (EFS)
- Disease-free survival (DFS)
- Progression-free survival (PFS)
- Overall survival (OS)

Endpoints

Primary Endpoint

For the binary primary endpoint (patient preference for rituximab SC versus rituximab IV), the proportion of patients who preferred rituximab SC over rituximab IV, along with the corresponding two-sided 95% confidence interval (CI), were estimated.

Secondary Endpoints

Safety endpoints: Safety was assessed by adverse events (AEs), AEs of Grade ≥ 3 , serious AEs (SAEs), premature withdrawal from the study and from study medication, laboratory parameters, vital signs, and Eastern Cooperative Oncology Group (ECOG) Performance Status. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs and SAEs was summarized by primary System Organ Class and Preferred Term. Laboratory parameters were presented in shift tables of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade at baseline against the worst grade recorded overall. Other safety variables were summarized. All clinical AEs and SAEs as well as laboratory abnormalities were recorded and graded according to the NCI CTCAE v 4.0.

Efficacy endpoints

The CR/CRu rate measured 28 (± 3) days after Day 1 of the last dose of induction treatment was summarized. The time-to-event endpoints, EFS, DFS, PFS, and OS, from randomization were summarized overall and by the two treatment sequence groups using the Kaplan-Meier approach. Patient-reported outcome variables: Patient-assessed satisfaction and convenience using RASQ and CTSQ were summarized and presented by treatment group. Study drug exposure variables: The time required for rituximab administration was summarized. Immunogenicity (anti-rituximab and anti-rHuPH20 antibodies) and the associated rituximab concentration level at each anti-rituximab sampling time point was summarized.

Eligibility Criteria

Inclusion Criteria

1. Signed, written informed consent form
2. Age ≥ 18 and ≤ 80 years at time of randomization
3. Histologically confirmed, previously untreated CD20+ DLBCL or CD20+ follicular NHL Grade 1, 2 or 3a, according to the World Health Organization (WHO) classification system. Note: lymph node excision or adequate core biopsy was required for the diagnosis of DLBCL or follicular NHL. Fine-needle aspiration samples were not used as the sole material for pathological diagnosis.
4. An IPI score of 1-4 or IPI score of 0 with bulky disease, defined as one lesion ≥ 7.5 cm, or FLIPI (low, low-intermediate, high-intermediate, high)
5. At least one bi-dimensionally measurable lesion defined as ≥ 1.5 cm in its largest dimension on computed tomography (CT) scan
6. ECOG performance status ≤ 3 .

Exclusion Criteria

1. Transformed lymphoma or follicular NHL 3b
2. Primary central nervous system (CNS) lymphoma, histologic evidence of transformation to a Burkitt lymphoma, primary mediastinal DLBCL, primary effusion lymphoma, primary cutaneous DLBCL or primary DLBCL of the testis

3. History of other malignancy that could affect compliance with the protocol or interpretation of results. This included a malignancy that was treated but not with curative intent, unless the malignancy was in remission without treatment for ≥ 5 years prior to enrolment. Note: Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix were eligible for the study.

4. Prior therapy for DLBCL or follicular NHL, with the exception of nodal biopsy or local irradiation
Note: lymph node excision or adequate core biopsy is required for the diagnosis of DLBCL or follicular NHL. Fine-needle aspiration samples should not be used as the sole material for pathological diagnosis.

5. Prior treatment with cytotoxic drugs (with the exclusion of intrathecal methotrexate for CNS prophylaxis in DLBCL) or rituximab for another condition (e.g., rheumatoid arthritis) or prior use of an anti-CD20 antibody

6. Prior use of any monoclonal antibody within 3 months prior to randomization

7. Chemotherapy or other investigational therapy within 28 days prior to randomization

8. Ongoing corticosteroid use > 30 mg/day of prednisone or equivalent. Note: (i) patients receiving corticosteroid treatment with ≤ 30 mg/day of prednisone or equivalent had to be on a documented stable dose of at least 4 weeks' duration prior to randomization; (ii) a pre-phase of high dose prednisolone (e.g. 100 mg/day for 5 days) was acceptable for patients with aggressive NHL.

9. Inadequate renal function, defined as:

- creatinine > 1.5 times the upper limit of normal (ULN) (unless normal creatinine clearance), or calculated creatinine clearance < 40 mL/min (using the Cockcroft– Gault formula)

10. Inadequate hematologic function, defined as:

- Hemoglobin < 9 g/dL
- Absolute neutrophil count $< 1.5 \times 10^9/L$
- Platelet count $< 75 \times 10^9/L$

Note: no transfusions were allowed within 2 weeks prior to the start of study drug administration.

11. Inadequate hepatic function, defined as:

- aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $> 2.5 \times$ the ULN
- total bilirubin $\geq 1.5 \times$ the ULN. Note: patients with documented Gilbert disease could enroll if total bilirubin was $\leq 3.0 \times$ the ULN.

12. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products

13. For patients with DLBCL - Contraindication to any of the individual components of CHOP, including prior receipt of anthracyclines

14. Other serious underlying medical conditions, which, in the Investigator's judgment, could impair the ability of the patient to participate in the study (e.g., significant cardiovascular disease, uncontrolled diabetes mellitus, gastric ulcers, active autoimmune disease).

15. Recent major surgery (within 4 weeks prior to randomization), other than for diagnosis

16. Active and/or severe bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization within 4 weeks prior to randomization

17. Active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection (ruled out during screening). Patients with occult or prior HBV infection (defined as positive total hepatitis B core antibody (HBcAb) and negative or positive HBsAg with undetectable HBV deoxyribonucleic acid [DNA]) could be included but these patients were to be followed closely. Patients who were positive for HBsAg and were PCR negative had to be treated with lamivudine (or other standard antiviral therapy) beginning prior to the initiation of study treatment and continuing for 6 months after completing study treatment. Patients positive for HCV antibody were eligible only if polymerase chain reaction (PCR) testing for HCV ribonucleic acid (RNA) was negative.

18. History of HIV seropositive status.

19. Inability to provide informed consent. Furthermore, any patients who could not read and/or write required an independent to help complete the questionnaires.

20. Life expectancy of less than 6 months

21. A positive serum pregnancy test in women of childbearing potential within 7 days prior to randomization or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to randomization. Women of childbearing potential were defined as pre-menopausal women or women who were < 2 years after the onset of menopause and were not surgically sterile.

22. Fertile men or women of childbearing potential who do not agree to use a highly effective measure of contraception (such as oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) throughout the study and for at least 12 months after the last dose of rituximab.

Treatment plan

Study treatment in both treatment arms consisted of eight cycles of rituximab administration in combination with CHOP, CVP, or bendamustine. Interim staging occurred after completion of Cycle 4.

Arm A: Patients randomized to Arm A received one cycle of rituximab IV, then three cycles of rituximab SC, followed by four cycles of rituximab IV after interim staging.

Arm B: Patients randomized to Arm B received four cycles of rituximab IV followed by four cycles of rituximab SC after interim staging.

Rituximab SC: Each treatment cycle consisted of a single SC injection of rituximab administered at a fixed dose of 1400 mg. Rituximab was administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Rituximab IV: Rituximab was administered at a dose of 375 mg/m² body surface area (BSA) as a single IV infusion, followed by administration of chemotherapy. At Cycle 1, Day 1, the first rituximab dose for both Arms A and B was always administered as a slow IV infusion, according to local standard practice. Faster infusion rates were permitted after Cycle 1, according to local practice. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Approved, commercially available chemotherapy was used in combination with rituximab SC or rituximab IV. Each participating investigator decided before patient randomization which chemotherapy regimen would be used in combination with rituximab for an individual patient. The chemotherapy options were:

- CHOP every 14 days, Cycles 1-8
- CHOP every 21 days, Cycles 1-8
- CHOP every 28 days, Cycles 1-8
- CHOP every 14 days, Cycles 1-6
- CHOP every 21 days, Cycles 1-6
- CVP or bendamustine every 21 days, Cycles 1-8
- Bendamustine every 21 days, Cycles 1-8
- Bendamustine every 28 days, Cycles 1-8
- CVP every 21 days, Cycles 1-6
- CVP every 28 days, Cycles 1-6
- CHOP every 21 days, Cycles 1-3; CVP every 21 days, Cycles 4-6

Patients whose treatment plan included 6 cycles of chemotherapy received rituximab monotherapy for Cycles 7 and 8.

Toxicity Management

Section 5 of the MO28457 protocol version 3 describes the safety plan, specifically management of adverse events.

Patient Preference and Patient Reported Outcome Instruments

Table 1 Summary of the Patient Preference and Patient Reported Outcome (PRO) Instruments

Patient Assessment	Brief Description
Patient Preference Questionnaire (PPQ)	The PPQ is a 3-item self-reported questionnaire developed by the Applicant to assess patients' preference for a route of treatment administration (SC vs. IV). The three PPQ questions are: Question 1: All things considered, which method of administration did you prefer? (IV/SC/No preference) Question 2: If you have a preference for one of the administration routes, how strong is this preference? (Very strong/Fairly strong/Not very strong) Question 3: If you have a preference for one of the administration routes, what are the two main reasons for your preference? ☐ Feels less emotionally distressing ☐ Requires less time in the clinic ☐ Lower level of injection-site pain ☐ Feels more comfortable during administration ☐ Other reason; please specify
Cancer Treatment Satisfaction Questionnaire (CTSQ)	The CTSQ is a 16-item PRO instrument designed to measure treatment satisfaction in individuals with cancer. The CTSQ is comprised of three domains related to patients' satisfaction with cancer therapy: expectations of therapy, feelings about side effects, and satisfaction with therapy. Each item is rated on a 5-point verbal rating scale and assessed with a recall period of 4 weeks. The CTSQ is scored on a 0-100 point scale, where a lower score indicates greater dissatisfaction with treatment and a higher score indicates greater satisfaction with treatment.
Rituximab Administration Satisfaction Questionnaire (RASQ)	The RASQ is a 20-item PRO instrument designed to measure "treatment satisfaction" (covering subconcepts of "overall preference/satisfaction", "convenience", "confidence", and "bothersomeness") and "impact of treatment administration" (covering subconcepts of "physical impact", "psychological impact," "impact on activities of daily life," and "impact on the interaction with health care providers"). The Applicant utilized two similar versions of the RASQ for each method of administration (RASQ-IV and RASQ-SC) in the PrefMab study. Sixteen items were rated on a 5-point verbal rating scale, two items were rated on a 3-point verbal rating scale, and one Yes/No item. Each item was assessed with a recall period based on the recall of their most recent SC or IV administration. The RASQ is scored on a 0-100 point scale, where a lower score indicates greater dissatisfaction with treatment and a higher score indicates greater satisfaction with treatment.

See the clinical outcome assessment (COA) staff review for details regarding how the above instruments were developed, the conceptual framework, and the scoring methods.

Schedule of Assessments

Study Period	Screening/ Baseline	Induction Treatment Rituximab IV or SC + chemotherapy				Post-Treatment Follow-up	Early Treatment Termination/ End of Study
Visit		V1–V4 (Cycles 1-4)	V5 Interim Staging	V6–V9 (Cycles 5-8)	V10 Final Staging	V11–V23	
Timing/Assessments	D -28 to D -1	D1 Every 14–21 days 4 cycles	14-28 days after 4 cycles ^a	D1 Every 14–21 days 4 cycles	End of study treatment ^b	From Visit 9: Every 3 months ($\pm$ 2 weeks) for the first 2 years according to country standards, then every 6 months ($\pm$ 2 weeks) until end of study ^c	Within 4 weeks of last dose or last follow-up ^d
Written informed consent ^e	X						
Demographic data	X						
Medical history	X						
DLBCL or follicular NHL diagnosis and WHO classification ^f	X						
Documentation of/testing for HIV, active hepatitis, and other infections ^g	X	As clinically indicated					
Tumor evaluation ^h	X		X		X	X (until PD) according to local practice	
Physical examination, infection assessment, vital signs ⁱ	X	X	X	X	X	If clinically indicated	X
Height, weight, and BSA ^j	X	X		X			
12-lead ECG	X						
IPI, FLIPI score ^k	X						
ECOG Performance Status ^l	X		X		X		X
Serum pregnancy test ^m	X	If clinically indicated					

Patient Preference and Patient Reported Outcomes Review
Vishal Bhatnagar, MD
BLA 761064
Rituxan Hycela (rituximab/hyaluronidase)

Study Period	Screening/ Baseline	Induction Treatment Rituximab IV or SC + chemotherapy				Post-Treatment Follow-up	Early Treatment Termination/ End of Study
Visit		V1–V4 (Cycles 1-4)	V5 Interim Staging	V6–V9 (Cycles 5-8)	V10 Final Staging	V11–V23	
Timing/Assessments	D -28 to D -1	D1 Every 14–21 days 4 cycles	14-28 days after 4 cycles ^a	D1 Every 14–21 days 4 cycles	End of study treatment ^b	From Visit 9: Every 3 months ($\pm$ 2 weeks) for the first 2 years according to country standards, then every 6 months ($\pm$ 2 weeks) until end of study ^c	Within 4 weeks of last dose or last follow-up ^d
Laboratory: hematology, biochemistry, coagulation tests ⁿ	X	X	X	X	X	If clinically indicated	X
Randomization by IxRS ^o		Prior to Cycle 1 dosing					
Rituximab + chemotherapy administration ^p		X		X			
AE recording ^q	X	X	X	X	X	X	X
Immunogenicity (anti-rituximab antibodies, anti-rHuPH20 antibodies, and rituximab concentration level) ^r		X	X	X	X	X (at 6 and 12 months)	X
Concomitant treatments & therapies ^s	X	X	X	X	X	X	X
PPQ ^t				Cycle 6+8			
RASQ, CTSQ ^u		Cycle 4		Cycle 8			
Survival						X	X

AE=adverse event; BSA=body surface area; CHOP=cyclophosphamide, hydroxydaunorubicin (doxorubicin, Adriamycin), Oncovin (vincristine), prednisone/prednisolone; CR=complete response; CTSQ=Cancer Therapy Satisfaction Questionnaire; CVP=cyclophosphamide, vincristine, prednisolone/prednisone; D=day; DLBCL=diffuse large B-cell lymphoma; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FLIPI=Follicular Lymphoma International Prognostic Index; HIV=human immunodeficiency virus; IPI=International Prognostic Index; IV=intravenous; IWG=International Working Group; IxRS=interactive voice/web response system; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NHL=non-Hodgkin's lymphoma; PD=progressive disease; PPQ=Patient Preference Questionnaire; RASQ=Rituximab Administration Satisfaction Questionnaire; rHuPH20=human recombinant hyaluronidase; SAE=serious adverse event; SD=stable disease; SC=subcutaneous; SD=stable disease; V=visit; WHO=World Health Organization.

^aInterim staging of patients occurred 14–28 days after Day 1 of Cycle 4 of rituximab and chemotherapy (CHOP, CVP, or bendamustine, independent of whether the CHOP regimen was given every 14 days or every 21 days). All interim staging assessments associated with Visit 5 must have been completed prior to Visit 6 (initiation of Cycle 5). Patients with SD or PD at interim staging had study medication permanently discontinued.

^bFinal staging assessment performed at 28 days ($\pm$ 3 days) after the last dose of induction treatment. Any response assessment was also to occur prior to any planned radiotherapy.

^cFollow-up schedule was calculated from Visit 9. Patients with PD or initiating any new anti-lymphoma treatment after the end of induction treatment were followed only for survival until the end of the study. Randomized patients who did not complete the study per protocol for any reason underwent the early termination assessment and entered the post-treatment follow-up phase. These patients were followed until the end of the study according to local practice for resolution of SAEs related to rituximab therapy, tumor response/progression (if PD not yet documented), new treatments for lymphoma, and survival.

^dRandomized patients who did not complete the induction treatment as per protocol underwent early termination assessments within 4 weeks after their last dose of induction treatment and entered the post-treatment follow-up phase.

^eSigned informed consent must have been obtained prior to any study-required screening/baseline assessments or other study-related changes to the patient's management.

^fDiagnosis of DLBCL or follicular NHL before treatment must have included histological diagnosis and initial CD20 expression confirmation. Lymph node excision or adequate core biopsy was required for the diagnosis DLBCL or follicular NHL. Fine-needle aspiration samples were not to be used as the sole material for pathological diagnosis.

^gPatients known to have human immunodeficiency virus, active hepatitis C virus (HCV), active hepatitis B virus (HBV), or signs or symptoms of other active and/or severe infection were not to be included in the study. Patients with occult or prior HBV infection (defined as positive total hepatitis B core antibody, and negative or positive hepatitis B surface antigen with undetectable HBV deoxyribonucleic acid [DNA]) may have been included, but these patients must have been followed closely, with testing for HBV DNA levels approximately every 4 weeks during induction treatment and for 1 year after completing study treatment. Patients with positive for hepatitis B surface antigen that were negative for HBV DNA by polymerase chain reaction (PCR) test and negative PCR must have been treated with lamivudine (or other standard antiviral therapy) beginning prior to the initiation of study treatment and continuing for 6 months after completing study treatment. Patients positive for HCV antibody were eligible only if PCR testing was negative for HCV ribonucleic acid

(RNA). During treatment with rituximab, additional serology was to be performed according to clinical judgment. Local guidelines for patient consent to viral testing must have been adhered to.

^hComputed tomography (CT) and magnetic resonance imaging (MRI) are currently the best available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT or MRI was to be performed according to institutional standards. Tumor assessment at baseline, after 4 cycles of treatment (interim staging), and at end of treatment was based on CT scans of the neck, chest, and abdomen, as applicable; CT scan of the pelvis was to be included if clinically indicated. Computed tomography scan with contrast was the recommended technique. However, MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan may have been used in patients for whom CT scans with contrast were contraindicated (e.g., patients with contrast allergy or impaired renal clearance). Owing to the global nature of this study, and due to limited availability of [¹⁸F]deoxyglucose positron emission tomography (FDG-PET) scanners, an FDG-PET scan could not be mandated, unless specified as standard country-specific practice. The CT scan used for eligibility assessment may have been performed up to 35 days before randomization. The end-of-treatment response assessment including radiology/imaging report must have been obtained 28 (± 3 days) after Day 1 of the last dose of induction treatment. Response was to be determined on the basis of radiographic and clinical evidence of disease according to the IWG guidelines, or if not applicable, institutional standards should have been used for tumor evaluation. Disease progression was evaluated by the investigator according to the IWG response criteria for NHL (Cheson et al. 1999) or other country-specific standards until PD. Patients with SD or PD at the interim staging were to come off study treatment. Screening/baseline bone marrow examinations included biopsy and aspirate for morphology (flow studies were optional) for staging purposes unless it had been performed within 4 months prior to the start of study drug administration and was done for the purpose of diagnosis and staging of DLBCL. Subsequent bone marrow assessments were required to confirm any suspected CR in patients with bone marrow involvement at baseline. If a confirmatory bone marrow assessment was not obtained, these patients were to be considered only having a partial response.

ⁱAs part of the physical examination, SC injection sites were checked at every treatment visit (in applicable patients). As part of tumor assessments, physical examinations should also have included the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Patients were to be assessed for presence of active infections throughout the treatment periods. Vital signs assessment included resting heart rate, body temperature, and blood pressure.

^jPatients were weighed prior to each treatment so that BSA may have been re-calculated if necessary. Cyclophosphamide, vincristine, doxorubicin, and bendamustine doses were to be recalculated only if the patient's weight changed by more than ± 10% from baseline.

^kInternational prognostic index (IPI) (according to Shipp et al. 1993) and FLIPI score determined at baseline (prior to Cycle 1). Where possible, the baseline IPI or FLIPI score was to be calculated from the patient notes. Missing IPI/FLIPI scores did not preclude enrollment/randomization.

^lEastern Cooperative Oncology Group (ECOG) performance status needed to be ≤3 for inclusion of the patient into the study.

^mWomen of childbearing potential (defined as premenopausal women or women who were <2 years after the onset of menopause and not surgically sterile) must have undergone a serum pregnancy test within 7 days prior to randomization or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to randomization.

ⁿHematology parameters included hemoglobin, red blood cell count, white blood cell count, neutrophils, lymphocytes, and platelet count. Biochemistry parameters at screening included sodium, potassium, alanine aminotransferase/serum glutamate pyruvate transaminase, aspartate aminotransferase/serum glutamate oxaloacetic transaminase, total bilirubin, serum creatinine, alkaline phosphatase, albumin, blood urea nitrogen, C-reactive protein, and lactate dehydrogenase (LDH). Biochemistry parameters at any further time point during the study included sodium, potassium, alanine aminotransferase/serum glutamate pyruvate transaminase, aspartate aminotransferase/serum glutamate oxaloacetic transaminase, total bilirubin,

and serum creatinine. Patients with abnormal LDH, alkaline phosphatase, albumin, blood urea nitrogen, or C-reactive protein at screening also had these tests repeated as part of their interim and final staging assessments. Coagulation tests included at least one of the following: international normalized ratio, prothrombin time, activated partial thromboplastin time. The results from the safety laboratory assessments must have been available on treatment days, prior to the rituximab administrations. Note: If Visit 5 (interim staging) was within 3 days of Visit 6 (initiation of Cycle 5), all laboratory samples only needed to be done once, and were labelled as being associated with Visit 6.

^aRandomization occurred prior to dosing on Day 1 of Cycle 1. It could only occur after all screening assessments had been completed and the patient's eligibility had been confirmed.

^bIn both randomized groups, the first rituximab dose was administered by IV infusion on Day 1 of Cycle 1, at a dose of 375 mg/m² BSA (rounded to the nearest 10 mg), followed by administration of chemotherapy. The initial dose of rituximab could also be administered 1 day before chemotherapy (depending on institutional practice), or over 2 consecutive days in case the patient was at high risk of developing tumor lysis syndrome. Patients randomized to Arm A, who tolerated the full first dose of rituximab IV, received rituximab SC at a fixed dose of 1400 mg in Cycles 2 to 4, while patients randomized to Arm B, who tolerated the first full dose of IV rituximab, continued receiving rituximab IV in Cycles 2 to 4. Patients must have been observed for at least 15 minutes following rituximab SC administration. A longer period may have been appropriate in patients with an increased risk of hypersensitivity reactions. Patients not having SD or PD at interim staging (after Cycle 4) continued treatment with the alternative treatment administration method for Cycles 5 to 8.

^cAfter informed consent had been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention were to be reported (e.g., SAEs related to invasive procedures such as biopsies). All clinical and laboratory AEs reported during the study were documented and graded using the NCI CTCAE criteria, v4.0. Special attention was given to any acute infusion-related toxicities. After initiation of study drug, all AEs/SAEs, regardless of relationship to study drug, were reported until study closure, with the exception of unrelated AEs/SAEs occurring in an off-study patient who had started a new anti-cancer treatment. After the end of study, all SAEs (regardless of causality) occurring in a patient after the treatment of that patient had ended were to be reported to the Sponsor if the investigator became aware of them. The investigator was not required to actively monitor patients after the study had ended.

^dAll patients were evaluated for anti-rituximab, anti-rHuPH20 (and the associated rituximab concentration level at each anti-rituximab sampling time point; at predose during Cycles 1 to 8 (according to the treatment arm), at the interim and final staging, at 6 and 12 months follow-up, and at End of Study. Note: If Visit 5 (interim staging) was within 3 days of Visit 6 (initiation of Cycle 5), all laboratory samples only needed to be done once, and were labelled as being associated with Visit 6.

^eDuring the post-treatment follow-up, only new anti-lymphoma treatments were recorded.

^fAll patients were required to complete the PPQ for the route of administration at the end of Cycle 6 and at the end of Cycle 8. Patients prematurely discontinuing study treatment during Cycles 4 or 5 were to complete the questionnaire at the time of discontinuation, as long as they had taken at least one dose via each treatment route post randomization.

^gPatient-reported outcomes: Treatment satisfaction for rituximab SC or rituximab IV administration was assessed using the CTSQ and the RASQ in Cycle 4 and Cycle 8. At these visits, CTSQ was completed prior to rituximab administration, whereas RASQ was completed immediately after rituximab administration and before chemotherapy administration.

Source: MO28457 CSR, table 1

Efficacy Assessments

During study treatment, patients were assessed for safety and efficacy as detailed in the Schedule of Assessments. The PPQ was applied after rituximab administration in Cycles 6 and 8. In Cycles 4 and 8, the CTSQ was applied before rituximab administration and the RASQ was applied after rituximab administration. The efficacy of rituximab was evaluated in terms of CR/CRu, PFS, EFS, DFS, and OS. Response assessments after four cycles (interim staging) and 28 (± 3) days after Day 1 of the last dose induction treatment were based on the investigator's assessment, completed according to the International Working Group response criteria, or other country-specific standards. After induction treatment had been completed after Cycle 8, patients were followed every 3 months (± 2 weeks) calculated from Visit 9 for the first 2 years and then every 6 months (± 2 weeks) until the end of the study. Follow-up assessments included evaluations of safety, disease progression, new anti-lymphoma treatment, and survival.

Statistical Methods

The primary analysis of patient preference took place when all patients had completed induction treatment. Secondary endpoints were also summarized at this time. There were no formal statistical hypothesis tests performed. The final analysis for the efficacy endpoints (CR/CRu, EFS, DFS, PFS, and OS) will be performed when the last patient completes at least 24 months of follow-up, has disease recurrence, is withdrawn from the study, is lost to follow-up, or dies, whichever occurs first. Safety monitoring of data was performed periodically by the independent data monitoring committee (IDMC). For the binary primary endpoint (patient preference for rituximab SC versus rituximab IV), the proportion of patients who preferred rituximab SC over rituximab IV, along with the corresponding two-sided 95% confidence interval (CI), were estimated. Safety was assessed by AEs, AEs of Grade ≥ 3 , SAEs, premature withdrawal from the study and from study medication, laboratory parameters, vital signs, and ECOG performance status. Adverse events were coded using MedDRA. The incidence of AEs and SAEs was summarized by primary System Organ Class and Preferred Term. Laboratory parameters were presented in shift tables of NCI CTCAE grade at baseline against the worst grade recorded overall. Other safety variables were summarized. All clinical AEs and SAEs as well as laboratory abnormalities were recorded and graded according to the NCI CTCAE v 4.0. The CR/CRu rate measured 28 (± 3) days after Day 1 of the last dose of induction treatment was summarized. The time-to-event endpoints, EFS, DFS, PFS, and OS, from randomization were summarized overall and by the two treatment sequence groups using the Kaplan-Meier approach. Patient-reported outcome variables: Patient-assessed satisfaction and convenience using RASQ and CTSQ were summarized and presented by treatment group. Study drug exposure variables: The time required for rituximab administration was summarized. Immunogenicity (anti-rituximab and anti-rHuPH20 antibodies) and the associated rituximab concentration level at each anti-rituximab sampling time point was summarized.

Key Revisions

Protocol Version 2 – Summary of Changes (February 21, 2013):

- For each anti-rituximab sample taken, drug-concentration analysis was added as a requirement at each scheduled time point.
- The 30-minute post-dose anti-rHuPH20 samples were removed from every cycle.
- Additional anti-rituximab and anti-rHuPH20 samples were required during the follow-up period (i.e., at 6 and 12 months).
- The screening/baseline anti-rituximab sample was removed (because the Cycle 1 predose sample could also act as the baseline sample).

- The Schedule of Assessments and applicable footnotes were revised to reflect the above changes and to correct some inconsistencies. Immunogenicity sampling schedules for Treatment Arms A and B were included for ease of reference during the study.
- The prephase corticosteroid course was increased from 3 days to 5 days in patients with aggressive NHL.
- The reporting requirements for SAEs and AEs of special interest after the end of study were revised in alignment with recent global requirements.
- The needle gauge was revised to include both 25- and 27-gauge needles.
- The word “MabThera” (trade name) was replaced with the word “rituximab” (generic name) in the PPQ for consistency within the protocol.

Protocol Version 3 - Summary of Changes (June 2, 2014):

- It was originally anticipated that the proportion of patients preferring rituximab SC would be approximately 60%. In order to have a sample size of 720 patients for analysis of the primary endpoint, the enrollment target was originally 900. However, a preplanned interim analysis revealed that approximately 80% of patients preferred rituximab SC. After a discussion with the IDMC, the sample size was recalculated, decreasing the required number of patients from 720 to 560 patients and the enrollment target to 700 patients.
- Although patients with active hepatitis B or hepatitis C virus were excluded from the study, some hepatitis-related conditions were permitted. Further details are provided in version 3 of the protocol.
- As the blastic variant of mantle cell lymphoma is neither DLBCL nor NHL, this was removed as an exclusion criterion from the study.
- Patients receiving prior intrathecal methotrexate for CNS prophylaxis in DLBCL were not excluded.
- For study entry, patients had to have histologically confirmed, previously untreated CD20+ DLBCL or CD20+ follicular NHL Grade 1, 2, or 3a, according to the World Health Organization (WHO) classification system. The patient’s diagnosis was to be histologically confirmed prior to randomization. Clarification was provided that fine needle aspiration samples were not be used as the sole material for pathological diagnosis. Lymph node excision or adequate core biopsy was required for the diagnosis of DLBCL or follicular NHL.
- For assessment of hematologic function for study eligibility criteria, clarification was provided that transfusions were not permitted within 2 weeks prior to the start of study drug administration.
- The acceptable length of a cycle delay was increased from 10 days to 3 weeks, making it consistent with the 3-week window allowed for the treatment of toxicities and/or AEs.
- To allow investigators to decide how best to manage specific hematologic and nonhematologic AEs associated with rituximab-CHOP treatment, the protocol “guidelines” were changed to be considered as “recommendations.” Patient management decisions that did not adhere to these recommendations were no longer to be considered as major protocol violations.
- To comply with doxorubicin’s prescribing information, patients receiving rituximab- CHOP treatment who had a bilirubin value in the range of 20–50 µmol/L had their dose of doxorubicin reduced by 50%.
- Corticosteroids could now be given as part of premedication to reduce the incidence and severity of injection-related reactions.
- Clarification was provided that long-term treatment (>1 month) with intermittent corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of autoimmune conditions was permitted.

- To comply with the guidance given in the current rituximab SC Investigator's Brochure, patients were now to be observed for at least 15 minutes following rituximab SC administration. A longer period may have been appropriate in patients with an increased risk of hypersensitivity reactions.
- To conform to standards of clinical practice, patients with a high risk of CNS involvement could now receive prophylactic intrathecal methotrexate. Intrathecal methotrexate was to be administered according to local standards.
- To better follow clinical practice, patients were weighed prior to each treatment so that BSA could be recalculated if necessary. Cyclophosphamide, vincristine, doxorubicin, and bendamustine doses were to be recalculated only if the patient's weight changed by more than $\pm 10\%$ from baseline.
- It was clarified that non-investigational medicinal products given as part of the patient's chemotherapy must have been approved for this indication.
- Additional chemotherapy regimens of CHOP every 14 days $\times$ 8 cycles, CHOP every 28 days $\times$ 8 cycles, CVP every 21 days $\times$ 6 cycles, and CVP every 28 days $\times$ 6 cycles were now permitted.
- The wording about stability and storage of rituximab SC was updated according to the latest Investigator's Brochure.
- It was clarified that the end-of-treatment response assessment, including radiology and imaging report, must have been obtained 28 ($\pm$ 3) days after Day 1 of the last dose of induction treatment. The protocol previously stated that this must have been obtained between 4 and 8 weeks after Day 1 of the last treatment cycle, which was inconsistent with other parts of the protocol describing the final staging assessment.
- As some study sites were only able to perform an international normalized ratio test, coagulation tests were modified to include at least one of the following tests: international normalized ratio, prothrombin time, and activated partial thromboplastin time.
- Lactate dehydrogenase (LDH) was previously only required to be tested at screening. However, as normalization of LDH was part of the response assessment according to the International Working Group, patients with an abnormal LDH at screening also had LDH included as part of their interim and final staging assessments. In addition, patients with abnormal alkaline phosphatase, albumin, blood urea nitrogen, or C-reactive protein at screening had these tests repeated as part of their interim and final staging assessments.
- Neutrophil and lymphocyte counts were added to hematology tests to better monitor safety and to be consistent with other rituximab clinical trial protocols.
- It was clarified that it was acceptable for patients to have an MRI if they had a contraindication to CT scans (e.g., patients with contrast allergy or impaired renal clearance).
- It was clarified that CT scans of the pelvis need only be done if clinically indicated. CT scans of the neck, chest, and abdomen continued to be required for all study patients.
- To minimize discrepancy between the calculation of follow-up visit dates and CT scan intervals, the wording was modified to allow sites to follow the CT frequency according to local standard of care.
- The follow-up of patients after induction treatment occurred every 3 months ($\pm$ 2 weeks). It was clarified that the visit schedule would be calculated based on Visit 9.
- The wording around the timing of Visit 5 (interim staging) was clarified. All interim staging and Visit 5 must have occurred prior to Visit 6 (initiation of Cycle 5), regardless of whether the CHOP regimen was given every 14 or 21 days.
- To reduce redundant sampling, if Visit 5 (interim staging) was within 7 days of Visit 6 (initiation of Cycle 5), there was no need to collect the samples for Visit 6, i.e., only Visit 5 samples were to be collected and labeled as Visit 5.

- During the post-treatment follow-up (observation) period, laboratory assessments and physical examinations were performed only if clinically indicated.
- In the definition of DFS and PFS, it was clarified that in terms of the event (relapse, progression, or death as relevant), these outcomes were to be assessed based on the event that occurred first.
- The protocol wording was updated to reflect the latest Roche protocol template regarding the following:
 - If an adverse event worsened in severity and became serious.
 - If the electronic data capture system was not available and a pregnancy reporting form needed to be submitted.
- Investigators were to document and explain any protocol deviations.
- If a new anti-lymphoma treatment had been started, any response to therapy was documented in the electronic Case Report Form; however, it was clarified that response assessments were not specifically mandated by this study.
- After study closure initiation, unrelated AEs/SAEs occurring in an off-study patient who had started a new anti-cancer treatment did not need to be reported.
- Based on current recruitment rates, the study recruitment period was increased from 12 to 18 months, and the study duration was correspondingly adjusted from 3.5 to 4 years.

3. Study Results

Subject Population

The intent-to-treat (ITT) population was defined as all patients randomized into the study. The modified intent-to-treat (mITT) population, consisting of 645 patients (323 in Arm A and 322 in Arm B), was defined as all patients randomized into the study who received both routes of administration and completed the primary question in the PPQ at either Cycle 6 or Cycle 8. The safety population, consisting of 740 patients (371 in Arm A and 369 in Arm B), included all patients who received at least one dose of rituximab.

Table 2 Subject Population

	Arm A	Arm B	Total
Subjects randomized	372	371	743
Intent to treat population (ITT)	372	371	743
Modified intent to treat population (mITT)	323	322	645
Safety population	371	369	740

Arm A: Cycle 1 IV, Cycles 2-4 SC, Cycle 5-8 IV

Arm B: Cycle 1-4 IV, Cycles 5-8 SC

Source: FDA Analysis

Subject Disposition

Of subjects who received study treatment, 121 subjects discontinued study treatment as described in Table 3.

Table 3 Reasons for Treatment Discontinuation by Arm

	Arm A	Arm B	Total
Progression of disease	6	7	13
Stable Disease at interim staging	6	8	14
Adverse Event	25	27	52
Withdrew consent	12	9	21
Investigator request	7	6	13
Lack of compliance	3	1	4
Need for prohibited treatment	1	1	2
Lost to follow-up	0	1	1
Missing	0	1	1

Arm A: Cycle 1 IV, Cycles 2-4 SC, Cycle 5-8 IV

Arm B: Cycle 1-4 IV, Cycles 5-8 SC

Source: FDA Analysis

Demographics

Table 4 Demographics, ITT Population

	Arm A N=372 (%)	Arm B N=371 (%)	Total N=743 (%)
Age (years)			
Mean	58	59	59
Standard Deviation	13.2	12.6	12.9
Median	60	60	60
(Min, Max)	(18, 80)	(23, 80)	(18, 80)
Sex			
Male	185 (50)	190 (51)	375 (50)
Female	187 (50)	181 (49)	368 (50)
Race			
White	258 (69)	262 (71)	520 (70)
Black	1 (<1)	3 (<1)	4 (<1)
Asian	82 (22)	74 (20)	156 (21)
Other	24 (6)	25 (7)	49 (7)
Missing	7 (2)	7 (2)	14 (2)

Arm A: Cycle 1 IV, Cycles 2-4 SC, Cycle 5-8 IV

Arm B: Cycle 1-4 IV, Cycles 5-8 SC

Source: FDA Analysis

The PrefMab trial was conducted ex-US. The highest enrolling country was Germany (27%) followed by Italy (8%) and Australia (7%).

Table 5 Listing of Subjects by Country, ITT Population

Country	ITT population (N=743)	Proportion of ITT population %
Germany	201	27%
Italy	60	8%

Country	ITT population (N=743)	Proportion of ITT population %
Australia	49	7%
Korea	31	4%
Romania	31	4%
Thailand	30	4%
Brazil	26	3%
Indonesia	25	3%
Hungary	24	3%
Panama	22	3%
Canada	20	3%
Malaysia	20	3%
Philippines	18	2%
Sweden	18	2%
Taiwan	16	2%
Austria	15	2%
Turkey	15	2%
Denmark	13	2%
Netherlands	12	2%
El Salvador	11	1%
Argentina	10	1%
Chile	10	1%
Egypt	10	1%
Peru	10	1%
Portugal	10	1%
Guatemala	8	1%
Hong Kong	8	1%
Vietnam	6	1%
New Zealand	5	1%
Dominican Republic	4	1%
Colombia	3	<1%
Croatia	2	<1%

Source: FDA Analysis

Disease Characteristics

Table 6 Baseline Disease Characteristics by Lymphoma Type and Arm, ITT Population

	Arm A N=372 (%)	Arm B N=371 (%)	Total N=743 (%)
DLBCL	236 (63)	234 (63)	470 (63)
IPI Low	87 (23)	83 (22)	170 (23)
IPI Low Intermediate	65 (18)	67 (18)	132 (18)
IPI High Intermediate	53 (14)	49 (13)	102 (13)
IPI High	31 (8)	35 (10)	66 (9)
Follicular Lymphoma	136 (37)	137 (37)	273 (37)
FLIPI Low	29 (8)	33 (9)	62 (8)

	Arm A N=372 (%)	Arm B N=371 (%)	Total N=743 (%)
FLIPI Intermediate	50 (14)	51 (14)	101 (14)
FLIPI High	57 (15)	53 (14)	110 (15)

Arm A: Cycle 1 IV, Cycles 2-4 SC, Cycle 5-8 IV

Arm B: Cycle 1-4 IV, Cycles 5-8 SC

Source: FDA Analysis

Treatment Regimen

The majority of subjects in both arms received CHOP every 21 days for 8 cycles. The second most common regimen was CHOP every 21 days for 6 cycles; however as mentioned above, subjects who were to receive 6 cycles of chemotherapy received two additional doses of rituximab monotherapy to complete a total of 8 cycles of rituximab therapy.

Table 7 Treatment Regimen by Arm, ITT Population

	Arm A N=372 (%)	Arm B N=371 (%)	Total N=743 (%)
CHOP-21 x 8	143 (39)	139 (37)	282 (38)
CHOP-21 x 6	111 (30)	117 (32)	228 (30)
Bendamustine-28 x 6	52 (14)	50 (14)	102 (14)
CHOP-14 x 6	26 (7)	23 (6)	49 (7)
CVP-21 x 8	20 (5)	19 (5)	39 (5)
Bendamustine-28 x 8	8 (2)	11 (3)	19 (3)
Other*	12 (3)	12 (3)	24 (3)

*Other includes CVP-21 x 6, CHOP-14 x 8, CHOP-28 x 8, Bendamustine-21 x 8, Bendamustine-21 x6, CVP-21 x 3 + CHOP-21 x 3, CVP-28 x 6

Arm A: Cycle 1 IV, Cycles 2-4 SC, Cycle 5-8 IV

Arm B: Cycle 1-4 IV, Cycles 5-8 SC

Source: FDA Analysis

Preference Results

The PPQ was administered after Cycle 6 and 8. Cycle 6 was administered to 653 subjects, and 620 subjects completed the PPQ. The following table summarizes preferences at Cycle 6.

Table 8 Rituximab Administration Preference after Cycle 6

	Arm A N=328 (%)	Arm B N=325 (%)	Total N=653 (%)
Preference for SC	246 (75)	249 (77)	495 (76)
95% CI	70.0, 79.4	71.7, 80.9	72.4, 78.9
Strength of Preference			
Very strong	121 (37)	103 (32)	224 (34)
Fairly strong	105 (32)	108 (33)	213 (33)
Not very strong	19 (6)	38 (12)	57 (9)
Patient did not answer	1 (<1)	0 (0)	1 (<1)
Reason for preference			

	Arm A N=328 (%)	Arm B N=325 (%)	Total N=653 (%)
Requires less time in the clinic	219 (67)	205 (63)	424 (65)
Feels more comfortable during administration	118 (36)	113 (35)	231 (35)
Feels less emotionally distressing	87 (27)	85 (26)	172 (26)
Lower level of injection site pain	35 (11)	52 (16)	87 (13)
Other: Fewer side effects*	4 (1)	1 (<1)	5 (1)
Preference for IV	33 (10)	29 (9)	62 (10)
Strength of Preference			
Very strong	7 (2)	10 (3)	17 (3)
Fairly strong	18 (6)	14 (4)	32 (5)
Not very strong	8 (3)	5 (2)	13 (2)
Patient did not answer	0 (0)	0 (0)	0 (0)
Reason for preference			
Feels more comfortable during administration	20 (6)	19 (6)	39 (6)
Feels less emotionally distressing	19 (6)	17 (5)	36 (6)
Lower level of injection site pain	14 (5)	8 (3)	22 (4)
Requires less time in the clinic	8 (3)	0 (0)	8 (1)
Other: Fewer side effects*	1 (<1)	4 (1)	5 (1)
No Preference	32 (10)	31 (10)	63 (10)
Did not state a preference	17 (5)	16 (5)	33 (5)

* Subjects who stated fewer side effects could have stated this generally or named a specific side effect.

Arm A: Cycle 1 IV, Cycles 2-4 SC, Cycles 5-8 IV

Arm B: Cycle 1-4 IV, Cycles 5-8 SC

Source: FDA Analysis

After Cycle 8, 591 subjects completed the PPQ. Table 9 summarizes preferences at Cycle 8.

Table 9 Rituximab Administration Preference after Cycle 8

	Arm A N=311 (%)	Arm B N=309 (%)	Total N=620 (%)
Preference for SC	226 (73)	251 (81)	477 (77)
95% CI	67.4, 77.3	76.5, 85.2	73.5, 80.0
Strength of Preference			
Very strong	117 (38)	115 (37)	232 (37)
Fairly strong	92 (30)	111 (36)	203 (33)
Not very strong	16 (6)	25 (8)	41 (7)
Patient did not answer	1 (<1)	0 (0)	1 (<1)
Reason for preference			
Requires less time in the clinic	205 (66)	205 (66)	410 (66)
Feels more comfortable during administration	98 (32)	120 (39)	218 (35)
Feels less emotionally distressing	82 (26)	91 (29)	173 (28)
Lower level of injection site pain	40 (13)	52 (17)	92 (15)
Other: Fewer side effects*	3 (1)	4 (1)	7 (1)
Preference for IV	37 (12)	29 (9)	66 (11)
Strength of Preference			
Very strong	7 (2)	15 (5)	22 (4)

	Arm A N=311 (%)	Arm B N=309 (%)	Total N=620 (%)
Fairly strong	15 (5)	7 (2)	22 (4)
Not very strong	15 (5)	6 (2)	21 (4)
Patient did not answer	0 (0)	1 (<1)	1 (<1)
Reason for preference			
Feels more comfortable during administration	25 (8)	19 (6)	44 (7)
Lower level of injection site pain	18 (6)	14 (5)	32 (5)
Feels less emotionally distressing	16 (6)	15 (5)	31 (5)
Requires less time in the clinic	3 (1)	4 (1)	7 (1)
Other: Fewer side effects*	1 (<1)	3 (1)	4 (<1)
No Preference	30 (10)	18 (6)	48 (8)
Did not state a preference	18 (6)	11 (4)	29 (5)

* Subjects who stated fewer side effects could have stated this generally or named a specific side effect.

Arm A: Cycle 1 IV, Cycles 2-4 SC, Cycle 5-8 IV

Arm B: Cycle 1-4 IV, Cycles 5-8 SC

Source: FDA Analysis

Of the 495 subjects who had a preference for rituximab SC at Cycle 6, 296 (60%) had DLBCL and 199 (40%) had follicular NHL. Of the 477 who had a preference for rituximab SC at Cycle 8, 286 (60%) had DLBCL and 191(40%) had follicular NHL.

Retention of Preference between Cycle 6 and Cycle 8

In the population of subjects who completed PPQ question 1 in both Cycle 6 and 8 (n=566), 471 patients (83%) retained their preference between Cycle 6 and 8. Of the subjects who changed their preference between Cycle 6 and 8 (n=95), the majority changed from “no preference” to SC (27 subjects). A similar number of subjects changed their preference from IV to SC (16 subjects) and SC to IV (18 subjects) between Cycle 6 and 8.

Missing Preference Data

Cycle 6 was administered to 653 subjects, and Cycle 8 was administered to 620 subjects. Per Table 8 and Table 9, 620 and 591 subjects completed the PPQ in Cycle 6 and 8, respectively. Missing preference data is defined as the population of subjects who received rituximab but did not complete the PPQ. Using this definition, 5% of subjects at Cycle 6 and 8 received rituximab but did not complete the PPQ.

Reviewer comment: The PPQ had a high completion rate at both Cycle 6 and 8. The breakdown of patients who preferred SC was similar to the distribution in the ITT population as a whole (DLBCL 63%, follicular NHL 37%); therefore, preference was unlikely to be influenced by disease subtype. In general, the retention of preference between Cycle 6 and 8 was high. For those subjects who made a change in preference between Cycle 6 and 8, the majority moved toward a preference for SC.

Satisfaction Results

Refer to the Clinical Outcomes Assessment (COA) staff review for a description of the satisfaction questionnaire domains, how the satisfaction questionnaires were scored, and an analysis of the content validity of the satisfaction instruments. Refer to Table 1 in this review for a summary of each instrument.

RASQ Results

The RASQ favored the SC method of administration in four out of five domains: psychological impact, impact on activities of daily living (ADLs), convenience, and satisfaction. Table 10 describes the RASQ results.

Table 10 Summary of RASQ Results by Domain

Domain	RASQ Score after IV n=743 (SD)	RASQ score after SC n=687 (SD)
Physical Impact	82 (15.6)	82 (15.9)
Psychological Impact	78 (16.4)	84 (14.4)
Impact on ADLs	58 (25.2)	84 (16.5)
Convenience	59 (20.8)	81 (13.1)
Satisfaction	75 (19.4)	87 (15.0)

Note: The population is different between IV and SC, as all subjects received IV, but there was a proportion of subjects who did not receive SC. These were subjects who discontinued therapy due to disease progression, AE, etc. prior to Cycle 2 of arm A or Cycle 5 of arm B. See Table 3 for subject disposition.

Source: FDA Analysis

In response to RASQ question 18, “If given the option, which would you prefer?” (IV administration, SC injection, or no preference), a similar percentage of patients favored SC injections regardless of the route of administration they had initially received: 82% preferred SC after an SC injection and 78% preferred SC after an IV infusion.

Reviewer comment: The RASQ was administered immediately after Cycle 4 and 8. The following are sample questions from the RASQ:

6. When you receive the Rituximab IV infusion do you worry that your condition would get worse?	Not at all	A little bit	Somewhat	Quite a bit	Very much
7. When you receive the Rituximab IV infusion do you feel anxious thinking about your disease?	Not at all	A little bit	Somewhat	Quite a bit	Very much
8. Thinking about the Rituximab IV infusion, how confident are you that the Rituximab IV infusion is treating your disease?	Not at all	A little bit	Somewhat	Quite a bit	Very much

Source: PrefMab protocol v3

Isolating the effect of rituximab in the treatment of the disease may have been difficult because all subjects were receiving other therapies in addition to rituximab (CHOP, CVP, or Bendamustine). Therefore, querying subjects regarding their satisfaction with rituximab IV versus SC may have been confounded by the other chemotherapies being administered and may have been influenced by what the practitioner had told the subject about their disease. Although subjects were relatively balanced in terms of disease subtype and severity, controlling for how subjects were educated and their level of understanding of the disease would have been difficult.

CTSQ Results

The CTSQ results were similar between IV and SC administration methods in all domains. Table 11 describes the CTSQ results.

Table 11 Summary of CTSQ Results by Domain

Domain	CTSQ Score after IV n=743 (SD)	CTSQ Score after SC n=687 (SD)
Expectation of therapy	81 (18.3)	82 (17.9)
Feelings about side effects	61 (22.3)	62 (22.3)
Satisfaction with therapy	85 (12.2)	85 (11.3)

Note: The population is different between IV and SC, as all subjects received IV, but there was a proportion of subjects who did not receive SC. These were subjects who discontinued therapy due to disease progression, AE, etc. prior to Cycle 2 of arm A or Cycle 5 of arm B. See Table 3 for subject disposition.

Source: FDA Analysis

Reviewer comment: *The CTSQ was not modified for the purpose of comparing rituximab IV versus rituximab SC. The majority of the questions stated “(IV/pills)” as the description of the treatment in question. For example, question 14 of the CTSQ asked the following:*

14. How satisfied were you with the **form** of your cancer therapy (IV/pills)?

☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

Source: PrefMab protocol v3, page 122

The wording of the CTSQ questions may have confused subjects, as they were being asked regarding their satisfaction of a subcutaneously administered therapy. As with the RASQ, the CTSQ was not designed to isolate satisfaction with individual elements of a chemotherapy regimen. The CTSQ asked the following question:

13. **Overall**, were the **side effects** of cancer therapy (IV/pills) as you expected?

☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Much better than I expected	Somewhat better than I expected	Exactly as I expected	Somewhat worse than I expected	Much worse than I expected

Source: PrefMab protocol v3, page 122

Subjects received rituximab on the same day as other intravenous chemotherapy agents with overlapping toxicities. Querying subjects regarding side effects in the manner specified in question 13 of the CTSQ incorrectly assumes subjects will be able to isolate the side effects attributable solely to rituximab.

Clinical Efficacy

Refer to the statistical review by Jingjing Ye for an analysis of the efficacy endpoints in this trial.

Safety

The rate of adverse events was similar comparing IV and SC rituximab. Any grade TEAE was similar between arms: 642 of 740 subjects who received rituximab IV had a TEAE. Similarly, 530 of 687 subjects who received rituximab SC had a TEAE. The rate of TEAEs by system organ class and preferred terms was similar between administration methods. Grade 3 or greater TEAEs occurred in 268 of 740 subjects (36%) receiving rituximab IV versus 185 of 687 subjects (26%) receiving rituximab SC.

The applicant performed an analysis of safety events between arms which are summarized in Table 12.

Table 12 Summary of Adverse Events between Arms

Events (n [%])	Arm A n=371	Arm B n=369	Total N=740
Any TEAE	344 (92.7)	340 (92.1)	684 (92.4)
Any SAE	126 (34.0)	118 (32.0)	244 (33.0)
Any related TEAE	206 (55.5)	215 (58.3)	421 (56.9)
Any TEAE of ≥Grade 3	173 (46.6)	186 (50.4)	359 (48.5)
TEAEs leading to death	8 (2.2%)	9 (2.4%)	17 (2.3%)
Discontinuations due to AE	34 (7.3)	17 (6.2)	51 (6.9)

AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Source: PrefMab CSR, Table 5, page 50

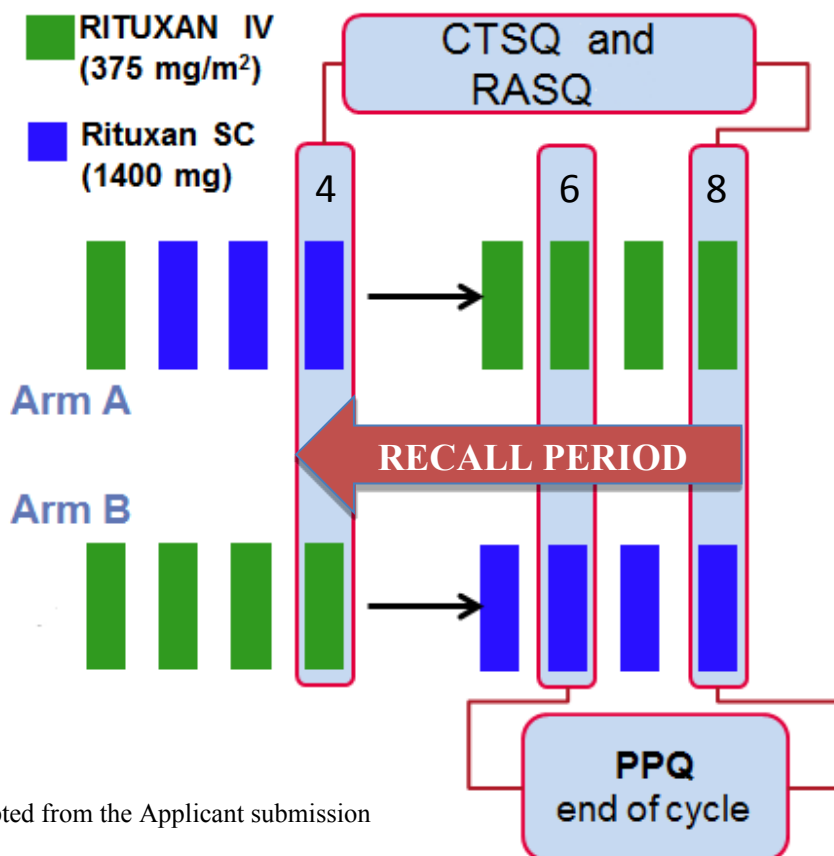
Reviewer comment: *The incidence of adverse events was similar between administration methods and treatment arms.*

4. Discussion

Overall, the study design was appropriate for evaluating patient preference and the strength of the data for the PPQ analysis is supportive of inclusion in the USPI.

One limitation in the design of PrefMab was the long recall period. Subjects were asked to compare the current method of administration to the method they last received four cycles prior. Depending on the type of chemotherapy regimen, the recall period between the end of Cycle 8 and the beginning of Cycle 4 could be up to 5 months (e.g., R-Bendamustine x 28 day cycle). Although the recall period between Cycle 4 and 8 is long, the similar results seen at Cycle 6 and the strong retention of preference between Cycle 6 and 8 help mitigate concerns with the length of the recall period.

Figure 2 Recall Period



Source: Adapted from the Applicant submission

Strengths of the PrefMab study include a high completion rate of the patient preference instruments and a large sample size. In terms of preference, a similar high rate of preference for rituximab SC was noted at multiple time points using the PPQ. This preference was corroborated by the results of question 18 of the RASQ which also demonstrated a preference for rituximab SC.

The results of question 3 of the PPQ (reasons for why subjects had a preference) are reasonable to include in labeling, as based on examination of the “other” responses, there was adequate saturation of potential reasons why subjects had a preference.

The CTSQ and RASQ had disparate results despite overlap of content and timing. There are multiple reasons why the results of these satisfaction questionnaires cannot be clearly interpreted, including presence of vague and misleading questions. Furthermore, satisfaction is difficult to gauge in the context of multi-agent chemotherapy in the setting of a life threatening disease.

Advisory Committee

This application was discussed at an Oncology Drugs Advisory Committee (ODAC). The topics discussed were the PK bridging study, relative safety of rituximab/hyaluronidase, and the patient preference data. The ODAC members voted 11-0 “Yes” to the following question:

Patient Preference and Patient Reported Outcomes Review

Vishal Bhatnagar, MD

BLA 761064

Rituxan Hycela (rituximab/hyaluronidase)

“Does the committee consider that efficacy and safety have been established for rituximab and hyaluronidase administered subcutaneously for the same oncologic indications as Rituxan (rituximab IV)?”

Labeling Recommendation

This reviewer recommends inclusion of the PPQ results, inclusive of preferences for SC, IV and no preference in section 14 of the rituximab SC USPI. This reviewer also recommends exclusion of the RASQ and CTSQ results in section 14, for the reasons described above.

References:

Theodore-Oklota C, Humphrey L, Wiesner C, Schnetzler G, Hudgens S, Campbell A. Validation of a treatment satisfaction questionnaire in non-Hodgkin lymphoma: assessing the change from intravenous to subcutaneous administration of rituximab. *Patient Preference and Adherence*. 2016;10:1767–1776.

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/s/

VISHAL BHATNAGAR
05/17/2017

ROMEO A DE CLARO
05/18/2017

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

Template version: January 05, 2017

COA CONSULT TRACKING NUMBER	AT 2016-211
BLA NUMBER	761064
REFERENCED IND FOR NDA/BLA	Pre-IND 126650
ESTABLISHED NAME/TRADE NAME	Rituximab and hyaluronidase
APPLICANT	Genentech
INDICATION	Treatment of follicular lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia
SUBMISSION NUMBER	1
PDUFA GOAL DATE	June 26, 2017
DATE OF CONSULT REQUEST	October 11, 2016
REVIEW COMPLETION DATE	February 22, 2017
REVIEW DIVISION	Division of Hematology Products (DHP)
MEDICAL REVIEWER/TEAM LEADER (TL)	Alexandria Schwarsin, MD, Clinical Reviewer Vishal Bhatnagar, MD, DHP PRO Reviewer
REVIEW DIVISION PM	Laura Wall
COA REVIEWER	Nikunj B. Patel, PharmD
COA TL	Selena Daniels, PharmD, MS
ASSOCIATE DIRECTOR, COA STAFF	Elektra J. Papadopoulos, MD, MPH
INSTRUMENT(S)	1. Patient Preference Questionnaire 2. Rituximab Administration Satisfaction Questionnaire 3. Cancer Therapy Satisfaction Questionnaire
COA TYPE	Patient-Reported Outcome
ENDPOINT(S) CONCEPT(S)	Treatment (method of administration) preference, satisfaction, and impacts
INTENDED POPULATION(S)	Adult patients (≥ 18 years) with follicular lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia
<i>Please check all that apply:</i>	☐ Rare Disease/Orphan Designation ☐ Pediatric

Clinical Outcome Assessment Review

Nikunj B. Patel, PharmD

BLA 761064

Rituximab and hyaluronidase subcutaneous injection

PPQ; RASQ; CTSQ; (treatment preference, satisfaction, and impacts)

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Hematology Products (DHP) regarding BLA 761064. The Applicant completed five pivotal clinical trials outside the United States (U.S.) to support the approval of rituximab and hyaluronidase subcutaneous injection. The proposed indication is treatment of follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia in adult patients (≥ 18 years). The Applicant implemented the following instruments to assess treatment (method of administration) preference, satisfaction, and impacts in their phase 3b patient preference study (PrefMab; MO28457):

Instrument	Concept(s)	Endpoint ¹	Copy of Instrument
Patient Preference Questionnaire (PPQ) Question 1	Treatment preference	Primary	Appendix A
Rituximab Administration Satisfaction Questionnaire (RASQ)	Treatment satisfaction; Treatment impacts	Secondary	Appendices B and C
Cancer Therapy Satisfaction Questionnaire (CTSQ)	Treatment satisfaction	Secondary	Appendix D

The DHP requested COA Staff input on the validity of the PPQ, RASQ, and CTSQ and the appropriateness of proposed labeling claims. The subject of this review was restricted to the aforementioned instruments and not the pharmacoeconomic and health-care professional reported outcomes. The select proposed targeted labeling claims are²:

(b) (4)

The intended use of the PPQ is to assess treatment preference rather than a health outcome. As such, it is not a patient-reported outcome (PRO) instrument and the review criteria for this instrument were not the same as would be required for PRO instruments (e.g., RASQ and CTSQ). Instead, the review focused on whether the PPQ was fit-for-purpose in the context of the clinical development program to assess patient preference of a method administration in the clinical trial.

The review concludes the following:

Patient Preference: Based on review of face validity and supportive evidence submitted by the Applicant, the PPQ Question 1 (pre-specified primary endpoint) appears to be fit-for-purpose to

¹ Please see Section C 1.3 for a select list of efficacy endpoints.

² Refer to Section C 1.4 of this review for complete labeling language for the PPQ, RASQ, and CTSQ instruments.

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PPQ; RASQ; CTSQ; (treatment preference, satisfaction, and impacts)

assess patient preference for method of treatment administration (subcutaneous versus intravenous) without labeling implications (e.g., false or misleading claims) despite being developed for the context of use in breast cancer patients. However, because there is no evidence to support U.S. patients would have the same treatment preference, it will be important to caveat that this data is from patients outside the U.S., if it is decided to describe these data in product labeling. Additionally, there are concerns regarding labeling data from PPQ Question 3, as it was not a pre-specified endpoint and may not provide a balanced description of both methods of administration, which could potentially generate misleading conclusions. For example, the data may suggest that one method is less painful than the other is; however, pain was not assessed as a study endpoint.

Ultimately, COA Staff defers to the Clinical and Statistical reviewers whether the study design is appropriate to evaluate patient preference and the Division whether the data can be supportive of labeling claims. As the targeted labeling claims are non-clinical claims (patient preference), it is advised that you also seek input from the Labeling Development Team and Office of Prescription Drug Promotion.

Patient Satisfaction: Due to limited evidence submitted by the Applicant to support the content validity of the RASQ and CTSQ instruments, it cannot be determined whether the instruments are adequate to measure treatment satisfaction and impacts for this context of use. For example, the RASQ and CTSQ instruments assessed broad and ambiguous concepts (e.g., how “worthwhile” was the treatment) with lengthy recall period (e.g., 4 weeks). Furthermore, the CTSQ instrument was developed based on input from different patient populations (breast, colorectal, lung and melanoma cancer patients). Additionally, the use of “pill/IV” parenthetical throughout the instrument is problematic as the intended purpose of CTSQ in the PrefMab study was to assess patient’s experience related to SC versus IV treatment options.

Satisfaction is a complex, multidimensional concept and can include multiple components as evidenced by the qualitative data provided for the RASQ. Qualitative interviews demonstrated that patients considered a variety of elements while rating their overall satisfaction on the method of administration (e.g., improved health; treatment administration; absence or presence of side effects; etc) and there was inter-patient variability in these considerations.

Based on the abovementioned concerns, the PRO data from the RASQ and CTSQ instruments may be difficult to interpret or describe clinical benefits without labeling implications. Nonetheless, COA Staff defers to the Division regarding whether the treatment satisfaction concept is acceptable for labeling claims.

B. BACKGROUND

The Applicant (Genentech) submitted the Biologics License Application (BLA 761064) rituximab and hyaluronidase subcutaneous injection solution, a co-formulation of rituximab and hyaluronidase, for treatment of patients with follicular lymphoma (FL), diffuse large B-cell

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lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL). FDA approved the RITUXAN® (rituximab) intravenous (IV) infusion formulation in 1997 (BLA 103705).

The Applicant completed five clinical trials (SABRINA, MabEase, SAWYER, PrefMab, and SparkThera) outside the United States to support the BLA 761064. The Applicant developed rituximab and hyaluronidase solution for subcutaneous injections to provide an alternative to the established RITUXAN (rituximab) IV for infusion formulation for patients and clinicians.

The Division of Hematology Products (DHP) requested Clinical Outcome Assessments (COA) Staff advice regarding instruments used to collect patient preference and patient-reported outcome (PRO) data in the PrefMab study (MO28457). The Division requested COA Staff input on (1) the validity of Patient Preference Questionnaire (PPQ), Rituximab Administration Satisfaction Questionnaire (RASQ-SC and RASQ-IV), Cancer Therapy Satisfaction Questionnaire (CTSQ), and (2) appropriateness of including labeling claims based on these instruments.

Materials reviewed:

- BLA 761064 Documents
 - o Draft Labeling Text (eCTD Section 1.14.1.3)
 - o Clinical Overview (eCTD Section 2.5)
 - o Clinical Study Report - PrefMab MO28457 (eCTD Section 5.3.5.1 NHL)
- BLA 761064 Information Request (eCTD Section 1.11.3; January 30, 2017)

eCTD=Electronic Common Technical Document

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

1.1 Clinical Trial Population

PrefMab Study (MO28457): The PrefMab study included previously untreated patients with CD20-positive diffuse large B-cell lymphoma (DLBCL) or CD20-positive follicular non-Hodgkin's lymphoma (FL) grades 1, 2, or 3a.

Select Inclusion Criteria:

- Aged 18-80 years
- Histologically confirmed, previously untreated CD20-positive DLBCL or CD20-positive follicular non-Hodgkin's lymphoma of grades 1, 2, or 3a according to the World Health Organization (WHO) classification system
- Eastern Cooperative Oncology Group (ECOG) performance states of ≤ 2

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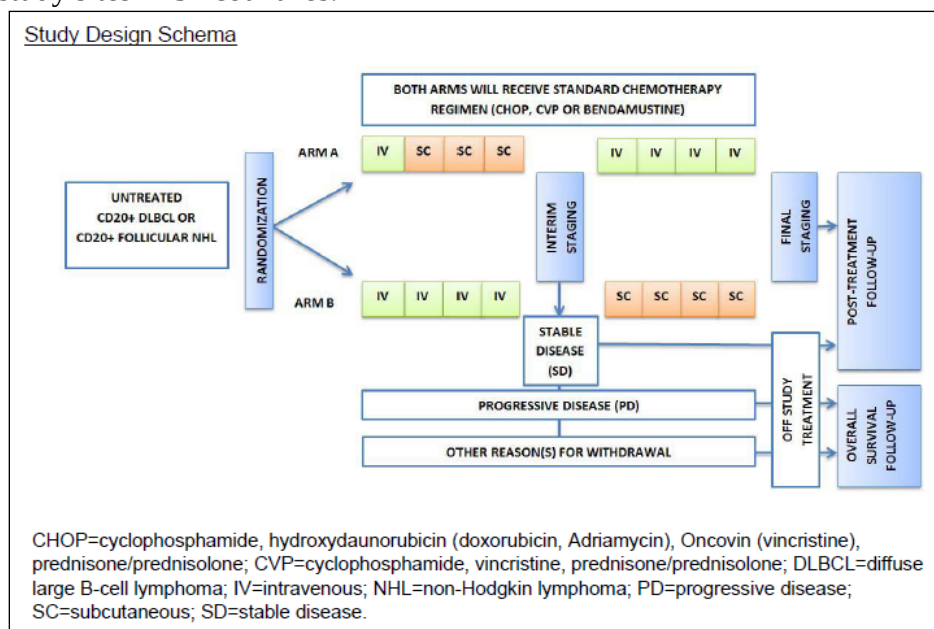
Select Exclusion Criteria:

- Transformed lymphoma or FL 3b
- Primary CNS lymphoma, histologic evidence of transformation to a Burkitt lymphoma, primary mediastinal DLBCL, primary effusion lymphoma, primary cutaneous DLBCL or primary DLBCL of the testis

Please refer to the Clinical review and clinical study reports for complete list of study inclusion and exclusion criteria.

1.2 Clinical Trial Design

PrefMab Study (MO28457): This was an ex-United States, phase 3b, prospective, multi-center, multinational, open-label, cross-over randomized study to evaluate patient preference with subcutaneous (SC)- versus intravenous (IV)-administered rituximab in combination with chemotherapy in previously untreated patients with CD20-positive diffuse large B-cell lymphoma (DLBCL) or CD20-positive follicular non-Hodgkin's lymphoma (FL) of grades 1, 2, or 3a. Patients were randomized at a 1:1 ratio to one of the two treatment arms with different treatment sequences. The Applicant randomized 743 patients (372 in Arm A and 371 in Arm B) across 201 study sites in 32 countries.



The Clinical review provides further details regarding the PrefMab study design. Refer to the PrefMab (MO28457) Clinical Study Report in the BLA 761064 eCTD Section 5.3.5.1 for complete overview of the clinical development program.

***Reviewer Comments:** The open-label study design is not an issue in the context of this study to assess patient preference using the PPQ.*

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PPQ; RASQ; CTSQ; (treatment preference, satisfaction, and impacts)

1.3 Endpoint Hierarchy and Definition

The table below describes select efficacy endpoints included in the PrefMab study.

Concept	Endpoint	Assessment
Primary Endpoint		
Patient preference	Proportion of patients who preferred rituximab SC over rituximab IV	PPQ Question 1
Secondary Endpoints		
Treatment satisfaction	Patient-assessed satisfaction and convenience	CTSQ
Treatment (administration) satisfaction	Patient-assessed satisfaction and convenience	RASQ
Efficacy	Time-to-event endpoints (Event-free Survival, Disease-free Survival, Progression-free Survival, and Overall Survival),	--

Please refer to the PrefMab (MO28457) Clinical Study Report to the BLA 761064 eCTD Section 5.3.5.1 NHL and the corresponding Clinical review for a complete list of study endpoints (efficacy and safety).

Reviewer Comments: The applicant did not specify PPQ Question 2 and Question 3 analyses in the Statistical Analysis Plan (SAP). Additionally, the SAP stated that there were no formal statistical hypothesis tests performed for any of the endpoints.

1.4 Labeling or promotional claim(s) based on the COA

The Applicant proposed the following labeling claims in the Section 14.4 of the package insert based on the PPQ, RASQ, and CTSQ instruments in the PrefMab study:

(b) (4)

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(b) (4)

Refer to the BLA 761064 eCTD Section 1.14.1.3 for complete labeling text.

Reviewer Comments: Labeling claims based on PPQ Question 1 may be reasonable. However, labeling claims based on PPQ Questions 2-3, RASQ, and CTSQ may not be appropriate because inadequate evidence provided to support content validity (See Section C 4). There is concern that patients may not have understood and interpreted the items of these instruments consistently. This reviewer defers to the Division on acceptability of the proposed labeling claims.

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the instruments are summarized below within the assessment's conceptual frameworks. (Note: The conceptual frameworks for the PPQ and CTSQ were constructed based off the copies of the assessments submitted by the Applicant)

The table below (created by this reviewer) shows the PPQ conceptual framework.

Items	Domain	General Concept
1. All things considered which method of administration did you prefer?	Patient preference for method of administration	Treatment (method of administration) preference
2. How strong is this preference	Strength of preference for method of administration	
3. What are the two main reasons for your preference?	Reasons for preferred method of administration	

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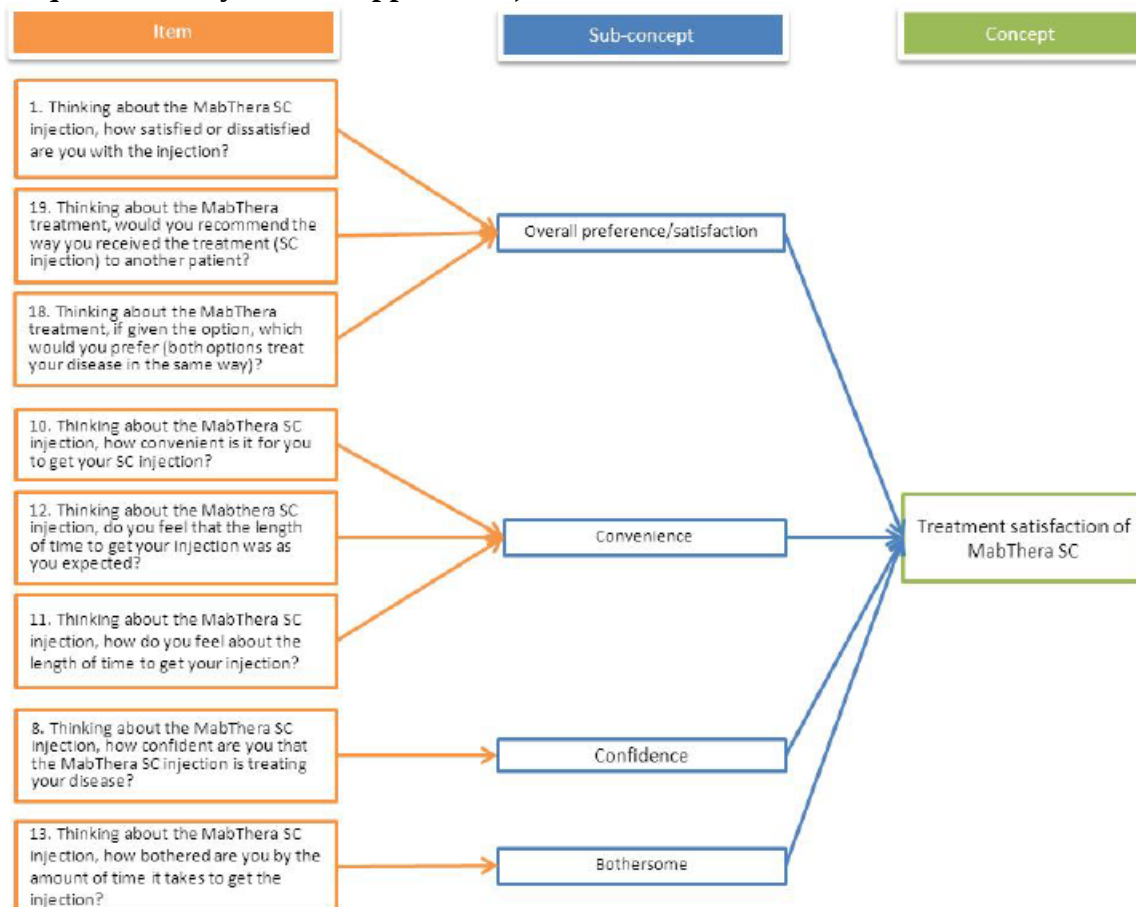
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The figure below shows the RASQ-SC conceptual framework³ (Source: FDA Information Request January 30, 2017, pp254-256).



³ The RASQ-IV conceptual framework was nearly identical to the RASQ-SC; therefore, RASQ-IV conceptual framework is not included in this section.

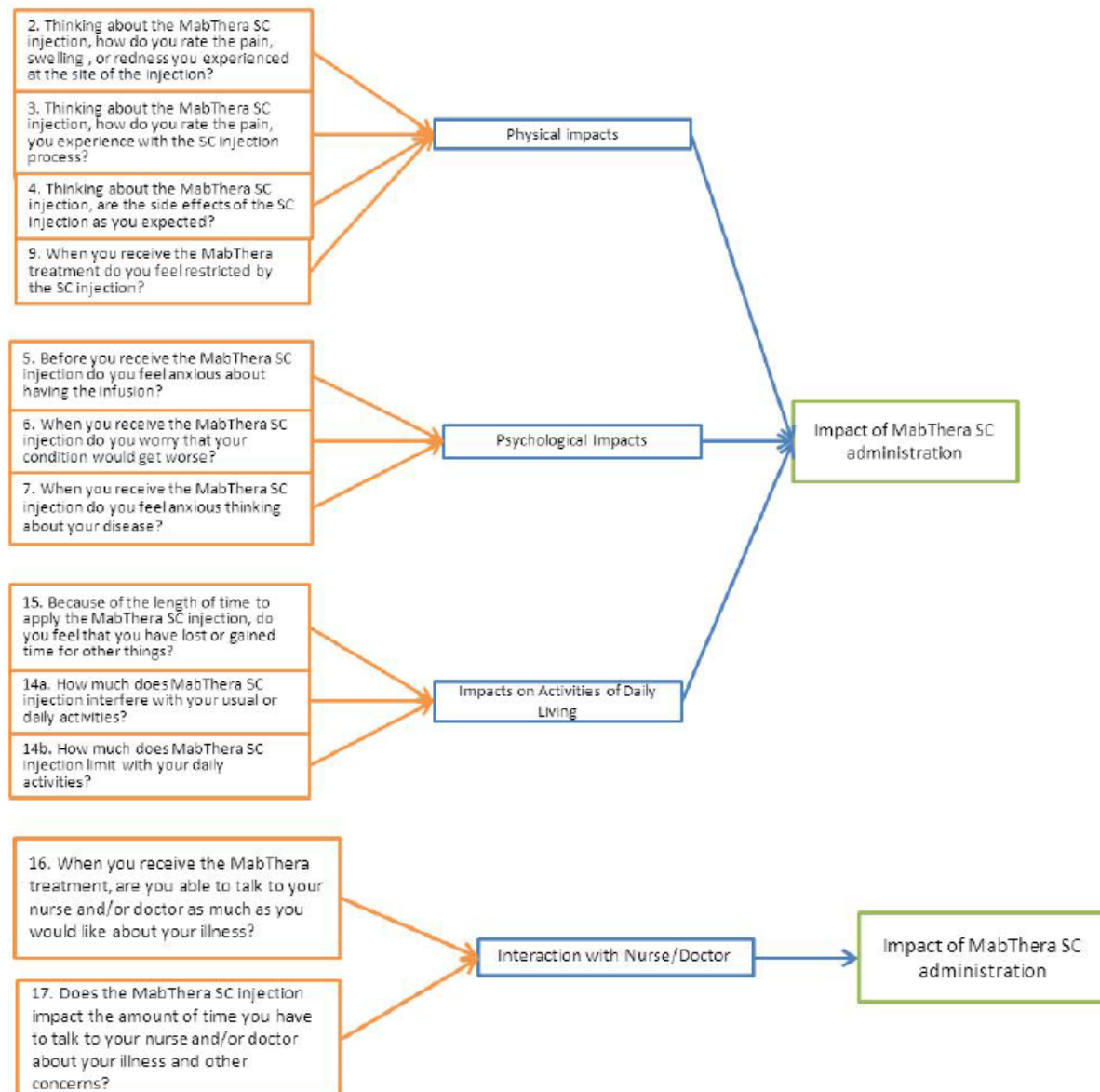
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The table below (created by this reviewer) shows 16-item CTSQ conceptual framework (Source: Trask et al, 2008)⁴

Items	Domain	General Concept
Items 1, 2, 3, 4, and 8	Expectations of Therapy	Cancer Therapy Satisfaction
Items 5, 6, 11, and 13	Feelings about Side Effects	
Items 7, 9, 10, 12, 14, 15, and 16	Satisfaction with Therapy	

3 CLINICAL OUTCOME ASSESSMENT(S)

Instruments:

- Patient Preference Questionnaire (PPQ): The PPQ is a 3-item instrument designed to measure patients' preference for a method of treatment administration (subcutaneous (SC) versus intravenous (IV)). The response scale varies for each question. The first question inquires about the preferred method of administration with the following responses: SC, IV, or no preference. The other two questions ask patients about the strength of preference (response options ranging from 'very strong' to not 'very strong') and rationale for their preferred method of administration (response options include a checklist of specific reasons including an 'other' option). Items are assessed without the use of a specific recall period; however, the respondents are asked to reflect on their experience with both methods of administration (IV or SC) and preference when completing the instrument. Please see Appendix A for a copy of the instrument.
- Rituximab Administration Satisfaction Questionnaire (RASQ): The RASQ is a 20-item PRO instrument designed to measure "treatment satisfaction" (covering subconcepts of "overall preference/satisfaction", "convenience", "confidence", and "bothersomeness") and "impact of treatment administration" (covering subconcepts of "physical impact", "psychological impact", "impact on activities of daily life", and "impact on the interaction with health care providers"). The Applicant utilized two similar versions of the RASQ for each method of administration (RASQ-IV and RASQ-SC) in the PrefMab study. Sixteen items were rated on a 5-point verbal rating scale, two items were rated on a 3-point verbal rating scale, and one Yes/No item. Each item was assessed with a recall period based on the recall of their most recent SC or IV administration. Please see Appendices B (RASQ-SC) and C (RASQ-IV) for copies of the instruments.
- Cancer Therapy Satisfaction Questionnaire (CTSQ): The CTSQ is a 16-item PRO instrument designed to measure treatment satisfaction in individuals with cancer. The CTSQ is comprised of three domains related to patients' satisfaction with cancer therapy: expectations of therapy (five items), feelings about side effects (four items), and satisfaction with therapy (seven items). Each item is rated on a 5-point verbal rating

⁴Task el al. developed the 21-item CTSQ instrument to assess cancer therapy expectations and satisfaction. The applicant (Genentech) modified the 21-item CTSQ to 16-item CTSQ after removing five items. The PrefMab study implemented the modified version (16-item CTSQ instrument) to assess cancer therapy expectations and satisfaction.

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PPQ; RASQ; CTSQ; (treatment preference, satisfaction, and impacts)

scale and assessed with a recall period of 4 weeks. Please see Appendix D for a copy of the instrument.

Prior versions: This submission did not include any prior versions of the PPQ, RASQ, and CTSQ instruments. The PPQ instrument was a modified version of a similar instrument (Patient Interview Schedules 2 or PINT2) used in the PrefHer study (NCT01401166)⁵ to evaluate preference of either IV or SC trastuzumab administration in adult breast cancer patients.

User manuals: There are no existing user manuals for the corresponding instruments.

Timing, data collection method, and mode of administration: The PPQ was self-administered in the PrefMab study and completed following rituximab therapy in cycles 6 and 8. The RASQ and CTSQ instruments were self-administered in cycles 4 and 8. The CTSQ was completed prior to rituximab administration, whereas the RASQ was completed immediately after rituximab administration and before chemotherapy administration. All instruments used paper or pen method.

Scoring algorithm:

PPQ Scoring: The PPQ instrument is consisted of categorical and verbal rating scale response options. The results for the PPQ were described by item distribution by categories of response for each item.

RASQ Scoring: The RASQ instruments were scored according to a scoring algorithm provided by the Theodore-Oklotka et al. (2016) publication. Scoring is completed by summing each of the five domains: physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction (most items offered five response options) where higher scores are more positive.

CTSQ Scoring: The modified CTSQ instrument was scored according to the algorithm published in Trask et al (2008) paper. All items were scored on a 1-5 scale, with a value of 1 associated with the worst response and a value of 5 representing the best response. Four of the items (Q5, Q6, Q9, and Q11) were reverse-coded.

For each domain, if the number of completed items is greater than or equal to the pre-specified minimum number (3 out of 5 for expectation of therapy domain; 4 out of 4 for feelings about side effects domain; and 5 out of 7 for satisfaction with therapy domain), the domain will be scored using the formula: Domain score = [(Sum of completed

⁵ The PrefHer study was an international, open-label, randomized study (NCT01401166) with a cross-over design in women with HER2 positive primary breast adenocarcinoma, assessing preference for either intravenous (IV) or subcutaneous (SC) delivery of trastuzumab.

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item responses / Number of completed items) - 1] x 100 / (Maximum possible item response value – Minimum possible item response value).

However, if fewer items are completed than the minimum number indicated above, then the domain will not be scored (i.e. a missing value is assigned). Since the maximum possible item response value is 5 and the minimum possible response value is 1 for all CTSQ items, a simpler way to represent the above formula for the CTSQ domains is: CTSQ domain = (mean of completed item response – 1) X 25.

A higher score on CTSQ indicated response that is more positive.

Training materials/methods: The Applicant trained study investigators and staff personnel on the instruments prior to study initiation. The Applicant also included language in the informed consent form (ICF) asking patients to complete the instruments throughout the study.

4 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- ☒ Literature review and/or publications
- ☐ Documentation of expert input
- ☐ Qualitative study protocols and interview guides for focus group or patient interviews
- ☐ Chronology of events for item generation, modification, and finalization (item tracking matrix)
- ☐ Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
- ☐ Qualitative support for meaningful change
- ☐ Quantitative study summary with evidence to support item retention and scoring
- ☒ Transcripts (if available)

Reviewer comments: *Transcripts were only provided for RASQ.*

The development of the PPQ instrument implemented in the PrefMab study was informed by the Applicant's earlier qualitative research conducted for a similar instrument implemented in the PrefHer study (NCT01401166)⁵. Additionally, the Applicant provided literature references and qualitative research documentation to help support the content validity of the RASQ-SC and RASQ-IV instruments. The applicant also furnished literature references to help support the content validity of the CTSQ.

This section describes relevant content validity findings from the referenced literature and information submitted in the application for each instrument.

PPQ: The PPQ instrument was a modified version of a similar instrument (Patient Interview Schedules 2 or PINT2) used in the PrefHer study to evaluate preference of either IV or SC trastuzumab administration in adult breast cancer patients. The PINT2 development incorporated patient input to understand the issues associated with the administration of

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trastuzumab, patients' preference for treatment method of administration, the strength of their preference, other influencing factors, and reasons for the preferred method of administration. The PINT2 instrument was administered via telephone interview in the PrefHer study. The Applicant confirmed that a final qualitative summary report on the development of the PPQ was not available.

RASQ-SC and RASQ-IV: The Applicant conducted a literature review and combined concept elicitation and cognitive debriefing interviews in non-Hodgkin lymphoma (NHL) patients (n=10) to help support the content validity. Most patients were female (n=7) and Caucasian (n=8), with a mean age of 60.8 years. Seven patients had indolent B-cell lymphoma and three had DLBCL. The instrument developer claimed the items and responses were generally well understood and interpreted consistently and correctly.

CTSQ: Abetz et al. (2005) developed CTSQ based on input from breast or lung cancer patients (n=110), oncologists (n=7), and nurses (n=14) in the United States, United Kingdom, and France, to assess issues oncology patients consider when evaluating chemotherapy in terms of expectations and satisfaction. The CTSQ was developed for use in a variety of cancer types and stages, particularly where patients are taking IV and/or oral anticancer therapies.

Reviewer Comments:

PPQ: At face value, the PPQ instrument Question 1 (preferred method of treatment administration) may be reasonable to assess patient preference of IV vs. SC method of administration. The evidence to support content validity for Question 2 (strength of preference) and Question 3 (reasons for the preference) appears inadequate, as the applicant provided limited qualitative documentation supporting their relevance, importance, and patient interpretation and understanding. Additionally, there is concern that patients may not have understood and interpreted the items of the PPQ consistently because the Applicant did not provide documentation of patient understanding in the context of use (e.g., cognitive interviews). Furthermore, there is no evidence to support United States (U.S.) patients would have the same treatment preference, because the preference data provided were from patients outside the U.S.

There are concerns regards to labeling data from PPQ Question 3, as it was not a pre-specified endpoint and may not provide a balanced description of both methods which could potentially generate misleading conclusions (e.g., data may suggest that one method is less painful than the other is; however pain was not a study endpoint). Additionally, the PPQ instrument item content was informed by a different patient population (i.e. breast cancer patients) other than the PrefMab study patient population (i.e. non-Hodgkin's lymphoma). Although there is potential for recall error, the recall period is not a critical issue in the context of this study.

This reviewer recommends in the future, that instruments that assess patient preference be developed with patient input to ensure relevance and patient understanding of item content, recall, and instructions in the proposed context of use. Additionally, this reviewer recommends

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the qualitative research patient sample be representative of the clinical trial and patient populations at large. COA Staff recommends drug sponsors engage FDA early (e.g., Pre-IND) and throughout the clinical development to discuss patient preference studies including the instruments to assess patient preference.

Comments regarding RASQ and CTSQ: Due to limited evidence submitted by the Applicant to support the content validity of the RASQ and CTSQ instruments, it cannot be determined whether the instruments are adequate to measure treatment satisfaction and impacts for this context of use. Satisfaction is a complex, multidimensional concept and can include multiple components as evidenced by the qualitative data provided for the RASQ and the referenced CTSQ literature. The qualitative interviews for RASQ development demonstrated that patients factored in a variety of elements while rating their overall satisfaction on the method of administration (e.g., improved health; treatment administration; absence or presence of side effects; etc), as well as inter-patient variability.

Additionally, the CTSQ instrument is intended to assess broad quality of life concepts that appear ambiguous (e.g., how “worthwhile” was the treatment). Further, this instrument was developed based on input from a patient population that is not a representative sample of the PrefMab study context of use. The use of “pill/IV” parenthetical throughout the instrument is problematic as the intended purpose of CTSQ in the PrefMab study was to assess patients’ experiences related to SC versus IV treatment options.

Overall, the use of broad and ambiguous concepts, lengthy recall period (e.g., 4 weeks), and incorrect instructions undermines the content validity of RASQ and CTSQ instruments. Testing other measurement properties (reliability, construct validity, and ability to detect change), while important, will not replace or rectify these problems with the RASQ and CTSQ content validity. Based on these concerns, the data from these instruments may be difficult to interpret or describe clinical benefits without labeling implications. Nonetheless, COA Staff defers to the Division regarding whether treatment satisfaction concept is acceptable for labeling claims.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The Applicant did not evaluate PPQ psychometric properties (reliability, construct validity, and ability to detect change) in the PrefMab study or provide supporting literature.

For the RASQ-SC and RASQ-IV and CTSQ instruments, the Applicant provided literature references in an effort to support their psychometric properties. Despite evidence to support psychometric properties, it is important to note that this data will not replace or rectify the problems with the content validity for these instruments. As such, this data was not reviewed. RASQ: Theodore-Oklota et al (2016) referenced psychometric findings for the RASQ-IV and RASQ-SC using the clinical trial data from the PrefMab (NCT01724021) and PrefCute (NCT01461928) studies. A total of 1051 patients were included in the psychometric evaluation,

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however, only 556 of these patients provided data based on early cycles for the quantitative phase of the study: 294 at cycle 4 from PrefMab and 262 from MabCute. The instrument developer evaluated item scale distribution, reliability (internal consistency), concurrent validity, and convergent validity. The observed Cronbach's alphas were 0.791 (PrefMab) and 0.756 (MabCute). A low to moderate concurrent validity was observed ($r=0.11$ to 0.50) when compared to CTSQ constructs (expectations of therapy, feelings about side effects, and satisfaction with therapy).

CSTQ: According to Trask et al (2008), the CTSQ psychometric properties were evaluated in 361 individuals with breast, colorectal, lung cancer, or melanoma who had received in the last 6 months or were currently receiving more than one cycle of chemo, biological, or hormonal therapy. Internal consistency (Cronbach's alpha) for the CTSQ domains ranged from 0.60 to 0.87 while the test retest reliability (intraclass correlation coefficients) ranged from 0.56 to 0.82. Additionally, the results indicated low to moderate Spearman correlations of CTSQ against various constructs of EORTC QLQ-C30 instrument. The instrument developer also assessed concurrent and known groups validity.

Reviewer Comments: The psychometric results for the RASQ and CTSQ instruments were not reviewed because of the relevant problems with content validity.

6 INTERPRETATION OF SCORES

The Applicant did not provide corresponding documentations for review.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The Applicant translated the PPQ, RASQ, and CTSQ instruments to 24 different languages for use in the multinational trial. The Applicant noted locally translated CTSQ and RASQ instruments were used in error instead of validated translated version in Philippines. The Applicant provided corresponding translation certificates and copies of translated or adapted instrument versions.

Refer to the PrefMab (MO28457) Clinical Study Report located in BLA 761064 eCTD Section 5.3.5.1 NHL and BLA 761064 Information Request (eCTD Section 1.11.3; January 30, 2017).

Reviewer Comments: The Applicant utilized adequate methods (i.e. forward and backward translation with cultural adaptation where applicable) to translate the PPQ, RASQ, and CTSQ instruments to the relevant languages for the multinational trial, which were consistent to International Society For Pharmacoeconomics Outcomes Research best practices. However, because there is no evidence to support U.S. patients would have the same treatment preference, it will be important to caveat that this data is from patients outside the U.S. if labeled.

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8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable

9 REVIEW USER MANUAL

The applicant confirmed no corresponding user manuals are available for review.

10 KEY REFERENCES FOR COA

Abetz L, Coombs JH, Keininger DL, Earle CC, Wade C, Bury-Maynard D, Copley-Merriman K, Hsu MA. Development of the cancer therapy satisfaction questionnaire: item generation and content validity testing. *Value Health*. 2005 Nov-Dec;8 Suppl 1:S41-53.

Theodore-Oklota C, Humphrey L, Wiesner C, Schnetzler G, Hudgens S, Campbell A. Validation of a treatment satisfaction questionnaire in non-Hodgkin lymphoma: assessing the change from intravenous to subcutaneous administration of rituximab. *Patient Preference and Adherence*. 2016;10:1767–1776.

Trask PC, Tellefsen C, Espindle D, Getter C, Hsu M. Psychometric Validation of the Cancer Therapy Satisfaction Questionnaire. *Value in Health*. 2008;11:669-679.

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/s/

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