

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



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Food and Drug Administration
Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: BLA 761064
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Follicular Lymphoma (FL), Diffuse Large B-cell Lymphoma (DLBCL), Chronic Lymphocytic Leukemia (CLL), Progression-Free Survival, Objective Response Rate, Patient-Reported Outcome

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1. EXECUTIVE SUMMARY

Rituxan® is an intravenously administered CD20-directed cytolytic antibody approved for the treatment of patients with Non-Hodgkin lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL). The Applicant (Genentech, Inc.) submitted a biologic license application (BLA) to support approval for a co-formulation of rituximab and hyaluronidase via subcutaneous injection (rituximab SC) for oncologic indications in Follicular Lymphoma (FL), Diffuse Large B-cell Lymphoma (DLBCL) and CLL.

The Applicant used primarily a PK-bridging approach to establish the safety and effectiveness of a rituximab and hyaluronidase product intended for subcutaneous route of administration. A notable feature of the Applicant's approach was the targeting of a trough concentration (C_{trough}) for the rituximab SC product that would be at least as high as that achieved with the rituximab IV product. Additional changes include the use of a fixed-dose regimen instead of BSA-based dosing, and the addition of hyaluronidase to facilitate absorption and administration. Note that hyaluronidase has been approved as an adjuvant and one of its indications is to increase the dispersion and absorption of other injected medicines.

Clinical efficacy was evaluated in four randomized clinical trials: SABRINA in patients with FL, MabEase in patients with DLBCL, SAWYER in patients with CLL and PrefMab, a patient preference study in patients with FL and DLBCL. Objective response rates (ORR) were the primary efficacy endpoint in two main clinical studies: SABRINA and MabEase. Secondary endpoints included time-to-event endpoints of progression-free survival (PFS) and overall survival (OS). None of the studies had pre-specified hypotheses on the clinical efficacy, nor were multiple endpoints adjusted for multiplicity.

The results based on the patient-preference questionnaire (PPQ) instrument from the PrefMab clinical trial, demonstrate that 80% of the patients preferred rituximab SC over rituximab IV.

We conclude that the data from the studies support the applicant's claim. Although the clinical trials were not designed for efficacy hypothesis testing, the data tend to show that the rituximab SC and Rituximab IV arms are comparable and efficacy results are similar across studies.

FDA requested discussion at ODAC on Mar. 29, 2017 to obtain feedback and insights on the acceptability of the above development approach to support the approval of the rituximab SC product for the same oncologic indications as intravenous rituximab (Rituxan). In the ODAC meeting, the committee unanimously voted "Yes" on the question that the benefit-risk is favorable for the proposed indication for FL, DLBCL and CLL.

2. INTRODUCTION

2.1 Overview

Rituxan® is an intravenously administered CD20-directed cytolytic antibody approved for the treatment of patients with NHL (Non-Hodgkin lymphoma) and CLL. The initial oncology approval occurred in 1997. The Applicant (Genentech, Inc.) submitted a biologic license application (BLA) to support approval for a co-formulation of rituximab and hyaluronidase for the following oncologic indications:

a. Follicular Lymphoma (FL)

Rituximab SC (rituximab/hyaluronidase) for subcutaneous injection is a co-formulation of rituximab and recombinant human hyaluronidase (rHuPH20) and is indicated for the treatment of patients with:

- 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 *Rituximab SC* 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 cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.

b. Diffuse Large B-Cell Lymphoma (DLBCL)

Rituximab SC (rituximab/hyaluronidase) for subcutaneous injection is indicated for the treatment of patients with previously untreated DLBCL in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) or other anthracycline-based chemotherapy regimens.

c. Chronic Lymphocytic Leukemia (CLL)

Rituximab SC (rituximab/hyaluronidase) for subcutaneous injection is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CLL.

Hyaluronidase is a purified preparation of the enzyme recombinant human hyaluronidase. Hyaluronidase facilitates absorption and dispersion of subcutaneously injected drugs by cleaving glycosidic bonds of hyaluronic acid other acid mucopolysaccharides of the connective tissue. Hyaluronidase has been approved as an adjuvant as follows:

- in subcutaneous fluid administration for achieving hydration
- to increase the dispersion and absorption of other injected drugs
- in subcutaneous urography for improving resorption of radiopaque agent

The co-formulation of rituximab and hyaluronidase, hereafter referred to as rituximab SC, is subcutaneously administered, which offers patients a different route of administration compared to intravenous rituximab, hereafter referred to as rituximab IV.

The clinical development of rituximab SC was based on a pharmacokinetic bridging program to evaluate intravenously administered rituximab in patients with DLBCL, FL and CLL. Two different doses of rituximab SC were developed: a 1400 mg subcutaneous (SC) dose to represent the 375 mg/m² intravenous (IV) rituximab dose and a 1600 mg SC dose to represent the 500 mg/m² IV rituximab dose. This submission contains 5 clinical trials listed in Table 1.

Table 1 Clinical Trials Submitted

Protocol number and name	Patient Population	Design	Primary Objective
BO22334/SABRINA	FL	Phase 3, 2 stage trial, stage 1 with more intensive PK sampling of 1400 mg SC dose	Stage 1: Non-inferiority C _{trough} of rituximab SC vs IV Stage 2: Efficacy overall response rate (ORR) at end of induction
MO28107/MabEase	DLBCL	Phase 3b randomized trial	Complete response rate (CRR) at end of treatment
BO25341/SAWYER	CLL	Phase 1b Stage 1: dose-finding single SC injection Stage 2: Dose confirmation of 1600 mg SC dose	Non-inferiority of C _{trough} SC vs IV
BP22333/SparkThera	FL	Phase 1b Stage 1: dose finding single SC injection Stage 2: dose confirmation 1400 mg in maintenance setting	Non-inferiority of C _{trough} SC vs IV
MO28457/PrefMab	FL/DLBCL	Phase 3b randomized cross over trial	Patient preference of SC vs IV

The development of rituximab SC is based on the predicate that rituximab SC is “a different dose, regimen, or dosage form” of rituximab IV and that PK data can be used to bridge the two different formulations of the same molecular entity provided the role of hyaluronidase is to serve as an adjunct to facilitate the dispersion and subsequent absorption of rituximab from the subcutaneous tissue. The main differences between the two formulations are shown in Table 2.

Table 2 Comparison between rituximab IV and rituximab SC

Characteristics	Rituximab IV	Rituximab SC
Administration	IV infusion over 1.5 to 2.5 hours	SC injection over 5 minutes
Rituximab Concentration	10 milligrams (mg)/milliliters (mL)	120 mg/mL
Dosing regimen	Body surface area - based	Fixed
Co-formulation	none	Hyaluronidase
Doses	375 mg/m ² and 500 mg/m ²	1400 mg and 1600 mg

The statistical efficacy was evaluated in four of the five clinical trials. The summary of the clinical trial information is given in Table 3.

Table 3: List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Data cut-off/ Median Observation Time
BO22334/ SABRINA	Phase III, multi-center, randomized, open-label, active controlled to demonstrate C_{trough} Non-inferiority and comparable ORR of Rituxan SC vs IV in Previously untreated Follicular Lymphoma (FL)	<u>Induction:</u> q3w R-CHOP or R-CVP Cycle 1: 375 mg/m ² IV; Cycles 2–8: 1400 mg SC vs 375 mg/m ² IV <u>Maintenance:</u> q2m R Cycles 9-20: 1400 mg SC vs 375 mg/m ² IV	2 years follow-up	Rituximab SC+CHOP or CVP / 205 Rituximab IV+CHOP or CVP / 205	11 January 2016/ 37 months
MO28107/ MabEase	Phase IIIb, multi-center, randomized, open-label, active controlled in Previously untreated Diffuse Large B-cell Lymphoma (DLBCL)	R-CHOP-14 or R-CHOP-21 Cycle 1: 375 mg/m ² IV; Cycles 2–8: 1400 mg SC vs 375 mg/m ² IV	2 years follow-up	Rituximab SC+CHOP/ 381 Rituximab IV+CHOP/ 195	31 December 2015/ 28 months
MO28457/ PrefMab	Phase IIIb, multi-center, randomized, open-label, active controlled in Follicular Lymphoma (FL)/ Diffuse Large B-cell Lymphoma (DLBCL)	CHOP, CVP or bendamustine-14 or 21 Arm A: Cycle 1 375 mg/m ² IV, then 3 cycles of 1400 mg SC; after interim staging 4 cycles of 375 mg/m ² IV. Arm B: 4 cycles of 375 mg/m ² , four cycles of 1400 mg SC after interim staging.	2 years follow-up	Rituximab SC+chemo/ 372 Rituximab IV+chemo /371	NA/12.75 months
BO25341/ SAWYER	Phase Ib, previously untreated CLL	<u>Part 2:</u> dose confirmation q4w R-FCCycle 1: 375 mg/m ² IV; Cycles 2–6: 1600 mg SC vs 500 mg/m ² IV	4 years follow-up	Rituximab SC+FC /88 Rituximab IV+FC /88	07 May 2014/ 14 months

None of the studies had pre-specified hypotheses on the clinical efficacy, nor were multiple endpoints adjusted for multiplicity. The objective of the evaluation of efficacy is to ensure that the efficacy of Rituximab SC is not compromised compared to IV.

2.2 Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path: [\\CDSESUB1\evsprod\BLA761064\0000](#)

3. STATISTICAL EVALUATION

Study BO22334/SABRINA

3.1 SABRINA Data and Analysis Quality

The efficacy endpoints such as overall response rate (ORR) were derived and saved in analysis datasets “DEMOEXT”, time-to-event endpoints were derived and saved in analysis datasets “EVENT” for investigator assessment and IRC assessment respectively. The statistical reviewer is able to reproduce the derived ORR or time-to-event analysis datasets from the BLA tabulation datasets.

3.2 SABRINA Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

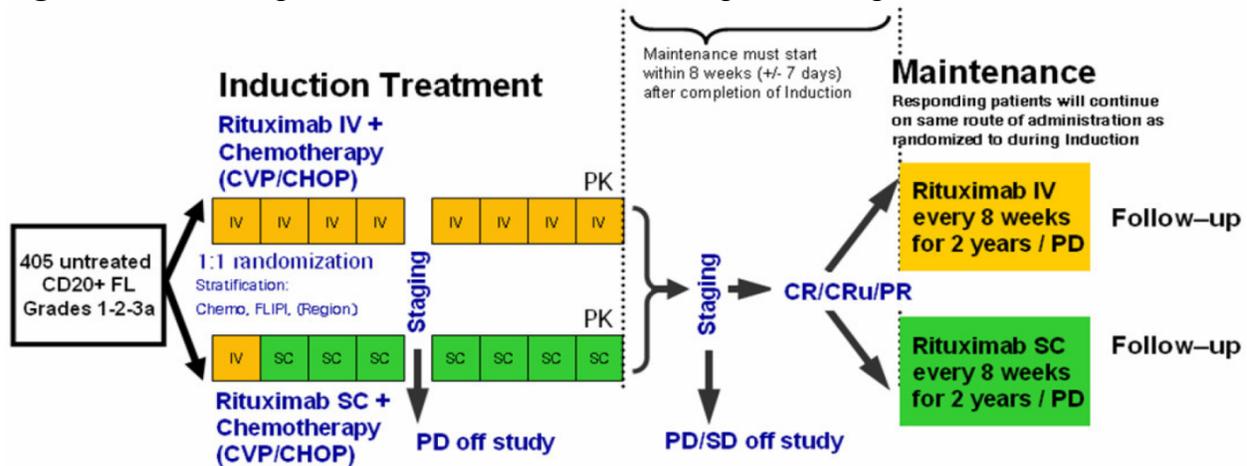
Study BO22334 or SABRINA was a two-stage Phase 3 randomized trial entitled “A two-stage phase III, international, multi-center, randomized, controlled, open-label study to investigate the pharmacokinetics, efficacy and safety of rituximab SC in combination with CHOP or CVP versus rituximab IV in combination with CHOP or CVP in patients with previously untreated FL followed by maintenance treatment with either rituximab SC or rituximab IV”. A total of 410 patients were randomized, 205 patients to rituximab IV and 205 to rituximab SC.

Randomization was centralized in a 1:1 fashion using the Pocock and Simon dynamic randomization algorithm. Patients were stratified by underlying chemotherapy backbone (CHOP vs CVP), Follicular Lymphoma International Prognostic Index (FLIPI) (low-risk vs intermediate-risk vs high-risk), and region (Europe and North America vs South and Central America vs Asia).

The primary objective of stage 1 was to obtain the ratio of serum C_{trough} concentrations (C_{trough} SC/ C_{trough} IV) at Cycle 7, 21 days after SC administration. The primary objective of stage 2 was to estimate the ORR including CR, CRu (complete response unconfirmed), and PR in the two arms at the end of induction. As shown in Figure 1, the design for the two-stages was the same except for more extensive PK sampling in stage 1. A total of approximately 125 patients were

planned to be enrolled into Stage 1 of the study and 280 were planned for stage 2. Data from both stages (total of approximately 405 patients) would be combined for the analysis.

Figure 1 : Trial Design for BO22334 SABRINA for stage 1 and stage 2



[Source: Clinical Study Report Hoffmann-La Roche Ltd Protocol BO22334 page 2774]

As shown in Figure 1, the rituximab SC arm consisted of the first cycle of rituximab IV 375 mg/m² followed by 7 cycles of rituximab SC 1400 mg both combined with a total of 8 cycles of CHOP or CVP chemotherapy. A cycle was defined as 3 weeks. Patients with at least a PR were to receive rituximab SC maintenance which was rituximab SC monotherapy every 8 weeks for 24 months. The rituximab IV arm was 8 cycles of rituximab IV 375 mg/m² in combination with CHOP or CVP every 3 weeks for 8 cycles. Patients with at least a PR after induction were to receive rituximab IV 375 mg/m² monotherapy maintenance every 8 weeks for a total of 24 months. Patients who received rituximab CHOP and who achieved a CR, CRu, PR or stable disease (SD) at the interim assessment could receive either 4 more cycles of rituximab-CHOP with rituximab IV or SC depending on assignment at randomization, or 2 cycles of rituximab-CHOP followed by two cycles of rituximab alone, either IV or SC depending on assignment at randomization.

The primary endpoint for Stage 1 was the estimated ratio of observed rituximab serum $C_{\text{trough SC}}/C_{\text{trough IV}}$ cycle 7 of induction treatment every 3 weeks. The primary endpoint for Stage 2 was the estimated overall response rate (ORR) consisting of complete response (CR), complete response unconfirmed (CRu) and partial response (PR) at the completion of induction.

The secondary objectives for stage 1 and 2 are:

- To compare peripheral blood B-cell depletion and repletion after rituximab SC and rituximab IV treatment.
- To compare complete response rates (CRR, comprising CR and CRu) of rituximab SC and rituximab IV given in combination with chemotherapy (CHOP or CVP) at the end/completion of the induction treatment.
- To compare ORR and CRR of rituximab SC and rituximab IV at the end/completion of the maintenance treatment.

- To compare progression-free survival (PFS), event-free survival (EFS), and overall survival (OS) of rituximab SC and rituximab IV when given in combination with chemotherapy during induction followed by maintenance as monotherapy.
- To compare observed rituximab serum C_{trough} levels (rituximab IV vs SC) during induction.
- To compare observed rituximab serum C_{trough} levels (rituximab IV vs SC) during maintenance treatment.
- To compare the safety profile of rituximab SC with the safety profile of rituximab IV according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.
- Adverse events (AEs) including laboratory values
- Incidence and severity of administration-related reactions (ARRs)
- Physical examination including weight, performance status, and vital signs (pulse rate and blood pressure)
- Prior and interval medical history, prior treatments for cancer, concomitant medications
- Immunogenicity.
- To gather physician/nurse opinions on resource savings with rituximab SC compared with rituximab IV.

The sample size was planned based on assumptions that 80% power, 0.05 type I error rate, 0.56 coefficient of variation, Rituximab SC is 5% higher than IV for C_{trough} and 20% patients do not have valid PK at cycle 8. Stage 1 needs 125 patients to be enrolled. For stage 2, 280 patients were planned. The ORR in Rituximab SC was assumed to arrange from 0.8-0.95. The 95% confidence intervals were given and the study was not designed to show non-inferiority.

An interim futility PK analysis was performed and reviewed by the independent (b) (4) as planned, using PK data from approximately 35 patients per arm who had completed Cycle 7. This interim analysis evaluated the non-inferiority of the C_{trough} levels between the rituximab SC and rituximab IV formulations based upon O'Brien-Fleming futility considerations (p-value boundary for futility). On the basis of this interim analysis, the study continued without modification.

3.2.1.2 Efficacy Endpoints

The primary endpoint is the investigator-assessed ORR. Independent review committee-assessed ORR was analyzed as supporting analysis for the primary endpoint.

ORR was defined as CR, CR_u and PR in each treatment arm at the end/completion of induction treatment.

The secondary endpoints are CRR (CR and CR_u) at the end/completion of induction treatment; ORR and CRR at the end/completion of maintenance treatment and time-to-event endpoints (Progression-free survival (PFS), Event-free survival (EFS), Overall Survival (OS)).

PFS was defined as time from randomization to disease progression/relapse or death due to any cause. If the specified event (i.e., disease progression/relapse or death) did not occur, PFS was censored at the last tumor assessment date either during the treatment period or the follow-up period.

EFS was defined as time from randomization to disease progression/relapse, death or initiation of new non-Hodgkin's lymphoma (NHL) therapy treatment. If the specified event (i.e., progression/relapse, death or new NHL treatment) did not occur, EFS was censored at the last tumor assessment date either during the treatment period or the follow-up period.

OS was defined as time from randomization to death due to any cause. Patients without death were censored at the last time known to be alive.

3.2.2 Statistical Methodologies

The sponsor focused on the estimation, therefore, the statistical hypothesis testing presented is considered to be exploratory. No multiplicity adjustments were made.

Response rates (ORR and CRR) were analyzed in frequency tables, including 95% two-sided Pearson-Clopper confidence intervals (CIs) by treatment arm. For the difference in response rates, 95% two-sided CIs (Hauck-Andersen) were calculated. The primary statistical analysis of ORR was based on investigator's assessment.

For each of the time-to-event secondary endpoints analyzed (PFS and OS), the median time to the event was estimated (if reached) for all patients by treatment arm using Kaplan-Meier methodology; the corresponding 95% two-sided CI for a median time to event was calculated using the method of Brookmeyer and Crowley.

Hazard ratio and corresponding 95% two-sided CIs and p-values were estimated using an unstratified Cox regression model. The statistical model was parameterized such that HR of <1 favored rituximab SC. Additionally, exploratory analysis of hazard ratios from a stratified Cox model was conducted for time-to-event endpoints, using the stratification information recorded in the randomization system (chemotherapy backbone [CHOP vs CVP], FLIPI risk [low vs intermediate vs high], and region [Europe and North America vs South and Central America vs Asia]).

The sponsor performed sensitivity analysis for ORR based on the assessment of the independent review committee.

The sponsor also conducted three sensitivity analyses for PFS:

1. Progression dates include only those based on radiological assessments. Clinical progression is not considered a progression endpoint. PFS is assigned to the first time when tumor progression was noted and deaths occurring after 2 or more missed visits are censored at the last visit
2. PFS was assigned dates for censoring and events only at scheduled visit dates

3. PFS was evaluated including all signs of clinical progression as an event, such as when PD is recorded as a reason for treatment discontinuation

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis population

All efficacy endpoints were analyzed based on intent-to-treat (ITT) population, which included all patients being randomized into study irrespective whether they received study drug or not. ITT population was the primary analysis population for all efficacy analyses, and was used for descriptions of patient disposition, demographics, and baseline disease characteristics.

Safety population was defined as all patients who received at least one dose of rituximab, either IV or SC.

The study BO22334 randomized 410 patients: 205 to rituximab IV and 205 to rituximab SC in the ITT population. One patient in rituximab IV arm discontinued before receiving any treatment and two patients in rituximab SC arm discontinued before receiving any treatment.

Subject disposition

The study BO22334 randomized 410 patients: 205 to rituximab IV and 205 to rituximab SC in the ITT population. A total of 284 (69%) patients completed the treatment period for both induction and maintenance: 146 (71%) patients in the rituximab IV arm and 138 (67%) in the rituximab SC arm. The most common reason for discontinuation of treatment was disease progression (12% vs 14%) followed by adverse events (AEs) (5% vs 7%).

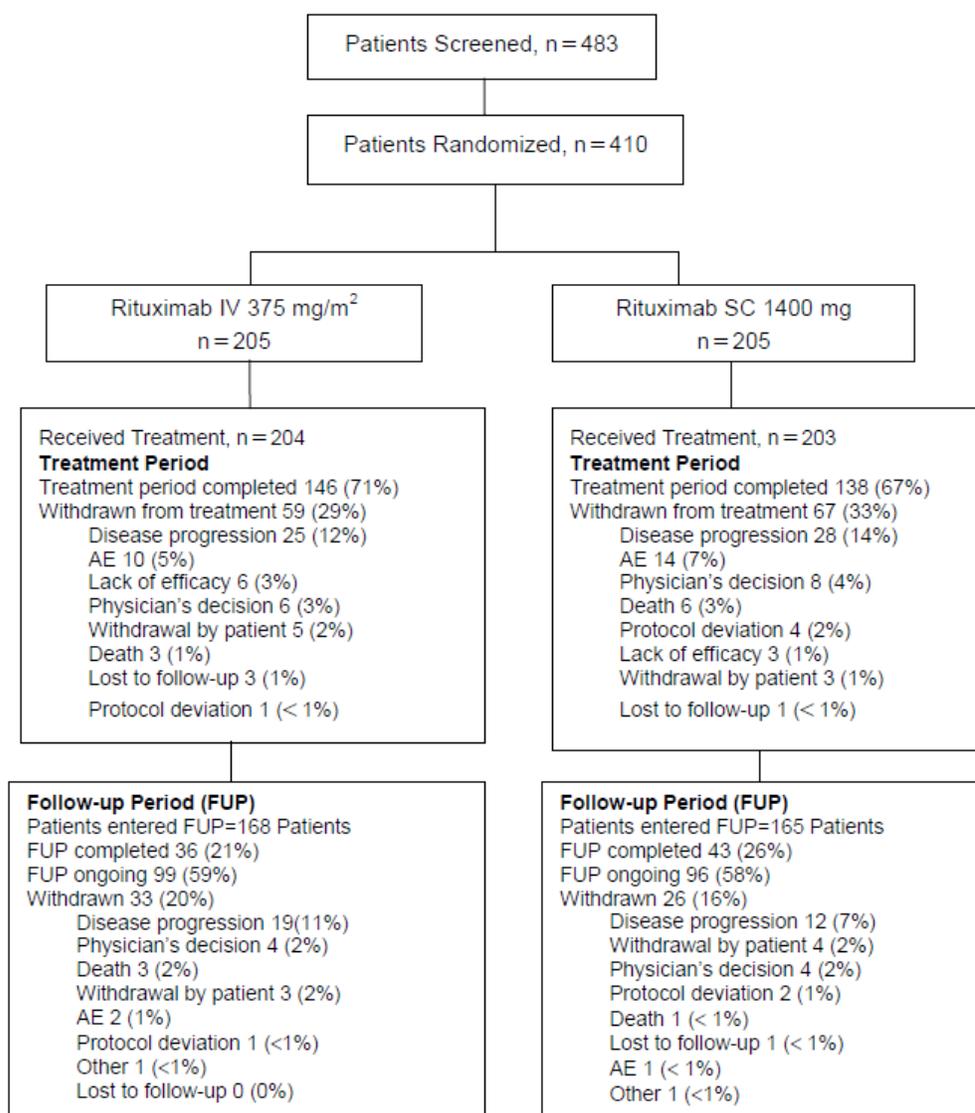
A total of 168/205 (82%) patients in the rituximab IV arm and 165/205 (80%) patients in the rituximab SC arm entered the 2-year follow-up period. Of those patients, 33/168 (20%) in the rituximab IV arm and 26/165 (16%) patients in the rituximab SC arm were withdrawn from the follow-up period. The most common reason for withdrawal was disease progression (11% vs 7%).

Of all patients, 37 (18%) in rituximab IV arm and 32 (16%) in rituximab SC arm withdrew from the study, most commonly due to death (10% vs 8%).

The median duration of observation at the clinical cut-off date was 36.8 months (range: 0.3-57.2) in rituximab IV arm and 37.2 months (range: 0.1-58.2) in the rituximab SC arm. The patient disposition was given in Figure 2:

Figure 2: SABRINA patient disposition

Figure 2 Patient Disposition (All Patients)



[Source: BO22334 study report page 71]

Subject demographics and baseline disease characteristics

Subject demographics and baseline disease characteristics listed in Table 4 and Table 5 appeared to be balanced between rituximab IV arm and rituximab SC arm.

Table 4: SABRINA Baseline Demographic Data (ITT population)

Protocol(s): BO22334 (C22334X)
 Analysis: Intent-To-Treat Population Center: ALL CENTERS
 Snapshot Date: 12FEB2016 Clinical Cutoff Date: 11JAN2016

	Rituximab IV + Chemo N = 205	Rituximab SC + Chemo N = 205	Total N = 410
Age (years)			
Mean	56.9	56.1	56.5
SD	12.69	12.66	12.67
Median	57.0	56.0	57.0
Min-Max	28 - 86	28 - 85	28 - 86
n	205	205	410
Age Category (years)			
<65	147 (72%)	154 (75%)	301 (73%)
>=65 - <=70	24 (12%)	22 (11%)	46 (11%)
>70	34 (17%)	29 (14%)	63 (15%)
n	205	205	410
Gender			
MALE	106 (52%)	85 (41%)	191 (47%)
FEMALE	99 (48%)	120 (59%)	219 (53%)
n	205	205	410
Weight (kg)			
Mean	76.660	73.565	75.112
SD	15.4141	16.0883	15.8116
Median	75.000	72.000	74.000
Min-Max	43.90 - 141.80	45.00 - 124.20	43.90 - 141.80
n	205	205	410
Height (cm)			
Mean	168.75	166.15	167.45
SD	9.880	9.761	9.895
Median	168.00	166.50	167.00
Min-Max	141.0 - 192.0	138.0 - 191.0	138.0 - 192.0
n	205	205	410
Body Surface Area (sqm)			
Mean	1.862	1.810	1.836
SD	0.2067	0.2251	0.2174
Median	1.840	1.800	1.830
Min-Max	1.34 - 2.49	1.36 - 2.51	1.34 - 2.51
n	205	205	410
Ethnicity			
HISPANIC	36 (20%)	42 (23%)	78 (21%)
NON-HISPANIC	143 (80%)	143 (77%)	286 (79%)
n	179	185	364
Race			
AMERICAN INDIAN/ALASKA NATIVE	1 (<1%)	3 (2%)	4 (1%)
ASIAN	11 (6%)	10 (5%)	21 (6%)
BLACK	1 (<1%)	-	1 (<1%)
OTHER RACE	14 (7%)	13 (7%)	27 (7%)
WHITE	160 (86%)	164 (86%)	324 (86%)
n	187	190	377
Tobacco Use History			
NEVER	115 (56%)	114 (56%)	229 (56%)
CURRENT	42 (20%)	47 (23%)	89 (22%)
PREVIOUS	48 (23%)	44 (21%)	92 (22%)
n	205	205	410
Chemotherapy Combination			
CHOP	130 (63%)	132 (64%)	262 (64%)
CVP	75 (37%)	73 (36%)	148 (36%)
n	205	205	410

n represents number of patients contributing to summary statistics.
 Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

[Source: BO22334 study report page 77 and statistical reviewer's calculation]

Table 5: SABRINA Baseline Disease Data (ITT Population)

Protocol(s): B022334 (C22334X)
 Analysis: Intent-To-Treat Population Center: ALL CENTERS
 Snapshot Date: 12FEB2016 Clinical Cutoff Date: 11JAN2016

	Rituximab IV + Chemo N = 205	Rituximab SC + Chemo N = 205	Total N = 410
Time to first diagnosis (days)			
Mean	157.1	173.3	165.2
SD	621.18	439.35	537.41
Median	50.0	47.0	48.0
Min-Max	3 - 8520	3 - 3038	3 - 8520
n	205	205	410
Time to first diagnosis (months)			
Mean	5.16	5.69	5.43
SD	20.408	14.435	17.656
Median	1.64	1.54	1.58
Min-Max	0.1 - 279.9	0.1 - 99.8	0.1 - 279.9
n	205	205	410
Ann Arbor Stage at diagnosis			
I	8 (4%)	9 (4%)	17 (4%)
II	30 (15%)	21 (10%)	51 (12%)
III	62 (30%)	71 (35%)	133 (32%)
IV	91 (44%)	94 (46%)	185 (45%)
UNKNOWN	14 (7%)	10 (5%)	24 (6%)
n	205	205	410
Ann Arbor Stage at study entry			
I	8 (4%)	6 (3%)	14 (3%)
II	25 (12%)	21 (10%)	46 (11%)
III	63 (31%)	65 (32%)	128 (31%)
IV	108 (53%)	113 (55%)	221 (54%)
UNKNOWN	1 (<1%)	-	1 (<1%)
n	205	205	410
FLIPI risk group			
LOW RISK (0-1 ADVERSE FACTOR)	44 (21%)	42 (20%)	86 (21%)
INTERMEDIATE RISK (2 ADVERSE FACTORS)	66 (32%)	73 (36%)	139 (34%)
HIGH RISK (EQUAL TO OR GREATER THAN 3 ADVERSE FACTORS)	95 (46%)	90 (44%)	185 (45%)
n	205	205	410
Follicular cell lymphoma grading			
1	45 (22%)	67 (33%)	112 (27%)
2	109 (53%)	93 (46%)	202 (49%)
3	9 (4%)	9 (4%)	18 (4%)
3A	42 (20%)	35 (17%)	77 (19%)
n	205	204	409
CD20 Positivity			
POSITIVE	205 (100%)	205 (100%)	410 (100%)
n	205	205	410
Follicular Lymphoma Confirmation (BL)			
CONFIRMED	167 (88%)	171 (90%)	338 (89%)
NOT CONFIRMED	2 (1%)	3 (2%)	5 (1%)
NOT DONE	19 (10%)	16 (8%)	35 (9%)
TISSUE EXHAUSTION;NO TUMOR CELLS PRESENT	1 (<1%)	-	1 (<1%)
n	189	190	379
Tumor Load			
Mean	7025.32	7165.22	7095.27
SD	8881.305	7285.672	8113.130
Median	4394.00	4851.00	4477.50
Min-Max	168.0 - 76371.0	165.0 - 47169.0	165.0 - 76371.0
n	205	205	410

n represents number of patients contributing to summary statistics.

[Source: B022334 study report page 79 and statistical reviewer's calculation]

Protocol deviation

Protocol deviations Table 6 were defined as: no informed consent, no treatment arm assigned, no rituximab administration, not treated for at least 4 cycles without an event, treated in a different treatment group as randomized and not all eligible criteria met.

Table 6: Protocol deviation

	Rituximab IV (N=205)	Rituximab SC (N=205)
	n (%)	n(%)
Patients with at least 1 violations	6 (3%)	11(5.4%)
No informed consent	0	0
No treatment arm assigned	0	0
No rituximab administered	2 (0.96%)	4 (1.95%)
Not treated for at least 4 cycles without an event	6 (3%)	9 (4.4%)
Treated in a different treatment group as randomized	0	6 (3%)
Not all eligible criteria met	2 (0.96%)	7 (3.4%)

Note: The numbers do not add to 100% because some patients have more than 1 violation.
[Source: Statistical Reviewer's Calculation]

3.2.4 SABRINA Results and Conclusions

The primary efficacy endpoint was ORR (comprising CR, CRu and PR) for stage 2 at the end/completion of induction treatment. The analysis of ORR at the end of induction based on investigator assessment and the Stage 1+2 population was updated based on the clinical cutoff date 11 January 2016. An independent review of response was conducted at the time of the Stage 2 analysis based on response data from both stages (clinical cutoff date 31 October 2013).

The results for the primary endpoint are presented in Table 7. The ORR difference between the rituximab SC arm and the rituximab IV arm is -0.5% with a 95% confidence interval of -7.7% to 6.8%. The response rate ratio is 0.99 with a 95% confidence interval of 0.92 to 1.08. The response rate ratio of 0.99 indicates that the estimated probability of patients achieving ORR in patients who received rituximab SC is 99% of the estimated probability in those who received rituximab IV. The results show that the rituximab SC arm and the rituximab IV arm are comparable in ORR.

Table 7: Primary Endpoint Result for FL

Study	Endpoints	IV; 95% CI	SC; 95% CI	Diff: SC-IV, 95% CI	Response Rate 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]

[Source: statistical reviewer's calculation]

The results for the secondary endpoints of CR/CRu at the end of induction, ORR at end of maintenance, and CR/CRu at end of maintenance period are presented in Table 8 (see below). The number of patients achieving response and the total number of patients in the evaluation are included in the parenthesis in the table. There is no observed difference in CR/CRu at the end of

induction period between the two arms; therefore, the estimated response rate ratio is 1.00. For ORR at the end of the maintenance period, the difference between the two arms is -0.2% with a 95% confidence interval of -9.2% to 8.8%. The estimated response rate ratio is 1.00 with the corresponding 95% confidence interval of 0.89 to 1.12. For CR/CRu at end of the maintenance period, rituximab SC achieved 5.6% less CR/CRu than rituximab IV arm. The 95% confidence interval for CR/CRu rate difference is -16.4% to 5.2%, covering 0. The response rate ratio of CR/CRu at end of the maintenance is 0.90, indicating the estimated probability of patients achieving CR/CRu at the end of the maintenance in rituximab SC is 90% of the estimated probability in rituximab IV arm.

Table 8: Secondary Endpoint Results for FL

Endpoints	IV	SC	Diff: SC-IV, 95% CI	Response Rate 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]

[Source: statistical reviewer's calculation]

The results of time-to-event secondary endpoints of PFS, EFS and OS are presented in Table 9. As shown in Figure 3 and Figure 4, the survival curves of rituximab SC arm and rituximab IV arm are close to each other and crossed at several time-points. The numbers of patients with events in the rituximab SC and rituximab IV arms are given in Table 9. The number of events in the rituximab SC arm is smaller than in the rituximab IV arm for each of PFS, EFS, and OS.

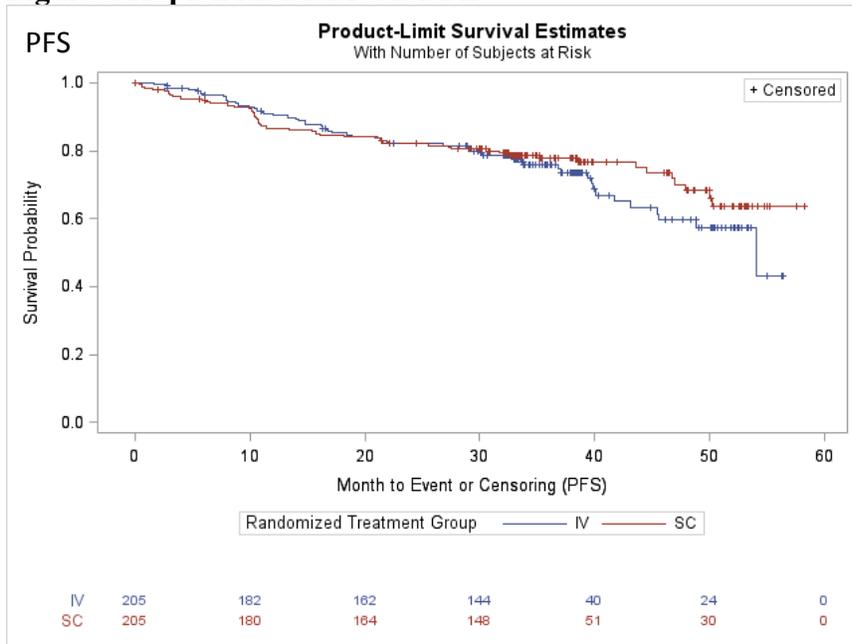
Table 9: Time-to-Event Endpoint Results for FL

	# of Patients with event (%); IV	# of Patients with event (%); SC	HR Stratified [95% CI]	2-Year Survival Rate, IV	2-Year Survival 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%

[Source: statistical reviewer's calculation]

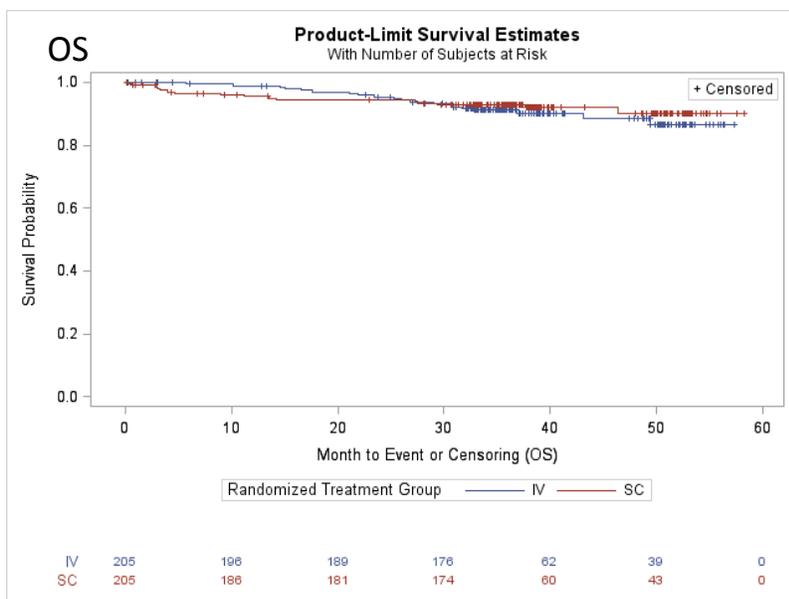
The 2-year survival rates are estimated using the Kaplan-Meier estimator and the estimated 2-year survival rates are similar in the rituximab SC and rituximab IV arms. The hazard ratio (HR) estimates are obtained through a Cox-regression model, stratified by the following stratification factors: underlying chemotherapy backbone (CHOP vs CVP), FLIPI (low-risk vs. intermediate-risk vs. high-risk), and region (Europe and North America vs. South and Central America vs Asia). The estimated HRs of PFS and EFS are close to 1. HR of OS is 0.82 with a 95% confidence interval of 0.41 to 1.63. The number of events is small in OS; therefore the confidence interval is relatively wide. Overall, the clinical efficacy of rituximab SC is comparable to rituximab IV.

Figure 3 Kaplan Meier PFS for FL



[Source: statistical reviewer’s calculation]

Figure 4 Kaplan Meier for OS for FL



[Source: statistical reviewer’s calculation]

3.2.5 SABRINA Sensitivity analysis

Sensitivity analysis of PFS

The sponsor performed three sensitivity analyses for PFS (A, B and C).

- In PFS-A, progression dates include only those based on radiological assessments; clinical progression is not considered a progression endpoint. PFS-A is assigned to the first time when tumor progression was noted, and deaths occurring after 2 or more missed visits are censored at the last visit.
- PFS-B corrects for potential bias in follow-up schedules for tumor assessment by assigning the dates for censoring and events only at scheduled visit dates.
- PFS-C evaluates PFS including all signs of clinical progression as an event, such as when PD is recorded as a reason for treatment discontinuation.

The sensitivity analysis results Table 10 were consistent with those from the secondary analysis.

Table 10: Sensitivity analysis of PFS

	HR and 95% CI
Sensitivity analysis PFS-A	0.96 [0.64, 1.42]
Sensitivity analysis PFS-B	0.95 [0.64, 1.41]
Sensitivity analysis PFS-C	0.95 [0.64, 1.41]

[Source: BO22334 Study Report Page 2366, 2367, 2368 and statistical reviewer’s calculation]

Analysis of ORR by Independent review committee (IRC)

Tumor response at the end/completion of the induction phase was verified by an analysis of response by an independent review committee of radiologists (Table 11). Available CT scans

were reviewed for 375/410 patients (91.5%) by independent radiologists (189 in rituximab IV and 186 in rituximab SC); data were missing for 35 patients (16 IV and 19 SC).

Table 11 Tumor Response Rate at the end of induction by IRC (ITT Population)

Endpoints	IV; N=205; 95% CI	SC; N=205; 95% CI	Diff: SC-IV; 95% CI
ORR	82.4% [77.6, 88.2]	79.0% [72.8, 84.4]	-4.4% [-12.2, 3.4]
CR	22% [16.5, 28.2]	23.9% [18.2, 30.3]	1.9% [-6.4, 10.4]
PR	61.5% [54.4, 68.2]	55.1% [48.0, 62.1]	-6.4% [-16.1, 3.5]

[Source: BO22334 study report page 91]

Concordance between investigator and independent review committee assessment

At the end of induction, available CT scans for 373/410 patients were reviewed both by investigators and the independent review committee: 188 patients in the rituximab IV arm and 185 patients in the rituximab SC arm. The results were presented in Table 12.

Table 12 Concordance/Discordance between investigator and independent review committee assessment of response at the end of induction

Cross-Tabulation of Response (ITT)		Independent Review Committee Assessment			
		Responder ^a	Non-Responder ^b	Missing	Total
Rituximab IV	Responder ^a	<u>162</u>	5	7	174
	Non-Responder ^b	8	<u>13</u>	3	24
	Missing	1	--	6	7
	Total	171	18	16	205
Rituximab SC	Responder ^a	<u>158</u>	10	5	173
	Non-Responder ^b	4	<u>13</u>	3	20
	Missing	--	1	11	12
	Total	162	24	19	205
Investigator and Independent Review Committee Response Agreement (ITT excl. Missing)					
	Rituximab IV	Rituximab SC	Total		
Agreement ^c	175 (93%)	171 (92%)	<u>346 (93%)</u>		
No Agreement	13 (7%)	14 (8%)	27 (7%)		
n	188	185	373		

^a Responder: CR, CRu and PR.

^b Non-Responder: SD, Progressive Disease, and invalid response assessment.

^c Sum of concordant assessments of patient as responder or non-responder (underlined in upper table), excluding patients with missing data. Overall concordance rate is underlined in lower table.

Percentages are based on n.

[Source: BO22334 study report page 93 and statistical reviewer's calculation]

3.3 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

3.4 Benefit-Risk Assessment

Overall, the clinical efficacy of rituximab SC is comparable to rituximab IV in SABRINA study. Whether the submission demonstrated an overall favorable risk-benefit profile on Rituximab SC over IV is deferred to the clinical team reviewing this submission.

Study MO28107/ MabEase

3.5 MabEase Data and Analysis Quality

The efficacy endpoints such as complete response (CR) were derived and saved in analysis datasets “ADRSA”, time-to-event endpoints were derived and saved in analysis datasets “ADRS” and “ADRSA” for investigator assessment and IRC assessment respectively. The statistical reviewer is able to reproduce the derived CR or time-to-event analysis datasets from the BLA tabulation datasets.

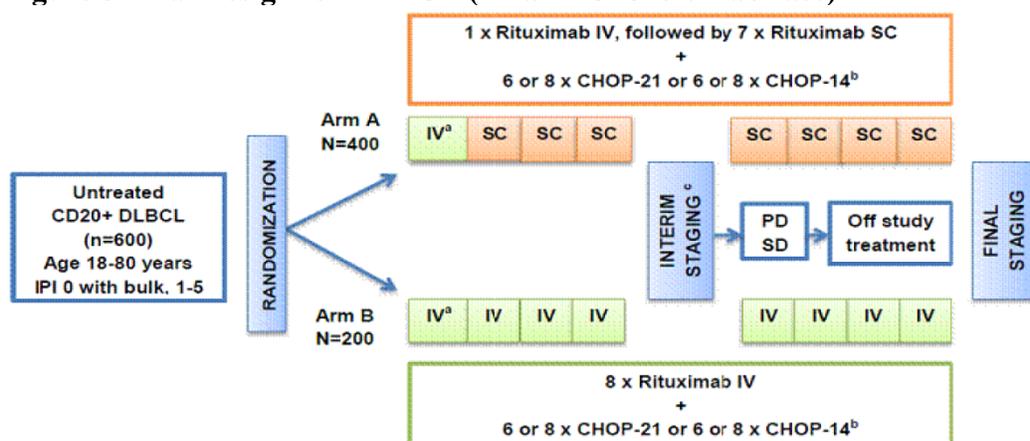
3.6 Evaluation of Efficacy

3.6.1 Study Design and Endpoints

3.6.1.1 Study Design

Study MO28107, or MabEase, was a randomized, multicenter, open-label trial entitled “A Comparative, Randomized, Parallel-group, Multi-center, Phase IIIB Study to Investigate the Efficacy of Subcutaneous Rituximab Versus Intravenous Rituximab Both in Combination with CHOP in Previously Untreated Patients with CD20-Positive Diffuse Large B-Cell Lymphoma”. The primary objective of this trial was to determine the CR and CRu rate one month after the end of treatment. As shown in Figure 5, treatment consisted of 8 cycles of rituximab with CHOP every 21 days, or 8 cycles of rituximab with CHOP every 14 days, or 6 cycles of rituximab with CHOP every 14 days followed by an additional 2 cycles of rituximab only.

Figure 5 Trial Design for DLBCL (Trial MO28107/MabEase)



[Source: Roche Clinical Study Report MO28107 page 29]

Patients were randomized 2:1 to the rituximab SC arm or the rituximab IV arm. Patients randomized to the rituximab SC arm received rituximab SC at a fixed dose of 1400 mg in Cycles 2 to 8 after the first cycle with rituximab IV 375 mg/m². Patients randomized to the rituximab IV arm received rituximab IV 375 mg/m². An interim staging was done after the first 4 cycles. The primary endpoint of CR/CRu was based on investigator assessment at the end of induction. The secondary endpoints include event-free survival (EFS), disease-free survival (DFS), progression free survival (PFS) and overall survival (OS).

Approximately 600 patients planned. Patients were stratified according to age (< 60 years, ≥ 60 years), International Prognostic Index (IPI) risk category (low, low-intermediate, high-intermediate, high), and chemotherapy regimen (CHOP administered every 21 days [CHOP-21] or CHOP administered every 14 days [CHOP-14]).

Follow-up of patients after induction treatment occurred every 3 months for the first 2 years and then every 6 months until the end of the study.

Patient satisfaction with administration of cancer therapy was evaluated using CTSQ and RASQ at Visit 3/Cycle 3 and Visit 8/Cycle 7. At these visits, CTSQ was completed prior to rituximab administration, whereas RASQ was completed immediately after rituximab administration and before chemotherapy administration.

3.6.1.2 Efficacy Endpoints

Primary endpoint:

- Complete response rate (CR/CRu) based primarily on the Investigator's assessment according to the International Working Group response criteria at the end of induction treatment (Visit 10). The primary efficacy variable was derived based on a combination of the Investigator's assessment as captured in the eCRF, and bone marrow results using a pre-defined algorithm.

Secondary endpoints:

- Progression-free survival (PFS): defined as the time from randomization to the first occurrence of progression of disease/relapse, or death from any cause.
- Event-free survival (EFS): defined as the time from randomization to first occurrence of progression of disease or relapse, or initiation of a non-protocol-specified anti-lymphoma therapy or death, whichever occurs first.
- Disease-free survival (DFS) in patients achieving CR/CRu: defined as the time from the date of the initial CR/CRu until the date of progression or death from any cause.
- Overall survival (OS): defined as the time from randomization until death from any cause.

The Two-year Follow-up Analysis therefore also examined additional secondary efficacy endpoints of:

- Event-free survival at 24 months (EFS24): defined for each patient on the basis of his/her EFS status at 24 months after the date of randomization i.e., on Study Day 730. EFS24 was set to "Yes" for patients with EFS duration \geq 730 days. All other patients had EFS24 set to "No".
- Progression-free survival at 24 months (PFS24): defined for each patient on the basis of his/her PFS status at 24 months after the date of randomization; a similar indicator was defined for PFS24, as for EFS24.

3.6.2 Statistical Methodologies

Response rates were analyzed by frequency tables including 90% and 95% 2-sided Pearson-Clopper confidence intervals (CIs) by treatment group. For the difference in response rates between the 2 treatment arms, 90% and 95% 2-sided binomial asymptotic CIs were calculated. Complete response rates were compared by a Wald chi-square statistic for descriptive purposes.

The RND and PP populations were used for a sensitivity analysis of the primary efficacy.

Secondary efficacy endpoints were presented graphically using Kaplan-Meier curves. The median and the corresponding 90% and 95% CIs were reported for each treatment group, as were Kaplan-Meier estimates of PFS, EFS, DFS and OS at 1 and 2 years (with associated 90% and 95% CIs) where 1-year and 2-year time points are 365 and 730 days, respectively. Hazard ratios (HRs) (and associated 90% and 95% CIs) were calculated to estimate the treatment effect between the 2 arms.

In addition, a stratified Cox regression, using the 3 randomization strata (age group [$<$ 60 years, \geq 60 years], IPI risk category [low, low-intermediate, high-intermediate, high], and chemotherapy regimen CHOP-21 or CHOP-14]) was performed for PFS, EFS, DFS and OS. The unstratified Cox model was also provided.

To supplement the summaries of OS, the median follow-up time (and associated 90% and 95% CIs) based on OS follow-up, were estimated for each treatment group and total patients. The median follow-up time was calculated using the reverse Kaplan-Meier method.

Three exploratory sensitivity analyses for PFS (PFS1, PFS2, PFS3) were conducted, considering different approaches for missing data.

- In PFS1, progression dates include only those based on radiological assessments; clinical progression is not considered a progression endpoint. PFS1 is assigned to the first time when tumor progression was noted, and deaths occurring after 2 or more missed visits are censored at the last visit.
- PFS2 corrects for potential bias in follow-up schedules for tumor assessment by assigning the dates for censoring and events only at scheduled visit dates.
- PFS3 evaluates PFS including all signs of clinical progression as an event, such as when PD is recorded as a reason for treatment discontinuation.

For all scenarios, patients were regarded as progressed or censored at the earliest such event.

For the primary efficacy variable, any patients with a missing or unknown response assessment were considered as not having a complete response to treatment in the analysis of complete response rates.

For the secondary efficacy variables, patients who had experienced none of the PFS, EFS, DFS and OS events at the time of analysis and patients who were lost to follow-up were censored as follows:

- PFS: censored at their last tumor or clinical assessment date
- EFS: censored at their last tumor or clinical assessment date
- DFS: censored at their last tumor or clinical assessment date
- OS: censored at the last known date they were alive - from the Survival Status page of the eCRF or latest clinical assessment if later than the dated survival status page.

For PFS, EFS and OS, any patient with no efficacy assessment after baseline was censored at Day 1.

3.6.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis Population

For the primary endpoint, the ITT population, which included all randomized patients with completed baseline and at least one on-treatment efficacy assessment, according to the patient's original randomization schedule, was used. The RND (all randomized patients) and PP (all patients in the ITT population who received at least 4 cycles of study treatment without an event [progression or death] and did not have a major protocol violation) populations were used for a sensitivity analysis of the primary endpoint.

The secondary efficacy analyses were performed for the RND, ITT and PP populations. The RND population was in agreement with the conventional definition of an ITT population (i.e., all randomized patients). The ITT population (which in this study also required an on-treatment efficacy assessment) was used as a sensitivity analysis of all secondary efficacy endpoints, and the PP population was used as a sensitivity analysis of key secondary efficacy endpoints (i.e., PFS, EFS, DFS, and OS).

Safety analyses were performed using the SAF population, which included all patients who received at least one dose of study drug, according to the treatment they received.

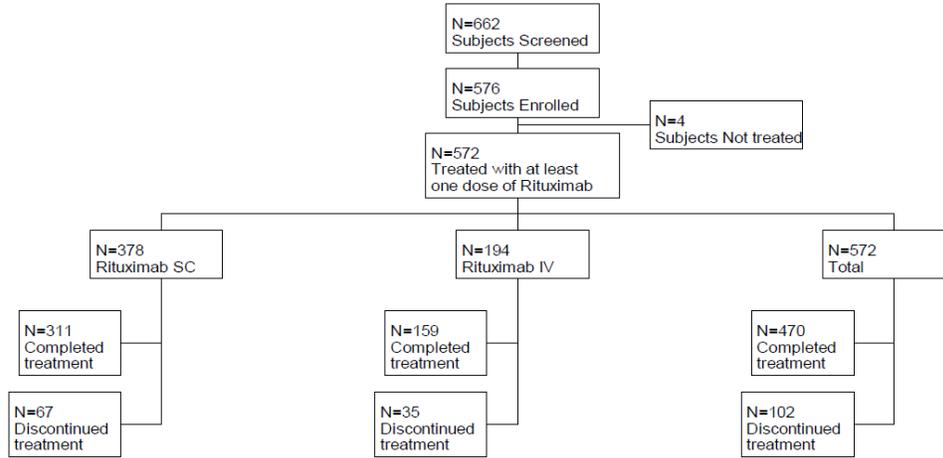
At the time of the Primary Analysis, the ITT_{CTSQ} and ITT_{RASQ} populations were used for analyses of patient-reported outcomes, and included all patients in the ITT population who completed the CTSQ and RASQ questionnaires, respectively, at Visit 3/Cycle 3 and Visit 8/Cycle 7.

A total of 572 patients received at least one dose of study drug; 369 patients received at least one administration of rituximab SC.

Subject disposition

A total of 662 patients were screened for entry into the study. Of these, 86 patients failed the screening procedure. Overall, 576 patients from 151 centers in 25 countries were enrolled into the study. These patients were randomized in a 2:1 ratio into the 2 treatment groups: 381 patients to rituximab SC and 195 patients to rituximab IV. The disposition of the patients was summarized below in Figure 6 and Table 13.

Figure 6 MabEase Study Disposition of Patients



Source data: [Figure 14.4](#) in Section 7.1.

[Source: MO28107 report page 51]

Table 13 All randomized patients

	Rituximab SC	Rituximab IV	Total
	N=381	N=195	N=576
Screened			662
Screened but not enrolled			86
Enrolled			576
Randomized	381	195	576
Treated with at least one dose	378 (99.2%)	194 (99.5%)	572 (99.3%)
Complete Study Treatment	311 (81.6%)	159 (81.5%)	470 (81.6%)
Withdrew from study treatment	67 (17.6%)	35 (17.9%)	102 (17.7%)
Primary reason for withdrawal from study treatment			
Withdrawal of consent by the patient	5 (1.3%)	3 (1.5%)	8 (1.4%)

Investigator decision	6 (1.6%)	2 (1.0%)	8 (1.4%)
Lack of compliance	3 (0.8%)	2 (1.0%)	5 (0.9%)
Treatment Failure	0	1 (0.5%)	1 (0.2%)
Progression disease	9 (2.4%)	5 (2.6%)	14 (2.4%)
Intercurrent illness	2 (0.5%)	0	2 (0.3%)
Protocol violation	6 (1.6%)	4 (2.1%)	10 (1.7%)
Adverse event	33 (8.7%)	16 (8.2%)	49 (8.5%)
Stable disease	2 (0.5%)	1 (0.5%)	3 (0.5%)
Lost to follow-up	1 (0.3%)	1 (0.5%)	2 (0.3%)
Discontinued from study	106 (27.8%)	57 (29.2%)	163 (28.3%)
Primary reason for study discontinuation			
Withdrawal of consent by the patient	14 (3.7%)	11 (5.6%)	25 (4.3%)
Protocol violation	5 (1.3%)	3 (1.5%)	8 (1.4%)
Treatment Failure	4 (1.0%)	2 (1%)	6 (1%)
Death	63 (16.5%)	29 (14.9%)	92 (16%)
SD at interim staging or pd at any time during the study	4 (1%)	2 (1%)	6 (1%)
Lost to follow-up	14 (3.7%)	8 (4.1%)	22 (3.8%)
Lack of compliance	2 (0.5%)	2 (1%)	4 (0.7%)
Missing	0	0	0

[Source: MO28107 report page 125-126 and statistical reviewer's analysis; Note: there is discrepancy in numbers in primary reason for study discontinuation between statistical reviewer's analysis and the sponsor's analysis; there is no impact on efficacy evaluation of the study]

Median observation (follow-up) time was approximately 28 months providing 13 months of additional follow-up since the Primary Analysis.

Subject demographics and baseline disease characteristics

Subject demographics appear to be balanced between Rituximab SC arm and Rituximab IV arm. Only all randomized patients (RND) demographics are included in Table 14:

Table 14 MabEase Demographic Information

	Rituximab SC N = 381	Rituximab IV N = 195	Total N = 576
Gender			
Male	209 (54.9%)	100 (51.3%)	309 (53.6%)
Female	172 (45.1%)	95 (48.7%)	267 (46.4%)
Race			
WHITE	298 (78.2%)	156 (80.0%)	454 (78.8%)
BLACK OR AFRICAN AMERICAN	1 (0.3%)	0	1 (0.2%)
ASIAN	23 (6.0%)	11 (5.6%)	34 (5.9%)
OTHER	33 (8.7%)	15 (7.7%)	48 (8.3%)
NOT APPLICABLE AS PER LOCAL REGULATION	26 (6.8%)	13 (6.7%)	39 (6.8%)
Ethnicity			
HISPANIC OR LATINO	35 (9.2%)	14 (7.2%)	49 (8.5%)
NOT HISPANIC OR LATINO	162 (42.5%)	100 (51.3%)	262 (45.5%)
OTHER	36 (9.4%)	10 (5.1%)	46 (8.0%)
NOT APPLICABLE AS PER LOCAL REGULATION	4 (1.0%)	1 (0.5%)	5 (0.9%)
MISSING	144 (37.8%)	70 (35.9%)	214 (37.2%)
Age (years)			
Mean (SD)	60.4 (13.86)	61.0 (12.37)	60.6 (13.37)
Median	64.0	64.0	64.0
25th - 75th Percentile	54 - 70	54 - 71	54 - 71
Minimum - Maximum	18 - 80	24 - 80	18 - 80
n	381	195	576
Age (years)			
<60	147 (38.6%)	76 (39.0%)	223 (38.7%)
>=60	234 (61.4%)	119 (61.0%)	353 (61.3%)
Age (years)			
18-64	204 (53.5%)	104 (53.3%)	308 (53.5%)
65-84	177 (46.5%)	91 (46.7%)	268 (46.5%)
Height (cm)			
Mean (SD)	167.8 (9.95)	167.1 (10.36)	167.6 (10.08)
Median	168.0	167.0	167.0
25th - 75th Percentile	160 - 175	160 - 174	160 - 175
Minimum - Maximum	140 - 197	135 - 200	135 - 200
n	381	195	576
Weight (kg)			
Mean (SD)	75.13 (17.996)	76.21 (17.824)	75.50 (17.929)
Median	73.00	74.00	73.75
25th - 75th Percentile	62.0 - 84.0	63.7 - 86.0	62.6 - 85.0
Minimum - Maximum	40.0 - 156.5	40.0 - 160.0	40.0 - 160.0
n	381	195	576
Body Surface Area (m2)			
Mean (SD)	1.840 (0.2363)	1.847 (0.2331)	1.842 (0.2351)
Median	1.830	1.850	1.830
25th - 75th Percentile	1.67 - 1.98	1.67 - 1.99	1.67 - 1.98
Minimum - Maximum	1.35 - 2.62	1.27 - 2.79	1.27 - 2.79
n	381	195	576
Body Surface Area (m2)			
Low-BSA (BSA <= 1.70 m²)	115 (30.2%)	56 (28.7%)	171 (29.7%)
Medium-BSA (1.70 m² < BSA <= 1.90m²)	123 (32.3%)	65 (33.3%)	188 (32.6%)
High-BSA (BSA > 1.90 m²)	143 (37.5%)	74 (37.9%)	217 (37.7%)

[Source: MO28107 report page 137-138 and statistical reviewer’s analysis]

Baseline characteristics are provided in Table 15. The baseline characteristics appear to be balanced between arms.

Table 15 MabEase Baseline characteristics

	Rituximab IV N=195 (%)	Rituximab SC N=381 (%)
IPI risk category		
Low	31.3	31.0
Low-intermediate	29.2	29.9
High-intermediate	24.1	24.7
High	15.4	14.4
Chemotherapy regimen		
CHOP-14	11.3	9.4
CHOP-21	88.7	90.6

[Source: statistical reviewer’s analysis]

Protocol deviation

Please refer to Table 13 for information on protocol violations.

3.6.4 Results and Conclusions

3.6.4.1 Primary analysis results

The primary analyses based on all randomized patients (RND) are summarized. The RND population is defined as ITT as other studies, while ITT population in this submission was defined differently.

The primary endpoint results are presented in Table 16. The difference in CR rate at the end of induction is 4.9% better in SC arm compared to IV arm. The 95% confidence interval of the difference is -3.6% to 13.5%. The response rate ratio is 1.12 favoring SC arm with a 95% confidence interval of 0.92 to 1.36.

Table 16 Primary Endpoint DLBCL

Study	Endpoints	IV; 95% CI	SC; 95% CI	Diff: SC-IV, 95% CI	Response Rate 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]

[Source: statistical reviewer's analysis]

3.6.4.2 Secondary endpoints analyses results

3.6.4.2.1 Analyses results

The time-to-event secondary endpoints results are presented in Table 17. Kaplan-Meier curves of PFS and OS are included as [Source: statistical reviewer's calculation]

Figure 7 and [Source: statistical reviewer's calculation]

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Figure 8 respectively. As shown in the figures, the Kaplan-Meier curves stayed closed to each other and crossed at several time points.

The numbers of patients with events in the rituximab SC and rituximab IV arms are given in Table 17. The number of events in rituximab SC arm is larger than the number of events in rituximab IV arm for all of these time-to-event endpoints. The 2-year PFS, EFS, DFS and OS rates are estimated using the Kaplan-Meier method. The rate is about 7 to 8% higher in the rituximab IV arms than in the rituximab SC for PFS, EFS, and DFS. The estimated 2-year overall survival rates are similar in two arms.

The hazard ratio (HR) estimates are obtained through a Cox-regression model stratified by stratification factors (age (< 60 years, ≥ 60 years), International Prognostic Index (IPI) risk

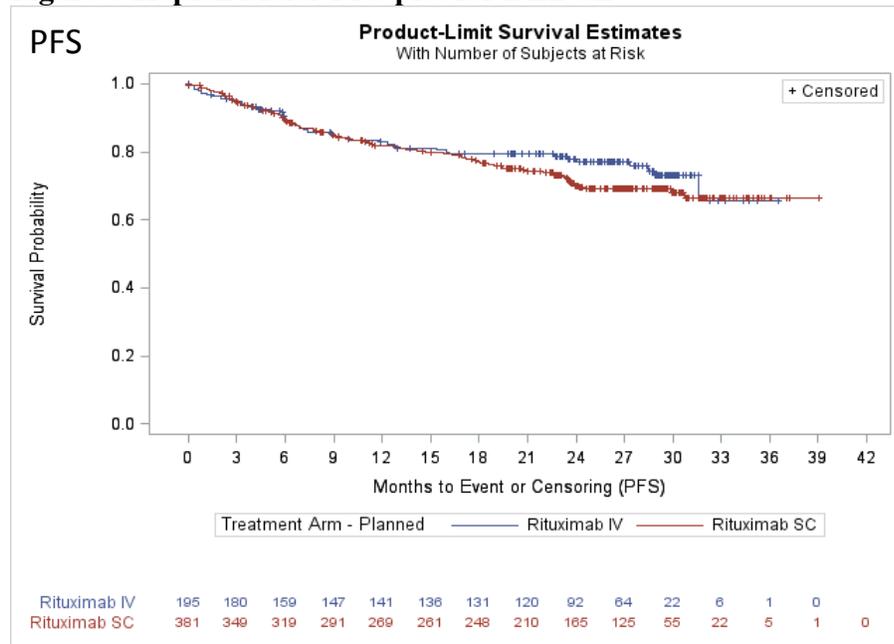
category (low, low-intermediate, high-intermediate, high), and chemotherapy regimen (CHOP administered every 21 days [CHOP-21] or CHOP administered every 14 days [CHOP-14])) in the trial. The point estimates of HRs (rituximab SC vs. rituximab IV) of PFS, EFS, DFS and OS are all above 1 and the 95% confidence intervals cover 1. The HRs of DFS and OS are 1.56 and 1.06 respectively. The number of events is relatively small in DFS and OS; therefore the confidence intervals are relatively wide. Overall, the clinical efficacy of rituximab SC is comparable to rituximab IV.

Table 17 Time-to-Event Secondary Endpoints DLBCL

	# of Patients with event (%); IV	# of Patients with event (%); SC	HR Stratified [95% CI]	2-Year Survival Rate, IV	2-Year Survival 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%

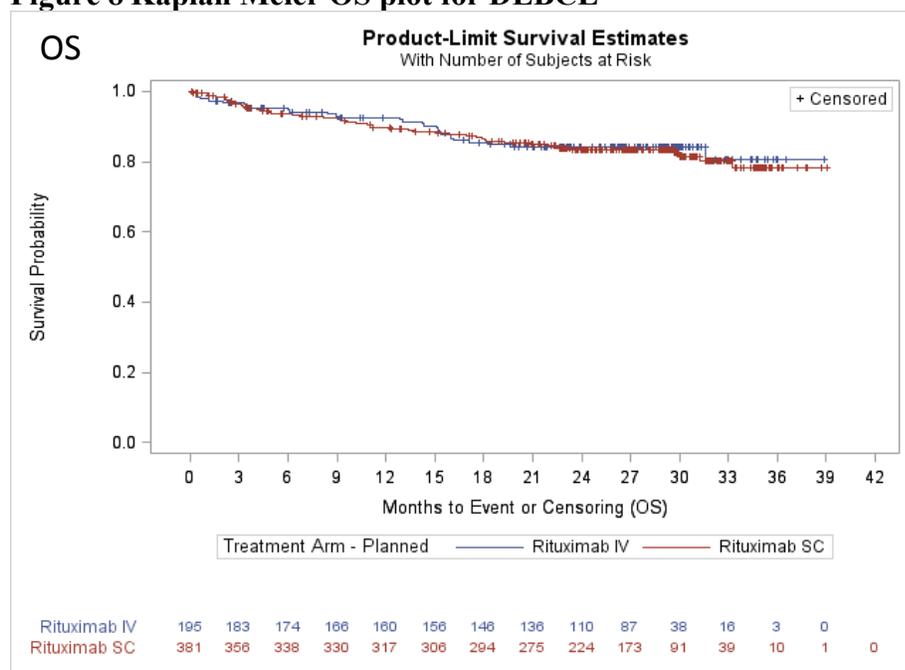
[Source: statistical reviewer’s calculation]

Figure 7 Kaplan Meier PFS plot for DLBCL



[Source: statistical reviewer’s calculation]

Figure 8 Kaplan Meier OS plot for DLBCL



[Source: statistical reviewer’s calculation]

3.6.4.3 Sensitivity analysis

The sponsor performed three sensitivity analyses for PFS (1, 2 and 3).

- In PFS1, progression dates include only those based on radiological assessments; clinical progression is not considered a progression endpoint. PFS1 is assigned to the first time when tumor progression was noted, and deaths occurring after 2 or more missed visits are censored at the last visit.
- PFS2 corrects for potential bias in follow-up schedules for tumor assessment by assigning the dates for censoring and events only at scheduled visit dates.
- PFS3 evaluates PFS including all signs of clinical progression as an event, such as when PD is recorded as a reason for treatment discontinuation.

The sensitivity analysis results Table 18 were consistent with those from the secondary analysis.

Table 18 MabEase Sensitivity Analysis on PFS

	HR and 95% CI
Sensitivity analysis PFS-1	1.17 [0.80, 1.71]
Sensitivity analysis PFS-2	1.17 [0.80, 1.71]
Sensitivity analysis PFS-3	1.15 [0.79, 1.65]

Sensitivity Analysis Method	Change from Original Analysis	Rituximab SC N = 381	Rituximab IV N = 195	Total N= 576
Table A. PFS 1	Censored at last radiological assessment based on new criteria	166 (43.6%)	90 (46.2%)	256 (44.4%)
	Censored at randomisation due to no baseline tumor assessments	1 (0.3%)	2 (1.0%)	3 (0.5%)
	Progression/Death based on new criteria	6 (1.6%)	4 (2.1%)	10 (1.7%)
	Progression/Death censored and brought forward due to two or more missed visits	13 (3.4%)	6 (3.1%)	19 (3.3%)
	Unchanged from original analysis	195 (51.2%)	93 (47.7%)	288 (50.0%)
Table B. PFS 2	Censored at last adequate assessment based on new criteria	164 (43.0%)	89 (45.6%)	253 (43.9%)
	Censored at randomisation due to no baseline tumor assessments	1 (0.3%)	2 (1.0%)	3 (0.5%)
	Progression/Death based on new criteria	6 (1.6%)	4 (2.1%)	10 (1.7%)
	Progression/Death censored and brought forward due to two or more missed visits	13 (3.4%)	6 (3.1%)	19 (3.3%)
	Unchanged from original analysis	197 (51.7%)	94 (48.2%)	291 (50.5%)
Table C. PFS 3	Censored at last adequate assessment based on new criteria	159 (41.7%)	87 (44.6%)	246 (42.7%)
	Censored at randomisation due to no baseline tumor assessments	1 (0.3%)	1 (0.5%)	2 (0.3%)
	Progression/Death based on new criteria	3 (0.8%)	3 (1.5%)	6 (1.0%)
	Progression/Death censored and brought forward due to two or more missed visits	13 (3.4%)	6 (3.1%)	19 (3.3%)
	Unchanged from original analysis	205 (53.8%)	98 (50.3%)	303 (52.6%)

[Source: MO28107 report page 270, 272, 274, 276 and statistical reviewer’s analysis]

3.6.4.4 Patient-reported outcomes analyses

Please refer to clinical outcome review of this application for patient-reported outcome results and conclusions for patient-reported outcome.

3.7 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

3.8 Benefit-risk assessment

Overall, the clinical efficacy of rituximab SC is comparable to rituximab IV in MabEase study. Whether the submission demonstrated an overall favorable risk-benefit profile on Rituximab SC over IV is deferred to the clinical team reviewing this submission.

Study MO28457/ PrefMab

3.9 PrefMab Data and Analysis Quality

The efficacy endpoints such as patient preference (PPQ) were derived and saved in analysis datasets “ADPREF”, time-to-event endpoints were derived and saved in analysis datasets “ADTTE” for investigator assessment and IRC assessment respectively. The statistical reviewer is able to reproduce the derived efficacy analysis datasets from the BLA tabulation datasets.

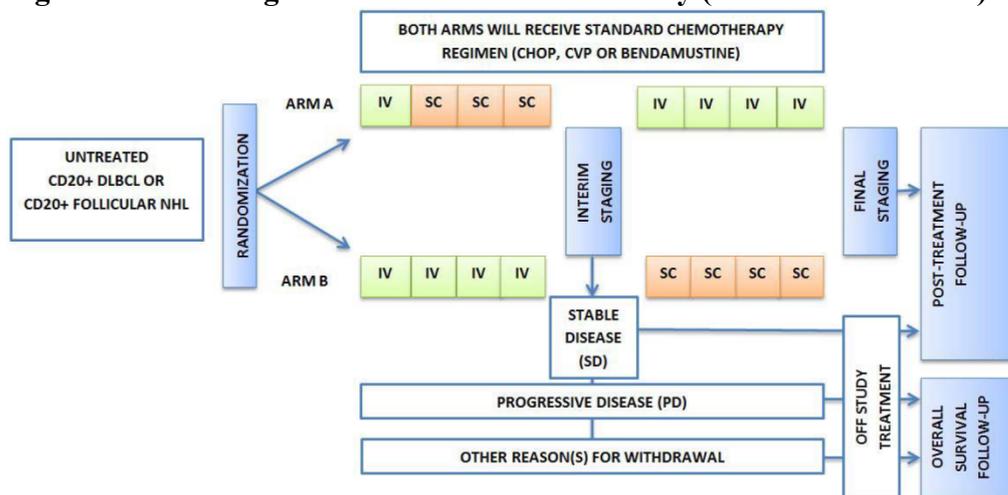
3.10 PrefMab Evaluation of Efficacy

3.10.1 Study Design and Endpoints

3.10.1.1 Study Design

PrefMab is a Phase IIIb, prospective, multi-center, multinational, open-label, randomized study in 743 adult patients with previously untreated CD20-positive DLBCL or CD20-positive FL Grade 1, 2, or 3a. Prior to starting therapy, all eligible patients were randomized in a 1:1 ratio to Treatment Arm A (or Arm B as shown in Figure 9). Patients received rituximab SC at a fixed dose of 1400 mg and received rituximab IV at a dose of 375 mg/m². Subjects were administered a patient preference questionnaire (PPQ) following cycles 6 and cycle 8, and 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 (CHOP; cyclophosphamide, vincristine, prednisone/prednisolone [CVP]; or bendamustine), which was selected by the investigator before randomization. The primary endpoint for PrefMab was the proportion of patients who preferred rituximab SC over rituximab IV.

Figure 9 Trial Design for Patient Preference Study (MO28457/PrefMab)



[Source: Roche Clinical Study Report MO28457 CSR Page 4]

A total of 619 patients (311 in Arm A and 308 in Arm B) completed the study. In the study, 465 patients (62.8%) were diagnosed with DLBCL and 273 (36.9%) with follicular NHL (two patients did not have a lymphoma type recorded but were included in the total).

The efficacy of rituximab was evaluated during induction and follow-up in terms of CR/CRu rate, PFS, EFS, DFS, and OS. Response was assessed on the basis of radiographic and clinical evidence of disease according to the International Working Group (IWG) response criteria using the following response categories: complete response/complete response unconfirmed (CR/CRu), partial response, stable disease, and progressive disease.

The sample size was estimated based on assumptions that 75% patients preferred rituximab SC and half width of the confidence limits is 3.6%, a total of 560 patients would be needed. To obtain evaluable preference information from 560 patients, approximately 700 patients were randomized to treatment. An interim analysis of patient preference was performed when approximately 100 patients had completed their preference questionnaire after the Cycle 6 rituximab dose. Patient-assessed satisfaction and convenience using RASQ (Rituximab

Administration Satisfaction Questionnaire) and CTSQ (Cancer Therapy Satisfaction Questionnaire), as well as safety data, were also summarized at this time.

3.10.1.2 Efficacy Endpoints

The primary analysis of patient preference took place when all patients had completed induction treatment. Secondary endpoints were also summarized at the same time. No formal statistical hypothesis tests performed.

The binary primary endpoint (patient preference for rituximab SC versus rituximab IV) is the proportion of patients who preferred rituximab SC over rituximab IV. This is the first question of the patient preference questionnaire (PPQ). Patient preference at cycle 8 is the primary endpoint.

The secondary endpoints of the efficacy of rituximab SC are evaluated:

- 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): time from randomization to first occurrence of progression or relapse, according to the International Working Group (IWG) response criteria or other country-specific standards, or initiation of a non-protocol-specified anti-lymphoma therapy or death, whichever occurred first
- Disease-free survival (DFS): period from the date of the initial CR/CRu until the date of relapse or death from any cause, whichever occurred first
- Progression-free survival (PFS): time from randomization to the first occurrence of progression or relapse, according to the IWG response criteria or other country-specific standards, or death from any cause, whichever occurred first
- Overall survival (OS): time from randomization to death from any cause

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.

The primary endpoint will be presented by the following subgroups:

- Age group (<60 years, \geq 60 years)
- IPI risk category (low, low-intermediate, high intermediate, high) and FLIPI risk category (low, intermediate, high).
- Diagnosis (DLBCL, NHL)
- Chemotherapy regimen (CHOP [including CVP+CHOP], CVP or bendamustine)
- Country

3.10.2 Statistical Methodologies

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.

For secondary endpoints, the CR/CRu rate measured 28 (\pm 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. In addition, the length of follow-up on the study will be summarized using the Kaplan-Meier estimate of potential follow-up using the reverse Kaplan-Meier.

For patient-reported outcome, patient-assessed satisfaction and convenience using RASQ and CTSQ were summarized and presented by treatment group.

3.10.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis Population

The intent-to-treat (ITT) population included all patients randomized into the study. Efficacy and patient-reported outcomes (patient preference, RASQ, and CTSQ) endpoints were summarized based on the ITT population.

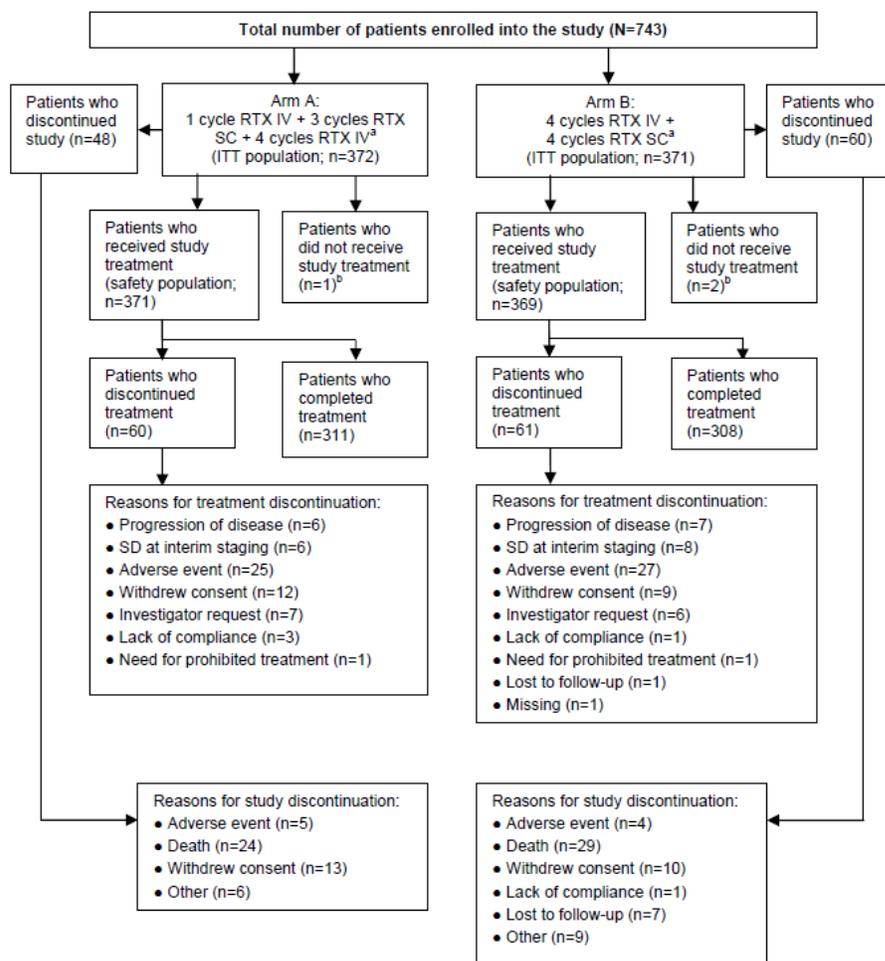
The modified intent-to-treat (mITT) population included all patients who were randomized into the study, received both routes of administration, and completed the primary question in the PPQ at either Cycle 6 or Cycle 8. The mITT population was used for sensitivity analyses of patient preference, RASQ, and CTSQ.

The safety population included all patients who received at least one dose of rituximab IV or rituximab SC. The safety data was summarized based on the safety population.

Subject disposition

The study MO28457 randomized 743 patients, 372 to Arm A and 371 to Arm B from 201 enrolling sites in 32 countries. One patient (0.27%) randomized to Arm A did not receive treatment because of death before first treatment administration. Two patients (0.54%) randomized to Arm B did not receive treatment because of death before first treatment administration. Of the patients who received treatment, 60 patients (16.2%) discontinued treatment in Arm A and 61 patients (16.5%) discontinued treatment in Arm B. The most common reason for treatment discontinuation is adverse event. The patient disposition was summarized in Figure 10.

Figure 10 PrefMab Patient Disposition



Abbreviations: ITT=intent-to-treat; IV=intravenous; RTX=rituximab; SC=subcutaneous; SD=stable disease.

[Source: Study report MP28457 page 34 and statistical reviewer's analyses]

Subject demographics and baseline disease characteristics

A total of 465 (62.8%) patients were diagnosed with DLBCL (235 patients [63.3%] in Arm A and 230 [62.3%] in Arm B), and 273 patients (36.9%) were diagnosed with follicular NHL (136 patients [36.7%] in Arm A and 137 [37.1%] in Arm B). Two patients did not have a lymphoma type recorded but were included in the safety population.

Median age at baseline in both groups was 60 years; 51% of patients were ≥ 60 years of age. The majority of patients were Caucasians (70%) or Asians (21%). Median BSA was 1.79 m². Thirty-seven percent of patients had FL: median age was 59 years, and the majority of patients with FL had FLIPI high risk or intermediate risk scores (40% and 37%, respectively). Sixty-three percent of patients had DLBCL: median age was 61 years, and a greater proportion of patients were considered as IPI low risk or low-intermediate risk (36% and 28%, respectively). A total of 620 patients (83.8%) completed all 8 cycles of treatment, with similar percentages

observed in Arm A and Arm B. The median duration of treatment exposure was 149.0 days (4.9 months).

The study demographics and baseline characteristics are summarized in Table 19:

Table 19 PrefMab Demographic and Baseline Characteristics (ITT population)

		Arm A (N=372)	Arm B (N=371)	Total (N=743)
Age	Mean (SD)	58.28 (13.2)	59.35 (12.6)	58.82 (12.9)
	Range	18-80	23-80	18-80
Weight	Mean (SD)	73.43 (18.2)	73.15 (17.3)	73.29 (17.7)
Body Surface Area	Mean (SD)	1.81 (0.24)	1.81 (0.24)	1.81 (0.24)
Height	Mean (SD)	166.8 (11.1)	166.5 (10.6)	166.7 (10.9)
Gender	Male	185 (49.7%)	190 (51.2%)	375 (50.5%)
	Female	187 (50.3%)	181 (48.8%)	368 (49.5%)
IPI Score	Low Risk	87 (23.4%)	83 (23.4%)	170 (22.9%)
	Low Intermediate Risk	65 (17.5%)	67 (18.1%)	132 (17.8%)
	High Intermediate Risk	53 (14.2%)	49 (13.2%)	102 (13.7%)
	High Risk	31 (8.3%)	35 (9.4%)	66 (8.9%)
Childbearing Potential (Female)	Yes	23 (6.2%)	36 (9.7%)	59 (7.9%)
	No	164 (44.1%)	145 (39.1%)	309 (41.6%)
FLIPI	Mean (SD)	2.21 (0.8)	2.15 (0.8)	2.18 (0.8)
	N	136	137	273
Ethnicity	Hispanic	65 (17.5%)	65 (17.5%)	130 (17.5%)
	Non-Hispanic	191 (51.3%)	199 (53.6%)	390 (52.5%)
	Other	57 (15.3%)	56 (15.1%)	113 (15.2%)

	Not applicable Per local regulation	59 (15.9%)	51 (13.7%)	110 (14.8%)
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[Source: statistical reviewer’s analyses]

Protocol deviation

Two patients were withdrawn due to protocol violations.

3.10.4 PrefMab Results and Conclusions

3.10.4.1 Primary analysis results

For the primary endpoint of patient preference, patients filled out the questionnaire after completing cycle 6 and cycle 8 of rituximab + IV chemotherapy treatment. After Cycle 6, 495 of 620 patients (79.8%) preferred SC administration (CI: 76.5%, 82.9%), with 36.1% showing a very strong preference for SC administration, and another 34.4% expressing a fairly strong preference for SC. A similar percentage of patients expressed a preference for rituximab SC administration after Cycle 8: 477 of 591 patients overall (80.7%; 95% CI: 77.3%, 83.8%), 226 of 293 patients in Arm A (77.1%; 95% CI: 71.9%, 81.8%), and 251 of 298 patients in Arm B (84.2%; 95% CI: 79.6%, 88.2%). A total of 471 patients (83.2%) retained their preference between Cycle 6 and Cycle 8. The results were summarized in Table 20.

Table 20 Patient Preference Results

		Prefer SC	Prefer IV	No Preference	Complete PPQ	Total
Cycle 8	n (%)	477 (80.7%)	66 (11.2%)	48 (8.1%)	591	743
	95% CI	77.3%, 83.3%	8.7%, 14.0%	6.0%, 10.6%		
	Arm A	226 (77.1%)	37 (12.6%)	30 (10.2%)	293	372
	95% CI	71.9%, 81.8%	9.0%, 17.0%	7.0%, 14.3%		
	Arm B	251 (84.2%)	29 (9.7%)	18 (6%)	298	371
	95% CI	79.6%, 88.2%	6.6%, 13.7%	3.6%, 9.4%		
Cycle 6	n (%)	495 (79.8%)	62 (10%)	63 (10.2%)	620	743
	95% CI	76.5%, 82.9%	7.8%, 12.6%	7.9%, 12.8%		
	Arm A	246 (79.1%)	33 (10.6%)	32 (10.3%)	311	372
	95% CI	74.2%, 83.5%	7.4%, 14.6%	7.1%, 14.2%		
	Arm B	249 (80.6%)	29 (9.4%)	31 (10%)	309	371
	95% CI	75.7%, 84.8%	6.4%, 13.2%	6.9%, 13.9%		

[Source: statistical reviewer’s analyses]

3.10.4.2 Sensitivity analysis

The sponsor did a sensitivity analysis on patient preference on modified ITT population. The results were summarized in **Table 21** and it showed consistent results as ITT population.

Table 21 Sensitivity analysis on patient preference on modified ITT population

Protocol no.: MO28457 (Final Analysis)

Table 5.1.2
Number (%) of Patients Indicating a Preference for Rituximab SC over Rituximab IV by Treatment Sequence
mITT Population

Variable	Arm A (N=323)	Arm B (N=322)	Total (N=645)
Patients Completing the Patient Preference Questionnaire - Cycle 6			
n	311	309	620
Patients who prefer SC, [n (%)]	246 (79.1%)	249 (80.6%)	495 (79.8%)
95% confidence interval	74.2%, 83.5%	75.7%, 84.8%	76.5%, 82.9%
Strength of preference			
Very Strong	121 (38.9%)	103 (33.3%)	224 (36.1%)
Fairly Strong	105 (33.8%)	108 (35.0%)	213 (34.4%)
Not Very Strong	19 (6.1%)	38 (12.3%)	57 (9.2%)
Patient didn't answer the question	1 (0.3%)	0	1 (0.2%)
Reason for preference			
Feels less emotionally distressing	87 (28.0%)	85 (27.5%)	172 (27.7%)
Requires less time in the clinic	219 (70.4%)	205 (66.3%)	424 (68.4%)
Lower level of injection site pain	35 (11.3%)	52 (16.8%)	87 (14.0%)
Feels more comfortable during administration	118 (37.9%)	113 (36.6%)	231 (37.3%)
Other reason	4 (1.3%)	4 (1.3%)	8 (1.3%)
Patient didn't answer the question	21 (6.8%)	22 (7.1%)	43 (6.9%)
Patients who prefer IV, [n (%)]	33 (10.6%)	29 (9.4%)	62 (10.0%)
Strength of preference			
Very Strong	7 (2.3%)	10 (3.2%)	17 (2.7%)
Fairly Strong	18 (5.8%)	14 (4.5%)	32 (5.2%)
Not Very Strong	8 (2.6%)	5 (1.6%)	13 (2.1%)
Patient didn't answer the question	0	0	0
Reason for preference			
Feels less emotionally distressing	19 (6.1%)	17 (5.5%)	36 (5.8%)
Requires less time in the clinic	8 (2.6%)	0	8 (1.3%)
Lower level of injection site pain	14 (4.5%)	8 (2.6%)	22 (3.5%)
Feels more comfortable during administration	20 (6.4%)	19 (6.1%)	39 (6.3%)
Other reason	0	3 (1.0%)	3 (0.5%)
Patient didn't answer the question	3 (1.0%)	7 (2.3%)	10 (1.6%)
Patients with no preference, [n (%)]	32 (10.3%)	31 (10.0%)	63 (10.2%)

* Change in preference calculated between cycles 6 and 8 questionnaires.

Source: Listing 5.1

Analysis dataset: ADPREF

[Source: Study report MP28457 page 926 and statistical reviewer's analyses]

3.10.4.3 Secondary endpoints analyses results

3.10.4.3.1 Analyses results

Table 22 gives the results of complete response rates for Arm A and Arm B. The complete response rate is about 43% for the two arms and about 78% for overall response. Please note the numbers reported are different from the applicant. The applicant calculated the response rate using the number of subjects without missing assessment as the denominator. It is given as small n in the table; while FDA used ITT (Intent-to-Treat) population, which includes all the patients randomized to the arm. The number is the capital N in the table. FDA's calculation is consistent with other studies.

Table 22 Complete response rate in PrefMab

	Arm A SC → IV	Arm B IV → SC
ITT	N=372	N=371
n	310	315
CR/CRu; n(%)	159 (42.7%)	165 (44.5%)
95% CI	37.7%, 47.9%	39.3%, 49.7%
CR/CRu/PR; n(%)	290 (78%)	290 (78.2%)
95% CI	73.4%, 82.1%	73.6%, 82.3%

[Source: statistical reviewer’s analyses]

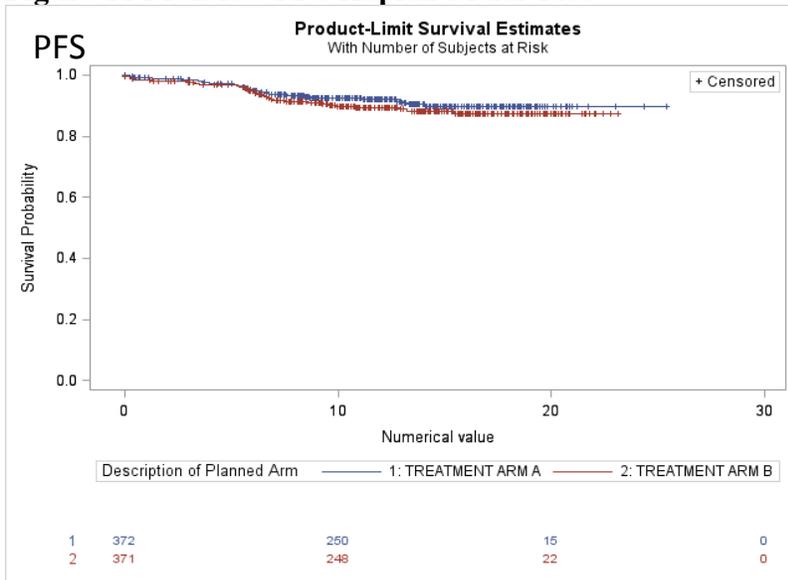
Secondary endpoints of time-to-event endpoints are summarized in Table 23. The number of events and 1-year survival rate calculated from Kaplan-Meier curves for two arms are given in the table. As can be seen from the table, the results are comparable between the two arms and the cross-over did not impact efficacy.

Table 23 PrefMab Time-to-event endpoints

Endpoints	# with event (%) ; Arm A	# with event (%) ; Arm B	Rate at 1 year, Arm A	Rate at 1 year, Arm B
PFS	31 (8.3%)	39 (10.5%)	92.0%	89.3%
EFS	121 (32.5%)	111 (29.9%)	65.1%	68.2%
DFS	3 (1.9%)	3 (1.8%)	97.2%	97.2%
OS	24 (6.5%)	33 (8.9%)	93.8%	91.1%

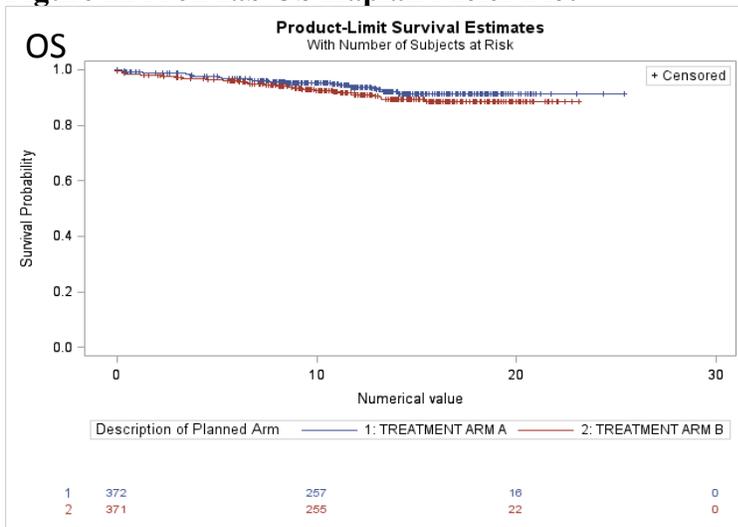
At 12 months, 92% of patients in Arm A and 89% of patients in Arm B were alive and had not experienced disease progression (i.e., PFS). No significant differences between the two treatment groups were observed for any of the survival variables. The Kaplan-Meier plots of PFS and OS are provided in Figure 11 and Figure 12.

Figure 11 PrefMab PFS Kaplan-Meier Plot



[Source: statistical reviewer’s analyses]

Figure 12 PrefMab OS Kaplan-Meier Plot



[Source: statistical reviewer’s analyses]

3.10.4.3.2 Patient-reported Outcome Analyses results

There were no major differences in the results of the CTSQ, between rituximab IV and rituximab SC administered at cycles 4 and 8. Mean scores for each of the three domains after rituximab SC treatment or rituximab IV treatment are summarized in Table 24.

Table 24 CTSQ Mean Scores by Domain, ITT population

Domain	CTSQ Score after IV n=740 (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)

[Source: Statistical reviewer's analysis]

Results from the RASQ, also administered at cycles 4 and 8, favored rituximab SC in four out of five domains. The results were summarized in Table 25.

Table 25 RASQ Mean Scores by Domain, ITT population

Domain	RASQ Score after IV n=740 (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)

[Source: Statistical reviewer's analysis]

Please refer to clinical outcome reviewer's review for summary and conclusions for patient-reported outcome.

3.11 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

3.12 Benefit-risk assessment

Overall, the clinical efficacy of rituximab SC is comparable to rituximab IV in PrefMab study. Whether the submission demonstrated an overall favorable risk-benefit profile on Rituximab SC over IV is deferred to the clinical team reviewing this submission.

Study BO25341/ SAWYER

3.13 Data and Analysis Quality

The efficacy endpoints such as tumor response were derived and saved in analysis datasets "RESPONSE" for investigator assessment. The statistical reviewer is able to reproduce the derived tumor response analysis datasets from the BLA tabulation datasets.

3.14 SAWYER Evaluation of Efficacy

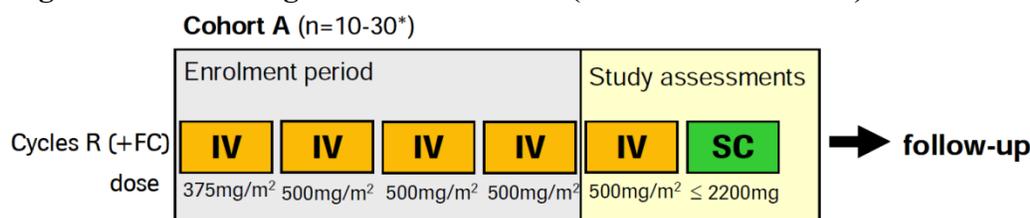
3.14.1 Study Design and Endpoints

3.14.1.1 Study Design

Study BO25341, also known as SAWYER, was a two part clinical trial entitled “An adaptive, comparative, randomized, parallel-group, multi-center, Phase Ib study of subcutaneous (SC) rituximab versus intravenous (IV) rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated Chronic Lymphocytic Leukemia”. This trial was designed with two parts, the primary objective of part 1 (pilot dose selection) was to confirm a selected rituximab SC dose that would result in a C_{trough} comparable to rituximab IV.

In Part 1, the first dose was rituximab IV 375 mg/m², doses 2 to 5 were rituximab IV 500 mg/m², and dose 6 was rituximab SC 1400 mg, 1600 mg or 1870 mg. PK parameters were assessed during cycles 5 (rituximab IV) and cycle 6 (rituximab SC). The schema for part 1 is displayed in Figure 13.

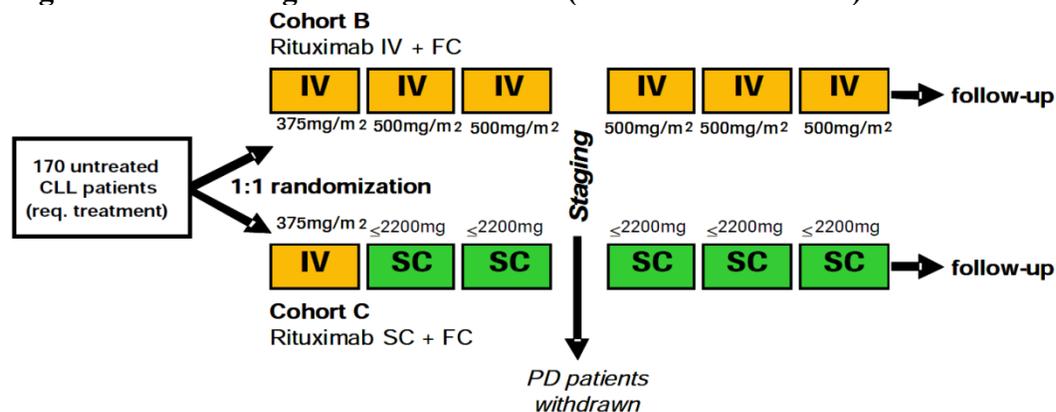
Figure 13 Trial Design for CLL – Part A (BO25341/SAWYER)



[Source: Roche Clinical Study Report- Protocol BO25341 page 42]

The primary objective for part 2 was to establish non-inferiority in observed C_{trough} levels between the selected rituximab SC dose and rituximab IV. For this part, patients were randomized 1:1 to rituximab IV (cohort B) or rituximab SC (cohort C). The schema for part 2 is displayed in Figure 14.

Figure 14 Trial Design for CLL – Part B (BO25341/SAWYER)



[Source: Roche Clinical Study Report- Protocol BO25341 page 43]

As shown in Figure 14, patients received 6 cycles of treatment with an interim staging after 3 cycles and patients with progressive disease at that point were withdrawn from the study. Rituximab was given as an IV infusion for the first cycle for all patients. Similar to part 1, the dose for the rituximab IV arm (cohort B) was 375 mg/m² for cycle 1 followed by rituximab IV 500 mg/m² for doses 2-6. For the rituximab SC arm, for first cycle was rituximab IV 375 mg/m², followed by rituximab SC 1600 mg SC for cycles 2-6. The primary endpoint of the Part 2 of the BO25341/SAWYER study was non-inferiority in C_{trough} between rituximab SC over rituximab IV arm. The secondary endpoint was response rate including CR, complete response with incomplete bone marrow recovery (CRi), and partial response (PR).

The sample size for part 2 was based on C_{trough} levels of rituximab. Non-inferiority margin 0.8 was used with 63% coefficient of variation for a power of 80% and type I error of 5%. The sample size also included 20% drop out.

For Part 2, a pre-planned futility analysis was performed after PK data from approximately 60 patients who had completed Cycle 5 were available (observed C_{trough} pre-dose Cycle 6). The analysis was performed to confirm the results from Part 1 and to exclude the possibility that a relevant difference in C_{trough} levels existed between the SC and IV rituximab formulations.

3.14.1.2 Efficacy Endpoints

For Part 2, the following one sided null hypothesis was tested in the primary analysis of the primary criterion (observed C_{trough} Cycle 5):

H₀: C_{troughSC}/C_{troughIV} ≤ 0.8 versus H₁: C_{troughSC}/C_{troughIV} > 0.8

Exploratory assessment of the efficacy of SC rituximab compared with IV rituximab, including:

- Response rate [complete response (CR), complete response with incomplete bone marrow recovery (CRi), partial response (PR)];
- Progression-free survival (PFS);
- Event free survival (EFS);
- Overall survival (OS).

PFS was defined as the time from randomization to disease progression/relapse or death due to any cause. If the specified event (disease progression/relapse, death) did not occur, PFS was censored at the last tumor assessment date showing no evidence of progression, either during treatment or follow up.

EFS was defined as the time from randomization to disease progression/relapse, death or initiation of new anti-CLL therapy treatment. If the specified event (progression/relapse, death or new anti-CLL treatment) did not occur, EFS was censored at the last tumor assessment date either during treatment or follow up.

OS was defined as the time from the date of randomization to the date of death, regardless of the cause of death. Subjects who were alive at the time of the analysis were censored at the date of the last follow-up assessment. Subjects without follow-up assessment were censored at the day

of last dose and subjects with no post-baseline information were censored at the time of randomization.

3.14.2 Statistical Methodologies

Efficacy endpoints analyses were considered exploratory. Response rates at the end of Part 2 (CR, CRi and PR), were analyzed in frequency tables including 95% Pearson-Clopper confidence intervals by treatment group. For the difference in response rates, 95% confidence intervals (Hauck-Andersen) were calculated.

For the analysis of tumor response rate, a patient was considered to be a responder if their response was either CR, CRi or PR. Patients whose disease was stable (SD), had progressed (PD) or patients who had a missing response assessment were considered to be non-responders.

Time-to-event endpoints (PFS, EFS and overall survival OS) for Part 2 have not been analyzed because these data are not yet mature. These parameters will be analyzed and presented in the final (follow-up) CSR.

3.14.3 Patient Disposition, Demographic and Baseline Characteristics

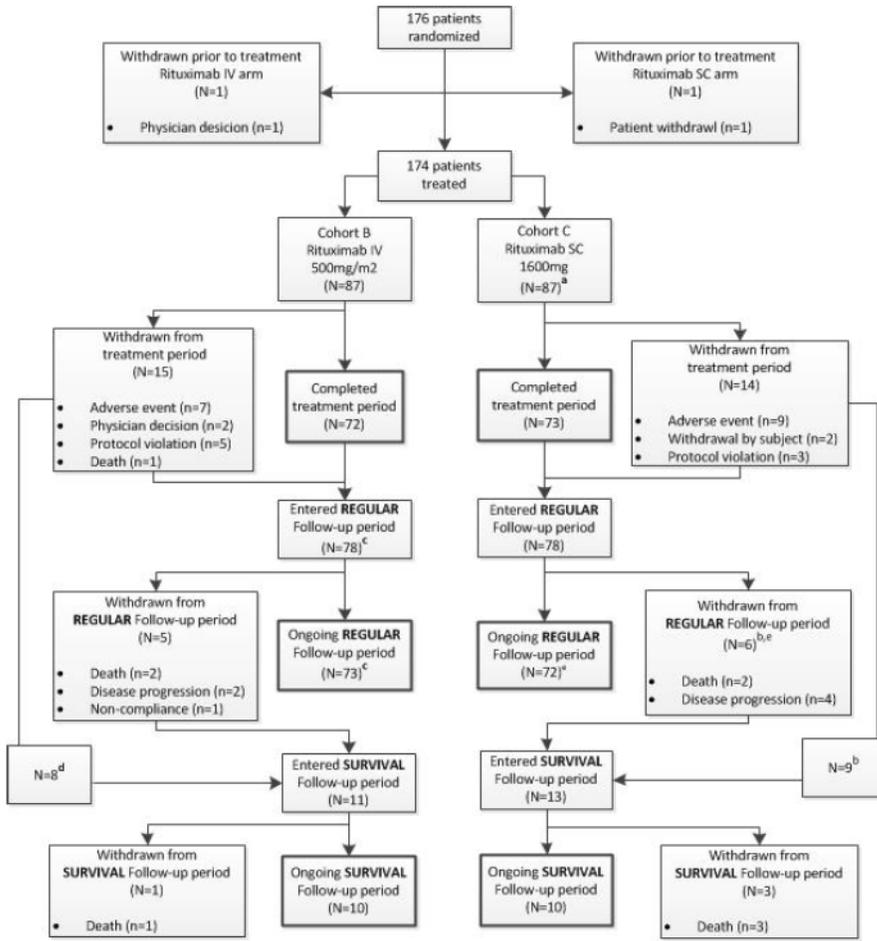
Analysis Population

All efficacy endpoints were analyzed according to the intent-to-treat (ITT) population, which included all patients randomized into Part 2, irrespective of whether or not they received study medication.

Subject disposition

Out of 176 patients randomized, there is 1 patient in each arm that was withdrawn prior to treatment. For the patients completed and withdrawn during study period and follow-up period, it is balanced between the two treatment arms. The most common reason for withdrawal from the treatment period was due to an adverse event, which affected 8% (7/88) and 10% (9/88) of rituximab IV and rituximab SC patients, respectively. The patient disposition was given in Figure 15 and Table 26.

Figure 15 SAWYER Patient Disposition



[Source: Study report BO25341 page 79]

Table 26 SAWYER Patient Disposition

	Rituximab IV 500 mg/m ² N=88	Rituximab SC 1600 mg N=88	Total N=176
Patients randomized	88 (100%)	88 (100%)	176 (100%)
Patients treated	87 (99%)	87 (99%)	174 (99%)
Treatment period:			
On-going	0 (0%)	0 (0%)	0 (0%)
Treatment period completed	72 (82%)	73 (83%)	145 (82%)
Treatment period withdrawal	15 (17%)	14 (16%)	29 (16%)
Study Follow-up period: §			
On-going	72 (82%)	73 (83%)	145 (82%)
Follow-up period completed	0 (0%)	0 (0%)	0 (0%)
Follow-up period withdrawal	5 (6%)	6 (7%)	11 (6%)
Survival Follow-up period: &			
On-going	10 (11%)	10 (11%)	20 (11%)
Follow-up period completed	0 (0%)	0 (0%)	0 (0%)
Follow-up period withdrawal	1 (1%)	3 (3%)	4 (2%)

§ Patients will go into 'study follow-up' after they have completed treatment, or if they withdrew from treatment (depending in part upon the reason of withdrawal).

& Patients will go into 'survival follow-up' after withdrawal from study follow-up or after withdrawal from the treatment period (depending in part upon reason for withdrawal).

- Percentages are based on N.

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Page 1 of 1

[Source: Study report BO25341 page 80 and statistical reviewer's calculation]

Subject demographics and baseline disease characteristics

The age demographics were balanced between the two groups. For part 2 the mean age of the combined arms was 58.8 years with a minimum age of 25 and a maximum age of 78. The majority of the patients were white 93.8%, 1.1% American Indian/Alaska Native, 2.8% other and 2.3% were blank. The mean time from first CLL diagnosis was 36.1 months with a range of 0.0 months to 388.5 months. The Binet stage and actual treatment received is displayed in Table 27.

Table 27 Baseline Demographic Characteristics (CLL)

	Rituximab IV N=88	Rituximab SC N=88
Binet Stage		
A	14.8	12.5
B	62.5	62.5
C	22.7	25.0
Actual chemotherapy route		
IV	67.0	68.2
Oral	31.8	29.5
Both	0.0	1.1

[Source: Statistical reviewer's calculation]

Protocol deviation

The information on protocol deviation was included in Table 28.

Table 28 SAWYER Protocol Violations

	Rituximab IV 500 mg/m ² (N=88)	Rituximab SC 1600 mg (N=88)	Total (N=176)
No. of Patients Randomized	88	88	176
No. Included in Enrolled Patients (ALL)	88	88	176
No. Excluded from Enrolled Patients (ALL)	0	0	0
No. Included in Intent-To-Treat Population (ITT)	88	88	176
No. Excluded from Intent-To-Treat Population (ITT)	0	0	0
No. Included in Pharmacokinetic Evaluable Population (PEP)	69	65	134
No. Excluded from Pharmacokinetic Evaluable Population (PEP)	19	23	42
No. Included in Per-Protocol Population (PPP)	69	60	129
No. Excluded from Per-Protocol Population (PPP)	19	28	47
Subject did not meet all eligibility criteria	6	8	14
Subject treated in a different treatment group as randomized	0	2	2
Not at least five cycles of trial treatment	14	10	24
Incomplete or partial PK data or administration information	19	23	42
No. Included in Safety Analysis Population (SAP)	87	87	174
No. Excluded from Safety Analysis Population (SAP)	1	1	2

[Source: Study report BO25341 page 83]

3.14.4 Results and Conclusions

3.14.4.1 Primary analysis results

Please refer to clinical pharmacology reviewer for this part of the evaluation.

3.14.4.2 Exploratory endpoints analyses results

3.14.4.2.1 Analyses results

The clinical efficacy of response rate is summarized in Table 29. The difference of response rate between rituximab SC and rituximab IV is 4.6% with a 95% confidence interval of -7.2% to 16.3%. The estimated response rate ratio is 1.06, favoring rituximab SC arm with a 95% confidence interval of 0.92 to 1.21.

Table 29 Response Rate Results CLL

Endpoints	IV (95% CI)	SC (95% CI)	Diff: SC-IV (95% CI)	Response Rate 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]

[Source: Statistical reviewer's analysis]

The results of time-to-events endpoints are summarized in Table 30. Rituximab SC arm has fewer events than rituximab IV arm and the hazard ratios are less than 1, favoring rituximab SC. However, all the 95% confidence intervals cover 1. Overall, the clinical efficacy results are comparable between rituximab SC and rituximab IV.

Table 30 Time-to-Event Results CLL

	# of Patients with Events IV; n(%) N=88	# of Patients with events SC; n(%) N=88	HR [95% CI]
PFS	23 (26.1%)	19 (21.6%)	0.89 [0.49, 1.64]
EFS	29 (33%)	22 (25%)	0.76 [0.44, 1.33]
OS	12 (13.6%)	7 (8%)	0.60 [0.24, 1.52]

[Source: Response to FDA’s request Dated Mar. 15, 2017, Page 3, 5, 7]

FDA Comment: The time-to-event results in Table 30 were provided by the applicant in a response to an FDA request. The applicant noted that the time-to-event endpoints including PFS, EFS and OS were not mature at the time of the analysis. The final analysis is planned to occur upon completion of 4 years of follow-up after the last treatment administration (estimated Q4/2017). The FDA has not verified the results because the sponsor has not submitted the patient level data for these endpoints.

3.14.4.3 Conclusions for efficacy

Overall, the clinical efficacy of rituximab SC is comparable to rituximab IV in SAWYER study given the assumption that the time-to-event results can be confirmed.

3.15 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

3.16 Benefit-risk assessment

Overall, the clinical efficacy of rituximab SC is comparable to rituximab IV in SAWYER study. Whether the submission demonstrated an overall favorable risk-benefit profile on Rituximab SC over IV is deferred to the clinical team reviewing this submission.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Study BO22334/SABRINA

4.1 SABRINA Gender, Race, Age and Region

The Table 31 summarizes the exploratory subgroup analysis of ORR by gender, age, region and race for the SABRINA study.

Table 31 ORR at the end of induction by subgroups of gender, race, age and geographic region

Subgroup	Overall Response Rate (CR, CRu, PR) at End of Induction [95% CI]		
	Rituximab IV+chemo N=205	Rituximab SC+chemo N=205	Difference [95% CI]
Gender			
Male	n = 106 83.0% [74.5; 89.6]	n = 85 89.4% [80.8; 95.0]	6.39% [-3.9; 16.7]
Female	n = 99 86.9% [78.6; 92.8]	n = 120 80.8% [72.6; 87.4]	-6.04% [-16.3; 4.2]

[Source: BO22334 study report page 106 and statistical reviewer's calculation]

Subgroup		IV; N=205; 95% CI	SC; N=205; 95% CI	Diff: SC-IV; 95% CI
Race	White	83.1% [76.4, 88.6]	86.6% [80.4, 91.4]	3.5% [-4.7, 11.6]
	Non-white	91.1% [78.8, 97.5]	75.6% [59.7, 87.6]	-15.5% [-32.5, 1.5]
Age	< 65 years	85.0% [78.2, 90.4]	87.7% [81.4, 92.4]	2.6% [-5.5, 10.8]
	>= 65 years	84.5% [72.6, 92.7]	74.5% [60.4, 85.7]	-10% [-26.3, 6.3]
Region	North America & Europe	83.4% [76.8, 88.8]	86.5% [80.3, 91.3]	3.1% [-5.0, 11.2]
	South and Central America	84.2% [60.4, 96.6]	66.7% [43.0, 85.4]	-17.5% [-46.8, 11.7]
	Asia	95.7% [78.1, 99.9]	85.7% [63.7, 97.0]	-9.9% [-29.9, 10]

[Source: statistical reviewer's calculation]

No outlier subgroup was discovered. Large confidence intervals, e.g. south and central America region, are due to small sample size.

4.2 SABRINA Other Special/Subgroup Populations

ORR by chemotherapy regimen and FLIPI score was given in Table 32. No outlier subgroup was discovered.

Table 32 ORR at the end of induction period by chemotherapy regimen and FLIPI scores

Subgroup	Overall Response Rate (CR, CRu, PR) at End of Induction [95% CI]		
	Rituximab IV + chemo N=205	Rituximab SC + chemo N=205	Difference [95% CI]
Chemotherapy Regimen			
CHOP	n = 130 86.2% [79.0; 91.6]	n = 132 87.9% [81.1; 92.9]	1.72% [-6.8; 10.3]
CVP	n = 75 82.7% [72.2; 90.4]	n = 73 78.1% [66.9; 86.9]	-4.58% [-18.1; 9.0]
FLIPI (low risk: FLIPI ≤ 1 ; intermediate risk: FLIPI = 2; high risk: FLIPI ≥ 3)			
Low	n = 44 81.8% [67.3; 91.8]	n = 42 81.0% [65.9; 91.4]	-0.87% [-18.7; 17.0]
Intermediate	n = 66 84.8% [73.9; 92.5]	n = 73 93.2% [84.7; 97.7]	8.30% [-2.9; 19.5]
High	n = 95 86.3% [77.7; 92.5]	n = 90 78.9% [69.0; 86.8]	-7.43% [-18.9; 4.1]

[Source: BO22334 study report page 106 and statistical reviewer’s calculation]

No outlier subgroup was discovered. Large confidence intervals are due to small sample size.

Study MO28107/ MabEase

4.3 MabEase Gender, Race, and Age

The Table 33 summarizes the exploratory subgroup analysis of CR by gender, age, and race for the MabEase study.

Table 33 MabEase CR by Age, Gender and Race

Subgroup	Complete Response Rate (CR, CRu) at End of Treatment [95% CI]		
	Rituximab SC n=381	Rituximab IV n=195	Difference [95% CI]
Age			
<60 years	n = 147 43.5% [35.5 to 51.6]	n = 76 46.1% [34.8 to 57.3]	-2.5% [-16.3 to 11.3]
≥60 years	n = 234 49.1% [42.7 to 55.6]	n = 119 39.5% [30.7 to 48.3]	9.6% [-1.2 to 20.5]
Gender			
Male	n = 209 49.3% [42.5 to 56.1]	n = 100 41.0% [31.4 to 50.6]	8.3% [-3.5 to 20.1]
Female	n = 172 44.2% [36.8 to 51.6]	n = 95 43.2% [33.2 to 53.1]	1.0% [-11.4 to 13.4]
Race			
White	n = 298 47.0% [41.3 to 52.6]	n = 156 42.9% [35.2 to 50.7]	4.0% [-5.6 to 13.6]
Non-White	n = 83 47.0% [36.3 to 57.7]	n = 39 38.5% [23.2 to 53.7]	8.5% [-10.1 to 27.2]

[Source: MP28107 report page 60 and statistical reviewer’s calculation]

No outlier subgroup was discovered. Large confidence intervals are due to small sample size.

4.4 MabEase Other Special/Subgroup Populations

CR by chemotherapy regimen, Body surface area and IPI score was given in Table 34. No outlier subgroup was discovered.

Table 34 MabEase CR by Other Special/Subgroup

Subgroup	Complete Response Rate (CR, CRu) at End of Treatment [95% CI]		
	Rituximab SC n=381	Rituximab IV n=195	Difference [95% CI]
<i>Chemotherapy Regimen</i>			
CHOP-21	n = 345 47.8% [42.6 to 53.1]	n = 173 43.9% [36.5 to 51.3]	3.9% [-5.2 to 13.0]
CHOP-14	n = 36 38.9% [23.0 to 54.8]	n = 22 27.3% [8.7 to 45.9]	11.6% [-12.9 to 36.1]
<i>Body Surface Area</i>			
Low BSA ≤ 1.70 m ²	n = 115 45.2% [36.1 to 54.3]	n = 56 42.9% [29.9 to 55.8]	2.4% [-13.5 to 18.2]
Medium 1.71 m ² -1.90 m ²	n = 123 48.8% [39.9 to 57.6]	n = 65 46.2% [34.0 to 58.3]	2.6% [-12.4 to 17.6]
High BSA > 1.90 m ²	n = 143 46.9% [38.7 to 55.0]	n = 74 37.8% [26.8 to 48.9]	9.0% [-4.7 to 22.8]
<i>IPI Risk Category</i>			
Low	n = 118 51.7% [42.7 to 60.7]	n = 61 57.4% [45.0 to 69.8]	-5.7% [-21.0 to 9.7]
Low-intermediate	n = 114 54.4% [45.2 to 63.5]	n = 57 40.4% [27.6 to 53.1]	14.0% [-1.6 to 29.7]
High-intermediate	n = 94 42.6% [32.6 to 52.5]	n = 47 34.0% [20.5 to 47.6]	8.5% [-8.3 to 25.3]
High	n = 55 29.1% [17.1 to 41.1]	n = 30 26.7% [10.8 to 42.5]	2.4% [-17.4 to 22.3]

[Source: MP28107 report page 60 and statistical reviewer's calculation]

Study MO28457/ PrefMab

4.5 PrefMab Gender, Race, Age, and Geographic Region

The Table 35 summarizes the exploratory subgroup analysis of CR by gender, age, and race for the MabEase study.

Table 35 PrefMab CR by gender, race, age and geographic region

Subgroup		Arm A; N=372; 95% CI	Arm B; N=371; 95% CI
Race	White	92.6% [88.7, 95.5]	91.6% [87.6, 94.7]
	Non-white	86.8% [79.2, 92.4]	89.0% [81.6, 94.2]
Age	< 60 years	87.8% [82.2, 92.2]	88.4% [82.8, 92.7]
	>= 60 years	93.7% [89.3, 96.7]	93.2% [88.6, 96.3]
Region	North America &	91.8% [87.1, 95.1]	90.9% [86.3, 94.3]

	Europe		
	Other	89.8% [84.1, 93.9]	90.8% [85.0, 94.9]
Sex	Male	91.9% [87.0, 95.4]	91.6% [86.7, 95.1]
	Female	89.8% [84.6, 93.8]	90.1% [84.7, 94.0]

[Source: Statistical reviewer's calculation]

No outlier subgroup was discovered. Large confidence intervals are due to small sample size.

4.6 PrefMab Other Special/Subgroup Populations

CR by chemotherapy regimen, Body surface area and IPI score was given in Table 36. No outlier subgroup was discovered.

Table 36 PrefMab CR by IPI score and FLIPI score

Subgroup		Arm A; N=372; 95% CI	Arm B; N=371; 95% CI
IPI Score	Low Risk	86.2% [77.2, 92.7]	90.4% [81.9, 95.8]
	Low Intermediate Risk	86.2% [75.3, 93.5]	83.6% [72.5, 91.5]
	High Intermediate Risk	92.5% [81.8, 97.9]	89.8% [77.8, 96.6]
	High Risk	96.8% [83.3, 99.9]	94.3% [80.8, 99.3]
FLIPI Score	LOW RISK (0-1 ADVERSE FACTORS)	93.1% [77.2, 99.2]	90.9% [75.7, 98.1]
	INTERMEDIATE RISK (2 ADVERSE FACTORS)	94.0% [83.5, 98.8]	94.1% [83.8, 98.8]
	HIGH RISK (>_3 ADVERSE FACTORS)	94.7% [85.4, 98.9]	96.2% [87.0, 99.5]

Study BO25341/ SAWYER

4.7 SAWYER Gender, Race, and Age

The Table 37 summarizes the exploratory subgroup analysis of response rate by gender, age, and race for the SAWYER study.

Table 37 Response Rate by Gender, Race

Subgroup	Response Rate (CR, CRi, PR) at 3 Months of Follow up [95% CI]		
	Rituximab IV N=88	Rituximab SC N=88	Difference [95% CI]
Gender (male vs. female)			
Male	n=53 81.1% [68.0%; 90.6%]	n=62 90.3% [80.1%; 96.4%]	9.19% [-4.7%; 23.1%]
Female	n=35 80.0% [63.1%; 91.6%]	n=26 73.1% [52.2%; 88.4%]	-6.92% [-30.8%; 17.0%]

Subgroup		IV; N=88; 95% CI	SC; N=88; 95% CI	Diff: SC-IV; 95% CI
Race	White	80.3% [69.9, 88.3]	84.5% [75.0, 91.5]	4.3% [-8.0, 16.6]
	Non-white	85.7% [42.1, 99.6]	100% [39.8, 100]	14.3% [-26.2, 54.8]
Age	< 65 years	83.6% [72.5, 91.5]	89.2% [79.1, 95.6]	5.7% [-6.9, 18.2]
	65-70 years	73.3% [44.9, 92.2]	66.7% [38.4, 88.2]	-6.7% [-43.9, 30.5]
	>=70 years	66.7% [22.3, 95.7]	87.5% [47.4, 99.7]	20.8% [-35.5, 77.2]

[Source: Study report BO25341 page 114 and statistical reviewer's analysis]

No outlier subgroup was discovered. Large confidence intervals are due to small sample size.

4.8 SAWYER Other Special/Subgroup Populations

Response rate by Body surface area was given in Table 38. No outlier subgroup was discovered.

Table 38 Response rate by Body Surface Area

Subgroup	Response Rate (CR, CRi, PR) at 3 Months of Follow up [95% CI]		
	Rituximab IV N=88	Rituximab SC N=88	Difference [95% CI]
<i>BSA (low: BSA ≤ 1.81 m²; medium: 1.81 m² < BSA ≤ 2.00 m²; high: BSA > 2.00 m²)</i>			
Low	n=33 78.8% [61.1%; 91.0%]	n=26 73.1% [52.2%; 88.4%]	-5.71% [-30.1%; 18.6%]
Medium	n=29 79.3% [60.3%; 92.0%]	n=31 90.3% [74.2%; 98.0%]	11.01% [-9.1%; 31.1%]
High	n=26 84.6% [65.1%; 95.6%]	n=31 90.3% [74.2%; 98.0%]	5.71% [-13.9%; 25.3%]

[Source: Study report BO25341 page 114 and statistical reviewer's analysis]

5. SUMMARY AND CONCLUSIONS

5.1 Conclusions and Recommendations

Clinical efficacy was evaluated in four randomized clinical trials: SABRINA in patients with FL, MabEase in patients with DLBCL, SAWYER in patients with CLL and PrefMab, a patient preference study in patients with FL or with DLBCL. Although the clinical trials were not designed for efficacy hypothesis testing, the data tend to show that the rituximab and hyaluronidase product and IV arms are comparable and efficacy results are similar across studies.

The results based on the patient-preference questionnaire (PPQ) instrument from the PrefMab clinical trial, demonstrate that 80% of the patients preferred rituximab SC over rituximab IV.

We recommend approval of the rituximab and hyaluronidase product for FL, DLBCL and CLL, the ITT population as designed.

5.2 Labeling Recommendations

The clinical efficacy should be included as a new product labeling. Because the clinical trials were not designed for efficacy hypothesis testing, no inferential statement should be made on the clinical efficacy.

APPENDICES

Results on 2-year survival estimates using Kaplan-Meier survival curves with 95% confidence interval and the corresponding difference and the 95% confidence intervals are provided in Table 39 and Table 40 for SABRINA study and Table 41 and Table 42 MabEase study. Similar results for PrefMab are provided in Table 43.

Table 39 SABRINA 2-year survival estimates; FL

	2-year # with event (%); IV	2-year # with event (%); SC	Rate at 2-Years, IV; 95% CI	Rate at 2-Years, SC; 95% CI	Diff: SC-IV; 95% CI
PFS	35 (17.1)	35 (17.1)	82.1% [76.0, 86.8]	82.1% [76.0, 86.8]	0.0% [-7.6, 7.6]
EFS	40 (19.5%)	42 (20.5%)	79.5% [73.2, 84.6]	78.5% [72.1, 83.7]	-1.0% [-9.1, 7.1]
OS	9(4.4%)	11 (5.4%)	95.4% [91.3, 97.6]	94.4% [90.1, 96.7]	-1.0% [-5.3, 3.4]

Table 40 SABRINA Time-to-event endpoint results

	IV Med (month, 95% CI)	SC Med (month, 95% CI)	# with event (%); IV	# with event (%); SC	HR unstratified; 95% CI	HR Stratified; 95% CI
PFS	54 [45.5, .]	NR	57 (27.8%)	50 (24.4%)	0.84 [0.57,1.23]	0.97 [0.65,1.44]
EFS	54 [45.4, .]	NR [50.2, .]	61 (29.8%)	57 (27.8%)	0.91 [0.64,1.31]	1.03 [0.71,1.50]
OS	NR	NR	20 (9.8%)	16 (7.8%)	0.81 [0.42,1.57]	0.82 [0.41,1.63]

Table 41 MabEase Time-to-event endpoint results

	IV Med (month, 95% CI)	SC Med (month, 95% CI)	# with event (%); IV	# with event (%); SC	HR unstratified; 95% CI	HR Stratified; 95% CI
PFS	NR [31.6,.]	NR [. ,.]	44 (22.6%)	104 (27.3%)	1.22 [0.85,1.73]	1.23 [0.86,1.76]
EFS	NR [31.6,.]	NR [. ,.]	59 (30.3%)	129 (33.9%)	1.11 [0.82,1.51]	1.14 [0.84,1.56]
DFS	NR [28.62,.]	NR [. ,.]	12 (10.4%)	38 (16.0%)	1.52 [0.79,2.91]	1.55 [0.80,3.01]

OS	NR [.,.]	NR [.,.]	29 (14.9%)	63 (16.5%)	1.08 [0.70,1.68]	1.06 [0.68,1.65]
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Table 42 MabEase 2-year survival estimates; DLBCL

	2-year # with event (%); IV	2-year # with event (%); SC	Rate at 2- Year, IV; 95% CI	Rate at 2- Year, SC; 95% CI	Diff: SC-IV; 95% CI
PFS	39 (20%)	100 (26.2%)	77.9% [71.0, 83.4]	69.9% [64.6, 74.7]	-8.0% [-16.0, 0.0]
EFS	53 (27.2%)	124 (32.5%)	70.5% [63.2, 76.7]	64% [58.6, 69.0]	-6.5% [-15.0, 2.0]
DFS	10 (5.1%)	38 (10%)	88.8% [79.5, 94.1]	80.5% [74.0, 85.6]	-8.3% [-17.4, 0.7]
OS	28(14.4%)	59 (15.5%)	84.4% [78.2, 89.0]	83.3% [79.0, 86.8]	-1.1% [-7.7, 5.5]

Table 43 PrefMab 1-year survival estimates

Endpoints	1-year # with event (%); Arm A	1-year # with event (%); Arm B	Rate at 1-Year, Arm A; 95% CI	Rate at 1- Year, Arm B; 95% CI	Diff: Arm A-Arm B; 95% CI
PFS	27 (7.3%)	36 (9.7%)	92.0% [88.6, 94.5]	89.3% [85.5, 92.2]	2.7% [-1.7, 7.1]
EFS	113 (30.4%)	103 (27.8%)	65.1% [59.6, 70.2]	68.2% [62.8, 73.1]	-3.1% [-10.5, 4.3]
DFS	3 (1.9%)	3 (1.83%)	97.2% [90.8, 99.2]	97.2% [91.6, 99.1]	0.0% [-4.6, 4.5]
OS	20 (5.4%)	29 (7.8%)	93.8% [90.5, 96.0]	91.1% [87.4, 93.8]	2.7% [-1.4, 6.9]

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